Research Article

An Integrated Approach of Proposed Pruning Based Feature Selection Technique (PBFST) for Phishing E-mail Detection

(E-pub Ahead of Print)

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Journal Name: Recent Advances in Computer Science and Communications

Formerly Recent Patents on Computer Science (https://www.eurekaselect.com/node/676/)

DOI : 10.2174/2666255814666210322162129 (https://doi.org/10.2174/2666255814666210322162129)

Article ID: e220321192418 (https://www.eurekaselect.com/192418/article)

Journal Home (/node/174415)

Abstract:

Introduction: The entire world is shifting towards electronic communication through Email for fast and secure communication. Millions of people, including organization, government, and others, are using Email services. This growing number of Email users are facing problems; therefore, detecting phishing Email is a challenging task, especially for non-IT users. Automatic detection of phishing Email is essential to deploy along with Email software. Various authors have worked in the field of phishing Email classification with different feature selection and optimization techniques for better performance.

Objective: This paper attempts to build a model for the detection of phishing Email using data mining techniques. This paper's significant contribution is to develop and apply Feature Selection Technique (FST) to reduce features from the phishing Email benchmark data set.

Methods: The proposed Pruning Based Feature Selection Technique (PBFST) is used to determine the rank of feature based on the level of the tree where feature exists. The proposed algorithm is integrated with already developed Bucket Based Feature Selection Technique (BBFST). BBFST is used as an internal part to rank features in a particular level of the tree.

Results: Experimental work was carried out with open source WEKA data mining software using a 10-fold cross-validation technique. The proposed FST was compared with other ranking based FSTs to check the performance of C4.5 classifier with Phishing Email data set.

Conclusion: The proposed FST reduces 33 features out of 47 features which exist in phishing Email dataset and C4.5 algorithm produces remarkable accuracy of 99.06% with only 11 features and it has been found to be better than other existing FSTs.

Keywords: Phishing e-mail detection (https://www.eurekaselect.com/search/aws_search.php?searchvalue=Phishing e-mail detection), Pruning Based Feature Selection Technique (PBFST) (https://www.eurekaselect.com/search/aws_search.php?searchvalue= Pruning Based Feature Selection Technique (PBFST)), classification (https://www.eurekaselect.com/search/aws_search.php?searchvalue= classification), Decision Tree (DT) (https://www.eurekaselect.com/search/aws_search.php?searchvalue= Decision Tree (DT)), gain ratio (https://www.eurekaselect.com/search/aws_search.php?searchvalue= gain ratio), data mining. (https://www.eurekaselect.com/search/aws_search.php?searchvalue= data mining.)

Article Details

Article ID: e220321192418 (https://www.eurekaselect.com/192418/article)
(E-pub Ahead of Print)
DOI: 10.2174/2666255814666210322162129
(https://doi.org/10.2174/2666255814666210322162129)
Price: $95

Article Metrics

PDF: 458

(/terms/termandcondition.html?1)

(https://www.projectcounter.org/counter-user/bentham-science/)

The *HBG2* rs7482144 (C > T) Polymorphism is Linked to HbF Levels but not to the Severity of Sickle Cell Anemia

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J Pediatr Genet

Abstract

Sickle cell anemia (SCA) is a severe disease characterized by anemia, acute clinical complications, and a relatively short life span. In this disease, abnormal hemoglobin makes the red blood cells deformed, rigid, and sticky. Fetal hemoglobin (HbF) is one of the key modulators of SCA morbidity and mortality. Interindividual HbF variation is a heritable trait that is controlled by polymorphism in genes linked and unlinked to the hemoglobin β gene (HBB). The genetic polymorphisms that determine HbF levels are known to ameliorate acute clinical events. About 190 well-characterized homozygous SCA patients were included in this study. Complete blood count (CBC), high-performance liquid chromatography (HPLC), and clinical investigations were obtained from patient's records. Severity scores were determined by using the combination of anemia, complications, total leucocyte count, and transfusion scores. *HBG2* rs7482144 polymorphism was genotyped by using the polymerase chain reaction and restriction fragment length polymorphism. The association between *HBG2* rs7482144 polymorphism and HbF levels as well as the disease severity of SCA were assessed. SCA patients carrying TT genotype were found to have higher HbF levels. In addition, SCA patients with increased severity showed significantly lower levels of hemoglobin, HbF, and hematocrit values. However, the genotypes of *HBG2* rs7482144 polymorphism were not found to be associated with the risk of disease severity. In summary, this study demonstrated that *HBG2* rs7482144 polymorphism is linked with HbF levels, but it does not affect disease severity. The sample sizes used and the pattern of association deduced from our small sample size prevents us from extrapolating our findings further.

Keywords

- sickle cell anemia
- *HBG2* rs7482144 polymorphism
- fetal hemoglobin
- severity scores

Introduction

Sickle cell anemia (SCA) is a widespread and severe single-gene hemoglobin (Hb) disorder.[1] The substitution of nucleotide T for A in codon 6 of HBB gene results in the substitution Glu to Val amino acid leading to impaired β-globin chain synthesis.[2] Sickle cell anemia is characterized by sickle-shaped red blood cells (RBCs) with a relatively short life span and varying degrees of anemia. Complications of SCA includes severe episodes of pain, acute chest syndrome, stroke, hepatomegaly, splenomegaly, renal failure, and susceptibility to bacterial infection.[3] There is a considerable

received
April 27, 2021
accepted after revision
July 8, 2021

Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI https://doi.org/10.1055/s-0041-1733950.
ISSN 2146-4596.

Journal of Applied Biology & Biotechnology Vol. 9(05), pp. 64-69, September, 2021
Available online at http://www.jabonline.in
DOI: 10.7324/JABB.2021.9509

HBB gene cluster haplotype diversity in sickle cell anemia patients of Chhattisgarh, India

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ARTICLE INFO

Article history:
Received on: December 30, 2020
Accepted on: February 09, 2021
Available online: September 01, 2021

Key words:
Sickle cell anemia, *HBB* haplotypes, clinical complications, hematological variables, severity scores

ABSTRACT

Sickle cell anemia (SCA) is one of the hereditary hemoglobin disorders in Indian populations. An exceptionally high prevalence of SCA is observed in the populations of Chhattisgarh. Restriction fragment length polymorphism (RFLP) haplotypes of the beta globin (*HBB*) gene cluster are important as population data, anthropological purpose for tracing migration of SCA allele and predicting the severity of SCA disease. The purpose of this study was to elucidate the *HBB* haplotypes and their correlation with clinical and hematological profile of SCA patients of Chhattisgarh population. The *HBB* gene cluster haplotypes were determined in 190 SCA patients by the polymerase chain reaction-restriction fragment length polymorphism method. Medical records of patients were reviewed to obtain pertinent clinical features, hemoglobin fractions, and other biochemical variables. Among the analyzed patients, 74% had Arab-Indian (AI) haplotype, followed by 21% atypical haplotypes. Senegal, Benin, and Cameroon types of *HBB* haplotypes represented 3%, 1%, and 1% of the patients, respectively. Comparison of various biochemical and hematological variables and clinical complications among various haplotypes did not reveal significant differences. The high frequency of atypical haplotypes observed may have been generated by single and double crossing-over between AI haplotype and normal *HBB* haplotype. Considering the Indian population's genetic structure and diversity, the results of our study should be considered as introductory, and our study can serve as a possible tool for additional studies of SCA in India.

1. INTRODUCTION

Sickle cell anemia (SCA) is an autosomal recessive hemoglobin disorder caused by a mutation in the *HBB* gene. This mutation leads to substitution of valine for glutamic acid at the 6th amino acid position of the β-globin chain. SCA has been found to be more common in Africa, USA, Mediterranean region, Middle-Eastern countries, and in the Indian subcontinent [1]. In 1952, Lehmann and Cutbush [2] reported the first case of SCA in the Indian subcontinent among the Indian tribal population of Nilgiri hills. In the same year, the case of SCA was reported and documented among the tea garden laborers in upper Assam [3]. SCA is common among the populations of India and a higher prevalence is seen among the ST, SC, and OBC population of Chhattisgarh [4]. The clinical presentation of SCA is very diverse and can be modified by many factors that include age, gender, genetics, hematological, and environmental factors [5,6]. The other factors include fetal hemoglobin (HbF), *HBB* gene cluster haplotypes, and simultaneous presence of α-thalassemia or glucose-6-phosphate dehydrogenase deficiency [7].

The *HBB* gene cluster includes epsilon, gamma-G, gamma-A, delta, and beta globin genes. This *HBB* gene cluster spans approximately 70 kilobases on chromosome 11. Several polymorphic sites flanking the *HBB* gene cluster have resulted in the delineation of five *HBB* haplotypes [8,9]. These haplotypes are important for understanding and tracing migration of SCA allele and predicting the severity of SCA disease [10–12]. A better understanding of the *HBB* haplotypes that influence disease severity is important to predict the clinical outcomes in SCA patients. Hence, the purpose of this study was to elucidate the *HBB* haplotypes and their correlation with clinical and hematological profile of SCA patients of Chhattisgarh population.

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ISSN 0974-3618 (Print)
0974-360X (Online)

www.rjptonline.org

RESEARCH ARTICLE

Association of Clinical and Hematological variables with the disease severity in Indian Sickle cell anemia patients

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ABSTRACT:

Sickle cell anemia (SCA) is the most common genetic disorder that is caused due to mutation of the β globin gene. Although SCA is a monogenic disorder, the clinical presentation varies greatly among patients. The present study was designed to be a cross sectional study, aimed at analysing the SCA severity and its association with different clinical, biochemical and hematological variables in SCA patients of Indian origin. About 190 random homozygous SCA patients confirmed by hemoglobin electrophoresis were used in the study. Routine biochemical laboratory (liver function test and Renal function test) and hematologic tests (Total hemoglobin, fetal hemoglobin, hematocrit, MCV and MCH) were done. Values pertaining to complete blood count (CBC), Hb-HPLC and clinical investigations were collected from patient's records. The mean age of patients with severe disease was significantly lesser than the moderate and mild disease patients. The body mass index (BMI) was also significantly lower in severe disease patients compared to the moderate and mild disease. The patients with severe disease had low levels of red blood cells, total hemoglobin (tHb) and fetal hemoglobin (HbF) compared to the other groups. There is no significant difference in the kidney and liver function among various degrees of disease severity. In summary, this study demonstrates that the tHb and HbF and total leucocyte count (TLC) are major prognostic factors for several clinical complications in SCA. Baseline measurement of these important variables is paramount in predicting important aspects of clinical course and improves the quality lives of these children.

KEYWORDS: Sickle cell anemia, Clinical complications, Hematological variables, Severity scores.

INTRODUCTION:

Sickle cell anemia (SCA) is the most common genetic disorder that is caused due to mutation of the β globin gene[1]. Hypoxemia in these individuals leads to hemoglobin polymerization, formation of sickled red blood cells (RBCs) and many of the hallmark events in SCA[2]. RBCs of SCA patients are prone to endogenous free radical mediated oxidant damage[3]. Further, vaso-occlusion or disruption of microvasculature by sickled erythrocyte produces distinctive signs and symptoms of the disease and makes them susceptible to a number of serious complications[4].

Received on 08.11.2020 Modified on 20.12.2020
Accepted on 15.01.2021
Research J. Pharm. and Tech. 2021; 14(10):5254-5257.
DOI: 10.52711/0974-360X.2021.00915

Painful crises are the most common external manifestation of vascular occlusion and are the main reason for hospitalization and medical costs[5]. Other vaso-occlusive events included splenic sequestration and priapism. Recurrence of vaso-occlusion causes progressive organ damage, leading to kidney failure, heart failure, stroke, avascular necrosis, gallstone formation, cognitive impairment, predisposition to infections and other complications[6,7].

Although SCA is a monogenic disorder, the clinical presentation varies greatly among patients. Further, the complication associated with SCA begins in the first year of life and varies with age[8]. In addition, the severity of a particular clinical feature found to vary in different individuals[9,10].

Several studies have proposed methods for estimating severity scores, none satisfying to capture the general severity of the disease due to its unusual clinical

http://journalrip.com doi: 10.34172/jrip.2021.35

Journal of Renal Injury Prevention

Sodium-glucose co-transporter 2 inhibitors (SGLT2i); as a preventive factor of kidney failure in patients with type 2 diabetes; a meta-analysis of randomized controlled trials

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ARTICLE INFO

Article Type:
Review

Article History:
Received: 3 June 2021
Accepted: 23 August 2021
Published online: 9 September 2021

Keywords:
Sodium-glucose transporter 2 inhibitors, Chronic kidney disease, Type 2 diabetes mellitus, Acute kidney injury, Meta-analysis

ABSTRACT

Introduction: Sodium-glucose co-transporter 2 inhibitors (SGLT2i) are a new class of anti-diabetic drugs. SGLT2 inhibitors lower blood glucose levels by decreasing glucose reabsorption in the proximal renal tubule, resulting in increased urinary glucose and sodium excretion.
Objective: This study was conducted to investigate the effects of SGLT2i on individual renal outcomes in diabetic patients.
Methods: This study was a systematic review and meta-analysis of clinical trials. A comprehensive search of Cochrane Central Register of Controlled Trials was conducted in the Cochrane Library and PubMed, to identify relevant articles focusing on SGLT2i and chronic kidney disease (CKD) in diabetic patients. The most recent article search was conducted on July 12, 2021.
Results: Seven randomized controlled trials (RCTs) were included in the meta-analysis. Two trials were comparing dapagliflozin, two comparing empagliflozin, one comparing ertugliflozin, one comparing canagliflozin, and one comparing sotagliflozin. Composite renal outcome and acute kidney injury (AKI) was found in seven and four studies, respectively. Data on end-stage kidney disease (ESKD) and albuminuria or initiation of renal replacement therapy were reported in the two studies. The pooled risk ratio (RR) 95% confidence interval (CI) for the composite renal outcome was 0.54 (0.50–0.59), with 92 % heterogeneity. The pooled RR for AKI was 0.77 (0.66–0.89), with no heterogeneity. A significant lower incidence of albuminuria (RR: 0.69; 95% CI: 0.59–0.81), initiation of renal replacement therapy (RR: 0.71; 95% CI: 0.58–0.87), was observed following the use of SGLT2 inhibitors.
Conclusion: Our findings confirm that the SGLT2 inhibitors can reduce the risk of albuminuria, AKI and renal replacement therapy in ESKD patients with T2D (type 2 diabetes). These meta-analyses provide substantial evidence supporting the beneficial effect of SGLT2 inhibitors on reducing CKD events in individuals with T2D.

Review

Implication for health policy/practice/research/medical education:
Sodium-glucose co-transporter 2 inhibitors (SGLT2i) lower blood glucose by reducing glucose reabsorption. SGLT2i was found to be beneficial in diabetic patients in randomized controlled trials. The current meta-analysis found that SGLT2 inhibitors may reduce the risk of kidney damage in T2D patients..

Please cite this paper as: Jahangiri D, Padhi UN, Kumar Verma HK, Lakkakula BVKS, Valizadeh R, Nasri H. Sodium-glucose co-transporter 2 inhibitors (SGLT2i); as a preventive factor of kidney failure in patients with type 2 diabetes; a meta-analysis of randomized controlled trials. J Renal Inj Prev. 2021; 10(4): e35. doi: 10.34172/jrip.2021.35.

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Journal of Oral Biosciences xxx (xxxx) 1–6

Contents lists available at ScienceDirect

Journal of Oral Biosciences

journal homepage: www.elsevier.com/locate/job

Original Article

Interleukin-6 gene -174G>C promoter polymorphism reduces the risk of periodontitis in Brazilian populations: A meta-analysis

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ARTICLE INFO

Article history:
Received 10 May 2021
Received in revised form 20 August 2021
Accepted 24 August 2021

Keywords:
Genetic factors
Periodontitis
IL6 -174G > C polymorphism
Meta-analysis

ABSTRACT

Introduction: Periodontitis is a multifactorial host-mediated oral disease caused by microbes. Previous studies suggested that interleukin-6 (IL-6) gene promoter polymorphism (-174G > C) are associated with the risk of periodontitis, although the results were inconclusive. This study investigated the association between IL-6 -174G > C polymorphism and susceptibility to periodontitis.

Method: A comprehensive search was conducted in PubMed, EMBASE, Web of Science, and Google Scholar databases to retrieve relevant studies. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to assess the strength of the association between 174G > C polymorphism and the risk of periodontitis. Cochrane Q and I^2 statistics were used to measure heterogeneity between studies. Publication bias was estimated using Begg's funnel plots and Egger's test.

Results: Our results showed significant differences in the allelic (C vs. G: OR = 0.82, CI = 0.65–1.03), recessive (CC vs. GC + GG: OR = 0.69, CI = 0.42–1.13), and dominant (GC + CC vs. GG: OR = 0.85, CI = 0.68–1.18) genetic models of the IL6 -174G > C polymorphism and risk of periodontitis. Further, subgroup analysis showed decreased susceptibility to periodontitis associated with IL6 -174 G > C in a Brazilian population (C vs. G: OR = 0.60, CI = 0.41–0.88; GC + CC vs. GG: OR = 0.57, CI = 0.42–0.78) but not in Asian or Caucasian populations.

Conclusion: The findings of this study revealed that the IL6 -174 "C" allele is protective against periodontitis in the Brazilian population.

1. Introduction

Periodontitis is a multifactorial host-mediated oral disease caused by microbes associated with chronic inflammation of the gums, progressive bone loss, and destruction of tooth-supporting structures [1]. Indigenous bacterial environments and adapted host responses play crucial roles in the development and progression of disease [2]. Periodontitis etiology is influenced by genetic factors, particularly those involved in the development of the immune response [3]. Specific pathogen-associated molecular patterns, such as lipopolysaccharide and bacterial virulence factors, have been found to induce inflammatory host responses through the regulation of cytokine expression [4]. It was previously reported that there is a correlation between the risk of periodontitis and human genetic polymorphisms in various populations [5].

Certain cytokine gene polymorphisms have recently been shown to play a crucial role in the development of periodontitis-related immune pathogenesis, including interleukin-6 (IL-6), IL-1, IL-8 IL-10 and tumor necrosis factor-α [6]. Thus, qualitative changes in the levels of these markers might be of diagnostic and therapeutic significance. In this context, periodontitis can be considered a complex disease, with genetic and environmental factors influencing its clinical phenotype. IL-6 is a pleiotropic cytokine released by different tissues, including leukocytes, adipocytes, endothelial cells, fibroblasts, and myocytes [7]. In addition to innate immune activation, IL-6 is involved in bone metabolism and hematopoiesis [8]. The discovery of increased levels of IL-6 in cervical gingival fluid and gingival tissues led to extensive studies on the association between IL-6 and periodontitis [9]. The gene encoding

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https://doi.org/10.1016/j.job.2021.08.003
1349-0079/

Original Article

American Cleft Palate–Craniofacial Association

The Cleft Palate-Craniofacial Journal
1-6

DOI: 10.1177/1055665621 1046486
journals.sagepub.com/home/cpc
SAGE

Association Between *MTHFD1* 1958G > A Variant and non-Syndromic Cleft lip and Palate: An Updated Meta-Analysis

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Abstract

Introduction: Non-syndromic cleft lip and palate (NSCLP) is one of the most common and challenging congenital deformities worldwide. Previous research has linked the methylenetetrahydrofolate dehydrogenase1 (MTHFD1) gene to orofacial cleft (OFC) susceptibility via a complex metabolism. Studies analyzing the *MTHFD1* 1958G > A variant and NSCLP are contradictory. This study aims to evaluate the association between the *MTHFD1* 1958G > A variant and NSCLP by meta-analysis.

Methods: PubMed, Web of Science, MEDLINE, and Google Scholar databases were searched to retrieve the eligible studies. A fixed- or random-effect model was used to calculate pooled odds ratio (OR) and 95% confidence interval (CI). All analyses were calculated by Metagenyo software. To detect heterogeneity, the Cochrane Q and I^2 statistics were used. The publication bias was estimated using funnel plots and Egger's test.

Results: Our study suggested that the *MTHFD1* 1958G > A variant allele "A" does not appear to increase the risk of NSCLP (A vs G random effect model: Overall $P = .501$, OR = 1.07, CI = 0.88–1.31; Asians $P = .245$, OR = 1.29, CI = 0.84–1.97; Caucasians $P = .658$, OR = 0.95, CI = 0.76–1.19). Similarly, mutant genotypes also did not exhibit increased risk for NSCLP in the overall populations as well in subgroup analysis by ethnicity (AA + AG vs GG: Overall $P = .684$, OR = 1.06, CI = 0.80–1.39; Asians $P = .240$, OR = 1.47, CI = 0.77–2.78; Caucasians $P = .923$, OR = 0.99, CI = 0.85–1.16).

Conclusions: Our data suggest no association between the *MTHFD1* 1958G > A variant and NSCLP. Additional well-designed studies are needed to better understand the role of *MTHFD1* polymorphisms in the etiopathogenesis of NSCLP.

Keywords
MTHFD1, rs2236225, 1958G > A, NSCLP, SNP, meta-analysis

Introduction

Non-syndromic cleft lip and palate (NSCLP) is one of the most challenging congenital deformities with complex phenotypes that can leave the patients with a lifelong disability (Mossey et al., 2011; Wehby et al., 2012). Several epidemiological studies have shown that the prevalence of NSCLP is ~0.37%–1.53%, but birth defects vary by gender, ethnicity, and geographic location. American Indians had the highest prevalence rate of 2.62 per 1000 live births. While Caucasians had an intermediate birth rate of 1 per 1000 live births, Africans had the lowest prevalence rate of about 1 in 2000 (Panamonta et al., 2015). Based on anatomy, the orofacial clefts (OFCs) can be divided into the cleft palate and palate (CLP), cleft palate only (CPO), and the cleft lip only (CL). Non-syndromic CLPs account for about 70% of CLP.

Precise gene identification for NSCLP is difficult and complex due to the involvement of genetic and environmental factors (Howe et al., 2019). The complex nature of the NSCLP is attributed to multiple interactive genes, which confer moderate effects and are proposed to provide susceptibility to the OFCs. Recent studies have shown that folic acid may have a

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J Prev Epidemiol. 2021;6(1):e08 Review

doi 10.34172/jpe.2021.08 Journal of Preventive Epidemiology http jprevepi.com

World Kidney Day 2021 with the theme of living well with kidney disease; a review of current concepts

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Received: 17 Apr. 2021
Accepted: 20 May 2021
ePublished: 3 Aug. 2021

Keywords: World Kidney Day (WKD), Women, Obesity, Aging, Hypertension, Diabetes, Poverty, Acute renal injury

Citation: Bahadoram M, Labaykee S, Lakkakula BVKS, Keikhaei B, Nekouei Shahraki M, Mohammadi Jouabadi S, Onuigbo M, Ahmadizar S, Mahmoudian-Sani MR, Peymani P. World Kidney Day 2021 with the theme of living well with kidney disease: a review of current concepts. J Prev Epidemiol. 2021;6(1):e08. doi: 10.34172/jpe.2021.08.

Abstract

Since 2006, by considering one dimension of kidney disease, each year, the International Society of Nephrology (ISN) and the International Federation of Kidney Foundations (IFKF) have consistently and unanimously declared a World Kidney Day (WKD) around a specific kidney disease to increase the global awareness about kidney diseases. WKD, which is celebrated in more than 150 countries worldwide, is an international kidney health awareness campaign emphasizing the importance of the kidneys to reduce the global prevalence of kidney diseases and their related health problems by promoting patients and providing education. The present review aims to summarize the themes of previous WKD campaigns and the advocacy of the 2021 WKD campaign theme "Living well with kidney disease". The 2021 WKD Steering Committee advocates for the empowerment of CKD patients, their family members, and care partners, along with both drug and non-drug therapeutic programs to achieve better health outcomes.

Introduction

The International Society of Nephrology (ISN) and the International Federation of Kidney Foundations (IFKF) have jointly celebrated the "World Kidney Day (WKD)" on the second Thursday of March each year. Since 2006, WKD has been celebrated to increase awareness of the importance of the kidneys on our health to reduce the global burden of kidney diseases and their associated health problems. WKD is commemorated every year in more than 150 countries around the world. This review covered all the WKD's experiences and campaigns from the time of initiation of WKD to date to highlight the activities of the ISN and the IFKF during these years.

Methods of study

For this narrative review, a comprehensive search was conducted in PubMed, Google Scholar and Web of sciences databases. The keywords included World Kidney Day, chronic kidney disease and acute kidney injury. To summarize the current state of research on this topic, case reports, review articles, and original articles related to this topic were retrieved.

Key point

Chronic kidney disease (CKD) is associated with many complications and results in significant hardship for their care-partners. Unawareness of illness and lack of health professionals support make it difficult to live with a person with a chronic illness. The 2021 WKD Steering Committee calls for increased awareness and preventive measures using both drug and non-drug therapeutic programs.

Retrospection on previous WKD campaigns

The theme for WKD in 2006 was "Are your kidneys OK?", which was a very successful campaign to raise awareness about the importance of kidney disease and kidney health among policymakers and the general public. Through interviews with patients and other community awareness programs, and with the help of the media, public attention and the attention of policy makers have continued to increase. The mission was to positively influence behaviors and attitudes of individuals towards early detection, prevention, and early treatment of kidney diseases (1). Further, the focus of this campaign was on early detection, treatment,

BLOOD RESEARCH
VOLUME 56 · NUMBER 2
June 2021
REVIEW ARTICLE

Association of hypercoagulation with severe acute respiratory syndrome coronavirus 2 infection

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p-ISSN 2287-979X / e-ISSN 2288-0011
https://doi.org/10.5045/br.2021.2021011
Blood Res 2021;56:61-64.

Received on January 20, 2021
Revised on April 19, 2021
Accepted on April 26, 2021

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic has emerged as a major threat to all healthcare systems across the globe, and it was declared a public health emergency of international concern by the World Health Organization (WHO). The novel coronavirus affects the respiratory system, producing symptoms such as fever, cough, dyspnea, and pneumonia. The association between COVID-19 and coagulation has been previously reported. Due to several inflammatory changes that occur in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections such as alterations in the levels of clotting factors, platelet activation leads to thrombus formation in coronary and cerebral vessels, leading to myocardial infarction and cerebrovascular accidents, respectively. Unfortunately, the progression of hypercoagulability in COVID-19 is rapid in patients with and without comorbidities. Hence, the proper monitoring of thrombotic complications in patients with COVID-19 is essential to avoid further complications. The implementation of guidelines for antithrombotic treatments based on the presentation of the disease is recommended. This review discusses the symptoms and mechanisms of upregulated coagulation in patients with COVID-19.

Key Words COVID-19, SARS-CoV-2, Hypercoagulation, Thrombosis, Stroke, D-dimer

INTRODUCTION

At the end of December 2019, there was an unusual emergence of pneumonia cases of unknown origin in Wuhan, Hubei province, China [1]. All the patients had a history of exposure to the Huanan seafood market. Throat swabs were collected from all the suspected patients, and the causative agent was found to be a coronavirus by the Chinese Centre for Disease Control and Prevention; subsequently, the disease was named as coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) [2, 3]. COVID-19 is known to be caused by SARS-CoV-2, a member of the human-infecting betacoronavirus. Previous outbreaks such as severe acute respiratory syndrome (SARS) in China in 2002–2003 and Middle East respiratory syndrome in Saudi Arabia in 2011 were also attributed to the zoonotic origin of betacoronavirus [4]. These coronaviruses can also cause respiratory, hepatic, and central nervous system-related diseases [5]. Further epidemiological investigation showed that the zoonotic origins were rhinolophid bats (natural hosts) and pangolin mammals (intermediate hosts) [6]. An increasing number of COVID-19 cases were reported from other countries, and the WHO has raised a public health emergency of international concern [3].

The virus infects humans through various modes of transmission such as direct contact with an infected person via coughing, sneezing, or through other body fluids; inhalation of infected droplets; and, indirect contact with the surface used by infected persons (according to the WHO) [7]. When the SARS-CoV-2 enters the lower respiratory tract, it binds to the angiotensin-converting enzyme 2 (ACE) receptors, causing the downregulation of the renin-angiotensin system and increased vascular permeability, resulting in pulmonary edema and acute respiratory distress syndrome (ARDS) [1, 5, 8]. An attack of SARS-CoV-2 on ACE2 receptors triggers the activation of T cells and increases the release of pro-inflammatory mediators, causing various other outcomes [9]. A recent study in China reported that the most common symptoms of the SARS-CoV-2 infection were fever (98%), cough (76%), and fatigue (44%), and the least-common symptoms were headache (8%), hemoptysis (5%), and diarrhea

Seminars in Cancer Biology 69 (2021) 293–306

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Review

Engineered nanoparticles for imaging and drug delivery in colorectal cancer

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ARTICLE INFO

Keywords:
Colorectal cancer
Chemotherapy
Nanoparticle
Imaging
Drug delivery

ABSTRACT

Colorectal cancer (CRC) is one of the deadliest diseases worldwide due to a lack of early detection methods and appropriate drug delivery strategies. Conventional imaging techniques cannot accurately distinguish benign from malignant tissue, leading to frequent misdiagnosis or diagnosis at late stages of the disease. Novel screening tools with improved accuracy and diagnostic precision are thus required to reduce the mortality burden of this malignancy. Additionally, current therapeutic strategies, including radio- and chemotherapies carry adverse side effects and are limited by the development of drug resistance. Recent advances in nanotechnology have rendered it an attractive approach for designing novel clinical solutions for CRC. Nanoparticle-based formulations could assist early tumor detection and help to overcome the limitations of conventional therapies including poor aqueous solubility, nonspecific biodistribution and limited bioavailability. In this review, we shed light on various types of nanoparticles used for diagnosis and drug delivery in CRC. In addition, we will explore how these nanoparticles can improve diagnostic accuracy and promote selective drug targeting to tumor sites with increased efficiency and reduced cytotoxicity against healthy colon tissue.

1. Introduction

Colorectal Cancer (CRC) is the third-most commonly diagnosed cancer in the US after breast and lung cancers and ranks second in mortality. CRC is more commonly diagnosed in males than females. Approximately 1.096 million CRC cases were diagnosed in 2018 with 551,269 estimated deaths [1]. Hence, CRC represents the most prevalent cause of cancer-related deaths, resulting from its distant metastatic nature. Conventional adjuvant therapies for CRC including chemo, radiotherapies and biological agents have improved cancer therapy, but they

Abbreviations: AuNPs, gold nanoparticles; CEA, carcino embryonic antigen; CLM, colorectal liver metastasis; DOX, doxorubicin; DPYD, dihydropyrimidine dehydrogenase; EPR, enhanced permeability and retention; hENT1, human equilibrative nucleoside transporter 1; HPβCD, hydroxypropyl β-cyclodextrin; ICD, immunogenic cell death; IDO, indoleamine 2,3-dioxygenase; ITM, immunosuppressive microenvironment of tumor; isoCA-4, isocombretastatin A-4; LbL, layer-by-layer carrier system; LCL, long circulating liposome; LDH, layered double hydroxide; MCM, mobil composition of matter; MDR, multidrug resistance; MDT, magnetic drug targeting; MSN, mesoporous silica nanoparticle; MUC, mucin; NPs, nanoparticles; PCL, poly capro lactone; PDL, programmed cell death ligand; PDT, photodynamic therapy; pDNA, plasmid DNA; PEG, polyethylene glycol; PLGA, poly lactic-co-glycolic acid; PNA, peanut agglutinin; PTT, photothermal therapy; QD, quantum dots; SERS, surface enhanced Raman spectroscopy; SLN, solid lipid nanoparticle; SQ, squalene; VEGF, vascular endothelial growth factor.

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https://doi.org/10.1016/j.semcancer.2019.06.017
Received 2 June 2019; Received in revised form 18 June 2019; Accepted 27 June 2019
Available online 29 June 2019
1044-579X/

World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2021 February 14; 27(6): 449-469

DOI: 10.3748/wjg.v27.i6.449

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Current understanding of the impact of COVID-19 on gastrointestinal disease: Challenges and openings

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Author contributions: Verma HK contributed to the conceptualization, investigation and supervision; Verma HK and Bhaskar LVKS contributed to the methodology; Verma HK and Vishvakarma NK contributed to the software; Sahu T, Mehta A, Jaiswal A and Ratre YK contributed to the article search and writing the original draft; Sahu T, Ratre YK, Verma HK, Vishvakarma NK and Bhaskar LVKS contributed to the writing, reviewing, and editing of the manuscript.

Conflict-of-interest statement: No conflict of interest.

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Abstract

The novel coronavirus disease-2019 (COVID-19) is caused by a positive-sense single-stranded RNA virus which belongs to the Coronaviridae family. In March 2019 the World Health Organization declared that COVID-19 was a pandemic. COVID-19 patients typically have a fever, dry cough, dyspnea, fatigue, and anosmia. Some patients also report gastrointestinal (GI) symptoms, including diarrhea, nausea, vomiting, and abdominal pain, as well as liver enzyme abnormalities. Surprisingly, many studies have found severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral RNA in rectal swabs and stool specimens of asymptomatic COVID-19 patients. In addition, viral receptor angiotensin-converting enzyme 2 and transmembrane protease serine-type 2, were also found to be highly expressed in gastrointestinal epithelial cells of the intestinal mucosa. Furthermore, SARS-CoV-2 can dynamically infect and replicate in both GI and liver cells. Taken together these results indicate that the GI tract is a potential target of SARS-CoV-2. Therefore, the present review summarizes the vital information available to date on COVID-19 and its impact on GI aspects.

Key Words: SARS-CoV-2; COVID-19; Gastrointestinal symptoms; Recommendation; Diagnosis; Therapeutics

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CNS & Neurological Disorders - Drug Targets, , 2021, 1-0

REVIEW ARTICLE

A Review on Hematopoietic Stem Cell Treatment for Epilepsy

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ARTICLE HISTORY

Received: June 30, 2020
Revised: October 11, 2020
Accepted: November 23, 2020

DOI:
10.2174/1871527320666210218085816

Abstract: Epilepsy responds to pharmacotherapy in its initial stages. The response of some forms of epilepsy, like the refractory epilepsy, is extremely low. Surgical management of epilepsy is associated with complications, which necessitates the search for novel and modern strategies for the treatment of epilepsy. Neuroprotection and neuronal regeneration are the major targets that must be accomplished by the new strategies. Hematopoietic stem cell (HSCs) therapy for epilepsy has shown promising results in pre-clinical studies with marginal clinical effects. This review explores the characteristics, mechanism of action, and clinical significance of HSCs therapy for the treatment of epilepsy.

Keywords: Neuroprotection, neuronal regeneration, antiepileptic property.

1. INTRODUCTION

Epilepsy is defined as constant and unprovoked seizures. Seizure is caused due to excessive, hyper synchronous, and paroxysmal discharge of neurons in the brain. The seizure caused by reversible insult cannot be considered as epilepsy [1]. Epilepsy is a neurological disorder with an incidence of 50 per 1,00,000 persons per year. Around 75% of epilepsy initiates during childhood [2]. In 2016, the global burden of this, according to Neurology Collaborators, was reported to be 46 million worldwide [3]. The incidence rate was reported to be elevated in low and middle-income countries (LMIC) (139/100000 population) as compared to high-income countries (HIC) (48.9/100000 population) [4, 5]. Male preponderance was reported in both incidence and prevalence of epilepsy [6]. The mortality ratio in HIC and LMIC was reported to be 1.6 to 3.0 and 19.8, respectively [7, 8].

Epilepsies are classified based on lesion site and etiology [9]. The International league against epilepsy classified seizures as generalized, focal, and epileptic spasms [9-11]. Seizure is generally focal in the beginning and later becomes generalized. The focal seizures originate from neuronal pathways confined to one part of the brain. The generalized seizures originate from bilateral neuronal pathways. The generalized/grand mal seizures are further classified into tonic-clonic seizures, absence seizures, myoclonic seizures, and atonic seizures. The absence/petit mal seizures may be typical or atypical. The generalized seizures are characterized by convulsive movements of all limbs with bilateral symmetry and disturbance in consciousness. The focal seizure manifestations are based on the area of brain which is involved. The myoclonic seizures are characterized with sudden and brief movements without disturbance in consciousness. Atonic seizures are characterized by loss of body tone associated with head drop and falls.

The etiology of epilepsy includes intracranial neoplasms, head injury, hippocampal sclerosis, congenital brain malformation, and birth trauma [12]. Pathophysiologically, a seizure may result from an imbalance between inhibitory GABA and excitatory glutamate/aspartate (Fig. 1). The potential membrane recordings during seizures exhibit a paroxysmal depolarization shift and upshift in internal potential causing recurrence in action potentials [13]. Diagnosis of epilepsy is mainly based on the history of the patient and neurological examinations. The electroencephalography (EEG), imaging techniques, and laboratory investigations are adjunctives. The EEG can detect abnormal activities characterized as focal spikes that are observed in focal seizures and diffuse bilateral waves for generalized seizures [14]. Only 50% of the patients exhibit abnormal EEG [13]. The neuroimaging techniques include CT, MRI, fMRI, MR, PET, SPECT, and MEG techniques [15]. MRI is preferred over CT due to its high sensitivity for detection of hippocampal sclerosis and cortical malformations. MRI findings may be correlated with EEG recordings. fMRI and MR localize the seizure activity [16]. All these imaging techniques aid the pre-surgical evaluations and surgical interventions [17]. Laboratory investigations for mitochondrial diseases, glucose transporter defects, neurotransmitter defects may demonstrate the type of seizure. Mitochondrial disease is evaluated with serum amino acids, blood lactate, and urine organic acids [18, 19]. Various antiepileptic treatments have been addressed in this review. Ineffective antiepileptic drug therapies and adverse events associated with alternative treatment strategies have warranted the development of novel therapeutic strategies. Stem cell therapies hold the most significance amongst these novel approaches with a rationale of stabilising the pathological events both locally and systemically

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1871-5273/ $65.00+.00

Contents lists available at ScienceDirect

International Journal of Pediatric Otorhinolaryngology

journal homepage: http://ees.elsevier.com

Genetic variations at 10q26 regions near FGFR2 gene and its association with non-syndromic cleft lip with or without cleft palate

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ARTICLE INFO

Keywords
FGFR2
TDT analysis
NSCL/P
Haplotype transmission
Parent-of-origin effects

ABSTRACT

Objectives: In our study, we focussed on three SNPs in the non-coding regions near *FGFR2* gene, as studies on non-coding variants in the genome are the novel trends to identify the susceptible loci for nonsyndromic cleft lip with or without cleft palate (NSCL/P). *FGFR2* gene is selected as a candidate gene based on knock out animal models and the role played in syndromic forms of clefting. *FGFR2* gene also plays an important role in FGF signaling pathway during craniofacial development.

Methods: In the present study 148 case-parent triads were assessed for three SNPs rs10749408, rs11199874 and rs10788165 near *FGFR2* gene by using TaqMan allelic discrimination method. Transmission disequilibrium test (TDT) was used to find the allelic association. Linkage disequilibrium (LD) between the markers was analysed using Haploview program 4.2. Haplotype transmission effects were estimated using FAMHAP package. The possible parent-of-origin effects were assessed by likelihood based approach.

Results: TDT analysis of three SNPs failed to show significant transmission distortion from heterozygous parents to the affected child and are not associated with NSCL/P. Linkage disequilibrium analysis showed strong LD between rs11199874 and rs10788165 SNPs. In the haplotype TDT analysis, GG haplotype of rs11199874-rs10788165 showed significant undertransmission to affected child. No significant parent-of-origin effects were observed.

Conclusion: The present study on noncoding variants near *FGFR2* gene is not associated with NSCL/P. As the numbers of triads included in the study are less, further studies are needed including large sample size to find association with NSCL/P.

1. Introduction

Nonsyndromic cleft lip with or without cleft palate (NSCL/P) is a polygenic multifactorial disorder characterized by complex inheritance pattern including the involvement of environmental factors contributing to its etiology [1]. By applying genetic and epidemiological methods, several candidate genes and loci associated with NSCL/P have been identified. Genes responsible for growth factors and their receptors, transcription factors, polarizing signals, cell adhesion molecules and extracellular molecules have been identified as major contributing factors [2,3]. Of these, various studies have shown that the genes in the fibroblast growth factor (FGF) signalling pathway are excellent candidate genes for nonsyndromic oral clefts [4–6]. Various birth defects that affect the craniofacial structural development are attributed to several members of this family of signalling molecules. Around 22 mammalian FGF ligands and seven receptors (FGFRs) have been recognized as of the date [7]. Mutations in FGFR genes 1–3 are strongly associated with craniosynostosis syndrome [8] These FGF proteins forms four highly conserved FGF receptors (FGFR 1–4) with FGFR2 being the most commonly mutated FGF receptor [8–10]. And mutations in *FGFR2* gene are associated with more than five craniosynostosis syndromes such as Crouzon syndrome, Jackson-Weiss syndrome, Apert syndrome, Pfeiffer syndrome and Beare-Stevenson syndrome. Till now four different mutations in *FGFR2* have been identified as a causative factor in Apert syndrome [11]. Moreover 75% of Apert syndrome patients have developed cleft in the palate [4]. Stanier et al., in 2004, proposed that candidate genes for NSCL/P can also be selected based upon their role in syndromic forms which exhibit cleft phenotype and common variants in these genes could contribute to the development of relatively less severe non-syndromic forms of clefts [12]. In addition this gene is also known to play significant role in orofacial development particularly in epithelial-mesenchymal interaction during the fusion of facial prominence [4–6]. Activation of Sonic hedgehog *(Shh)* proteins is the downstream target of FGFR2 signalling pathway in human orofacial development [13]. Gene knock out animal model of *fgfr2b−/−*have also been reported to develop cleft in the palate. Taking these factors into consideration *FGFR2* gene from FGF signalling pathway and 3 SNPs from the non-coding regulatory regions of this gene were selected to find its association with NSCL/P.

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https://doi.org/10.1016/j.ijporl.2021.110648

Meta Gene 28 (2021) 100870

Contents lists available at ScienceDirect

Meta Gene

journal homepage: www.elsevier.com/locate/mgene

Susceptibility to vascular complications in sickle cell anemia patients is associated with intron 4a/b polymorphism of the *NOS3* gene: A meta-analysis

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ARTICLE INFO

Keywords:
NOS3
Polymorphisms
Vascular complications
Sickle cell anemia
Meta-analysis

ABSTRACT

Background: Sickle cell anemia (SCA) is characterized by chronic hemolysis and vaso-occlusive episodes. The endothelial dysfunction in SCA may be due to the deficiency of nitric oxide. The association between nitric oxide synthase (*NOS3*) gene polymorphisms (−786 T > C, 894G > T and Intron 4a/b) and risk of vascular complications remains elusive.

Objective: Here we performed a meta-analysis to evaluate the relationship between NOS3 gene polymorphisms and vascular complications of SCA.

Methods: Ten previously published articles were retrieved from PubMed, and Embase bibliographic databases. This meta-analysis included, eight papers (463 SCA patients with complications and 333 without complications) that pertained to the NOS3 -786 T > C, five papers (235 SCA patients with complications and 191 without complications) that corresponded to the NOS3 894G > T polymorphism and six papers (391 SCA patients with complications and 292 without complications) that involved the *NOS3* intron 4a/b polymorphism. Pooled analysis, sensitivity analysis and assessment of publication bias were performed.

Results: Results of pooled analysis revealed that the *NOS3* Intron 4a/b polymorphism was significantly associated with an increased risk of vascular complications (aa+ab Vs. bb: odds ratio = 3.28, 95% confidence interval = 1.19–9.02, $p = 0.022$, random-effect model). However, no significant association was found for NOS3 -786 T > C and 894G > T polymorphisms.

Conclusion: Despite some limitations, our meta-analysis suggests that *NOS3* Intron 4a/b polymorphism is associated with four fold-increased risk of vascular complications in sickle cell anemia.

1. Introduction

Sickle cell anemia (SCA) is an autosomal recessive genetic disorder that affects hemoglobin structure, and is characterized by chronic hemolysis (Bhaskar and Patra, 2015). The clinical outcomes range widely from mild to severe with acute to chronic clinical complications, including vaso-occlusive episodes (VOE), multi-organ damage, painful crisis and higher early mortality risk (Adewoye et al., 2008; Lakkakula et al., 2018). The development of tissue and organ complications in childhood is postponed to older ages with the application of the vaccination program and the development of clinical care (Ballas, 2018). Recurrent acute vaso-occlusive episodes are the main clinical problem responsible for the frequent hospitalizations for these patients (Bunn, 1997). Vaso-occlusive crisis is a characteristic manifestation of SCA and is associated with abnormalities in the ratio of vasoconstrictor to vasodilator prostanoids (Potoka and Gladwin, 2015). The endothelial dysfunction in SCA may be due to the deficiency of nitric oxide. In transgenic sickle cell mice model, it has been shown that nitric oxide (NO) synthesized by endothelial nitric oxide synthase (eNOS) protects the mice from VOEs (Bartolucci et al., 2007).

NO is a small gaseous free radical molecule exerting a variety of biological actions under both physiological and pathological conditions (Hirst and Robson, 2011). Over the past decade, much research has been conducted to known the importance of NO in SCA patients. It is now established that the decreased NO availability play a major role in SCA pathophysiology (Mack and Kato, 2006). A strong correlation between low levels of nitrite (reflect high NO concentration) and high levels of fetal hemoglobin in SCA patients at baseline was documented (Ellas et al., 2012). Moreover, a recent study demonstrated a significant reduction in mean NO levels during vaso-occlusive complication in

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https://doi.org/10.1016/j.mgene.2021.100870
Received 22 October 2020; Received in revised form 19 December 2020; Accepted 7 February 2021
Available online 16 February 2021

Journal of Drug Delivery Science and Technology 63 (2021) 102487

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Review article

Nanotechnology based drug delivery system: Current strategies and emerging therapeutic potential for medical science

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ARTICLE INFO

Keywords:
Nanotechnology
Nano medicine
Therapeutics
Diagnosis
Drug delivery
Drug development

ABSTRACT

Nanotechnology or Nano medicine has been identified as the dominant and most commercially invented technology that aims to improve the quality of health care strategies. Although nanotechnology has some limitations, many pharmaceutical and medical equipment companies have already adhered to medical nanotechnology. In some cases, drugs with high toxic potential, such as chemotherapeutic cancer drugs, can be administered with a better safety profile using nanotechnology. It is important to note that Living cells are tiny virtual machines involved in all biological activities, including cell signalling, metabolism, energy generation and nutrient transport. Therefore it can be considered a major candidate technology to deal with biology and medicine for therapeutic purposes. In this review, we discuss the importance of nanoscience with different nanotechnology platforms being used in other aspects of medicine. Besides, we are also addressing the future opportunities of nanotechnology in human health.

1. Introduction

Nanoscience is the only platform to discover the new properties of matter by collaborating with conventional fields such as applied health, molecular chemistry, molecular science, pharmaceutical science, optics, and even engineering. In the recent few decades, the combination of science and technology are often well architected to defence the challenges in the field of medicinal and health sciences by providing a more effective health system, nano-medicinal tools, and therapeutic approaches. Historically, the term nanotechnology was first time coined in 1974 by Professor N. Taniguchi. Soon after, Drexler developed and published the first concept (Feynman's ideas) of nanotechnology in the book entitled "Vehicles of creation: the arrival of the nanotechnology era" in 1986 [1]. Currently, the impact of nanotechnology on human and animal can be arising new avenue for investigation and transformation of health science and becomes the imperative subject for consideration as a therapeutic tool. Nanotechnology is a very shady multidisciplinary area invented to engineering biological matters such as atoms, molecules, and supramolecules at nanoscale range approx 1–100 nm to hold promise against existing challenges by creating new devices and characterisation of material structure technologies with unique properties to study and understand the lethal biological problems followed by diagnosis and cure of disease [2,3]. Nanotechnology has highlighted as the most dominating and commercially invented technology of these decades, considerably being very crucial for human lives. Of note, living cells component are extremely crucial machinery with very tiny size (nanoscale). They are robustly involved in almost all biological activity, including cell signalling, metabolism, energy production, and nutrient transport. Therefore, it can be deemed that nanotechnology as an essential candidate that can offer new technologies at the individual matter level to deal with biology and medicine for therapeutic purposes [4]. Various nanoscale materials are invented with several clinical advantages; nano-medicine is emerging as a gold standard in health sciences [5,6]. The pathophysiological and clinically

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https://doi.org/10.1016/j.jddst.2021.102487
Received 2 January 2021; Received in revised form 7 March 2021; Accepted 15 March 2021

Annals of Hematology
https://doi.org/10.1007/s00277-020-04390-y

REVIEW ARTICLE

Erythrocyte microRNAs: a tiny magic bullet with great potential for sickle cell disease therapy

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Received: 17 July 2020 / Accepted: 21 December 2020

Abstract

Sickle cell disease (SCD) is a severe hereditary blood disorder caused by a mutation of the beta-globin gene, which results in a substantial reduction in life expectancy. Many studies are focused on various novel therapeutic strategies that include re-activation of the γ-globin gene. Among them, expression therapy caused by the fetal hemoglobin (HbF) at a later age is highly successful. The induction of HbF is one of the dominant genetic modulators of the hematological and clinical characteristics of SCD. In fact, HbF compensates for the abnormal beta chain and has an ameliorant effect on clinical complications. Erythropoiesis is a multi-step process that involves the proliferation and differentiation of a small population of hematopoietic stem cells and is affected by several factors, including signaling pathways, transcription factors, and small non-coding RNAs (miRNAs). miRNAs play a regulatory role through complex networks that control several epigenetic mechanisms as well as the post-transcriptional regulation of multiple genes. In this review, we briefly describe the current understanding of interactions between miRNAs, their molecular targets, and their regulatory effects in HbF induction in SCD.

Keywords Sickle cell disease · miRNA · Fetal hemoglobin · Non-coding RNAs · Therapeutic

Abbreviations

SCD	Sickle cell disease
HbF	Fetal hemoglobin
miRNAs	MicroRNAs
RBCs	Red blood cells
VOCs	Vaso-occlusive crises
HU	Hydroxyurea
FDA	Food and Drug Administration

Henu Kumar Verma and Yashwant Kumar Ratre contributed equally to this work.

Highlights

- Micro-RNA (miRNA) is involved in the epigenetic regulation of sickle cell disease.
- Up- and downregulation of several miRNAs in red blood cells can be a potential biomarker for diseases.
- We summarized the evidence of human miRNAs as a new, effective tool for re-activation of the γ-globin gene and fetal Hb induction.
- Molecular mechanisms that underlie the positive association of miRNAs with sickle cell disease.

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Published online: 04 January 2021

3 Biotech (2021) 11:94
https://doi.org/10.1007/s13205-021-02657-3

REVIEW ARTICLE

Molecular mechanism, diagnosis, and potential treatment for novel coronavirus (COVID-19): a current literature review and perspective

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Received: 3 October 2020 / Accepted: 12 January 2021

Abstract

Novel coronavirus disease 2019 (COVID-19) is a positive-sense single-stranded RNA virus which belongs to the Coronaviridae family. COVID-19 outbreak became evident after the severe acute respiratory syndrome coronavirus and the Middle East respiratory syndrome coronavirus in the twenty-first century as the start of the third deadly coronavirus. Currently, research is at an early stage, and the exact etiological dimensions of COVID-19 are unknown. Several candidate drugs and plasma therapy have been considered and evaluated for the treatment of severe COVID-19 patients. These include clinically available drugs such as chloroquine, hydroxychloroquine, and lopinavir/ritonavir. However, understanding the pathogenic mechanisms of this virus is critical for predicting interaction with humans. Based on recent evidence, we have summarized the current virus biology in terms of the possible understanding of the various pathophysiologies, molecular mechanisms, recent efficient diagnostics, and therapeutic approaches to control the disease. In addition, we briefly reviewed the biochemistry of leading candidates for novel therapies and their current status in clinical trials. As information from COVID-19 is evolving rapidly, this review will help the researcher to consider new insights and potential therapeutic approaches based on up-to-date knowledge. Finally, this review illustrates a list of alternative therapeutic solutions for a viral infection.

Keywords Coronavirus · COVID-19 · Diagnosis · Therapeutic · Molecular mechanism

Yashwant Kumar Ratre and Namrata Kahar are contributed equally to this work.

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Abbreviations

CoVs	Coronaviruses
HCoVs	Human coronaviruses
SARS-CoV	Severe acute respiratory syndrome
MERS-CoV	Middle East Respiratory Syndrome
ORFs	Open reading frames
ACE2	Angiotensin-converting enzyme 2
APCs	Antigen-presenting cells
TH1	T-helper
ER	Endoplasmic reticulum
HLA	Human leukocyte antigen
MBL	Mannose-binding lectin
ARDS	Acute respiratory distress syndrome
PRRS	Porcine reproductive and respiratory syndrome
ESR	Erythrocyte sedimentation
CRP	C-reactive protein
PCR	Polymerase chain
RT-PCR	Real-time reverse transcription PCR
HRCT	High-resolution computed tomography scans
ELISA	Enzyme-linked immunosorbent assay
LAMP	Loop-mediated isothermal amplification

Published online: 25 January 2021

Diagnostic and Prognostic Implications of Cardiac Markers for Hepatocellular Carcinoma

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ABSTRACT: Hepatocellular carcinoma (HC) is a malignant type of primary liver cancer with poor treatment outcomes for advanced stages. Unfortunately, many HC patients present with advanced stages. Incidence of death due to HC increases as a result of ineffective treatment during advanced-stage disease. Early diagnosis and management offer proven benefits both for survival and quality of life. Currently, very few biomarkers are available to provide diagnostic and prognostic benefits to HC patients. The present review elaborates on cardiac marker association in HC. HC pathology includes many cardiovascular events including hypoxia and other parameters with roles in disease advancement that may help in identifying diagnostic and/or prognostic markers. The scientific lacuna in the association/role of HC cardiac markers also discussed in this review may be helpful for future research and to develop cost-effective biomarkers for early HC diagnosis.

KEY WORDS: hepatocellular cancer, cardiac markers, early diagnosis

ABBREVIATIONS: ANP, atrial natriuretic peptide; **BCLC**, Barcelona clinic liver cancer; **CAD**, coronary artery disease; **CK-MB**, creatinine kinase–muscle/brain; **CRP**, C-reactive protein; **CT**, computerized tomography; **DCP**, des-γ-carboxy prothrombin; **HBV**, hepatitis B virus; **HC**, hepatocellular carcinoma; **HCV**, hepatitis C virus; **H-FABP**, heart-type fatty acid–binding protein; **MRI**, magnetic resonance imaging; **NAFLD**, nonalcoholic fatty liver disease; **pro-BNP**, probrain natriuretic peptide; **PUFAs**, polyunsaturated fatty acids; **sCD40L**, soluble cluster of differentiation 40 ligand

I. INTRODUCTION

Hepatocellular carcinoma (HC) is a malignant major type of primary liver cancer.[1] Etiologically, HC is a sequel to chronic liver disorders ranging from steatosis to cirrhosis. In HC, viral infections account for the major etiology.[2,3] Recent epidemiological studies revealed HC to be fifth (854,000/yr) among all cancer incidence and second (810,000/yr) in cancer-related mortalities worldwide.[4] During the past two decades, HC incidence has shown a twofold increase, from 2 to 5/lakh population.[5] More prevalence is seen in developing countries compared to underdeveloped countries. Highest incidence was seen in China (37.4/lakh population), Japan (40/lakh population), Africa (41.2/lakh population), Korea (49/lakh population), and Mongolia (99/lakh population), and the least is in United States (1.6–4.9/lakh population). With high incidence in Italy, Greece, and Spain, the European incidence rate was higher than that of the United States. In India, ~ 7.5/lakh population experienced HC.[6–8] This may infer that HC is more prevalent in developing countries. A male preponderance is seen in HC occurrence. This preponderance is due to environmental exposure, body-mass index, androgens, and higher chances of viral hepatitis infections.[9–11]

A. Risk Factors

HC risk factors include excess alcohol intake, viral hepatitis infections, chronic liver diseases, and cirrhosis. Viral hepatitis mostly includes hepatitis B virus (HBV) and hepatitis C virus (HCV) infections that cause chronic hepatitis.[12] HBV is characterized by circular double-stranded DNA and exists in eight genotype forms.[12] HC risk with HBV is significant, with 10% to 25% incidence and can occur even without cirrhosis.[13] HCV is a single-stranded RNA virus that exists in six genotype forms.[14] HCV develops into HC through cirrhosis and advanced fibrosis.[15,16] With alcohol

0893-9675/21/$35.00

www.nephropathol.com DOI: 10.34172/jnp.2021.xx J Nephropathol. 2021;10(x):exx

Journal of Nephropathology

Interleukin-10 gene promoter variants and susceptibility to diabetic nephropathy; a meta-analysis

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ARTICLE INFO

Article type:
Original Article

Article history:
Received: 14 August 2020
Accepted: 5 October 2020
Published online: 27 October 2020

Keywords:
Diabetic nephropathy
Interleukin-10
Promoter polymorphisms
Meta-analysis

ABSTRACT

Introduction: Diabetic nephropathy (DN) is a leading cause of chronic kidney disease (CKD) in diabetes patients. There is ample evidence that the inflammatory pathways are central to both diabetes and DN. Several studies that examined the link between the interleukin-10 (IL10) polymorphisms and DN risk yielded conflicting results.

Objectives: The purpose of this meta-analysis is to evaluate the associations between IL10 promoter polymorphisms and DN risk.

Methods: A bibliographic search was carried out on PubMed, Google scholar and Web of Science from the beginning until July 30, 2020. Association between IL10 promoter variants (-1082 A>G, -819 C>T and -592 C>A) and DN risk were assessed by considering diabetes without nephropathy (DWN) as well as healthy controls. Data were retrieved and the pooled odds ratio (OR) with 95% confidence interval (CI) was calculated.

Results: For the IL10 -1082 A> G analysis, a total of 4 studies with DWN controls (682 cases and 529 controls) and 5 studies with healthy controls (1025 cases and 1625 controls) were considered. For the IL10 -819 C> T analysis, a total of three studies with DWN controls (9619 cases and 445 controls) and 5 studies with healthy controls (1005 cases and 1537 controls) were considered. For the IL10 -592 C> T analysis, a total of 5 studies with DWN controls (819 cases and 645 controls) and 5 studies with healthy controls (1005 cases and 1537 controls) were considered. In addition, there was no evidence of publication bias for IL10 promoter variants. No substantial association was observed between IL10 promoter variants and DN risk.

Conclusion: Our study signifies that polymorphisms of IL10 -1082 A>G, -819 C>T and -592 C>A are not linked with DN risk.

Original Article

Implication for health policy/practice/research/medical education:
In the present study, we investigated the association between diabetic nephropathy and IL10 promoter variants using meta-analysis. This study demonstrated that the IL10 gene promoter variants (-1082 A>G, -819 C>T and -592 C>A) are not associated with the development of diabetic nephropathy.

Please cite this paper as: Mishra G, Gautam S, Kumara Reddy TP, Lakkakula BVKS. Interleukin-10 gene promoter variants and susceptibility to diabetic nephropathy; a meta-analysis. J Nephropathol. 2021;10(x):exx. DOI: 10.34172/jnp.2021.xx.

Introduction

Diabetic nephropathy (DN) causes serious health problems and is a leading cause of morbidity and mortality. The occurrence of DN is relatively high among type 2 diabetes mellitus (T2DM) patients representing huge health and economic burden (1). DN is the leading cause of chronic kidney disease (CKD), which leads to end-stage renal disease (ESRD). DN is characterised by micro albuminuria, loss of glomerular filtration rate to progressive CKD in patients with long standing diabetes (2). Several lines of research revealed that the DN is a complex disorder involving both genetic and environmental components (3). Diabetic kidney disease (diabetic nephropathy) is induced by inadequate glycaemic control in diabetic

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J Nephropharmacol. 2021; 10(1): x-x.

http://www.jnephropharmacology.com DOI: 10.34172/npj.2021.xx

Journal of Nephropharmacology

Understanding kidney injury in COVID-19; a pressing priority

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ARTICLE INFO

Article Type:
Mini Review

Article History:
Received: 16 October 2020
Accepted: 10 November 2020
ePublished: 17 November 2020

Keywords:
COVID-19, Kidney injury, Renal transplant, Hemodialysis, Angiotensin-converting enzyme 2, Cytokine storm, SARS-CoV-2, Acute kidney injury

ABSTRACT

The 2019 novel coronavirus disease (COVID-19) is a newly defined infectious and highly contagious acute disease caused by the severe acute respiratory syndrome coronavirus 2 ((SARS-CoV-2). COVID-19 is mainly characterized by an acute respiratory disease however it can also affect multiple other organ systems such as the kidney, gastrointestinal tract, heart, vascular system, and the central nervous system. Kidney involvement is frequent in patients with COVID-19 and this review aims to explore the available data on kidney and COVID-19. In conclusion, COVID-19 infection can affect renal function and may cause acute kidney injury (AKI), due to several mechanisms that need to be fully elucidated. As only supportive management strategies are available for treating AKI in COVID-19, it is necessary to identify and preserve renal function during SARS-CoV-2 infection.

Mini Review

Implication for health policy/practice/research/medical education:
Numerous studies have shown that, acute kidney injury was independently associated with higher mortality in COVID-19.
Please cite this paper as: Ahmadipour E, Lakkakula BVKS, Vahdani G, Tolouian R, Ragati Haghi H, Delgado D, da Silva LAF, Hafizi M. Understanding kidney injury in COVID-19; a pressing priority. J Nephropharmacol. 2021;10(1):x-x. DOI: 10.34172/npj.2021.xx.

Introduction

Novel coronavirus disease (COVID-19) is a newly discovered serious infectious and highly contagious acute disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It first appeared in Wuhan, China, in early December 2019, and rapidly evolved into a global pandemic recognized by the World Health Organization (WHO). COVID-19 can be transmitted directly from human to human via contact or respiratory droplets. COVID-19 is characterized by acute respiratory disease, with most patients (80%) presenting mild and self-limited flu-like symptoms, however 20% may have a severe presentation with acute respiratory distress syndrome (ARDS) (1). The first face of the disease comprises an incubation period for individuals infected with COVID-19 that may vary from 1 to 14 days (most commonly, 3-10 days). The second phase of the disease, which is related closely to the risk of mortality, usually begins between days 7 to 10 from the onset of symptoms that is associated with growing requirements of oxygen supply and respiratory support. This condition is likely to be secondary to hyper inflammatory and cytokine release syndromes (2).

Although, COVID-19 is characterized by interstitial and alveolar pneumonia, it can also affect multiple other organ systems such as kidney, gastrointestinal tract, heart,

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J Renal Inj Prev. 2021; 10(x): x-x.

http://journalrip.com doi: 10.34172/jrip.2021.xx

Journal of Renal Injury Prevention

COVID-19 and the kidney; mechanisms of tubular injury by SARS-CoV-2

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ARTICLE INFO

Article Type:
Review

Article History:
Received: 7 September 2020
Accepted: 5 October 2020
Published online: 8 October 2020

Keywords:
Chronic kidney disease, COVID-19, Acute respiratory distress syndrome, SARS-CoV-2, Angiotensin-converting enzyme II, Hemodialysis, Acute renal failure, End-stage renal disease, Acute kidney injury,

ABSTRACT

Coronavirus disease 2019 (COVID-19) is an ongoing pandemic, reported to cause asymptomatic to severe disease and eventually death. Multi-organ failure and death in patients with severe COVID-19 is associated with increased release of pro-inflammatory cytokines into the blood stream. Renal impairment is reported in a significant proportion of COVID-19 patients and is associated with high mortality. Acute kidney injury (AKI) is multifactorial and involving overlapping pathogenic mechanisms. This review updates the reader of recent publications dealing with the mechanisms underlying AKI in patients with COVID-19. A full understanding of all the possible ways in which the system plays its role in AKI is still a matter of research. Further studies are warranted to better understand the causes of AKI in COVID-19 patients.

Review

Implication for health policy/practice/research/medical education:
Acute kidney injury (AKI) is more common in severely ill patients with COVID-19. AKI is strongly correlated with the occurrence of respiratory failure disease severity. Acute kidney injury in COVID-19 patients conferred a poor prognosis and outcomes.
Please cite this paper as: Chegini R, Mojtahedi Z, Lakkakula BVKS, Pezeshgi A, Niazi S, Nasri H. COVID-19 and the kidney; mechanisms of tubular injury by SARS-CoV-2. J Renal Inj Prev. 2021; 10(x): x-x. doi: 10.34172/jrip.2021.xx.

Introduction

The disease caused by a SARS-CoV-2 infection, which is called coronavirus disease 2019 (COVID-19), is an ongoing pandemic. Although the catastrophic pulmonary effects of COVID-19 have been well documented, damage to other organ systems, such as the heart, kidneys, and liver, has also been reported (1). The predominant clinical symptoms of COVID-19 are similar to those of common cold and flu, including dry cough, dyspnea, myalgia pneumonia, fatigue and fever (2). Clinical manifestation of COVID-19 has been reported to range from asymptomatic to severe (hyperinflammatory shock) and eventually death (3). Numerous studies have shown that increased pro-inflammatory cytokines could release into the bloodstream and cause a ~~syndrome~~ "cytokine storm" leading to multi-organ failure and death in patients with severe COVID-19. Further, acute respiratory distress syndrome (ARDS) is the most significant pulmonary complication severely infected patients (1-3).

Renal impairment is also reported in a significant

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J Nephropharmacol. 2021; 10(2): e16.

http://www.jnephropharmacology.com DOI: 10.34172/npj.2021.16

Journal of Nephropharmacology

Potential of renin-angiotensin system inhibition to improve metabolic bone disorders

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ARTICLE INFO

Article Type:
Review

Article History:
Received: 7 June 2020
Accepted: 18 September 2020
Published online: 17 October 2020

Keywords:
Metabolic bone disorder, Renin-angiotensin system, Dual blockade

ABSTRACT

Metabolic bone disorder is an abnormality of bones indicated by reduced bone mass and high risk of fractures. Several lines of evidence have demonstrated that the local bone tissue renin-angiotensin system (RAS) is directly involved in bone metabolism and influences the bone health. This review aimed to assess the role of RAS in bone metabolism and comparative effectiveness of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in reducing the bone fractures. In summary, the clinical trials, in vivo studies, and functional - pharmacological experiments suggested that the RAS regulates bone marrow metabolism and influences the bone health. Hence, it warrants further investigation on the role of ACEIs and ARBs in reducing risk fractures.

Review

Implication for health policy/practice/research/medical education:
Several studies have demonstrated that the local bone tissue renin-angiotensin system (RAS) is directly involved in bone metabolism and influences the bone health.
Please cite this paper as: Momenzadeh M, Khosravian M, Lakkakula BVKS. Potential of renin-angiotensin system inhibition to improve metabolic bone disorders. J Nephropharmacol. 2021;10(2):e16. DOI: 10.34172/npj.2021.16.

Introduction

Metabolic bone disorder (MBD) is an abnormality of bones characterized by the reduced bone mass and high risk of fractures (1). MBD is the most common endocrine dysfunction after diabetes and thyroid disease. The common MBD includes osteoporosis, osteomalacia, fluorosis, and primary hyperparathyroidism, while the rare MBDs include Paget's disease, tumor-induced osteomalacia, fibrous dysplasia, and osteogenesis imperfect (2). MBD is usually caused by abnormalities in minerals such as calcium and phosphorus and hormones interfering with mineral metabolism such as parathyroid hormone (PTH) and vitamin D (1). Recent studies demonstrated that the bone tissue renin-angiotensin system (RAS) is directly involved in bone metabolism (3). The RAS is an endocrine system that controls blood pressure, blood volume, and fluid balance. The dysfunction of RAS system induces various disorders such as hypertension, nephropathy, preeclampsia, polycystic ovary syndrome, and kidney allograft dysfunction (4). The elements of RAS include angiotensinogen (AGT), renin, angiotensin-converting enzyme (ACE), angiotensin II (Ang II), and the angiotensin II receptor 1 (AT1) and angiotensin II receptor 2 (AT2). The RAS include three main components such as renin, angiotensin, and aldosterone. Angiotensin II as the major biologically dynamic hormone which is created by the successive cleavage of peptides derived from AGT. AGT is synthesized and secreted from the liver and converted to angiotensin I (Ang I) by renin that released from the juxtaglomerular cells of the kidney. Then, Ang I is effectively activated to Ang II by angiotensin-converting enzyme (ACE), which predominantly exists in high levels on the endothelial cells' surface within the pneumonic circulation (3,4).

As the best dynamic component of the RAS, Ang II can act on certain receptors. The RAS blockade may

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http://www.jnephropharmacology.com DOI: 10.34172/npj.2021.13

Journal of Nephropharmacology

Metformin induced acute kidney injury; a systematic review

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ARTICLEINFO

Article Type:
Review

Article History:
Received: 17 June 2020
Accepted: 30 August 2020
Published online: 9 September 2020

Keywords:
Acute kidney injury
Type 2 diabetes mellitus
Metformin
Glomerular filtration rate

ABSTRACT

Introduction: Metformin is the best proven first-line treatment for type 2 diabetes (T2DM), based on both national and international guidelines. The present systematic review is aimed to examine the acute kidney injury (AKI) risk associated with metformin.

Methods: A systematic literature search was performed in MEDLINE, PubMed and google scholar, to retrieve the literature related to the metformin use. A bibliographic management software (Endnote X9) was used for managing the literature. The following keywords were used: "Acute renal injury OR ARI", "Acute kidney injury OR AKI"," Metformin", " Type 2 diabetes mellitus OR T2DM", "Diabetic patients", "Renal function", "CKD".

Results: About 28 relevant articles were found during the electronic and manual search. Finally, a total of four articles that fulfill the inclusion criteria were used for this systematic literature review. There is no evidence to suggest that metformin increases the incidence of AKI and is associated with an increased survival of 28 days following AKI event. Further, there was no difference in the incidence of AKI in patients who continued metformin after arterial contrast exposure compared with the control group.

Conclusion: In summary, there is no evidence that metformin increases the incidence of AKI. More clinical trials are needed in this area, to investigate more evidence so that we can better understand the outcome.

Review

Implication for health policy/practice/research/medical education:
There is no evidence that metformin increases incidence of acute kidney injury.
Please cite this paper as: Momenzadeh M, Lakkakula BVKS. Metformin induced acute kidney injury; a systematic review. J Nephropharmacol. 2021;10(2):e13. DOI: 10.34172/npj.2021.13.

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic condition, long-term T2DM can leads to both microvascular and macrovascular complications (1). The advancement of kidney disease is related to poor controlled T2DM and other complications (2). Hence, preventing kidney disease and abating the progression of kidney disease is one point of therapy (3). It has been hypothesized that the drugs used to treat T2DM play a major role in protecting the kidneys by regulating blood sugar levels and may have extra-protective effects according to particular drug profiles (4). Metformin is used in T2DM to reduce the amount of glucose produced by the liver and to enhance the body's response to insulin secreted by the pancreas. The mean renal clearance of metformin is diminished in patients with renal failure (acute or chronic), leading to lactic acidosis, which is associated with a mortality rate of 50% (5,6). Having a half-life of about 4-8 hours, 90% of metformin is eliminated via renal excretion, in the setting of normal kidney function. Although metformin is not directly associated with nephrotoxicity, it has been suggested that the metformin can inhibit gluconeogenic pathway of lactate metabolism resulting to lactate accumulation in conditions such as acute renal failure (7). In any case, as kidney function interrupt, treatment choices for T2DM become restricted due to prescribing limitations (8, 9). Following the FDA's announcement, the European Medicines Agency (EMA) also recently reported that metformin-containing drugs may be used in patients with moderately impaired kidney function (eGFR 30 to 59 mL/min per 1.73 m^2) (1). However, serum creatinine levels allow the detection of mild AKI (stage

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Journal of Parathyroid Disease

Journal of Parathyroid Disease 2021;9, e02

Mini Review

Perspectives on the relationship of urolithiatic markers and primary hyperparathyroidism

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Abstract

Abnormal parathyroid hormone (PTH) secretion by parathyroid glands leads to hypoparathyroidism or hyperparathyroidism. Most of the hyperparathyroidism cases are asymptomatic and occult urolithiasis is present in about one-fifth of these patients. The marker associated with hyperparathyroidism and urolithiasis may aid in early diagnosis and prophylactic management of these conditions. The aim of the present review is to list the most widely measured markers in urolithiasis. The literature related to urolithiasis and hyperparathyroidism was collected from PubMed and Google Scholar. Serum, urine and genetic markers that were found associated with both urolithiasis hyperparathyroidism were discudded. Further studies on these markers may provide scope for early risk identification and management of the hyperparathyroidism.

Keywords: Parathyroid hormone, hyperparathyroidism, urolithiasis, hypercalcemia, serum creatinine.

Please cite this paper as: Ghanta MK, Lakkakula BVKS. Perspectives on the relationship of urolithiatic markers and primary hyperparathyroidism. J Parathyr Dis. 2021;9:e02.

Introduction

There are usually four parathyroid glands, two superior and two inferior parathyroid glands located behind the thyroid gland. The main function of this gland is synthesis and secretion of parathyroid hormone (PTH) which regulates serum calcium homeostasis (1). At the level of bone, it enhances calcium release from bone to serum by activating the osteoclast functions and impeding osteoblast functions (2). At the level of kidney, calcium reabsorption is facilitated by PTH through up-regulation of TRPV5 receptors at thick ascending loop of Henle, distal convoluted tubule and collecting duct (3).

The main disorders of parathyroid glands are hypoparathyroidism and hyperparathyroidism caused due to abnormal PTH secretion. Hypoparathyroidism is etiologically classified as primary and secondary or acquired (4). Hyperparathyroidism is caused due to increased secretion of PTH. Hyperparathyroidism may be classified as primary, secondary or tertiary. Primary hyperparathyroidism is seen in parathyroid hyperplasia, adenoma or carcinoma. The prevalence of hyperparathyroidism was varying from 1-7/1000 adults (5). Urolithiasis and nephrolithiasis are the major complications of primary hyperparathyroidism (6). Urolithiasis is a common disorder of hyperparathyroidism and also may signify incidence of benign adenoma (7). The recurrence of urolithiasis was suggestive of hyperparathyroidism(8). This review elaborates the biochemical and genetic markers associated with hyperparathyroidism induced urolithiasis. The serum, urinary, genetic and other markers associated were described.

Urolithiatic markers and primary hyperparathyroidism

Urolithiatic markers imply the risk of lithiasis in urinary tract. Different urolithiatic markers demonstrated by various studies may be classified as serum markers, urine markers, genetic markers and others. The serum markers are creatinine, uric acid, calcium, magnesium, blood urea nitrogen (BUN), albumin and blood pH. The urine markers include creatinine, calcium, phosphate, uric acid and vitamin D. Genetic markers are CaSR, PH1, *NaPi2a*, *NHERF1*, *FGF23*, *DMP1*, *ENPP1*, *PHEX* and *GNAS-1*. Other miscellaneous markers are cAMP and ulcerative colitis.

Serum markers

Hypercalcemia is the commonly seen in hyperparathyroidism. The increased PTH augments intestinal reabsorption of calcium through calcitriol

Received: 6 July 2020, Accepted: 11 August 2020, ePublished: 28 August 2020

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J Nephropharmacol. 2021; 10(2): e12.

http://www.jnephropharmacology.com DOI: 10.34172/npj.2021.12

Journal of Nephropharmacology

Strive for kidney health for everyone during COVID-19; the possible theme for the world kidney day 2021

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ARTICLE INFO

Article Type:
Mini Review

Article History:
Received: 10 August 2020
Accepted: 1 September 2020
Published online: 7 September 2020

ABSTRACT

Increasing awareness regarding CKD and self-care during COVID-19 pandemic has become the most important aspect for the nephrologists. Hence it is appropriate that the theme of the forthcoming World Kidney Day on 11 March 2021 should be "Strive for kidney health for everyone during COVID-19"

Keywords: Chronic kidney disease, COVID-19, World Kidney Day, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Collapsing glomerulopathy, End-stage renal disease, Hemodialysis, Renal failure

Mini Review

Implication for health policy/practice/research/medical education:
Proteinuria, hematuria, and acute kidney injury are some of the clinical manifestations of renal failure in COVID-19 patients. Additionally, collapsing glomerulopathy with de novo nephrotic syndrome with acute renal impairment in COVID-19 patients has been described and recently been linked with APOL1 (apolipoprotein L1) in African American patients.

Please cite this paper as: Aleebrahim-Dehkordi E, Mazaheri E, Roshan B, Lakkakula BVKS, Hasanpour-Dehkordi A, Khosravian M, et al. Strive for kidney health for everyone during COVID-19; the possible theme for the world kidney day 2021. J Nephropharmacol. 2021;10(2):12. DOI: 10.34172/npj.2021.12.

Introduction

Since 2006, World Kidney Day (WKD) is observed on the second Thursday of March each year in more than 150 countries around the world. WKD provides an opportunity to raise concerns about kidney disease and its impact on public health worldwide. Kidney failure is one of the major global public health problems and the number of individuals with chronic kidney disease (CKD) is increasing every year (1,2). The growing global prevalence of CKD and high economic burden it imposes on the healthcare systems is making it a global health concern by all healthcare administrators (3). CKD and progressive kidney failure are associated with major adverse health consequences, including cardiovascular disease and death (4,5). Despite many efforts to prevent ESRD (end-stage renal disease), the number of these patients is increasing worldwide (6). ESRD treatment options such as hemodialysis and kidney transplantation, adversely affect the life expectancy and social life of the patient leading to impaired quality of life (7,8). Patients undergoing hemodialysis have higher levels of inflammation and oxidative stress, which are the main risk factors for cardiovascular mortality in these patients (9,10). Although a lot of people around the world suffer from CKD, many do not have necessary information about their disease. Hence it is necessary to take effective measures to promote the knowledge about CKD and its burden on overall health status of an individual.

Methods

International databases including Google Scholar, Web of Science, Scopus, EBSCO and PubMed were considered

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http://www.jnephropharmacology.com DOI: 10.34172/npj.2021.07

Journal of Nephropharmacology

Glomerulonephritis associated with SARS-CoV-2 infection

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ARTICLE INFO

Article Type:
News and Views

Article History:
Received: 7 June 2020
Accepted: 29 June 2020
Published online: 24 July 2020

Keywords:
COVID-19, Nephropathy, Glomerulonephritis, kidney injury, Collapsing glomerulopathy

Implication for health policy/practice/research/medical education: Post-infectious glomerulonephritis (PIGN) can develop secondary to infections associated with bacterial, viral, fungal, protozoal, and helminthic parasites. Recently, there is a serious concern regarding the occurrence of kidney dysfunctions and subsequent acute kidney injury (AKI) among COVID-19 patients. The outcome data of COVID-19 in neonates and children demonstrated that the fatality rate is significantly higher in patients with AKI than in patients without AKI. In the current COVID-19 pandemic, few instances of glomerulonephritis (GN) in patients affected by SARS-CoV-2 have been reported. In this review, we investigated the PIGN concentrating on the COVID19-nephropathy, as well as its prevention and diagnosis strategies.

Please cite this paper as: Akhavan Sepahi M, Lakkakula BVKS, Roshan B, Yalameha B. Glomerulonephritis associated with SARS-CoV-2 infection. J Nephropharmacol. 2021;10(1):07. DOI: 10.34172/npj.2021.07.

News and Views

Introduction

Post-infectious glomerulonephritis (PIGN) is one of the most common forms of glomerulonephritis (GN) (1-3). Among children, acute 'post-streptococcal glomerulonephritis' (APSGN) is the most common cause of PIGN, whereas viral infections are accounting for less common forms of PIGN (4,5). Further, viral infections can occur at any age (2,4). Recognizing the pattern of GN has paramount importance for causative diagnosis, treatment guidance, and prognostication of many GNs and thus frequently kidney biopsy is required (6,7). Typical APSGN and typical nephrotic syndrome in children are two major exceptions that can be initially managed without biopsy.

The immune system, with direct or indirect activation of the complement system, plays a substantial role in different forms of immune GNs such as lupus nephritis and many infectious related GN (8,9).

Although the exact cause is not known, different factors including environmental agents, immune dysregulation and genetic predisposition can lead to the formation and accumulation of immune complexes in the glomeruli (10-13). Furthermore, chronic GN is most often associated with other systemic diseases such as hypertension, diabetes mellitus, and hepatitis (14,15). Mild cases of GN do not cause any clear symptoms and may not need any treatment. The most common clinical features of GN include hypertension, macroscopic hematuria, proteinuria, and edema (16), together called nephritic syndrome. In cases where the proteinuria is severe (more than 2 g/m^2 of body surface area), patients may develop significant edema, hypoalbuminemia and hyperlipidemia, called nephrotic syndrome. Some other common symptoms of kidney failure due to GN include fatigue, nausea and tremulousness. In severe GN cases, confusion or coma may develop (17). Glomerular disease can clinically be asymptomatic and detected as asymptomatic proteinuria or microscopic hematuria, or may be clinically detected with overt nephrotic syndrome or nephritic syndrome or mixed nephrotic-nephritic syndrome and ultimately with progressive to chronic renal failure (3, 4).

COVID-19 and kidney injury

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a novel coronavirus. A series of publications have reported multiple organ dysfunction including acute respiratory distress syndrome (ARDS) and acute renal injury (AKI) in COVID-19. Recently, there is more concern regarding AKI among COVID-19

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J Nephropharmacol. 2021; 10(1): e03.

http://www.jnephropharmacology.com DOI: 10.34172/npj.2021.03

Journal of Nephropharmacology

Herbal antioxidants and renal ischemic-reperfusion injury; an updated review

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ARTICLE INFO

Article Type:
Review

Article History:
Received: 4 February 2020
Accepted: 6 May 2020
Published online: 28 May 2020

Keywords:
Acute kidney injury, Renal ischemia-reperfusion, Oxidative stress, Antioxidant

ABSTRACT

Renal ischemia-reperfusion (RIR) is a pathological condition due to transient restriction of blood flow to the kidneys, which is followed by the subsequent recovery of perfusion and re-oxygenation. RIR injury contributes to the progression of renal dysfunction including acute kidney injury (AKI) in native and renal allograft transplant. The generation of reactive oxygen species (ROS) during oxidative stress contributes to the occurrence of RIR. Hence, the use of antioxidant compounds can improve oxidative stress due to RIR. This review highlights herbal antioxidant efficacy against RIR injury. The findings of this study indicate that antioxidant compounds with herbal origin could reduce complications due to oxidative stress related to RIR through diminishing lipid peroxidation, decreased production of malondialdehyde (MDA), apoptosis and increasing antioxidant enzymes activity. Reducing oxidative stress with the pharmacological approach of antioxidants can be a desirable target for ameliorating RIR.

Review

Implication for health policy/practice/research/medical education:
Antioxidants diminish the oxidative damage caused by renal ischemia-reperfusion (RIR) through inhibiting the lipid peroxidation and increasing the activity of antioxidant enzymes. Hence, targeting the oxidative stress pathway with antioxidants can be a pharmacological approach to ameliorate RIR injury.

Please cite this paper as: Asgharpour M, Tolouian A, Bhaskar LVKS, Tolouian R, Massoudi N. Herbal antioxidants and renal ischemic-reperfusion injury; an updated review. J Nephropharmacol. 2021:10(1):e03. DOI: 10.34172/npj.2021.03.

Introduction

Renal ischemia-reperfusion (RIR) is a pathological condition caused by transient restriction of blood flow to the kidneys that is followed by the subsequent recovery of perfusion and re-oxygenation. Under different conditions RIR injury may be caused by shock, cardiac arrest, sepsis, surgical interventions, and organ transplantation (1). Acute kidney injury (AKI) is recognized as a major complication of RIR, leading to a significant decrease in kidney function and a concomitant elevated serum creatinine level (2,3). The occurrence of RIR injuries involves various pathways such as apoptosis, the production of reactive oxygen species (ROS), activation of neutrophils, and inflammatory mediators including cytokines and adhesion molecules (4,5). Oxidative stress is one of the main events that occur during RIR, which induces cytotoxic effects; including DNA damage, proteins oxidation, lipids peroxidation, production of malondialdehyde (MDA) and induction of apoptosis (6,7).

Reperfusion following ischemia leads to re-oxygenation, re-warming and a throwback to aerobic metabolism. However, the increased renal oxygen concentration in reperfusion condition can contribute to the production of ROS (H_2O_2, $\cdot O^{-2}$ and $\cdot OH$), resulting in injury to the functional and cytoskeletal cellular components (8,9). RIR also has a significant role in early renal allograft dysfunction (10). Different strategies to reduce the complications of RIR injury through ROS scavenging is depicted in Figure 1 (11). The compounds extracted from medicinal plants including antioxidants have long been

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Malaysian Journal of Human Genetics (MJHG) | Vol. 1 (2) December 2020
OFFICIAL JOURNAL

ORIGINAL ARTICLE

Coinheritance of -3.7 Alpha-Thalassaemia Deletions Among Sickle Cell Anaemia Patients in Chhattisgarh, India

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Abstract

Background: Alpha (α)-thalassaemia is inherited as an autosomal recessive disorder characterised by microcytic hypochromic anaemia. In children with homozygous sickle cell anaemia (SCA), coinheritance of α-thalassemia reduces the risk of cerebral vasculopathy and alters the disease severity. This study aimed to detect the occurrence of α-thalassemia in homozygous SCA patients in Chhattisgarh state (India) and to evaluate their clinical and haematological profiles. ***Methods:*** In this study, a total of 203 well-characterized homozygous SCA patients who were diagnosed by Hb electrophoresis and Restriction Fragment Length Polymorphism (RFLP) methods were included. Genotypes of most common two deletional mutations of the α-thalassaemia genes were screened using multiplex gap-PCR. The calculation of gene frequency for α-thalassaemia mutations was done based on the gene counting method. ***Results:*** The average age at enrolment was 12.1 years for SCA. The average fetal haemoglobin was 18.7%. Out of 203 SCA patients, 9.85% and 5.4% were heterozygous ($-\alpha^{3.7}/\alpha\alpha$) and homozygous ($-\alpha^{3.7}/-\alpha^{3.7}$) for the α-thalassemia 3.7 kb deletions respectively and this distribution deviated from Hardy-Weinberg equation. There were significant differences in MCH values found in SCA with and without α-thalassaemia. Symptoms like abdominal pain and headache were significantly different between SCA with and without α-thalassaemia. **Conclusions:** In SCA patients coinheriting α-thalassemia, the clinical and laboratory results indicated improvement in overall clinical presentation of disease. Coinheritance of -3.7 alpha-thalassaemia deletions among sickle cell anaemia patients significantly resulted in milder clinical course.

Keywords: Sickle cell anaemia, Alpha thalassaemia, Co-inheritance, Genetic analysis, α-3.7 deletion

Introduction

Sickle cell anaemia (SCA) is a severe monogenic genetic disorder occurs because of a mutation in the haemoglobin gene and is associated with erythrocytes sickling. SCA is more common in Africa, America, the Mediterranean region, Middle Eastern countries and the Indian subcontinent (Bhaskar and Patra, 2015). In Equatorial Africa, the prevalence of sickle cell anaemia ranges from 10-40%, whereas in West African countries, the range is 15-30% (Uyoga *et al.*, 2019). In 1952 Lehmann and Catbush reported the first case of SCA in the tribal population of the Nilgiri hills of Indian subcontinent (Lehmann and Cutbush, 1952). A study conducted by Indian Council of Medical Research (ICMR) in Maharashtra, Orissa, Andhra Pradesh and Tamil Nadu revealed the prevalence of HbS allele as 5-34% in these populations (Jain *et al.*, 2013; Tewari and Rees, 2013). Sickle cell anaemia is more prevalent in Chhattisgarh populations and some communities; the prevalence of the sickle cell trait is as high as 30%. However, the frequency of the homozygous SCA in Chhattisgarh is 0.21 % (Patra *et al.*, 2015).

Received: 30 May 2020; **accepted revised manuscript:** 15 December 2020 **Published online:** 27 December 2020
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Meta Gene 26 (2020) 100815

Contents lists available at ScienceDirect

Meta Gene

journal homepage: www.elsevier.com/locate/mgene

Genetic association of *GSTM1*, *GSTT1*, and *GSTP1* polymorphisms with sickle cell disease complications: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Glutathione S-transferase
GSTM1
GSTT1
GSTP1
Sickle cell disease
Polymorphism
Meta-analysis

ABSTRACT

Background: Sickle cell disease (SCD) is a monogenic blood disorder characterized by vaso-occlusive crises (VOC) also recurrent episodes of severe pain. Glutathione S-transferase enzyme plays a crucial role in the defense mechanism of cells and tissue damage from oxidative stress during vaso-occlusive crises. Polymorphic variants in the *GSTT1*, *GSTM1*, and *GSTP1* genes are known to influence glutathione enzyme activity and modulate the clinical severity of SCD.

Objectives: We conducted a meta-analysis to synthesize evidence and to assess the relative impact of GST gene polymorphisms on SCD risk.

Methods: Comprehensive search in the PubMed, Google Scholar, EMBASE, Chinese National Knowledge Infrastructure (CNKI) and the Web of Science Databases was conducted to identify the relevant studies. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the strength of association between GST polymorphisms and SCD risk. The Cochrane Q and I^2 statistics were used to detect heterogeneity. Funnel plots and Egger 's test were used to estimate the publication bias.

Results: Eight studies involving 394 SCD patients / 593 controls of *GSTM1*, 397 SCD patients / 595 controls of *GSTT1*, and 178 SCD patients / 178 controls of *GSTP1* polymorphism were ultimately considered for meta-analysis. Pooled analysis of *GSTT1* (OR = 1.814; 95% CI: 1.34–2.45; $P < 0.001$) and *GSTP1* (OR = 1.746; 95% CI: 1.42–2.66; $P < 0.010$) polymorphisms revealed significantly increased risk of complications in SCD, while *GSTM1* null genotypes (OR = 0.867, 95% CI: 0.633–1.189; $P < 0.376$) did not show association with SCD complications. Significant between study heterogeneity ($I^2 > 50\%$) was observed for in all three polymorphisms (*GSTM1* = 68.7%), (*GSTT1* = 71.6%), (*GSTP1* = 83%).

Conclusion: The carriers of *GSTT1* null allele and *GSTP1* Val allele are associated with the increased risk of SCD complications. However, *GSTM1* deletion allele is not associated with the risk of SCD complications. A large number of studies must be evaluated for a more precise association of these polymorphisms.

1. Introduction

Sickle cell disease (SCD) is a monogenic disorder caused by a point mutation at the 6th amino acid position of the Beta-globin gene, which resulting in production of abnormal sickle hemoglobin (HbS). During deoxygenated conditions, HbS lead to the polymerization within erythrocytes and cause vaso-occlusive crises (VOC) also recurrent episodes of severe pain (Lakkakula et al., 2018). Further, this leads to acute chest syndrome, ocular manifestations, renal dysfunction, bone marrow aplasia, spleen damage, stroke, and pulmonary hypertension (Lakkakula et al., 2017; Shukla et al., 2017; Jain and Mohanty, 2018). The pathogenesis of SCD varies between different age groups and ethnicity. It also depends on haplotypes, while the Indo-Arab haplotype is milder due to higher fetal hemoglobin (HbF) (Nongbri et al., 2017). In current scenario Hydroxyurea (HU) is only SCD drug approved by The Food and Drug Administration (FDA), which can increase the level of fetal hemoglobin (HbF) (Verma et al., 2018). While increased the expression of γ-globin genes is extremely pleiotropic and influenced by several genes, such as *BCL11A*, *KLF-1* and *HBS1L-MYB* (Bhanushali et al., 2015). The prevalence of SCD in India is variable and HbS allele frequency ranging from 5 to 34% the HbS gene (Bhaskar and Patra, 2015). The frequency of the sickle cell anemia in Chhattisgarh is 0.21% which shows a relatively

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https://doi.org/10.1016/j.mgene.2020.100815
Received 17 June 2020; Received in revised form 12 October 2020; Accepted 18 October 2020
Available online 21 October 2020

CaSR gene A986S polymorphism contributes to the increased risk of primary hyperparathyroidism: A meta-analysis

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ABSTRACT

Primary hyperparathyroidism (PHPT) generally occurs due to mis-regulated secretion of parathyroid hormone. In humans, CaSR gene is responsible for calcium homeostasis, which regulates parathyroid hormone. By carefully evaluating published studies, the current meta-analysis assessed the association of *CaSR* gene R990G (rs1042636) and A986S (rs1801725) polymorphisms with the risk of primary hyperparathyroidism (PHPT). The meta-analysis includes five studies that focused on *CaSR* R990G and A986S polymorphisms. The effect size measures such as odds ratio (OR) and 95% confidence intervals (CI) were assessed for independent studies. The heterogeneity test showed no significant heterogeneity between studies; hence, pooled effects were assessed under fixed effect model. Meta-analysis of the *CaSR* polymorphisms demonstrated that only A986S polymorphism showed increased risk of PHPT in the dominant model (SS+AS vs. AA: OR = 1.40, 95% CI = 1.13-1.73, P = 0.002). Further, there is no evidence for publication bias for these polymorphisms. In conclusion, this meta-analysis supports that the *CaSR* A986S polymorphism correlates with an increased risk of PHPT.

KEYWORDS: Primary hyperparathyroidism, CaSR, R990G, A986S, rs1042636, rs1801725, Polymorphism, Meta-analysis.

Citation: Rakshit S et al. *CaSR* gene A986S polymorphism contributes to the increased risk of primary hyperparathyroidism: A meta-analysis. Polymorphism 2020; 5: 87-95.

Available online at www.sciencedirect.com

ScienceDirect

Biomedical Journal

journal homepage: www.elsevier.com/locate/bj

Correspondence

Reply to the comments on letter to the editor on review article "current updates and treatment strategy of the European and WHO registered clinical trials of coronavirus disease 2019"

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ARTICLE INFO

Article history:
Received 3 October 2021
Accepted 12 October 2021
Available online xxx

We would like to thank the authors for knowledgeable comments on our study and for clarifying aspects of our methodology in relation to these concerns. We would also like to thank author and his colleagues for their interest in our recently published paper "Current updates on the European and WHO registered clinical trials of coronavirus disease 2019 (COVID-19)" [1], and for taking the time to express their concerns.

One concern was whether the observational studies are to be considered in the clinical trials concerning health care. As per the clinical trials definition (https://clinicaltrials.gov/ct2/aboutstudies/learn#Observational Studies), they suggest that in an observational study, investigators can assess health outcomes in different groups of participants according to a research plan. Further, participants may receive interventions (which can include medical products such as any drugs). For example, investigators may observe a group of older patients to know more about the effects of the different medications on COVID-19 patients. However, as we mentioned in our study, the maximum studies were in the recruiting phase, and we did not have a clear idea about the drug target for the treatment of COVID-19. We have included both groups (interventional or observational) for the comparison to get some idea about the effect of the different combinational drugs on the SARS-CoV-2. However, it is clear that the observational study is not in the clinical trials phase as shown in Table 1.

Additionally, the second concern stated in the latter was selecting the Clinical Trials Registry Platform for the study. In this perspective, we would like to mention that the primary goal of our study was to accumulate all currently ongoing clinical trials database results (EU and ClinicalTrials.gov), which has included a majority of the worldwide data in the clinical trials registry platform. However, we selected only the three most extensive clinical trials platform for the analysis.

There are several master protocols available in which multiple treatment options are evaluated concurrently in observational and interventional studies. This design provides flexible features such as dropping treatment options, declaring one or more drug treatments, or adding new treatments to be tested during the course of a trial [2–4].

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Peer review under responsibility of Chang Gung University.
https://doi.org/10.1016/j.bj.2021.10.008

Please cite this article as: Verma HK et al., Reply to the comments on letter to the editor on review article "current updates and treatment strategy of the European and WHO registered clinical trials of coronavirus disease 2019", Biomedical Journal, https://doi.org/10.1016/j.bj.2021.10.008

Current Microbiology
https://doi.org/10.1007/s00284-020-02213-x

REVIEW ARTICLE

Dynamic Propagation and Impact of Pandemic Influenza A (2009 H1N1) in Children: A Detailed Review

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Received: 31 March 2020 / Accepted: 13 September 2020

Abstract

Influenza is a highly contagious respiratory infection caused by the circulating Swine flu virus. According to the World Health Organization (WHO), the unique blending strain of influenza A H1N1 2009 (Swine Flu) is a pandemic affecting several geographical regions, including India. Previous literature indicates that children are "drivers" of influenza pandemics. At present, satisfactory data were not available to accurately estimate the role of children in the spread of influenza (in particular 2009 pandemic influenza). However, the role of children in the spread of pandemics influenza is unclear. Several studies in children have indicated that the immunization program decreased the occurrence of influenza, emphasizing the significance of communities impacted by global immunization programs. This article provides a brief overview on how children are a key contributor to pandemic Influenza A (2009 H1N1) and we would like to draw your attention to the need for a new vaccine for children to improve disease prevention and a positive impact on the community.

Abbreviations

ALRI	Acute lower respiratory infections
WHO	World Health Organizations
HA	Hemagglutinin
NA	Neuraminidase
ARDS	Acute Respiratory Distress Syndrome
ILI	Influenza-like illness
POCT	Point of care testing
RIDT	Rapid influenza diagnostic tests
LAIV	Attenuated influenza vaccines
IIV	Inactivated influenza vaccine
ACIP	Advisory Committee on Immunization Practices
DCGI	Drug Controller General of India
AAP	American Academy of Pediatrics
IAV	Influenza A virus
IBV	Influenza B virus

Introduction

Influenza virus (commonly known as 'flu virus' or 'swine flu virus') is a life-threatening pathogenic circulating virus, preferably infecting the respiratory tract. It has a unique ability to cause a recurrence epidemic and pandemics in individuals of all ages. In growing children, it causes acute lower respiratory infections such as bronchitis and pneumonia [1]. The proportion of hospitalizations for children can reflect the severity of the disease. It is estimated that 10% of all hospitalizations in children below 18 years of age are due to respiratory diseases and cause 3% of post-neonatal deaths worldwide [2]. The transmission of influenza contributed to several factors, including the probability of infection, the susceptibility of the population and the risk of contact between highly prone and infected individuals. Swine flu virus is transmitted from person to person mainly through respiratory air droplets caused by the sneezing or coughing of infected persons [3]. Pandemic influenza A (2009 H1N1) is a viral disease that appears with influenza-like symptoms in children and young adults compared to the other adult population.

Unlike other respiratory infections, especially seasonal or recurrent influenza, the clinical severity and pathogenicity recorded with 2009 H1N1 was slightly milder; still, it is mysterious. A remarkable gene arrangement combining the genetic material from avian, human and swine flu viruses have been observed for this pandemic infection [4].

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Published online: 21 September 2020

[Frontiers in Bioscience, Elite, 13, 140-157, Jan 1, 2021]

Modulation of human ovarian function by melatonin

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1. ABSTRACT

Melatonin, a hormone which is primarily released by the pineal gland, has a wide range of actions in the female reproductive tract. While the melatonin receptor subtype, MT3, has been identified in amphibian animals and birds, in humans and other mammals, melatonin acts through, MT1 and MT2 receptor subtypes which are expressed in human ovaries. The rhythmic release of melatonin starts at puberty and continues throughout fertile female life, affecting and regulating diverse ovarian functions. Here, we discuss the importance of melatonin in regulating folliculogenesis, oocyte quality, ovulation and luteal function, sex steroid receptor gene expression, ovarian steroidogenesis including the production and steroidogenic enzyme activities in the egg and thecal cells. Melatonin improves the egg quality and increases the chance of success of *in vitro* fertilization (IVF). In view of such extensive actions, melatonin is central to the fertility in females. The objective of this review is to recapitulate the current understanding of the role of melatonin and its receptors.

2. INTRODUCTION

Melatonin (N-acetyl-5-methoxytryptamine), was identified 60 years ago as a neurohormone chiefly secreted by the pineal gland (epiphysis cerebri). Since then, various pinealogists have revealed the physiology and biochemistry of the pineal melatonin. Reports indicate, that its interaction is not limited to the endocrine organs, rather melatonin interacts with other non-endocrine tissues and hence participates in the regulation of various metabolic, immunologic, reproductive, and, other vital physiologic processes coordinating with neuroendocrine network system (1-4). Melatonin is an indoleamine, a tryptophan derivative, which is an

International Journal of Zoological Investigations

Contents available at Journals Home Page: www.ijzi.net

ISSN: 2454-3055

Melatonin and Alcoholic Seed Extract of *Tephrosia purpurea* (Linn.) Reverses Polycystic Ovarian Syndrome (PCOS) Induced Hematological Immune Suppression

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Received: 11th February, 2021
Accepted: 18th March, 2021
Published online: 31st March, 2021

https://doi.org/10.33745/ijzi.2021.v07i01.010

Abstract: Present study was designed to evaluate the effects of exogenous melatonin and alcoholic seed extract of *Tephrosia purpurea* (Linn.) on hematological/hematopoietic immune parameters in Letrozole induced polycystic ovarian (PCO) rat model. Letrozole was administrated (1 mg/kg bw) to the female rats for 28 days to induce the Polycystic Ovarian Syndrome **(**PCOS). The PCO condition was confirmed following preparation of vaginal smear with the persistent estrus cycle and presence of many cysts in the ovary. Exogenous melatonin (200 µg/100g bw) and alcoholic seed extract of *Tephrosia purpurea* (300 mg/kg bw) were given to letrozole induced polycystic ovarian (PCO) rats. Differential count of leucocyte demonstrated decreased numbers of neutrophils, lymphocyte and eosinophils, however, increase in the number of monocytes in PCO rats was noticed. This clearly indicates some inflammatory and pathogenic condition which might have led to immune suppression. Significant recovery of RBCs, hemoglobin, platelets and WBCs numbers were evaluated in rats administrated with exogenous melatonin and alcoholic seed extract of *Tephrosia purpurea* (Linn.). Therefore, combination of melatonin and alcoholic seed extract of *Tephrosia purpurea* (Linn.) may be used to up-regulate the blood and immune status during pathogenicity of PCOS.

Keywords: Polycystic ovarian syndrome, Letrozole, Melatonin, *Tephrosia purpurea,* Blood parameters

Citation: Rai Seema, Purohit Adyasha, Hajam Younis A., Ghosh Hindole, Basheer Muddasir and Kumar Yogesh: Melatonin and alcoholic seed extract of *Tephrosia purpurea* (Linn.) reverses polycystic ovarian syndrome (PCOS) induced hematological immune suppression. Intern. J. Zool. Invest. 7 (1): 98-109, 2021. **https://doi.org/10.33745/ijzi.2021.v07i01.010**

International Journal of Zoological Investigations Vol. 7, No. 2, 376-386 (2021)

International Journal of Zoological Investigations
ISSN: 2454-3055
Contents available at Journals Home Page: www.ijzi.net

Phytochemical Screening and Free Radical Scavenging Activity of *Cinnamomum tamala* Leaf Extract

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Received: 11th June, 2021; **Accepted:** 14th July, 2021; **Published online:** 19th July, 2021

https://doi.org/10.33745/ijzi.2021.v07i02.008

Abstract: Traditional plant-based medicines are still needed by the whole world for their primary healthcare benefits. The phytochemicals or plant extract could be used to treat different diseases and new formulation for the drug discovery in pharmaceuticals**.** *Cinnamomum tamala* is commonly called as Indian bay leaf or Tejpatta. The leaves and bark of *Cinnamomum tamala* are used to cure various diseases due to its various properties including astringent, stimulant and carminative. Hence, the objective of this study was to determine the comparative phytochemical screening and free radical scavenging activity of the leaf of *Cinnamomum tamala*. To achieve this, extract was prepared in three solvents (ethanol, ethanol, aqueous and chloroform). Phytochemical screening (qualitative and quantitative) was evaluated in all the three fractions to compare the solubility of various bioactive components. Phytochemical screening showed the presence of polyphenols, flavonoids, alkaloids, flavones and flavonols, tannins, carbohydrates, amino acids and proteins, saponins and glycosides in leaves of *Cinnamomum tamala*. Quantitative analysis showed that the total polyphenolic content, total flavonoids content, total alkaloids and total flavones and flavonols content in the hydroalcoholic extract was 48.1 mg GA (gallic acid)/g, 22.1 mg QE (Quercetin)/g, 59.9 mg/g and 1.75 mg RE (Rutin)/g, respectively. DPPH free radical assay revealed that *Cinnamomum tamala* hydroalcoholic leaf extract at a 100 µm/ml concentration showed 96.99± 0.99% inhibition activity. It can be concluded that most of the bioactive components are found soluble in hydroalcoholic solvent. *Cinnamomum tamala* hydroalcoholic leaf extract contains various bioactive and also exhibits significant free radical scavenging activity. Hence, it can be used as an alternative remedy for the treatment of various diseases.

Keywords: *Cinnamomum tamala*, Tejpatta, Medicinal plants, Bioactive components, Qualitative, Quantitative, DPPH, Scavenging activity

Citation: Rani Raksha, Kumar Rajesh, Sharma Preeti, Hajam Younis Ahmad and Rai Seema: Phytochemical screening and free radical scavenging activity of *Cinnamomum tamala* leaf extract. Intern. J. Zool. Invest. 7 (2): 376-386, 2021. **https://doi.org/10.33745/ijzi.2021.v07i02.008**

Introduction

Traditional plant-based medicines are still in need by the whole world for their primary healthcare benefits. This happens in many rural communities in Asia, Africa and Central and South America. In these countries the use of medicinal plants and knowledge about their medicinal use are available and inexpensive. In other nations, most of the traditional plant-based medicines are being

Current Pharmaceutical Biotechnology, 2020, *21*, 1489-1504

RESEARCH ARTICLE

Gallic Acid Protects from Acute Multiorgan Injury Induced by Lipopolysaccharide and D-galactosamine

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ARTICLE HISTORY

Received: December 16, 2019
Revised: March 30, 2020
Accepted: March 31, 2020

DOI:
10.2174/1389201021666200615165732

Abstract: ***Background*:** Secondary metabolites of plants, the polyphenols, play a vital role in protection from many health problems in human beings. Structurally favored phytochemicals may be studied to protect multiorgan injury. At pharmacological doses, gallic acid is nontoxic to mammals and is generally absorbed in the intestine.

***Aims*:** In this present study, gallic acid was evaluated for its protective efficacy against Lipo Polysaccharide (LPS) and d-Galactosamine (D-GalN) induced multiorgan injury, *i.e.*, liver, kidney and brain.

***Methods*:** Three different doses of gallic acid (5, 10 and 20 mg/kg p.o.) were administered to the experimental animals for 6 consecutive days, followed by exposure to LPS (50 µg/kg I.P.) and D-GalN (300 mg/kg I.P.) on the 6th day.

***Results*:** Exposure to LPS and D-GalN resulted in increased oxidative stress and proinflammatory cytokines. Altered hematology and serology due to LPS and D-GalN were restored towards control by gallic acid. Declined antioxidants such as reduced glutathione, superoxide dismutase and catalase due to injurious effects of LPS and D-GalN were rejuvenated by gallic acid.

***Discussion*:** Exposure to LPS and D-GalN severely increased lipid peroxidation, CYP2E1 activity and tissue lipids while lowered protein content. Gallic acid restored all these parameters towards control in dose dependent manner and 20 mg/kg dose provided the best protection. Histological study showed improved histoarchitecture of liver, kidney and brain that supported biochemical endpoints.

***Conclusion*:** Gallic acid minimized oxidative stress and provided best protection at 20 mg/kg dose against LPS and D-GalN induced multi organ acute injury.

Keywords: Gallic acid, biochemical, lipopolysaccharide, D-galactosamine, antioxidant, multiorgan injury.

1. INTRODUCTION

Acute Liver Failure (ALF) or fulminant hepatic failure is characterized by nephritis, encephalopathy and coagulopathy in patients with previously normal liver physiology [1], which consequently produce multi organ injury. Fulminant hepatic failure may be induced by bacteria, viral hepatitis, hepatitis B virus, alcohol and other hepatotoxic agents [2] like acetaminophen, which accounts for more than 50% of all cases in some western societies [3, 4]. The ALF is a result of a massive necrosis in liver. Due to high mortality in the patients, ALF has no better treatment except liver transplantation [5, 6]. About 90% of acute hepatitis happens due to viruses, which can also produce primary liver cancer and currently there are no effective therapeutic strategies against acute liver injury [7]. A combination of Lipopolysaccharide (LPS) and D-Galactosamine (D-GalN) causes acute liver injury in animals, which closely resembles the immunometabolic dysfunctions as seen in the clinical syndrome [8] and correlates with human acute liver failure complicated by endotoxemia or septicemia [9]. The LPS along with D-GalN enhances oxidative stress due to increased formation of reactive oxygen species, which may cause injury in various organs of the body, including liver, kidney and brain [10].

The medicinal plants attracted the attention of researchers for potential treatment of various ailments with highly safer use and minimal side effects [11]. Certain natural compounds or their derivatives were found to have the ability to protect cells from oxidative stress and related diseases [12]. Polyphenols have good oral bioavailability and have been used for disease prevention for decades [13]. Gallic acid, 3,4,5-trihydroxy benzoic acid is a colorless crystalline organic

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1873-4316/20 $65.00+.00

Received: 31 July 2020 | Revised: 8 December 2020 | Accepted: 14 December 2020

DOI: 10.1111/jfbc.13605

FULL ARTICLE

Journal of Food Biochemistry WILEY

Protective role of rutin against combined exposure to lipopolysaccharide and D-galactosamine-induced dysfunctions in liver, kidney, and brain: Hematological, biochemical, and histological evidences

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Abstract

Protective efficacy of rutin over liver, kidney, and brain dysfunctions was evaluated in this investigation. Rutin (5, 10, and 20 mg/kg) was administered continuously for 6 days followed by single dose of D-galactosamine (300 mg/kg I.P.) and lipopolysaccharide (50 μg/kg I.P.) on the 6th day. Hematological, serological, biochemical, and histological aspects were considered for this study. One-way ANOVA ($p \leq .05$) followed by Tukey's HSD *post hoc* test determined the statistical significance. Serum AST, ALT, ALP, urea, uric acid, and creatinine were increased significantly, whereas albumin and glucose were significantly decreased after combined exposure to LPS and D-GalN. Glutathione level and activity of SOD and catalase were decreased, whereas lipid peroxidation, triglycerides, and cholesterol were increased in tissue samples due to LPS- and D-GalN-induced toxicity. Prophylactic treatment of rutin maintained studied variables toward control claiming the protective role of rutin.

Practical application: Rutin is plenteous in a variety of commonly ingested foods such as onion, wine, grape, *citrus* fruits, tea, and buckwheat. Rutin supplement is recommended for the treatment of various diseases such as varicose veins, internal bleeding, or hemorrhoids. Rutin is better than well-known antithrombic agent, Juniferdin, or Bacitracin. In the present study, rutin showed protective effects against LPS- and D-GalN-induced multiorgan dysfunctions due to its anti-inflammatory and antioxidant properties. Therefore, rutin may be developed and practiced as a food supplement to cope with acute organ dysfunctions caused by inflammatory and oxidative damage.

KEYWORDS

Antioxidant, Biochemical, D-galactosamine, lipopolysaccharide, oxidative stress, rutin

1 | INTRODUCTION

In the era of industrial and social advancement, human being remain in the vicinity of a plethora of toxic substances, including drugs, which not only affect one organ at a time but also impose threat to other organ simultaneously. The two hit effect of combined exposure to lipopolysaccharide (LPS) and D-galactosamine (D-GalN) is well established model to study multiorgan damage and dysfunctioning. Combination of LPS and D-GalN induces hepatic injury is similar to clinical viral hepatitis; hence, this model

DRUG AND CHEMICAL TOXICOLOGY
https://doi.org/10.1080/01480545.2020.1774603

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RESEARCH ARTICLE

Evaluation of genotoxicity induced by herbicide pendimethalin in fresh water fish *Clarias batrachus* (linn.) and possible role of oxidative stress in induced DNA damage

Priyanka Gupta and Sushant Kumar Verma

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ABSTRACT

The present study was carried out in fish *Clarias batrachus* to evaluate the genotoxicity induced by herbicide pendimethalin and to find out the role of oxidative stress in induced DNA damage. The LC_{50} value (96 h) of pendimethalin was determined (3.55 mg/L) and based on this, sub lethal test concentrations were calculated as SL-I (1/20th LC_{50}), SLII (1/15th LC_{50}) and SL-III (1/10th LC_{50}) to which fish were exposed for 30, 45 and 60 days. Maximum DNA damage was observed in fish exposed to highest concentration of herbicide and for a particular concentration maximum damage occurs after 30 days then a time dependent decrease was observed. After 30 days the SOD and CAT activity was found to be significantly increased with respect to the control group while it was significantly decreased after 45 and 60 days as compared to 30 days of exposure. Level of lipid peroxidation in pendimethalin exposed fish followed the same pattern. GR activity remained same for all duration of herbicide exposure. The DNA damage is due to ROS generated by the metabolism of herbicide which is evident by alteration in LPO and anti-oxidant enzyme activities accompanied by incidence of DNA damage in a similar way. It can also be concluded that for pendimethalin genotoxicity testing *C. batrachus* can be used as model organism and comet assay and micronucleus test as effective tools.

ARTICLE HISTORY
Received 4 October 2019
Revised 3 April 2020
Accepted 20 May 2020

KEYWORDS
Genotoxicity; oxidative stress; pendimethalin; micronucleus frequency; comet assay; lipid peroxidation; antioxidant enzyme activities

1. Introduction

Herbicides are used to kill undesirable plants and are extensively used pesticides in all over the world with a consumption of about 47.5% of total pesticides (De *et al.* 2014). Herbicides put their detrimental effects on non target aquatic organisms in contaminated aquatic systems (Gilliom 2007) and are important environmental stressor (Liaud *et al.* 2016).

Belonging to the class di-nitroaniline the herbicide pendimethalin is generally used to remove annual grasses of agricultural fields. Being moderately persistent and bio-accumulative toxic compound (Roca *et al.* 2009) this herbicide has been identified as a contaminant not only in ground water with a concentration of 0.1 to 6 $\mu g\ L^{-1}$ but also in agricultural soil at around 13 mg kg^{-1} (Strandberg and Scott-Fordsmand 2004).

For fish pendimethalin is proclaimed as moderately to highly toxic compound. Due to its stability in environment it tends to accumulate in fish tissues (Garcia-Reyero and Denslow 2006). Nabela *et al.* (2011) observed reduced body weight and increased biochemical parameters like alkaline phosphatase, aspartate amino transaferase (AST), serum glucose, cholesterol and total protein in fish exposed to 10% and 5% of 96 h LC_{50} value of pendimethalin. Abd-algadir *et al.* (2011) observed skeletal muscles necrosis and gill lamellae swelling in *Tilapia nilotica* after its exposure to the herbicide pendimethalin. It induces oxidative stress in rainbow trout (Danion *et al.* 2014) and *Channa punctatus* (Ahmad and Ahmad 2016). To the best of our knowledge no work has been done so far to evaluate the toxicity of pendimethalin on cat fish.

The ability of all chemicals including xenobiotics to impair the genetic information contained within the cell is called genotoxicity which can be evaluated through different biomarkers like evaluation of structural modifications in chromosomes, sister chromatid exchanges, micronucleus frequency, DNA adducts and breaks (Bombail *et al.* 2001). Structural and numerical modifications in chromosomes result from abnormalities in DNA duplication during the 'S' phase. Many toxicants that cause chromosomal aberration were also found to induce sister chromatid exchanges. Among these biomarkers comet assay and micronucleus assay are simple, reliable and less time consuming. Comet assay is independent of chromosome number and do not require pretreatment with chemicals like mitotic inhibitors. Therefore it is most frequent and recommended method to detect DNA damage in organisms including fishes (Martins and Costa 2017). Previously it has been reported that herbicides and their commercial formulations induce genotoxicity in fishes (Moreno *et al.* 2014, Guilherme *et al.* 2015, Piancini *et al.* 2015, Ruiz *et al.* 2016, López González et al. 2017).

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Fish Physiol Biochem
https://doi.org/10.1007/s10695-020-00853-1

Impact of herbicide pretilachlor on reproductive physiology of walking catfish, *Clarias batrachus* (Linnaeus)

Rakesh Soni · Sushant Kumar Verma

Received: 20 April 2020 / Accepted: 28 July 2020

Abstract Herbicide pretilachlor is widely used in paddy fields to control annual weeds. The present study has been carried out in walking catfish, *Clarias batrachus*, to evaluate the impact of herbicide pretilachlor on reproductive physiology after chronic exposure. Based on the median lethal concentration value (96 h), fish were exposed to three nominal test concentrations of pretilachlor ((SL-I (1/20th LC_{50}), SLII (1/15th LC_{50}), and SL-III (1/10th LC_{50})) for 30, 45, and 60 days after which plasma sex steroid profile, plasma vitellogenin concentration, and gonadal aromatase activity were analyzed in both sexes. Plasma concentration of testosterone decreases in herbicide-exposed male fish. Significant increase in plasma 17β-estradiol, plasma vitellogenin concentration, and gonadal aromatase activity were observed in herbicide-exposed male fish. All these alterations in reproductive parameters in male fish are dependent on concentration and exposure duration of herbicide. On the other hand, significant decrease in plasma concentration of testosterone was observed in female fish which was also dependent on concentration and exposure duration of herbicide. No significant changes in plasma 17β-estradiol concentrations, plasma vitellogenin concentration, and gonadal aromatase activity were observed in female fish. Above findings clearly suggested that herbicide pretilachlor acts as endocrine disruptor in fish and affects overall reproductive physiology of fish, but its ability to induce reproductive toxicity in male and female differs considerably.

Keywords Pretilachlor · *Clarias batrachus* · Testosterone · 17β-estradiol · Vitellogenin · Gonadal aromatase activity

Introduction

Herbicides are mostly used in agricultural fields to remove unwanted plants. From agricultural fields, they may enter nearby water systems and impose harmful effects on fish including altered reproductive physiology. Herbicide reduces the reproductive capacity of fish by creating hormonal imbalance (Shioda and Wakabayashi 2000), by disrupting sex steroid metabolism (Moore and Waring 1998) and by altering normal function of hypothalamic pituitary gonadal axis (Li et al. 2009).

The chloroacetamide herbicide pretilachlor is widely used in paddy field. It inhibits cell division in herbs by interfering with the normal process of fatty acid synthesis (Kaushik et al. 2006). Chloroacetamide herbicides have been detected in surface water (Hladik et al. 2008), soil (Chao et al. 2007), and sediments (Xue et al. 2005). Some of them are suspected carcinogens (Coleman et al. 2000). They are found to be toxic for fish by several authors from time to time. Butachlor disrupts thyroid and sex steroid endocrine systems in zebra fish (Chang et al. 2013), induces genotoxicity in *C. batrachus* (Ateeq et al. 2002), causes irregular protrusion of the

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Published online: 09 August 2020

Bulletin of Environmental Contamination and Toxicology
https://doi.org/10.1007/s00128-020-03003-8

Genotoxic Potential Assessment of the Herbicide Bispyribac-Sodium in a Fresh Water Fish *Clarias batrachus* (Linn.)

Dibyajyoti Pradhan[1] · Rajendra Kumar Singh[1] · Sushant Kumar Verma[2]

Received: 20 May 2020 / Accepted: 16 September 2020

Abstract

Genotoxic potential of herbicide bispyribac-sodium was evaluated in fish *Clarias batrachus* using micronucleus (MN) test and comet assay. Fish were exposed to three environmentally relevant test concentrations of the herbicide for 20, 25 and 30 days. Significant effects ($p < 0.05$) for both concentration and duration of exposure were observed in herbicide exposed fish. Similar trend of DNA damage was observed through MN test and comet assay. Maximum DNA damage was observed in fish exposed to highest concentration of herbicide at all duration. Maximum damage was observed on day 25 at all concentrations followed by a decline. This study established *C. batrachus* as an ecotoxicological model for bispyribac-sodium induced genotoxicity testing. It further confirmed that both MN test and comet assay are useful tool for assessment of genotoxicity induced by water pollutants.

Keywords Genotoxicity · Bispyribac-sodium · Micronucleus test · Comet assay

Intense utilization of herbicides in agriculture fields has significantly contributed to water contamination which results in frequent detection of these chemicals in surface water and thus responsible for harmful effects on non-target organisms including fish (Gilliom 2007).

Fish are directly exposed to agricultural output containing several harmful chemicals including herbicides through surface runoff and thus play major role in toxicity evaluation of such xenobiotics at early stage (Van Der Oost et al. 2003). Toxicity of all such environmental pollutant can be evaluated through different biomarkers among which genetic, biochemical, reproductive, haematological and histopathological are the most important ones in eco-toxicological studies with fish.

Ability to impair the genetic information contained within the cell by chemicals is called genotoxicity. Different techniques have been identified from time to time to access the genetic damage caused by harmful chemicals among which evaluation of structural modifications in chromosomes, DNA adducts and breaks and micronucleus (MN) frequency are some important ones (Bombail et al. 2001). Comet assay or single cell gel electrophoresis and MN assay are most frequently used methods for accessing DNA damage in fishes as these methods are not only independent of chromosome number but also simple and do not involve mitotic inhibitors (Martins and Costa 2017). Exposure of fish to low concentration of herbicide lead to epigenetic changes and the most studied epigenetic changes in fish is DNA methylation (Kim et al. 2017). Genotoxicity testing of chemicals are of prime importance because such damages if occurring in gametes are heritable and risk factor for future generations (Wassom 1992). Genetic damages are responsible for induction of various types of cancer and well as reproductive impairments in the long term (Madle et al. 1987). These damages not only affect the health of fish, but may also a threat to the human health via food chain (Nagpure et al. 2007). Several herbicides have been shown to induce genotoxicity in fishes (Moreno et al. 2014; Guilherme et al. 2015; Piancini et al. 2015; Ruiz de Arcaute et al. 2016; Lopez González et al. 2017).

Bispyribac-sodium is a pyrimidinylcarboxy herbicide. This herbicide disrupts cell division by inhibiting the enzyme acetolactate synthase (ALS) which is first enzyme in the biosynthetic pathway for amino acids valine, leucine and isoleucine. Bispyribac-sodium is frequently used to control

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Published online: 24 September 2020

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Photoperiodic manipulation modulates the innate and cell mediated immune functions in the fresh water snake, *Natrix piscator*

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Objectives of the current work were to investigate the role of photoperiod and melatonin in the alteration of immune responses in a reptilian species. Animals were kept on a regimen of short or long days. Blood was obtained and leucocytes were isolated to study various innate immune responses. Lymphocytes were separated from blood by density gradient centrifugation and were used to study proliferation. Respiratory burst activity was measured through nitrobluetetrazolium reduction assay while nitric oxide production by leucocytes was assayed by nitrite assay. Lymphocytes were isolated and used to study proliferation with and without B and T cell mitogens. Photoperiodic manipulation acted differentially on leucocyte counts. Nitrite release was increased while superoxide production was decreased in cultures obtained from the snakes kept on the short day regimen. Significant enhancement of mitogen induced lymphocyte proliferation was observed in cultures from the animals kept in either long or short days compared to cultures from the animals kept in natural ambient day length. Use of in vitro melatonin showed that lymphocytes from the animals, kept in long days, were more reactive. Photoperiod induces changes in immune status which may permit adaptive functional responses in order to maintain seasonal energetic budgets of the animals. Physiological responses (like elevated immune status) are energetically expensive, therefore, animals have evolved a strategy to reduce immune functions at times when energy is invested in reproductive activities. *Natrix piscator* breeds from September to December and elevated pineal hormone in winter suppresses reproduction while immunity is stimulated.

Seasonal adaptations by organisms tend to reflect interactions and coordinations between changing environmental conditions and individual internal rhythms. It is well known that immune function and reproduction are energetically costly physiological processes hence incompatible simultaneously[1]. Photoperiodic information, which is considered as the most effective initial predictive cue, tends to initiate and terminate seasonal adaptations[2]. Well documented fluctuations in disease and pathogen load are natural threats faced by wild populations[3]. However, rapid adaptations have been documented in wild populations in response to seasonal oscillations in climate and pathogen load[4,5]. The endocrine system has been shown to mediate communication between reproduction and immunity[6]. A variety of environmental factors, such as day length, social interaction, food availability, and temperature, may have significant influence on endocrine system that can change reproductive function and immunity[7,8]. For example, the effects of photoperiodic alteration on immune functions have been well studied in mammals[8–11]. The involvement of melatonin has also been implicated in immune functions via experimental alteration in photoperiod[12–14]. Changes in the immune responses that occur in response to maintaining animals in short days are likely to be directly or indirectly related to elevated melatonin secretion. Along these lines, enhancement of immune function in winter has been studied in a variety of rodent species[15]. Authors of various

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DRUG AND CHEMICAL TOXICOLOGY
https://doi.org/10.1080/01480545.2021.1886306

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RESEARCH ARTICLE

Analysis of suppressive effects of pesticide triazophos on leucocyte immune responses in a teleost, *Channa Punctatus*

Ajay Kumar Bhardwaj, Rakesh Kumar Chandra and Manish Kumar Tripathi

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ABSTRACT

Triazophos is a commonly used organophosphate insecticide, which inhibits the acetylcholinesterase enzyme and causes paralysis and death of insects. Impact of the pesticides on immunity has scarcely been investigated, especially in fishes. The present study was designed to analyze the immunotoxic role of *in vitro* triazophos exposure to the leucocytes in freshwater teleost, *Channa punctatus*. Triazophos, at *in vitro* concentrations of 0.1, 0.5, and 1 μg ml^{-1}, was used to study leucocyte phagocytosis, superoxide production, nitrite release, and lymphocyte proliferation. Dose-dependent suppression of various immune responses was observed. Nitrite release and superoxide production by leucocytes were reduced in cultures incubated with triazophos. Mitogen-induced lymphocyte proliferation was significantly reduced at 0.5 and 1 μg ml^{-1} but not at 0.1 μg ml^{-1} concentration of pesticide. The biphasic suppressive effect was also discovered while evaluating phagocytic response. These investigations describe the effects of pesticide on immune responses in *C. punctatus*, which are helpful in understanding the immunotoxicity in fish. Substantially more researches are required to help design the measures to combat ecotoxicity in freshwater bodies.

ARTICLE HISTORY
Received 26 November 2020
Revised 13 January 2021
Accepted 20 January 2021

KEYWORDS
Pesticide; immunity; leucocytes; lymphocyte proliferation; *C. punctatus*

Introduction

Pesticides are produced at large scale and used worldwide to protect the food plants from insect pests. These chemicals, applied to the agricultural fields, often reach aquatic bodies along with runoff water and adversely affect aquatic fauna. The heavy quantity of pesticides is harmful to fish and leads to immediate mortalities, while lower concentrations result in accumulation in the water bodies leading to reduced immunity, metabolism and damage of the gills (Austin 1998). Water pollution is a great problem in many freshwater bodies. The effects of the pollutants may be either lethal or sub-lethal (Sures 2008). Triazophos (O, O-diethyl-O-(1-phenyl-1H-1, 2, 4-triazol-3-yl)) is an organophosphate insecticide that is used widely in most regions for controlling insect pests (Chen *et al*. 2014). In agriculture, it is used to control insect pests on grains. It is applied directly to the soil or used as a foliar spray. Organophosphate pesticides (OPs) are used on agricultural crops and then residual OPs reach water bodies either directly or indirectly, causing undesirable effects on nontarget organisms like fishes (Aydin and Koprucu 2005, Li *et al*. 2013). The immune system of fishes is the first-line defense against pathogenic organisms and at the same time very sensitive system to be altered by xenobiotics like pesticides (Li *et al*. 2013). Lysozyme activities have been shown to be differentially regulated by OPs as an acute concentration of diazinon increased while subacute and subchronic concentration decreased lysozyme activity (Ahmadi *et al*. 2014). Previous researches show that exposure of fishes to OPs provokes a decrease in the leucocyte counts. The differential leucocyte count showed that the percentage of lymphocytes, monocytes, and basophils were decreased, while the percentage of neutrophils and eosinophils increased after exposure to the pesticide (Banaee *et al*. 2008, Kaya *et al*. 2015). A decrease in leucocytes in Nile tilapia (*Oreochromis niloticus*) exposed to malathion and common carp exposed to phosalone has also been reported. In common carp (*Cyprinus carpio*), lymphocytes diminished significantly though the percentage of monocytes and neutrophils increased (Kaya *et al*. 2015). However, Ural (2013) reported an increase in the leucocyte number in common carp exposed to pesticide chlorpyrifos. Further, Hedayati and Tarkhani (2014) showed that in shark *Pangasius hypophthalmus*, exposed to diazinon, a significant increase in the total number of WBC was found, while the number of lymphocytes was not changed. Functions and structures of the different cells were also found to be altered by OPs. Diazinon exposure to *Lepomis macrochirus* caused changes in the size of macrophages of kidney and spleen (Dutta *et al*. 1997). Oxidative stress, as measured by respiratory burst activity of leucocytes, increased, while phagocytic activity decreased after treatment with diazinon (Giron-Perez *et al*. 2007, 2009). So far, cell-meditated immune function is concerned, proliferation of lymphocytes did not change after treatment of fishes with chlorpyrifos (Diaz-Resendiz and Giron-Perez 2014), while diazinon exposure resulted in a decrease in splenocyte proliferation (Giron-Perez *et al*. 2007).

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Comparative Biochemistry and Physiology, Part C 245 (2021) 109029

Contents lists available at ScienceDirect

Comparative Biochemistry and Physiology, Part C

journal homepage: www.elsevier.com/locate/cbpc

Evaluation of triazophos induced immunotoxicity of spleen and head kidney in fresh water teleost, *Channa punctata*

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ARTICLE INFO

Keywords:
Pesticide
Immunotoxicity
Phagocytosis
Lymphocyte proliferation
Fish

ABSTRACT

The utilization of pesticides has increased for destroying pests and protecting crops in the agriculture field. Triazophos is a commonly used organophosphorous insecticide that causes alterations in haematological and histological parameters in fish. The present study was designed to evaluate the effect of triazophos induced innate and cell mediated immunotoxicity in freshwater teleost, *Channa punctata*. Fishes were exposed to triazophos at concentrations 5 and 10% of LC_{50} value for 10 and 20 days. Splenic and head kidney macrophage phagocytosis, nitric oxide production and superoxide production were assayed to evaluate the innate immunity. Cell-mediated immunity was measured through splenic and head kidney lymphocyte proliferation in presence of T and B cell mitogens. Results of the present study revealed that macrophage phagocytosis was significantly reduced after in vivo triazophos treatment. Differential suppressive effect of triazophos was also observed where mitogen induced splenic and head kidney lymphocyte proliferations were reduced after 10 and 20 days treatment. Concentration dependent effect of triazophos was observed in in vivo studies where the production of reactive oxygen and nitrogen intermediates were suppressed. This study describes the first investigation of the effect of triazophos on immune functions and will help to determine appropriate ecotoxicity and immunotoxicity in freshwater teleosts.

1. Introduction

Organophosphorous pesticide (OP) formulations, applied to agricultural fields, often contaminate aquatic habitat, which in turn cause harmful effects to the aquatic biota particularly the economically important non-target organisms such as fishes (Tripathi and Harsh, 2002). It is assumed that about 70% of agricultural chemicals affect non-target species in India. Fishes are very sensitive to these chemicals and act as bio-indicator to environmental contamination of water. The use of pesticides has greatly increased recently to improve crop production. Triazophos (O, O-diethyl-O-(1-phenyl-1H-1, 2, 4-triazol-3-yl)) is an organophosphate insecticide and is widely used in most regions for controlling insect pests (Chen et al., 2014).

Residual organophosphate pesticides (OPs) reach water bodies either directly or indirectly, causing adverse effects on fishes (Aydin and Koprucu, 2005; Li et al., 2013). The innate immune response is the front line defense against pathogens and is very vigorous response, however, it is subjected to alteration by pesticides (Al-Ghanim, 2012; Li et al., 2013). Among various parameters of innate immune responses, macrophage phagocytosis is an important and primitive defense mechanism found in all vertebrates. The utility of the fish phagocytic function and the immunotoxicological measurement of phagocytic ability in presence of pollutants and immune-stimulants have been described in many studies (Anderson and Zeeman, 1995; Secombes, 1996; Secombes and Fletcher, 1992; Siwicki et al., 1990), however, toxicity mechanism in these studied are not clear. A few laboratory studies have shown that OPs display immunotoxicity (Galloway and Handy, 2003). Reactive oxygen species (ROS) formation in aquatic organisms is affected by insecticides (Monteiro et al., 2006) and the latter may cause changes in the antioxidant system.

Little is known about the toxicity of triazophos on the immune system in fishes. Experiments done till date show that the early life stages of fishes are severely affected by toxicants, very little is known about the immunotoxicity of OPs during further developmental stages. Although it is well studied that OPs interfere with a number of physiological processes such as neurotoxic, hematotoxic, development and reproduction, respiratory, genotoxic, hepatic and renal effects, very few reports are available regarding immunotoxic effects of OPs in teleosts. Diazinon

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https://doi.org/10.1016/j.cbpc.2021.109029
Received 14 January 2021; Received in revised form 20 February 2021; Accepted 11 March 2021
Available online 17 March 2021

Plant Archives Vol. 20, Supplement 2, 2020 pp. 4210-4216 **e-ISSN:2581-6063 (online), ISSN:0972-5210**

A REVIEW OF ANTITUBERCULOSIS DRUGS EMPHASISING ON PHYTOTHERAPEUTIC ASPECT

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Abstract

The long duration tuberculosis therapy makes causes several serious side effects, hepatotoxicity being the main. Hepatotoxicity is the most serious adverse effect related to tuberculosis treatment which interrupts the successful completion of tuberculosis treatment antioxidant system of the body effectively neutralises reactive oxygen species formed during the normal metabolic process. Any imbalance in this neutralization process causes oxidative stress leading to causation of various diseases. Research has enabledthe use of several medicinal plants from time to time to treat toxic manifestations from various toxigenic substances. This review is aimed to provide an insight for the phytotherapeutic intervention of the medicinal plants for the effectiveness of the existing tuberculosis therapy.
***Keywords*:** Tuberculosis, antituberculosis drugs, hepatotoxicity, medicinal plants.

Introduction

With the advent of modern scientific age, treatment for various diseases has been established in a sophisticated manner. However, in most of the cases, the therapeutic regimen is also responsible for causing secondary side effects, which directly or indirectly hamper functioning of various organs. These drugs have mostly been found to interact with the cellular biomolecules and thus cellular functioning is affected. The side effects are more prone incase the therapeutic regimen is too lengthy. Many of the approved drugs have been withdrawn from the market because of their adverse effect on liver. In western country, more than half of the cases of liver failure are because of the drug induced liver injury (DILI) and amongst them, paracetamol is found to be one of the main offending agents. The DILI has now became a clinical challenge because of large number of drugs with known hepatotoxicity are still in use and also because of broad spectrum of injuries that are caused to the liver by these drugs. Several drugs (e.g., astemizole, cisapride, grepafloxacin, terfenadine) have been withdrawn from clinical use as they have an effect on heart functioning. The antitumor drugs targeting the nuclear DNA exert their desirable toxic effects against tumor cells but besides that also exert their undesirable cytotoxic effects against rapidly dividing normal cells such as hematopoietic cells and small intestinal mucosal cells) by inducing apoptosis primarily via a p53-dependent mechanism. It is not surprising that most idiosyncratic drug reactions affect the liver, because this organ contains 80–90% of the body's fixed macrophages (i.e., Kupffer cells), because the liver is the first organ to be exposed to toxogenstranslocating from the intestinal lumen. Recently, an increase has been observed in the study of antituberculosis drug induced hepatorenal injury.

Tuberculosis

Tuberculosis (TB), a multisystemic disease is the most common cause of infectious disease related mortality worldwide. According to the World Health Organization (WHO, 2016) report, there were an estimated 10.4 million incident cases of TB in 2012 and 1.5 million deaths were attributed to the disease. The origin of genus mycobacterium is hypothesized to be originated some 150 million years ago (Hayman, 1984). The disease is distinguished by a multitude of symptoms as cough, sputum production, chest pain, and systemic symptoms such as night sweats, fevers, chills, and weight loss.

The history of tuberculosis drug development began in the 1940s with streptomycin (1946). A decade later, the discovery of isoniazid (INH) brought new hope. In the 1970s, (PZA) and rifampin (RIF) revolutionized TB treatment, resulting in robust cures with shortened durations of therapy. Historically, no new drugs have been introduced in the clinic since the discovery of rifampin, in spite of major advances made in the drug discovery process.

The regimen for treating drug-susceptible TB involves six month treatment with isoniazid, rifampin, pyrazinamide and ethambutol (EMB) for first 2 months followed by INH and RIF for 4 months (Koul *et al*., 2011). Currently available treatment regimens are prolonged, making the adherence to the therapy difficult. The occurrence, risk factors, morbidity and mortality of adverse events from isoniazid and rifampin have been well documented (White *et al*., 2012). Also Shih *et al*. (2012) proposed a novel mechanism which underlies the hepatotoxicity of pyrazinamide. Hepatotoxic effects decline treatment success rates, adversely affect therapy adherence and may escalate treatment failure, relapse, or drug resistance. Incomplete chemotherapy in long run may directly or indirectly result into multi-drug resistant (MDR) strains, extensively drug resistant (XDR)-TB or even total drug resistant (TDR) strains.

Antituberculosis drugs

Even though the causative agent of tuberculosis (TB) was first identified by Robert Koch over 100 years ago, the epidemic still continues. The TB remains a huge global public health problem with much of the burden felt by developing countries in south-east Asia, Africa and Eastern Europe. The reasons for continuing TB epidemic may include devastated health care systems in resource-poor countries and insufficient diagnostic tools. Most TB-affected populations are concentrated in poorer regions of the world and fatalities occur excessively in Africa. The chemotherapy for this disease is available in the form of first line (Isoniazid,

Egypt. J. Microbiol **Vol. 55,** pp. 29-44 (2020)

EgyptianJournalofMicrobiology
http://ejm.journals.ekb.eg/

Study on Antioxidant, Antidiabetic and Antibacterial Activity of Rhizospheric Fungi from Achanakmar Biosphere Reserve, Bilaspur

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FUNGAL derived bioactive compounds can be beneficial for the human immune system. They act as synergistic or agonistic molecules in the therapy of various human diseases. A total 18 rhizospheric fungi (ABRF1-ABRF18) were identified from rhizospheric soil of the medicinal plants of Achanakmar Biosphere Reserve, Bilaspur, India. The capacity of the fungi to produce metabolites with therapeutic potential was examined. Crude extract from these fungi demonstrated potent *in vitro* antioxidant activity with various antioxidant assays including Ferric reducing power, Phosphomolybdenum.2,2-diphenyl 1-picrylhydrazyl, and 2,2'-azino-bis3-ethylbenzthiazoline-6-sulfonic. Among different isolated fungi, four, (ABRF1-*Fusarium oxysporum,* ABRF2-*Talaromyces purpureogenus,* ABRF3-*Penicillium citrinum* and ABRF4- *Aspergillus carneus)* exhibited significant antioxidant potential. Active metabolites of the rhizospheric fungi obtained by extraction with solvents increasing in order of polarity, i.e. Toluene, Chloroform, Ethyl acetate, Methanol, Ethanol and Acetonitrile were examined for antibacterial activity. Variable zones of inhibition against the bacteria *Bacillus circulans, Bacillus subtilis, Escherichia coli, Staphylococcus aureus* and *Ralstonia eutrophae* were observed. Further, relatively purified extracts found in the ethyl acetate fraction of column chromatography demonstrated significant antidiabetic activity (up to 93.28±0.12) as measured by α amylase inhibition assay. The secondary metabolites extracted from these species may thus provide potential therapeutic ingredients for pharmaceutical applications worthy of future study.

Keywords: Antimicrobial activity, Antioxidant, Rhizospheric, Secondary metabolite.

Introduction

Medicinal plants have been used for treatments of various ailments in alternative medicine and as a source of bioactive pharmaceutical agents (Akerele et al., 1991). The growth, development and productivity of a medicinal plant is influenced by the soil quality and the organic and inorganic nutrients available to the plant through its roots. Rhizospheric regions of plants have a diverse array of microorganisms that may affect the growth period, cells and nutrient criteria (Simova-Stoilova et al., 2008). The rhizospheric regions are relatively active regions because microbes interact with plant cells as well as with other microbes to compete for food and growth. Utilization of microbes like fungi and bacteria for commercial production of secondary metabolites is an important research area, as microorganisms are easy to handle for any large-scale processes (Cragg & Newman, 2013). Fungi are eukaryotic microorganisms, easy to grow in the laboratory and known for secondary metabolite production. The fungi associated with plant roots are called rhizospheric fungi. Secondary products with therapeutic potential are formed by fungi to inhibit other microorganisms present in the rhizospheric range of a plant (Hibbing et al., 2010). Asperlicin, obtained from *Aspergillus alliaceus*, is effective in treating neurological conditions (Butler, 2008); strobilurin has been found to be effective as a fungicide (Reuveni, 2000); kojic acid is an antioxidant molecule (Pandit et al., 2018), and Lovastatin, isolated from *Aspergillus terreus* is hypocholesterolemic

#Corresponding author email: harit74@yahoo.co.in Telephone No: 9826630805
Received 20/6/ 2020; Accepted 10/8/ 2020
DOI: 10.21608/ejm.2020.31025.1160

MATERIALS TECHNOLOGY
https://doi.org/10.1080/10667857.2020.1782060

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Synthesis and characterization of lignin-poly lactic acid film as active food packaging material

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ABSTRACT

The present work describes the synthesis, characterisation and antimicrobial activity of lignin-polylactic acid (PLA) blended film. Film was prepared using co-polymerisation reaction of lignin and lactic acid in the presence of stannous chloride as a catalyst and poly(vinyl alcohol) to get the uniform film. The properties of the film was studied by scanning electron microscopy (SEM), X-ray diffraction (XRD), differential scanning calorimetry (DSC) and thermo-gravimetric analysis (TGA), respectively. The lignin-PLA film demonstrated a significant decrease in swelling ratio and tensile strength in contrast to PLA film. SEM analysis revealed proper blending of lignin into PLA matrix with slightly rough surface. Film was thermostable and amorphous in nature as confirmed from the thermal study and XRD analysis, respectively. Further, significant improvement was observed in antimicrobial activity and biodegradability of PLA film after addition of lignin, which suggest the putative application of lignin-PLA film as the food packaging and mulch film materials.

ARTICLE HISTORY
Received 7 February 2020
Accepted 30 May 2020

KEYWORDS
Lignin; poly lactic acid (PLA); biodegradability; antimicrobial activity

Introduction

Dependence on the petrochemical-based non-renewable polymers has become a serious threat to the environment. The use of non-degradable polymers from the non-renewable resource is one of the major reasons of environmental pollution. Hence, such problems have driven the efforts to replace the petroleum origin polymers with renewable and nature-derived biopolymers [1–3]. Natural resource fillers are abundant, inexpensive, renewable and fully biodegradable raw materials [4]. Consequently, the biocomposites with natural resource fillers have become a major part of the biodegradable plastic industry. Poly-lactic acid (PLA) is a linear aliphatic thermoplastic polyester which can be obtained from lactic acid derived from the fermentation of renewable agricultural-based feedstocks [5,6]. The global production growth of PLA is envisaged to approximately quadruple between 2013 and 2020 [7]. Furthermore, PLA is biodegradable and have some promising properties such as recyclable and compostable with good stiffness and strength, though the applicability of PLA is limited due to high brittleness, low softening temperature and weak water vapour and gas barrier properties, inferior moisture sensitivity, early physical ageing and poor impact resistance [2,8, 7]. Therefore, the best way to improve its properties and to extend its application field is to prepare blends, copolymers and to reinforce it with various inorganic and organic fillers.

Lignin, the most abundant polyphenolic compound found in biomass, can be used as a renewable organic filler. It is the main component of the plant cell wall and binds to the cellulose and hemicellulose to provide mechanical support [1,9-11]. Lignin is widely acceptable for application in the synthesis of value-added products such as resins, films, foams, stabilising agent for nanoparticles and nanofibers, it has various functional groups (hydroxyls, methoxyl, carbonyl, and carboxyl) in its structure [1,3,12,13]. The successful use of lignin in blends with different biopolymers, such as starch [14], alginate [1], gelatin [15] and synthetic polymers like poly(vinyl alcohol), poly(ethylene), poly(lactic acid)and poly(vinyl chloride) have also been reported in the literature [7,12,16,17]. Moreover, antibacterial and antioxidant activities of lignin have been reported, which might be helpful to augment the applicability of PLA in the food and pharmaceutical industries [18].

The objective of the current work was to synthesise the lignin-PLA blend for its plausible application in food packaging. The synthesised film was characterised by physicochemically, morphologically and structurally to evaluate the effect of lignin on the PLA matrix. At the end, antimicrobial and biodegradability properties of the film were investigated.

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Asian Journal of Psychiatry 53 (2020) 102426

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

journal homepage: www.elsevier.com/locate/ajp

Letter to the Editor

A physiological link for psychiatric symptoms in COVID-19: Role of amino acid deficiency

Dear Editor,

A variety of signs and symptoms are associated with SARS-CoV-2 infection. Clinical manifestations of COVID-19 include, but not limited to, acute respiratory distress syndrome, pneumonia, hyperthermia, intravascular disseminated coagulation, multi-organ damage, and gastrointestinal (GI) disturbance (Soni et al., 2020a). Psychiatric illnesses are also being invariably reported among COVID-19 patients (Tandon, 2020). Fear of adverse treatment outcome and mental trauma are linked with such psychosis. However, several other factors are also conjectured to prompt distress in SARS-CoV-2-infected patients, including socioeconomic state, nutritional practice, and immunity (Tandon, 2020). Cellular and physiological damage to body organs including lung, heart, vasculature, and intestine remains as collateral damage to physical health in recovered patients (Rozga et al., 2020). The abnormal physiological state is often correlated with psychotic manifestations. A significant fraction of recovered COVID-19 patients also experience post-traumatic stress disorder (PTSD). Moreover, major depression disorders (MDD) are also prevalent in patients and are predicted to have long-lasting consequences on mental as well as physical health (Tandon, 2020). Distorted physical well-being in COVID-19 patients, as well as recovered individuals, can be hypothesized to affect mental well-being. Therefore, it becomes imperative to explore the association of physiological disturbance and psychiatric compromise to identify targets and treatment of the later (Tandon, 2020).

One of the common clinical manifestations of SARS-CoV-2 infection is a disturbance in GI function. Abdominal pain, vomiting, and diarrhea are common GI symptoms in COVID-19 patients (Rozga et al., 2020; Ayres, 2020). Such GI symptoms lead to loss of appetite; and physiological damage caused by viral infection poses a hindrance in nutrient uptake culminating in malabsorption of nutrients. Rao et al. (2008) have reviewed the role of nutrients including omega fatty acids and other amino acids in maintenance of mental health; and a deficiency may lead to depression. A significant decline in uptake of nutrients was reported in COVID-19 patients (Ayres, 2020). Nutrient deficiency can invite physiological stress and provoke psychiatric symptoms (Ayres, 2020; Nisoli et al., 2020; Rao et al., 2008). Qualitative and quantitative set-up of amino acids has been shown to regulate various dimensions of psychiatric presentations including depression and schizophrenia (Rao et al., 2008). In Amine theory, reduced levels of neurotransmitters (dopamine, norepinephrine, and serotonin) act as foremost factors associated with depression. Besides being structural components of proteins, amino acids serve as precursors for neurotransmitters; and its malabsorption and nutritional deficiency can provoke mood change and depressive disorders. Dysfunction of angiotensin-converting enzyme-2 (ACE2), cellular anchor of SARS-CoV-2, can cause GI disturbance; and its cellular internalization during infection has been postulated to dwindle the expression sodium-dependent neutral amino acid transporter (B°AT1) in cells of the intestine (Nisoli et al., 2020). Hartnup disorder, an inherited condition with defective B°AT1 amino acid transporter encoded by mutated SLC6A19 gene, shares several psychiatric symptoms with COVID-19 (Nisoli et al., 2020). A reduced level of cofactors (vitamin C and zinc) may also cause a deficient conversion of amino acids into neurotransmitters; and thus corollary affects mental well-being.

Glutamine, glutamate, tryptophan, and tyrosine are among major amino acids that serve as the precursor for neurotransmitters like gamma-aminobutyric acid (GABA), norepinephrine, epinephrine, dopamine, serotonin, and melatonin (Rao et al., 2008). Adequate conversion of amino acids to these neurotransmitters can have regulatory consequences on brain function as well as the prevention of psychiatric illness. In COVID-19, a disrupted uptake of amino acid consequently drops off the level of neurotransmitters and may invite psychiatric symptoms (Nisoli et al., 2020). Moreover, a reduced level of brain interstitial amino acid correlates with the onset of depression (Kofler et al., 2019). Hasler et al. (2019) also demonstrated an association of prefrontal glutamine level, glutamine-glutamate ratio, and glutamatergic abnormality with the manifestation of anxiety, depression, and neuroticism. Tryptophan catabolites (TRYCATs) have pleiotropic effects in physiological and psychiatric health. TRYCATs also regulate the manifestation of depressive disorders (Rao et al., 2008); and have been postulated as a link for psychoneuroimmunomodulation in COVID-19 (Soni et al., 2020b)

Precursor amino acid therapy has shown significant success in pain management as well as in clinical management of psychosomatic disorders (Rao et al., 2008). Attempts for management of COVID-19 are not limited to physiological well-being; but also encompass the mental well-being (Tandon, 2020). An evidence-based analysis of medical nutrition therapy (MNT) for efficacy in COVID-19 was carried out. A supervised MNT, including micronutrients and conditional amino acid supplementation, was speculated to reduce the adverse effects of COVID-19 (Rozga et al., 2020). Considering the importance of amino acids as nutrients and regulators of mental well-being as well, a controlled and randomized clinical trial is underway for evaluation of amino acid supplementation in severely ill COVID-19 patients (clinicaltrials.gov, NCT04443673).

Collectively, it can be concluded that psychiatric symptoms in COVID-19 patients have a significant contribution from physiological injuries triggered by SARS-CoV-2-infection. Nutritional deficiency, especially those in level and ratio of amino acids may alter the balance of neurotransmitters in provoking a state of anxiety, depression, and mood change in COVID-19 patients. A supplementation of conditional amino acids may not only assist the mental well-being but also improves the immunity and treatment outcome of COVID-19.

https://doi.org/10.1016/j.ajp.2020.102426
Received 29 August 2020
Available online 25 September 2020

frontiers in Oncology

ORIGINAL RESEARCH
published: 06 October 2021
doi: 10.3389/fonc.2021.738961

Counteracting Action of Curcumin on High Glucose-Induced Chemoresistance in Hepatic Carcinoma Cells

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OPEN ACCESS

Edited by:
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Barretos Cancer Hospital, Brazil

Reviewed by:
Pritam Sadhukhan,
Johns Hopkins University,
United States
Giuseppina Di Stefano,
University of Bologna, Italy

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Specialty section:
This article was submitted to Cancer Metabolism, a section of the journal Frontiers in Oncology

Received: 09 July 2021
Accepted: 10 September 2021
Published: 06 October 2021

Citation:
Soni VK, Mehta A, Ratre YK, Chandra V, Shukla D, Kumar A and Vishvakarma NK (2021) Counteracting Action of Curcumin on High Glucose-Induced Chemoresistance in Hepatic Carcinoma Cells. Front. Oncol. 11:738961. doi: 10.3389/fonc.2021.738961

Along with direct anticancer activity, curcumin hinders the onset of chemoresistance. Among many, high glucose condition is a key driving factor for chemoresistance. However, the ability of curcumin remains unexplored against high glucose-induced chemoresistance. Moreover, chemoresistance is major hindrance in effective clinical management of liver cancer. Using hepatic carcinoma HepG2 cells, the present investigation demonstrates that high glucose induces chemoresistance, which is averted by the simultaneous presence of curcumin. Curcumin obviated the hyperglycemia-induced modulations like elevated glucose consumption, lactate production, and extracellular acidification, and diminished nitric oxide and reactive oxygen species (ROS) production. Modulated molecular regulators are suggested to play a crucial role as curcumin pretreatment also prevented the onset of chemoresistance by high glucose. High glucose instigated suppression in the intracellular accumulation of anticancer drug doxorubicin and drug-induced chromatin compactness along with declined expression of drug efflux pump MDR-1 and transcription factors and signal transducers governing the survival, aggressiveness, and apoptotic cell death (p53, HIF-1α, mTOR, MYC, STAT3). Curcumin alleviated the suppression of drug retention and nuclear condensation along with hindering the high glucose-induced alterations in transcription factors and signal transducers. High glucose-driven resistance in cancer cells was associated with elevated expression of metabolic enzymes HKII, PFK1, GAPDH, PKM2, LDH-A, IDH3A, and FASN. Metabolite transporters and receptors (GLUT-1, MCT-1, MCT-4, and HCAR-1) were also found upregulated in high glucose exposed HepG2 cells. Curcumin inhibited the elevated expression of these enzymes, transporters, and receptors in cancer cells. Curcumin also uplifted the SDH expression, which was inhibited in high glucose condition. Taken together, the findings of the present investigation first time demonstrate the ability of curcumin against high glucose-induced chemoresistance, along with its molecular mechanism. This will have implication in therapeutic management of malignancies in diabetic conditions.

Keywords: curcumin, chemoresistance, glucose, hepatic cancer, metabolism

International Journal of Biochemistry and Cell Biology 123 (2020) 105752

Contents lists available at ScienceDirect

International Journal of Biochemistry and Cell Biology

journal homepage: www.elsevier.com/locate/biocel

Curcumin circumvent lactate-induced chemoresistance in hepatic cancer cells through modulation of hydroxycarboxylic acid receptor-1

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ARTICLE INFO

Keywords:
Curcumin
HCAR-1/GPR81
Lactate
Chemoresistance

ABSTRACT

Curcumin has been demonstrated to affect the chemoresistance in cancer cells of various origins. However, its ability to modulate lactate-induced chemoresistance remains unclear. The Present investigation demonstrates that curcumin inhibits the survival of HepG2 and HuT78 cells and can modulate chemo-susceptibility of HepG2 cells. Experimental simulation of simultaneous and pre-treatment suggest cooperatively between curcumin and anticancer drugs as well as the modulation of molecular regulators. Inhibition of glucose consumption, lactate production, extracellular acidity and augmented level of Nitric oxide were observed. DAPI staining revealed hyper condensation of chromatin in curcumin-treated HepG2 cells. Curcumin also diminished the lactate-induced chemoresistance against doxorubicin in hepatic cancer cells along with down regulation of lactate receptor (*h*ydroxycarboxylic *a*cid *r*eceptor-1; HCAR-1/GPR81). Alteration of the extracellular milieu along with inhibited expression of genes (*hif-1α, ldh-a, mct-1, mdr-1* and *stat-3)* and proteins (HIF-1α and HCAR-1) are indicated to be involved in curcumin-induced reversal of chemoresistance in HepG2 cells. Findings of present investigation contribute to knowledge of curcumin mediated chemosensitization and its mechanism.

1. Introduction

Medicinal plant derivatives have achieved significant recognition for their bioactivity and antineoplastic activity (Rastegar et al., 2018; Aggarwal et al., 2003; Notarbartolo et al., 2005; Vishvakarma et al., 2011; 2012a; Vishvakarma, 2014; Abrahams et al., 2019). One of these, Curcumin, yellow pigment of turmeric, has displayed antitumor activity against cancer of a variety of origins (Aggarwal et al., 2003; Notarbartolo et al., 2005; Vishvakarma et al., 2011; Vishvakarma, 2014). The surfeits of investigations have been conducted to identify the potential and targets of curcumin (Aggarwal et al., 2003; Notarbartolo et al., 2005; Vishvakarma et al., 2012a; Vishvakarma, 2014; Adiwidjaja et al., 2017). Moreover, curcumin have been demonstrated to be exclusive of any toxic effect to the host (Aggarwal et al., 2003; Vishvakarma, 2014). Identified activity/targets of curcumin include anti-inflammatory, inhibition of cell growth, and modulation of regulators of cell death (Notarbartolo et al., 2005; Vishvakarma et al., 2011; Vishvakarma, 2014; Adiwidjaja et al., 2017). Curcumin has been proven to display effective therapeutic aptitude in laboratory as well as preclinical settings (Jantan et al., 2015; Vishvakarma, 2014). Interdisciplinary approaches are being exploited to overcome obstacles in the clinical exploitation of curcumin, such as low bioavailability etc. (Jantan et al., 2015; Adiwidjaja et al., 2017). Curcumin has also been shown to affect the various hallmarks of cancer. Modulations of deregulated cancer metabolism were reported in previous investigations (Siddiqui et al., 2018; Vishvakarma et al., 2011).

Cancer chemoresistance is one of the major obstacles in the efficient clinical management of malignant disorders (Rastegar et al., 2018; Lohitesh et al., 2018). The onset of chemoresistance not only increases required doses of anticancer drugs, they also invite other consequence harmful to the host (Rastegar et al., 2018; Su et al., 2018; Yoshida et al., 2017). The events of oncogenic transformation and metabolic niche at the earliest phases of neoplasm origin were shown to regulate the tumor phenotype. Various strategies have been adopted to identify the key

Abbreviations: DAPI, 4′,6-diamidino-2-phenylindole; HCAR1, Hydroxycarboxylic acid receptor 1; GPR81, G-protein-coupled receptor 81; MDR1, Multidrug resistance 1; HIF-1α, Hypoxia-inducible factor 1α; LDH-A, Lactate dehydrogenase A; MCT-1, Monocarboxylate transporter 1; β-Actin, Beta actin; NF-Kb, Nuclear factor kappa-light-chain-enhancer of activated B cells; DMSO, Dimethyl sulfoxide; MTT, 3-(4,5-dimethylthiazol-2 yl)-2,5-diphenyl tetrazolium bromide; PBS, Phosphate-buffered saline; Tris-EDTA, Tris Ethylenediaminetetraacetic acid; TCA, Tricarboxylic acid cycle; $NaNO_2$, Sodium nitrite; NO_2, Nitrogen dioxide; NO, Nitric oxide; H_3PO_4, Phosphoric acid; PIPES, Piperazine-N,N′-bis(2-ethanesulfonic acid; RPMI, 1640 Roswell Park Memorial Institute 1640

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https://doi.org/10.1016/j.biocel.2020.105752
Received 8 January 2020; Received in revised form 4 April 2020; Accepted 16 April 2020
Available online 20 April 2020

European Journal of Pharmacology 886 (2020) 173551

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Full length article

Curcumin, a traditional spice component, can hold the promise against COVID-19?

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ARTICLE INFO

Keywords:
COVID-19
Curcumin
Cytokine storm
Inflammation
Molecular targets

ABSTRACT

The severity of the recent pandemic and the absence of any specific medication impelled the identification of existing drugs with potential in the treatment of Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). Curcumin, known for its pharmacological abilities especially as an anti-inflammatory agent, can be hypothesized as a potential candidate in the therapeutic regimen. COVID-19 has an assorted range of pathophysiological consequences, including pulmonary damage, elevated inflammatory response, coagulopathy, and multi-organ damage. This review summarizes the several evidences for the pharmacological benefits of curcumin in COVID-19-associated clinical manifestations. Curcumin can be appraised to hinder cellular entry, replication of SARS-CoV-2, and to prevent and repair COVID-19-associated damage of pneumocytes, renal cells, cardiomyocytes, hematopoietic stem cells, etc. The modulation and protective effect of curcumin on cytokine storm-related disorders are also discussed. Collectively, this review provides grounds for its clinical evaluation in the therapeutic management of SARS-CoV-2 infection.

1. Introduction

An outburst of Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) infection causes COVID-19 pandemic; with millions of cases and approximately 540 thousands of deaths (WHO, 2020). Prophylactic and therapeutic measures are not yet available against COVID-19 (Scavone et al., 2020). Prompted responses throughout the world have been initiated to identify the therapeutic molecule against SARS-CoV-2; large number of drugs have been suggested for repurposing against COVID-19 (Wu et al., 2020). Several reviews have suggested a potential role of phytochemicals in the fight against SARS-CoV-2 infection and the onset of COVID-19 (Mani et al., 2020; McKee et al., 2020). Phytochemicals have been proven effective against previous episodes of virus outbreaks in the last two decades (Barnard and Kumaki, 2011; Kunnumakkara et al., 2017; Xu and Liu, 2017). Bioactive ingredients may offer potential candidates for the prevention and treatment of COVID-19. Turmeric is one of such plant products that provide benefits in a variety of medical ailments including respiratory infections (Barnard and Kumaki, 2011; Buhrmann et al., 2020; Kunnumakkara et al., 2019; Soni et al., 2020; Vishvakarma, 2014; Xu and Liu, 2017). A major bioactive component of turmeric, curcumin has been shown to confer curative and preventive effects in the diverse forms of pathology and disorders, infections, and malignancies (Barnard and Kumaki, 2011; Kunnumakkara et al., 2019; Soni et al., 2020; Vishvakarma, 2014; Xu and Liu, 2017).

Various demographic factors, including dietary habits, have been linked with low COVID-19 case fatality rate observed in South-East Asia and East-Mediterranean (WHO, 2020). Turmeric is an integral part of

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https://doi.org/10.1016/j.ejphar.2020.173551
Received 10 July 2020; Received in revised form 17 August 2020; Accepted 10 September 2020
Available online 12 September 2020

World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2021 February 14; 27(6): 449-469

DOI: 10.3748/wjg.v27.i6.449

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Current understanding of the impact of COVID-19 on gastrointestinal disease: Challenges and openings

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Author contributions: Verma HK contributed to the conceptualization, investigation and supervision; Verma HK and Bhaskar LVKS contributed to the methodology; Verma HK and Vishvakarma NK contributed to the software; Sahu T, Mehta A, Jaiswal A and Ratre YK contributed to the article search and writing the original draft; Sahu T, Ratre YK, Verma HK, Vishvakarma NK and Bhaskar LVKS contributed to the writing, reviewing, and editing of the manuscript.

Conflict-of-interest statement: No conflict of interest.

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Abstract

The novel coronavirus disease-2019 (COVID-19) is caused by a positive-sense single-stranded RNA virus which belongs to the Coronaviridae family. In March 2019 the World Health Organization declared that COVID-19 was a pandemic. COVID-19 patients typically have a fever, dry cough, dyspnea, fatigue, and anosmia. Some patients also report gastrointestinal (GI) symptoms, including diarrhea, nausea, vomiting, and abdominal pain, as well as liver enzyme abnormalities. Surprisingly, many studies have found severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral RNA in rectal swabs and stool specimens of asymptomatic COVID-19 patients. In addition, viral receptor angiotensin-converting enzyme 2 and transmembrane protease serine-type 2, were also found to be highly expressed in gastrointestinal epithelial cells of the intestinal mucosa. Furthermore, SARS-CoV-2 can dynamically infect and replicate in both GI and liver cells. Taken together these results indicate that the GI tract is a potential target of SARS-CoV-2. Therefore, the present review summarizes the vital information available to date on COVID-19 and its impact on GI aspects.

Key Words: SARS-CoV-2; COVID-19; Gastrointestinal symptoms; Recommendation; Diagnosis; Therapeutics

Asian Journal of Psychiatry 55 (2021) 102523

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

journal homepage: www.elsevier.com/locate/ajp

Letter to the Editor

Finding Horcrux of psychiatric symptoms in COVID-19: Deficiencies of amino acids and vitamin D

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ARTICLE INFO

Keywords
Amino Acids
COVID-19
Neurotransmitters
Psychiatric illness
Vitamin D

Dear Editor

A diverse range of psychiatric complications is involved in patients suffering from COVID-19 (Tandon, 2020). Moreover, psychiatric complications including anxious and depressive disorders are being reported even in those individuals who recovered from COVID-19 (Abrishami et al., 2020). Tandon (2020) has pressed the need for a multidisciplinary approach as a priority to combat ill-effects associated with the COVID-19 pandemic. The world has also been predicted to face a flood of psychiatric illness even in the post-pandemic era (Tandon, 2020). An intervened pyschoneuroendocrineimmune (PNEI) response governs the overall consequences of altered physiological and psychiatric presentation even in COVID-19. (Tandon, 2020; Soni et al., 2020a). Therefore the role of *'physiological spoils'* as *raison d'ètre* for psychiatric sequelae of COVID-19 cannot be overlooked. Physiological offend caused by COVID-19 culminate into gastrointestinal (GI) disturbances; leading to malabsorption. COVID-19 share psychiatric symptoms with Hartnup disorder, a genetic condition with GI expression of defective amino acid transporters (Soni et al., 2020b). The dysfunctional state of angiotensin-converting enzyme-2 (ACE-2), cellular doorway of SARS-CoV-2, downregulates the expression of amino acid transporters.

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https://doi.org/10.1016/j.ajp.2020.102523
Received 1 November 2020;
Available online 25 December 2020

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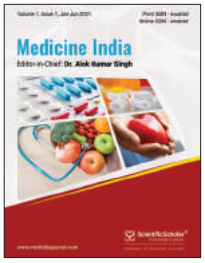
Article in Press



Immunology *Review Article*

Immunity boosters in COVID-19: Reality or myth?

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Received : 15 May 2021
Accepted : 27 June 2021
EPub Ahead of Print : 24 July 2021
Published :

DOI
10.25259/MEDINDIA_1_2021

Quick Response Code:

ABSTRACT

COVID-19 pandemic has posed an unprecedented threat to human beings. The emergence of pathogens always had been a threat as the designing and verification of treatment strategies and vaccines take time. In such a scenario, the use of strategies, formulations, or chemicals to improve immunity can provide protection, at least partially. The use of some traditional or folk medicinal preparations and other supplements derived from plants are among the most common agents used for keeping immunity tidy and tough. They are used by many with the belief that being herbal in origin these agents are safe. These formulations/preparations are regarded as "Immunity Boosters." Revolving information and advertisements in bulk and the strategies of "the attention economy" also propagate this belief. The term "Immunity Booster" is a misnomer for these agents and is scientifically not approved. However, the benefits of these herbal formulations cannot be denied. Few of these herbal formulations have benefits in preventive and therapeutic management infections including those of SARS-CoV-2. Due to lifestyle, diet habits, deficiencies and neuropsychological stress, the immunity of a large fraction of the population is not optimal. Uncertainty and fear prevalent in the time of pandemic also negatively affect the immunity threshold. Many phytochemicals have been proven to aid in maintaining the threshold of immune response to an optimal level in subjects with compromised states of immunity. The immunomodulatory potential of these traditional herbal formulations also offers advantages when used along with standard operating procedures in COVID-19. Proposed formulations and their components also have disadvantageous effects and must be used under supervision with scientific methods. Excessive use of these agents may not only affect the organ and tissues deleteriously, but it can also invite immunopathology. Experimental verification of benefits being offered by these herbal agents will aid in their rightful exploitation in the therapy of human ailments including COVID-19.

Keywords: COVID-19, Herbal formulation, Traditional medicine, Immunity booster, Immunomodulation

INTRODUCTION

In the time of the COVID-19 pandemic, the maximum possible efforts are being made throughout the globe to counter the detrimental and undesired consequences associated with SARS-COV-2 infection.[1,2] A strengthened immune system is always sought as a protective measure against infectious disorders. A large number of strategies or recommendations are being forwarded and spread through various means even by many authoritative organizations. There proposed beneficial role is largely based on traditional knowledge, and/or beliefs. In a large collection, it becomes hard as well as confusing to utilize these strategies.

Forces around the world are working together to their optimal level to design the cure and preventive measures against this deadly pandemic of COVID-19. Several therapeutic agents

JOURNAL OF BIOMOLECULAR STRUCTURE AND DYNAMICS
https://doi.org/10.1080/07391102.2021.1944911

Molecular docking and simulation studies of flavonoid compounds against PBP-2a of methicillin-resistant *Staphylococcus aureus*

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Communicated by Ramaswamy H. Sarma

ABSTRACT

Methicillin-Resistant *Staphylococcus aureus* (MRSA), a pathogenic bacterium that causes life-threatening outbreaks such as community-onset and nosocomial infections as emerging 'superbug'. Time and motion study of its virulent property developed resistance against most of the antibiotics such as Vancomycin. Thereby, to curb this problem entails the development of new therapeutic agents. Plant-derived antimicrobial agents have recently piqued people's interest, so in this research, 186 flavonoids compound selected to unmask the best candidates that can act as potent inhibitors against the Penicillin Binding Protein-2a (PBP-2a) of MRSA. Molecular docking performed using PyRx and GOLD suite to determine the binding affinities and interactions between the phytochemicals and the PBP-2a. The selected candidates strongly interact with the different amino acid residues. The 30 ns molecular dynamics (MD) simulations with five top-ranked compounds such as Naringin, Hesperidin, Neohesperidin, Didymin and Icariin validated the docking interactions. These findings are also strongly supported by root-mean-square deviation, root-mean-square fluctuation and the radius of gyration. ADME/T analysis demonstrates that these candidates appear to be safer inhibitors. Our findings point to natural flavonoids as a promising and readily available source of adjuvant antimicrobial therapy against resistant strains in the future.

ARTICLE HISTORY
Received 4 February 2021
Accepted 14 June 2021

KEYWORDS
Penicillin Binding Protein-2a; flavonoids compounds; methicillin-resistant staphylococcus aureus; molecular docking; molecular dynamic simulation; ADME/T properties

1. Introduction

Methicillin-Resistant *Staphylococcus aureus* (MRSA) is such a notorious pathogenic bacterium causing many infections that controlling the bacterium has become a serious issue worldwide (Kuehnert et al., 2005). The high outbreak of MRSA was observed in closed communities such as schools, prisons, sports teams and the disease has mainly been transmitted from fomite to person and from person to person and so on (David et al., 2011; Kokoska et al., 2019). The pathogenicity of the bacteria includes skin and soft tissue infections, bone, joint, implant infections, pneumonia and septicemia, etc. (Monecke et al., 2011). Recent reports have indicated the emergence of multidrug-resistant *Staphylococci* against all classes of β-lactam antibiotics. The antibiotic resistance is mainly due to the expression of PC1 β-lactamase and the acquisition of the mecA gene encoding a penicillin-binding protein, PBP-2a (Bai et al., 2021; Llarrull et al., 2009). Improving the affinity of β-lactams for MRSA-specific PBP-2a has been the purpose of intensive research. Recent work on the structure of PBP-2a and potential blocking β-lactams indicates that the active site of the enzyme is closed in the resting state and thus difficult to reach with the drug. However, when the enzyme is exposed to cell wall precursors or β-lactams with appropriate pharmacophores, allosteric interactions at other portions of PBP-2a trigger the opening of the active site, providing access to the precursors or the blocking drug (Figure 1). The bacteria initially penetrate the host's immune system via epidermal and mucosal epithelia and the antimicrobial peptides play a necessary role in the host's innate immune defense against the initial colonization of bacteria (Ouhara et al., 2008).

Recent studies revealed that strains of MRSA have gained resistance to traditional antibiotics and emerged as multi-drug-resistant superbugs. Hence, there is a large need for discovering better therapeutic agents. Many medicinal plants

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/07391102.2021.1944911.

Journal of Ecophysiology and Occupational Health, *Vol 21(2), DOI 10.18311/jeoh/2021/27108, 64-71, June 2021*

ISSN (Print): 0972-4397
ISSN (Online): 0974-0805

Biodecolorization of Azo Dye Acid Blue 113 by Soil Bacterium *Klebsiella variicola* RMLP1

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Abstract

The present study was aimed to isolate a new bacterial strain for the degradation/decolorization of azo dye Acid Blue 113 (AB 113). The physico-chemical method is inadequate for degradation of azo dyes; therefore, an environmental friendly and competent method such as use of the biological organism was studied for decolorization of AB 113. Bushnell and Hass (BHM) medium containing AB 113 dye were used to perform the decolorization study. 16S rRNA gene sequencing approach was used for identification of bacterial isolate as a *Klebsiella variicola*. The optimum process parameters for the decolorization of AB 113 were found at pH 8, 35°C temperature and 100 mg/L dye concentration during 72 h incubation. Glucose and ammonium sulphate was the carbon and nitrogen source suited well for the decolorization of dye. The results proved that the *Klebsiella variicola*, offer huge ability in treating textile wastewater containing the color AB 113.

Keywords: Acid Blue 113, Azo Dye, Decolorization, *Klebsiella Variicola,* 16S rDNA

1. Introduction

Synthetic dyes are xenobiotic, aromatic compounds which provide permanent color to various materials. These dyes offer broad range of color shades and consume minimum energy during their appliance in the textile, food, paper, paint, varnish, cosmetics and pharmaceutical industries[1]. On the basis of structure of chromophore, 20 different types of dye groups are available[2]. The textile processing industries produces huge quantity of azo dye[3]. It was estimated that globally $7x10^5$ metric tons of textile color is generated each year and 70% of this vast amount is contributed by azo dyes[4]. About 10-15% of the azo dyes used in dyeing process is unbound and are likely to be discharged into water bodies[5]. Azo dyes are cyclic organic preparations comprise one or more azo bond (–N=N–). These bonds are accountable for recalcitrant nature of dyes and give resistant capacity towards its natural degradation. Discharge of these dyes into environment decreases light dispersion into water which minimize the photosynthetic process of aquatic species[6]. These dyes are also mutagenic[7] and carcinogenic to human and other aquatic animals[8]. Number of physico-chemical techniques for example, flocculation, ion exchange, membrane filtration, coagulation, photo-oxidation, electrolysis and ozonation are used for textile wastewater treatment but, they have some limitations such as generation of large quantities of toxic chemical sludge and high operational and maintenance cost[9]. As physico-chemical techniques are associated with some limitation, there is a need to develop some more efficient and cost-effective methods for the removal of these dyes from wastewater. The biological methods include bacterial decolorization, fungal decolorization, phycoremediation, phytoremediation and enzymatic methods[10]. Thus, biological microorganisms such as bacteria, fungi, algae, and plants are successfully used in the decolorization and degradation of these dyes. These microbial based decolorization and degradation methods have some decisive advantages such as low operating cost, efficient and production of less sludge and eco-friendly nature[11]. The major benefits of biological methods are low preparation techniques and easy maintenance of microbes[12]. The decolorization process by fungi and algae attributed to adsorption rather than degradation which result in retention of dye in the environment. Bacterial degradation of dyes primarily begins under anaerobic conditions by an enzyme mediated step[13]. The ensuing degradation products for

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Toxicology International, *Vol 28(3), 177-186, 2021, DOI: 10.18311/ti/2021/v28i3/27736*

Original Research
ISSN (Print): 0971-6580
ISSN (Online): 0976-5131

Efficient Decolorization of Dye Acid Blue 113 by Soil Bacterium *Bacillus subtilis* RMLP2

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Abstract

In this study, a bacterial strain was isolated from soil and tested for the decolorization of azo dye Acid Blue 113 (AB 113). Decolorization of azo dyes by means of physico-chemical method is not environmentally friendly thus an alternative method based on bacteria was employed for decolorization of AB 113. The color removal studies were performed using Bushnell and Hass medium amended with AB 113 dye. Bacterial isolate *Bacillus subtilis* RMLP2 was identified by 16S rRNA gene sequence analysis. The effect of various physico-chemical parameters such as incubation condition, pH, temperature, carbon source, nitrogen source and dye concentration on decolorization of AB 113 by *Bacillus subtilis* RMLP2 were studied. The bacterial isolate showed the remarkable higher percentage (92.71%) of color removal of dye AB 113 at 100 mg/L concentration, 35^{0}C, pH 7 during 72 h of incubation period under static condition. Yeast extract and glucose was found as best nitrogen and carbon source for efficient decolorization of dye. These results confirmed that the *Bacillus subtilis* has enormous ability to degrade dye AB 113 present in textile effluents.

Keywords: Acid Blue 113, Azo Dye, *Bacillus subtilis*, Decolorization, 16S rDNA

1. Introduction

Our sacred environment is mainly polluted by the discharge of millions of liters of wastewater containing synthetic dyes[1]. Dyes are described by presence of chromophore group in their complex structures and are mainly classified as anthraquinone, phthalocyanine and azo dyes[2]. Around 2,000 diverse xenobiotic azo dyes are widely employed in several industries like textiles, leather, cosmetics, food and printing[3,4]. Textile industries utilized around 70% of azo dyes as a coloring material during dyeing process[5]. These dye contains typical one or more (-N=N-) azo bond[6,7]. Worldwide, it was reported that approximately 280,000 tons of textiles dye are discharged along with industrial wastewater every year[8]. Wastewater released from textile industries was proved to be toxic and mutagenic to aquatic inhabitants once discharged into the water ecosystem[9,10]. Hence, the release of textile wastewater into the water reservoir is of major environmental concern[11,12]. Azo dyes also induce allergic reactions and their degradative metabolites are extremely mutagenic and carcinogenic to humans[13]. The parent compound (dye) was quietly found less toxic as compared to their degradative metabolites, which was recalcitrant and more injurious[14]. The textile industry wastewater consists of dyes, stabilizers, detergents and additives, employed at various steps of dyeing process. These agents are accumulated in aquatic bodies and leads to diminished penetration of sunlight thereby inhibiting photosynthesis and respiration in flora and fauna[15,16]. The wastewaters are characterized by different factors like Chemical Oxygen Demand (COD), Biological Oxygen Demand (BOD), high pH, Suspended Solids (SS) and intense color quality[17]. The complex aromatic structures of dye contribute its resistance against the sunlight, temperatures

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Biologia
https://doi.org/10.2478/s11756-020-00575-y

REVIEW

Targeting type II diabetes with plant terpenes: the new and promising antidiabetic therapeutics

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Received: 17 March 2020 / Accepted: 31 July 2020

Abstract

Type II diabetes is a metabolic disorder characterized by hyperglycemia arising from defective insulin signaling. Several synthetic drugs are being used for diabetes treatment, but they have adverse effects. So as an alternative approach, compounds from plants with lesser/no side effects and comparatively cheaper are gaining momentum. Terpenes comprise a class of diversified phytochemicals, which have beneficial effects and important functions in plants. They have shown a series of biological properties that healthpromoting conduct in humans. Besides, a lot of terpenes have also been reported to be much less toxic as compared to synthetic compounds. Diabetic people could be benefited from terpenes obtained either from the diet or from plant-derived herbal medicines. Due to the natural origin of terpenes, they are supposed to be a safe and promising agent in eliminating the causes and effects of diabetes. This paper reviews the research reports of terpenes as their antidiabetic potential, mechanistic action, preclinical profile, shortcomings, and prospect in the effective management of diabetes.

Keywords Terpenes · Diabetes · Mechanistic action · Preclinical profile · Therapeutic molecules

Abbreviations

ACC	Acetyl-CoA carboxylase
ACE	Angiotensin converting enzyme
AGEs	Advanced glycation end products
AMPK	AMP activated protein kinase
AR	Aldose reductase
DAA	Dehyroabietic acid
DM	Diabetes mellitus
DPP IV	Dipeptidyl peptidase IV
DPPH	2,2-diphenyl-1-picryhydrazyl
ER	Endoplasmic reticulum
GADA	Glutamic Acid Decarboxylose
GLP	Glucagon like peptide
GSP	Glycosylated serum protein
HbA1c	Haemoglobin A1c
IA2A	Insulinoma associated autoantigen 2
IDDM	Insulindependent diabetes mellitus
IR	Insulin receptor
IRE1	Inositol requiring enzyme 1
IRS	Insulin receptor substrate
LC-MS	liquid chromatography-mass spectrometry
MAPK	Mitogen-activated protein kinase
MDA	Malondialdehyde
NF-kB	Nuclear factor kappa-B
NIDDM	Noninsulindependent diabetes mellitus
NLC	Nano-structured lipid carriers
NLRP3	Nod like receptor family pyrin domain containing 3
Nrf2	Nuclear factor erythroid 2-related factor
OGTT	Oral glucose tolerance test
PL	Pancreatic lipase
PPAR	Peroxisome proliferator activator receptor
PTP	Protein tyrosine phosphatase
ROS	Reactive oxygen species
SIRT1	Silent mating type information regulation 2 homolog 1 overexpression
SLN	Solid lipid nanoparticles
SOD	Superoxide dismutase
STZ	Streptozotocin
STZ-NA	Streptozotocin-Nicotinamide

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Published online: 12 August 2020

Computational perspectives revealed prospective vaccine candidates from five structural proteins of novel SARS corona virus 2019 (SARS-CoV-2)

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ABSTRACT

Background: The present pandemic COVID-19 is caused by SARS-CoV-2, a single-stranded positive-sense RNA virus from the *Coronaviridae* family. Due to a lack of antiviral drugs, vaccines against the virus are urgently required.

Methods: In this study, validated computational approaches were used to identify peptide-based epitopes from six structural proteins having antigenic properties. The Net-CTL 1.2 tool was used for the prediction of $CD8^+$ T-cell epitopes, while the robust tools Bepi-Pred 2 and LBtope was employed for the identification of linear B-cell epitopes. Docking studies of the identified epitopes were performed using HADDOCK 2.4 and the structures were visualized by Discovery Studio and $LigPlot^+$. Antigenicity, immunogenicity, conservancy, population coverage and allergenicity of the predicted epitopes were determined by the bioinformatics tools like VaxiJen v2.0 server, the Immune Epitope Database tools and AllerTOP v.2.0, AllergenFP 1.0 and ElliPro.

Results: The predicted T cell and linear B-cell epitopes were considered as prime vaccine targets in case they passed the requisite parameters like antigenicity, immunogenicity, conservancy, non-allergenicity and broad range of population coverage. Among the predicted CD8+ T cell epitopes, potential vaccine targets from surface glycoprotein were; YQPYRVVVL, PYRVVVLSF, GVYFASTEK, QLTPTWRVY, and those from ORF3a protein were LKKRWQLAL, HVTFFIYNK. Similarly, RFLYIIKLI, LTWICLLQF from membrane protein and three epitopes viz; SPRWYFYYL, TWLTYTGAI, KTFPPTEPK from nucleocapsid phosphoprotein were the superior vaccine targets observed in our study. The negative values of HADDOCK and Z scores obtained for the best cluster indicated the potential of the epitopes as suitable vaccine candidates. Analysis of the 3D and 2D interaction diagrams of best cluster produced by HADDOCK 2.4 displayed the binding interaction of leading T cell epitopes within the MHC-1 peptide binding clefts. On the other hand, among linear B cell epitopes the majority of potential vaccine targets were from nucleocapsid protein, viz; ^{59}-HGKEDLKFPRGQGVPINTNSS PDDQIGYYRRATRRIRGGDGKMKDLS-^{105}, ^{227}-LNQLE SKMSGKGQQQQGQT VTKKSAAEASKKPRQKRTATK-^{266}, ^{3}-DNGPQNQRNAPRITFGGP-^{20}, ^{29}-GERSG ARSKQRRPQGL-^{45}. Two other prime vaccine targets, ^{370}-NSASFSTFKCYGVSPTK LNDLCFTNV-^{395} and ^{260}-AGAAAYYVGYLQPRT-^{274} were identified in the spike

Submitted 22 April 2020
Accepted 11 August 2020
Published 29 September 2020

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Academic editor
Keith Crandall

Additional Information and Declarations can be found on page 28

DOI **10.7717/peerj.9855**

How to cite this article Anand R, Biswal S, Bhatt R, Tiwary BN. 2020. Computational perspectives revealed prospective vaccine candidates from five structural proteins of novel SARS corona virus 2019 (SARS-CoV-2). **PeerJ 8:e9855 DOI 10.7717/peerj.9855**

J. Exp. Zool. India Vol. 24, No. 1, pp. 609-615, 2021	www.connectjournals.com/jez	*ISSN 0972-0030*
DocID: https://connectjournals.com/03895.2021.24.609		eISSN 0976-1780

ISOLATION, SCREENING AND IDENTIFICATION OF POTENTIAL TANNASE PRODUCING BACTERIAL STRAIN

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(Received 21 September 2020, Accepted 26 October 2020)

ABSTRACT : A total of 14 different samples was collected for the isolation of bacteria from the soil, compost and excreta. Whereas, a total of 108 bacterial strains was isolated from the 14 different samples. In primary screening, 22 bacterial isolates were found tannase positive in tannic acid-containing medium. S11-01 strain was observed with maximum enzyme activity index 1.57 with a maximum hydrolysis zone diameter of 22 ± 3 mm (including 14 mm colony diameter). Primarily screened tannase positive bacteria were allowed for tannase production during secondary screening where S11-01 bacterial strain was also observed with maximum tannase production with 0.955 ± 0.047 U/mL activity. A potential tannase producing bacterial strain S11-01 was isolated from fish excreta and identified as *Klebsiella pneumoniae* on the basis of the microscopic, morphological and molecular study.

Key words : Tannase, *Klebsiella pneumoniae*, screening, identification.

How to cite : Amitabh Aharwar and Dharmendra Kumar Parihar (2021) Isolation, screening and identification of potential tannase producing bacterial strain. *J. Exp. Zool. India* **24**, 609-615. DocID: https://connectjournals.com/03895.2021.24.609

INTRODUCTION

Tannase (Tannin acyl hydrolase E.C.3.1.1.20) has an important role in the breakdown of tannins and gallic acid ester into gallic acid and glucose (Aharwar and Parihar, 2019). Tannins are the secondary metabolite and polyphenolic compounds of plants that are used in defense against microorganisms. They are also observed as anti-nutritional agents because they disrupt the function of proteins such as enzymes (amylase, protease, lipase, etc.) and also react with macromolecule (starch, cellulose, minerals, etc.). They are also observed with antimicrobial activity. Some microorganisms show tannins resistant because of the tannase production (Aharwar and Parihar, 2018).

Tannase is produced by plants, animals and microorganisms. Microorganisms produce tannase in large amounts therefore they are being used in industries. Among different microorganisms, fungi are major producer of tannase but in bacteria, *Bacillus* sp., *Enterobacter* sp., *Enterococcus* sp., *Lactobacillus* sp., *Serratia* sp., *Citrobacter* sp., *Klebsiella pneumonia*, *Streptococcus* sp. and *Pseudomonas citronellolis* are observed as tannase producers (Kumar *et al*, 2015). The isolation of maximum tannase producing microorganisms is essential for industrial purposes. Screening is also an important procedure for the identification of potential strains of microorganisms. It saves time for the selection of potential strain. Primary screening is a qualitative method whereas secondary screening may be both qualitative and quantitative (Kumar *et al*, 2010). Potential strains identification is essential that is done on the basis of rDNA sequencing, microscopic and macroscopic study.

Tannase has importance in food processing, beverages, tea processing and bioremediation. It has an application in the inhibition of tea cream formation, it also increases the clarity, flavor, strength, sweet after taste and antioxidant property of tea infusions whereas decreases the color, pH and turbidity of tea infusion as well. It also decreases the bitterness whereas enhances clarity and flavor of the fruit juices, beer, wine and refreshing drinks (Jana *et al*, 2014). It also has importance in the improvement of animal feed through detoxification of the tannin-rich animal feed. It also has importance for

Biomass Conversion and Biorefinery
https://doi.org/10.1007/s13399-020-01162-6

ORIGINAL ARTICLE

Talaromyces verruculosus tannase immobilization, characterization, and application in tea infusion treatment

Amitabh Aharwar[1] · Dharmendra Kumar Parihar[1]

Received: 1 August 2020 / Revised: 10 October 2020 / Accepted: 18 November 2020

Abstract

Partially purified tannase of *Talaromyces verruculosus* (305.6 U/mL) was immobilized on calcium alginate beads (8.0 ± 1.0 mm) using 1% glutaraldehyde as a cross-linking agent. Immobilized enzyme preparation retained (39.4%) 120.4 U/mL tannase activity, 79.6% immobilization yield, and 49.5% efficiency. Immobilized preparation was characterized by SEM and it revealed the changed topology of the immobilized bead. Functional groups present in immobilized beads were examined by FTIR spectra. Immobilized tannase was found optimally active at pH 8.0 and 60 °C, whereas the stability was obtained between 30 and 60 °C, but at high (9.0) and low pH (4.0), immobilized tannase was also found very stable. Beads were found stable up to 9th cycle of reuse with 49.27% relative activity. After the treatment by immobilized tannase, 78.02 ± 1.93, 72.24 ± 2.05, 65.29 ± 1.21, 59.06 ± 0.96, and 64.61 ± 1.07% tannin reduction were measured in black tea product 1, black tea product 2, black tea product 3, green tea product 1, and green tea product 2, respectively. The greatest change in pH, turbidity, and antioxidant activity was found in black tea product 2 infusion while the least change was obtained in green tea product 2 infusion after the tannase treatment.

Keywords Antioxidant activity · Immobilization · Tannase · *Talaromyces verruculosus* · Tea infusion

1 Introduction

Tannins are polyphenolic compounds abundantly found in plants and they are classified into hydrolyzable tannins and condensed tannins. Hydrolyzable tannins are easily degraded by tannase whereas condensed tannins have difficulty for the enzymatic hydrolysis [1]. Tannins provide protection to the plants against the microbial attack; furthermore, they also have an anti-nutritional effect on humans' and animals' health because they precipitate the digestive enzymes and macromolecules in the stomach [2]. Tea, fruit juices, wine, and beverages are bitter, haze, and astringent due to the presence of tannins. So, tannin treatment is necessary for health and industrial purposes [3].

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Tannase (EC 3.1.1.20) catalyzes the tannins and gallic acid ester degradation into gallic acid and glucose [4]. Gallic acid (3,4,5-trihydroxybenzoic acid) has an application in the production of trimethoprim (an antibacterial agent) and propyl gallate. In photography and printing inks, gallic acid is used as an important constituent. Furthermore, gallic acid also has antibacterial, antiviral, anticancer, antioxidant, and analgesic activities [5]. Tannase has extensive application in the detannification of fruit juices, tea, wine, beer, and refreshing drinks. Furthermore, it is also used in animal feed processing and tannery effluent treatment [6–8].

Tannase is present in different sources like plants, animals, and microorganisms but among them, the microbial source is the main source because of the high production yield and diversity of microbial tannases. Moreover, microorganisms have easy cultivation and downstream processing; therefore, industries mostly prefer them [8]. Fungi especially *Aspergillus* sp. and *Penicillium* sp. are the major tannase producers among different microorganisms and also being used in industries for large-scale tannase production [9]. Furthermore, *Aspergillus* sp. and *Penicillium* sp. have the potential to utilize both hydrolyzable and condensed tannins [10]. Solid-state fermentation (SSF) and submerged

Published online: 07 January 2021

Journal of Drug Delivery Science and Technology 57 (2020) 101682

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Molecular approaches for targeted drug delivery towards cancer: A concise review with respect to nanotechnology

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ARTICLE INFO

Keywords:
Nanocarriers
Cancer targeting
Nanotechnology
Apoptosis
Angiogenesis
Metastasis

ABSTRACT

Cancer is a leading cause of human death throughout the world. The lack of specificity associated with conventional anti-cancer therapeutics leads to several side effects in addition. Cancer initiation and progression involve complex and multi carcinogenesis processes along with diverse cellular physiological system activities like cell signaling and apoptosis. An erratic microenvironment and drug resistance mechanism of cancer cells further causes failure of the most conventional chemotherapy regimen. Such limitations of the conventional cancer therapy advocate well engineered and smart therapeutics for cancer treatment. An ideal cancer treatment needs a customized and specialized drug delivery technology, which is capable to eradicate even a last cancer cell that may be responsible for the relapse of disease. Targeted nanocarriers (NCs) navigate the loaded therapeutics towards the specific site of action with the reduced adverse effects on the healthy cells. This review presents an overview of various molecular mechanisms and cellular alterations associated with cancer cell development and how targeted formulations can be designed for cancer therapy. A brief focuses on the applications of nanotechnology to exploit these mechanisms and molecular ports for the development of a novel targeted formulation for cancer treatment has also been discussed.

1. Introduction

Cancer is the deadliest disease that accounts for the majority of deaths worldwide. As per GLOBOCAN 2018, about 18.1 million new cancer cases have been estimated worldwide and about 9.6 million cancer deaths in the year 2018 [1]. Cancer development is a complex multi carcinogenesis process concerning diverse cellular physiological systems like cell signaling and apoptosis [2]. Cancer involves rapid uncontrolled cell division with resistance and immortality to cell death. Cancerous cells proliferate rapidly and form an abnormal mass referred to as a tumor. Contradictory to the ability to form an abnormal mass, hematologic cancer illustrates a different pattern where such cells grow and extend throughout the circulatory system and bone marrow [3]. Cancer is termed as malignant based on the invasion potential. Each type involves its characteristic morphogenesis and an eternal state that illustrates different physiology [4]. Tumor is a condition that occurs randomly due to several mutations. The evolution of cancer is a result of damage and mutation in proto-oncogenes and tumor suppressor genes respectively. Proto-oncogene is basically coded for the expression of various proteins that control normal cell growth and proliferation whereas tumor suppressor genes coded for inhibitory signal proteins that check uncontrolled proliferation and/or stimulate apoptosis [5].

The loss of apoptosis and invasion and metastasis of cancerous cells to adjacent tissue and angiogenesis are well-known involved process of cancer. Apoptosis is a programmed cell death mechanism which undergoes with an approximate rate of 70,000 cells/minute [6]. The induction of apoptosis may be possible with associated targets proteins *i.e.*, Bcl-2, p53 genes, Fas ligand (FasL), tumor necrosis factor alpha (TNFα) and transcription nuclear factor (NF)-κβ etc [7,8]. Additionally, angiogenesis is another important event in cancer progression which is required for the development and growth of solid tumors beyond the size of 1–2 mm^3. It can be regulated by targeting proangiogenic factors such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (bFGF), and epidermal growth factor (EGF) etc [9,10]. This newly developed blood vessel's network provides a means to the detachment of mutant cells leading to metastasis and invasion of adjacent tissues [11]. The regulation of metastasis and invasion with various favorable proteins i.e., cadherins, integrins, CD44 protein family and matrix metalloproteinases (MMPs) etc. expression may protect from cancer cell metastasis [12]. The detailed biology showing unpredictable microenvironment and drug resistance mechanisms involved in diverse cancerous cells has been well

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https://doi.org/10.1016/j.jddst.2020.101682
Received 14 January 2020; Received in revised form 17 March 2020; Accepted 19 March 2020
Available online 24 March 2020

AAPS PharmSciTech (2020) 21:174
DOI: 10.1208/s12249-020-01690-4

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Research Article

Galactosylated TPGS Micelles for Docetaxel Targeting to Hepatic Carcinoma: Development, Characterization, and Biodistribution Study

Pawan Tekchandani,[1] Balak Das Kurmi,[1] Rishi Paliwal,[2] and Shivani Rai Paliwal[1,3]

Received 2 February 2020; accepted 13 April 2020

Abstract. Hepatocellular carcinoma (HCC) is a foremost type of cancer problem in which asialoglycoprotein receptors are overexpressed. In this study, asialoglycoprotein receptor–targeted nanoformulation (galactose-conjugated TPGS micelles) loaded with docetaxel (DTX) was developed to achieve its site-specific delivery for HCC therapy. The pharmaceutical characteristics like shape morphology, average particle size and zeta potential, drug entrapment efficiency, and *in vitro* release kinetics of developed system were evaluated. DTX-loaded galactosylated TPGS (DTX-TPGS-Gal) micelles and TPGS micelles (DTX-TPGS) were having 58.76 ± 1.82% and 54.76 ± 1.42% entrapment of the DTX, respectively. *In vitro* drug release behavior from micelles was controlled release. Cytotoxicitiy (IC_{50}) of DTX-TPGS-Gal formulation on HepG2 cell lines was significantly ($p \leq 0.01$) lower (6.3 ± 0.86 μg/ml) than DTX-TPGS (9.06 ± 0.82 μg/ml) and plain DTX (16.06 ± 0.98 μg/ml) indicating higher efficacy of targeted formulation. Further, *in vivo* biodistribution studies in animal model showed maximum drug accumulation at target site, *i.e.*, the liver in the case of DTX-TPGS-Gal as compared with non-targeted one. It is concluded from the findings that TPGS-Gal micelles can be utilized for targeted drug delivery of cytotoxic drugs towards HCC with minimized side effects.

KEY WORDS: nanoparticles; docetaxel; galactose; TPGS micelles; liver targeting.

INTRODUCTION

Liver cancer, also called hepatocellular carcinoma (HCC), is one of the emerging types of the human cancer and holds third category in the list of most common cancer types (1). Chemotherapeutic efficacy in the case of HCC becomes limited for the patients suffering with multiple locus/nodules and metastatic characteristics (2). Further, non-specificity of chemotherapeutics in the treatment of cancer including HCC creates poor therapeutic action and higher side effects of the administered cytotoxic drug. Therefore, it is quite needed that an effective and advanced drug delivery strategy should be adopted using cutting edge technology, *i.e.*, nanotechnology in particular for controlled delivery of chemotherapeutics to HCC cells, which require precise engineering and management at development stage.

One of the effective classes of chemotherapeutics is taxol group which acts upon inhibition of depolymerization of microtubules for their action (3). Docetaxel, one of the clinically effective representatives of taxanes, has been recommended for the treatment of cancers of many organs, *i.e.*, breast, gastric, pancreas, and urothelial tissues, alone or in combination therapy (4–7). However, its clinical use in the case of HCC is quite limited due to non-specific distribution in cirrhotic condition against hepatomas (8–10). This is why a concrete precise design of a delivery system is required to specifically target it to HCC cells for its future clinical applications.

Nanomedicine offers plenty of opportunities to knock the barriers of cancer therapeutics. Some of the well-established advantages of nanocarriers are tiny size capable of better targeting abilities due to improved permeability in leaky tumor vasculature, easy modification of surface as per need (drug targeting or stealthing), better stability at both *ex vivo* and *in vivo* biological mediums, solubility enhancement capability, extended blood circulation time, and improved pharmacokinetics (11). Out of the several available options of nanocarriers, functional micelle systems attract due to easy development process and solubilization to poor water-soluble drugs. Further, surface modification is quite simple and effective for targeted cancer nanomedicine.

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1530-9932/20/0000-0001/0

Published online: 16 June 2020

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5502 *Current Pharmaceutical Design, 2020, 26, 5502-5516*

REVIEW ARTICLE

Nanotheranostics for Cancer Therapy and Detection: State of the Art

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ARTICLE HISTORY

Received: March 15, 2020
Accepted: August 09, 2020

DOI:
10.2174/1381612826666201116120422

Abstract: Nanotheranostics, an approach of combining both diagnosis and therapy, is one of the latest advances in cancer therapy particularly. Nanocarriers designed and derived from inorganic materials such as like gold nanoparticles, silica nanoparticles, magnetic nanoparticles and carbon nanotubes have been explored for tremendous applications in this area. Similarly, nanoparticles composed of some organic material alone or in combination with inorganic nano-cargos have been developed pre-clinically and possess excellent features desired. Photothermal therapy, MRI, simultaneous imaging and delivery, and combination chemotherapy with a diagnosis are a few of the known methods exploring cancer therapy and detection at organ/tissue/molecular/sub-cellular level. This review comprises an overview of the recent reports meant for nano theranostics purposes. Targeted cancer nanotheranostics have been included for understating tumor micro-environment or cell-specific targeting approach employed. A brief account of various strategies is also included for the readers highlighting the mechanism of cancer therapy.

Keywords: Nanotheranostics, nanoparticles, cancer, imaging, therapy.

1. INTRODUCTION

Gradual advances in the number of cancer reports every year indicate that the disease is spreading day by day. Cancer therapy is always a challenging task due to its complicated mechanism of survival and replication. Cancer chemotherapy has limited success due to the factors including non-target distribution, multi-drug resistance, dose-associated side-effects and limited target accessibility [1-4]. Further, one to one detection of the correct cells (diagnosis) is the need of the hour for successful cancer treatment. Simultaneous detection of cancer cell and its therapy may be added advantages in more efficacious treatment strategies against cancer [5, 6].

Nano-sized carrier systems offering both diagnosis and therapy are known as nanotheranostics. Such carriers are fond of tumor microenvironment due to their small size. They may adhere to the correct cell type using cell-selective targeting and are able to treat/kill cancer cells either by releasing loaded cytotoxic agents or by phototherapy [7-8]. Nowadays, nanocargos made up of either carbon (carbon nanotubes, silica (mesoporous silica nanoparticles), iron (Magnetic nanoparticles), gold (Gold nanoparticles), lipids (liposomes or solid lipid nanoparticles), surfactants (multifunctional nanoparticles), FDA approved polymers (PLGA nanoparticles) or a comibination of two or more are being utilized as nanotheranostic agents [9-11].

Tumor microenvironment or over-expression of receptors on the cell surface in case of cancer can be explored to achieve the next level of drug targeting (Bio-targeting) for cancer therapy [12, 13]. For example, pH of the tumor environment (using Ph-sensitive linkages or carrier), leaky vasculature (EPR effect) and increased expression of estrone/folate/transferring/cyclic RGD receptors may be more efficacious approaches in cancer therapy [14-16]. Here, we have discussed the recent reports pertaining to either of the areas described above to understand the trends of nanotheranostics research and to weigh out the benefits of these approaches over conventional cancer therapy.

2. IMPACT OF NANOTHERANOSTICS IN CANCER THERAPY AND DETECTION

Nanotheranostics is one of the fastest-growing areas of research in cancer therapy that combines nanotechnology for simultaneous diagnosis and therapy [17]. An added advantage of theranostic nanoparticles (usually size range 10-60 nm) is that they have intrinsic accumulation capability in the vicinity of cancer cells via passive targeting. This is a consequence of altered vasculature of blood and lymph vessels in the tumor micro-environment, which is popularly known as the enhanced permeability and retention (EPR) effect. Further, it is an established fact that passive drug targeting enables high drug concentration at the target tumor site along with longer systemic circulation kinetics and reduced systemic toxicity [18-20]. Such alternation in pharmacokinetics depends upon the extent of density and pattern of vascularisation, angiogenesis, and the blood flow rate. These factors altogether are detrimental for restricted drug accumulation and poor drug distribution at the tumor site [21]. To achieve more tumor-specific drug delivery, targeting moieties could be attached directly on the nanoparticles' surface, which helps in navigating the carrier towards the target cancer cells via a ligand-receptor mechanism called as receptor-mediated endocytosis and release the loaded drug within the cell [22]. Detectable and measurable physical attributes of either biomaterials used for nanoparticles or the drug itself help in the detection of cancerous cells using MRI/fluorescent imaging. For example, nanosized dependent optical properties have been widely explored in nano theranostics applications. In fact, surface plasmon resonance (SPR) resulting from photon confinement to the small particle size is a remarkable property of noble metal nanoparticles, such as gold, which has found a multitude of biological and medical applications [23, 24]. Figure 1 shows the development of nanotheranostics and their possible interaction with cancer cells during diagnosis and therapy.

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1381-6128/20 $65.00+.00

International Journal of Biological Macromolecules 164 (2020) 2881–2894

Contents lists available at ScienceDirect

International Journal of Biological Macromolecules

journal homepage: http://www.elsevier.com/locate/ijbiomac

Dual cancer targeting using estrogen functionalized chitosan nanoparticles loaded with doxorubicin-estrone conjugate: A quality by design approach

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ARTICLE INFO

Article history:
Received 26 March 2020
Received in revised form 14 August 2020
Accepted 21 August 2020
Available online 24 August 2020

Keywords:
Nanoparticles
Chitosan
Doxorubicin
Estrogen receptor
Dual targeting
Quality by design
Box-Behnken design

ABSTRACT

In this study, estrone was used as targeting functionality in chitosan nanoparticles (DoxEs-CSEsNPs) carrying doxorubicin-estrone conjugate for dual targeted intracellular delivery to breast cancer cells. Estrone was conjugated with Dox and CS and characterized by FTIR and FT-NMR spectroscopy. Dox/DoxEs containing CSEsNPs were prepared with ionic gelation method and for the effect of formulation variables a 3-factor, 3-level Box-Behnken design (BBD) was explored, which predict the responses like particle size (Y_1) and percent entrapment efficiency (%EE) (Y_2) when CSEs: TPP ratio (X_1), sonication time (X_2) and stirring speed (X_3) were selected as independent variables. The Dox-CSEsNPs and DoxEs-CSEsNPs were characterized for size, shape, PDI, surface charge and thermal analysis. The drug entrapment efficiency was 66.33 ± 2.82% and 62.25 ± 2.63% for Dox-CSEsNPs and DoxEs-CSEsNPs formulation respectively. The in vitro release, haemolytic toxicity, and fluorescent microscopy studies were also assessed. Anticancer activity on the MCF-7 cell line indicated the higher potency of DoxEs-CSEsNPs as compared to Dox-CSEsNPs, DoxEs, and Dox solution. The findings are decisive for selective targeting of antineoplastic agents to the ERs, which indicate that the DoxEs loaded CSEsNPs were able to significantly improve the efficacy of Dox.

1. Introduction

Breast cancer is a frequently occurring cancer among women and presents significant challenges for its treatment. Conventional breast cancer therapy has several obstacles such as non-specific biodistribution of the drug, low intracellular drug concentration, and occurrence of multidrug resistance [1,2]. Tumor cell targeting could be an option for breast cancer treatment that would evade the limitations of conventional chemotherapy. A number of molecular targets have been identified on the basis of pathophysiology of cancer cells that can be utilized for targeted breast carcinoma therapy [3,4].

Breast cancer is classified on the basis of expression of hormone receptors or target protein such as hormone receptor positive cancer (i.e. estrogen receptor or progesterone receptor), epidermal growth receptor (EGFR or HER2) over expressed cancer and triple negative breast cancer (TNBC) that do not express any of these receptors means ER (-ve), PR (-ve) and HER 2 (-ve) as well [5]. The hormone responsive breast cancers are estrogen receptor positive (ER+), progesterone receptor positive (PR+) or both and among them majority of hormone-responsive breast cancer are ER+ (approximately 75%). Though, estrogen receptors are members of nuclear receptor super family; however, in cancerous conditions, they remain frequently present on cell surface as well [6]. These cell surface estrogen receptors are associated with the growth and proliferation of breast cancer. Such high level of expression of estrogen receptors has been widely exploited for targeted drug delivery as drug conjugates [7,8], as targeted nanocarriers [9,10] and also for gene delivery [11] to ER+ breast cancers. However, dual targeting of both nuclear ER and cell surface ER using specific drug delivery design is not reported till date.

Targeted nanoparticles have been widely explored for site specific drug delivery of chemotherapeutic agents with improved pharmacokinetics and lower systemic toxicity [12]. It is noteworthy that the properties of selected polymeric material for the preparation of such targeted nanoparticle play an important role as it affect not only the clinical performance of the delivery system but also affect the regulatory clearance at the time of translation of the product from bench to bedside. Chitosan, a natural biopolymer, is biocompatible, biodegradable, and safe material for the construction of nanoparticles. It offers modification opportunities due to the presence of several amino ($-NH_2$) group in its chemical structure that are resourceful for the tethering of various ligands and transforming it into a suitable carrier for biomedical application such as drug/gene targeting [13]. Doxorubicin (Dox) is one of the most popular and effective anticancer molecules commonly used in

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https://doi.org/10.1016/j.ijbiomac.2020.08.172
0141-8130/

International Journal of Quantitative Structure-Property Relationships
Volume 5 • Issue 2 • April-June 2020

QSTR Analysis of Acute Rat Oral Toxicity of Amide Pesticides

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ABSTRACT

The rodent acute toxicity is gaining much attention in the ecotoxicological assessment of chemicals. Among the available amide pesticides, the majority of compounds are lacking the experimental toxicity values of rat oral toxicity. In order to explore the structural alerts for toxicity and to fill the toxicity data gap through in silico studies, a series of statistically robust local quantitative structure-toxicity relationship (QSTR) models were developed for the prediction of acute oral toxicity of amide pesticides on rat following OECD principles. The mechanistic interpretation indicated types of amide, the presence of halogen, and SO_2 functionality were influential for the toxicity. Applicability domain (AD) analysis and prediction reliability indicators assured the robustness and reliability of the developed models. The detailed analyses of the AD as well the consensus predictions of the unknown compounds were commented for their toxic nature, and prioritization was done for similar classes of compounds without experimental values.

KEYWORDS

Acute Toxicity, AD, Amide Pesticides, Ecotoxicological, In Silico, OECD, Prioritization, QSTR

1. INTRODUCTION

The use of pesticides in agriculture has been in practice for long time. Sumeria used elemental sulphur dusting about 4,500 years ago as a pesticide and this was known to be use of the first pesticide. With the time, the development of newer pesticides was very quick. The use of pesticides is not only restricted to food/crop protection, but also in controlling many vector borne diseases like mosquito-borne disease malaria, dengue, etc. The subsequent toxicities (both living and non-living) associated with the indiscriminate use were the obvious observed outcomes and were/are regularly reported in the literature describing concerns related to the ecosystem. The nonstop development of pesticides and their use (≈2.5 million tons of pesticides used every year around the world) (Pimentel 1995) may perhaps become one of the causes of destruction of the ecosystem. Even many of the animal species are under the verge of extinction. Pesticide Action Network Europe (PAN) reported that many animal (mammals, birds, fish, bees, many amphibians, etc.) species are declining due to overuse of pesticides (https://www.paneurope.info/old/Resources/Briefings/Pesticides_and_the_loss_of_biodiversity.

DOI: 10.4018/IJQSPR.2020040103

Original research article

EJO European Journal of Ophthalmology

European Journal of Ophthalmology
1–10

DOI: 10.1177/1120672120962401
journals.sagepub.com/home/ejo
SAGE

Therapeutic effects of various renin angiotensin modulators on hyperglycemia-induced cataract formation in Sprague Dawley rats

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Abstract

Objects: Our previous research work reported the beneficial effects of angiotensin receptor blockers (ARBs) for the treatment of diabetes associated cataract which was induced by streptozotocin (STZ). The current study, evaluated the effects of topical administration of various renin angiotensin modulators on STZ-induced cataracts in rats.

Methods: Single dose of STZ (60 mg/kg, i.p.) was administered in the rats to induce diabetes. Animals were divided into normal and diabetic rats. Normal rats were administered with single dose of sodium citrate buffer (0.1 M, 10ml/kg, i.p.). Diabetic animals were divided into various treatment groups, each group contains six animals and received aliskiren, olmesartan, enalapril, and angiotensin 1–7 at a dose of 0.5% w/v topically on the cornea of the eye for a period of 8 weeks. During experimental protocol morphology of the eyes and lenticular opacity were monitored. Animals were sacrificed after 8 weeks of drug treatment, and various cataractogenic biochemical parameters were assessed.

Results: Topical administrations with aliskiren, enalapril, olmesartan, and angiotensin 1–7 showed non-significant alterations in the blood glucose level, but significantly decreased lenticular opacity, restored antioxidant level, restored MDA level and Nitrite content, and decreased the onset of cataract formation.

Conclusion: Overall, our findings suggest that topical treatment with renin angiotensin modulators delayed the onset of diabetes-induced cataract formation.

Keywords

Diabetic cataract, aliskiren, angiotensin 1–7, olmesartan, enalapril

Date received: 19 April 2020; accepted: 7 September 2020

Introduction

The results of many epidemiological studies indicate an increased risk of cataract formation in diabetic patients,[1,2] and other previous studies suggest that cataract serves as the other risk factors associated with diabetes.[2,3] Although the exact pathophysiology of role of the renin angiotensin system (RAS) in cataract formation due to diabetes is largely unknown. We recently established that topically administered angiotensin receptor blocker (ARB) prevented the progression of streptozotocin (STZ)-induced formation of cataracts.[4] On the basis of our recent study, one may postulate that the local RAS in the eyes may intensify formation of cataracts in hyperglycemic conditions. In addition, the ocular RAS has become a unique pathway for the treatment and the prevention of various eyes related disorders. Identification of prorenin/ renin, angiotensin II, and angiotensin-converting enzyme (ACE) 2/angiotensin 1–7 MAS axis, in the eyes has changed the scenario

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CURRENT EYE RESEARCH
https://doi.org/10.1080/02713683.2020.1782941

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Biochemical Evidence Indicates the Preventive Effect of Resveratrol and Nicotinamide in the Treatment of STZ-induced Diabetic Cataract

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ABSTRACT

Purpose: High glucose level is a strong initiator of both oxidative stress and DNA damage to various cellular proteins. This activates the poly ADP-ribose polymerase (PARP) enzyme, which is responsible for disturbing physiological energy metabolic homeostasis. The present study aimed to elucidate the association between stress and the PARP pathway by using resveratrol (RSV) and nicotinamide (NAM, PARP inhibitor) to treat diabetic cataract.

Method: Albino rats were used for the experimental study. A single streptozotocin administration (55 mg/kg, i.p.) prompted diabetes in the animals. The experimental groups were the normal group (non-diabetic) and the diabetic groups: the diabetic control animals (group D), the diabetic animals treated with RSV at 40 mg/kg/day, i.p. (D+ RSV group), NAM at 100 and 300 mg/kg/day, i.p. (D+ NAM100, D+ NAM300 groups, respectively), and a combination of RSV and NAM i.p. (D+ RSV+NAM100 = Combi 1 group, D+ RSV +NAM300 = Combi 2 group). Glucose levels and the eyes were examined biweekly; various cataractogenic parameters in the lenses were examined after completion of the eight-week experimental protocol.

Results: Compared to diabetic control, RSV monotherapy significantly decreased hyperglycemia and other lenticular alterations. NAM at the high dose only showed beneficial effects without altering the blood glucose level, lenticular aldose reductase (AR) activity, and sorbitol content, primarily restored the lenticular NAD level and decreased oxidative stress in diabetic rats. These findings regarding NAM treatment indicate that a pathway other than the antioxidant defense system and the polyol pathway, which might be due to PARP inhibition, is involved in diabetic cataracts. Moreover, compared to RSV monotherapy, combination treatments were effective.

Conclusion: These results indicate that hyperglycemia and oxidative-osmotic-nitrosative stress play central roles in the pathophysiology of diabetic cataracts. Moreover, our study also revealed that concurrent treatment with the RSV and NAM may prove useful in the pharmacotherapy of diabetes and its secondary complications such as cataract.

ARTICLE HISTORY
Received 2 July 2019
Revised 20 May 2020
Accepted 9 June 2020

KEYWORDS
Diabetic cataract; resveratrol; diabetes; oxidative stress; nicotinamide

Introduction

Hyperglycemia is the backbone of the pathophysiology of diabetes and leads to the development of a variety of secondary debilitating conditions such as diabetic cataract.[1] Many tangled cellular pathways, in which oxidative stress plays a common role, are associated with the pathogenesis of diabetic cataract.[2] The prevalence of cataract is 66% higher in patients with diabetes, which is an important factor in visual impairment.[3] Cataract will most certainly develop earlier in diabetic patients than in healthy people of the same age.[4] Additionally, a higher complication rate is encountered when diabetic patients undergo cataract surgery.[5] Diabetes-related hyperglycemia is also responsible for activating multiple pathways. For example, it increases aldose reductase (AR) enzyme activity, which is involved in limiting the reaction rate, leading to polyol formation.[6] Polyols play important roles in lenticular osmotic stress because they accumulate inside the cells; additionally, polyol accumulation induces reactive oxygen species (ROS), which cause oxidative damage to the eyes' lenses.[7]

Prolonged hyperglycemia increases oxidative stress, which is likely to cause various disorders, such as diabetic retinopathy, nephropathy, macular degradation, and diabetic cataract.[8] The streptozotocin (STZ)-induced diabetes animal model is useful for understanding the pathophysiology and the complications related to cataract in diabetic animals. STZ-induced diabetes may injure lens tissues and cause apoptosis of the lens' epithelial cells.[9] Oxidative damage and other related pathways are major contributors to the development of diabetic cataracts whereas antioxidant therapy may prevent or delay the onset and the progression of cataractogenesis. Resveratrol (RSV) is a well-established antioxidant with a wide variety of beneficial physiological activities.[10] Antioxidants are reported to have retinopathy protective action in animals with STZ-induced diabetes.[11] Additionally, the findings of Smith AJO et al. (2019) reported that RSV can have therapeutic benefits in a human lens.[12] Quenching of ROS by RSV is the primary mechanism for counteracting the contribution of oxidative stress to cataract formation. Moreover, RSV has been established as an agonist to the silent mating-type information regulation 2 homolog 1 (SIRT1) protein. The SIRT1 protein is a highly conserved nicotinamide adenine dinucleotide (NAD) and NAD/NADH ratio-dependent histone class III deacetylase that plays a very

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Current Drug Delivery

Expedition of Eudragit® Polymers in the Development of Novel Drug Delivery Systems

Authors: Jain, Sunil K.; Jain, Akhlesh K.; Rajpoot, Kuldeep
Source: Current Drug Delivery, Volume 17, Number 6, 2020, pp. 448-469(22)
Publisher: Bentham Science Publishers
DOI: https://doi.org/10.2174/1567201817666200512093639

Eudragit® polymer has been widely used in film-coating for enhancing the quality of products over other materials (*e.g.*, shellac or sugar). Eudragit® polymers are obtained synthetically from the esters of acrylic and methacrylic acid. For the last few years, they have shown immense potential in the formulations of conventional, pH-triggered, and novel drug delivery systems for incorporating a vast range of therapeutics including proteins, vitamins, hormones, vaccines, and genes. Different grades of Eudragit® have been used for designing and delivery of therapeutics at a specific site *via* the oral route, for instance, in stomach-specific delivery, intestinal delivery, colon-specific delivery, mucosal delivery. Further, these polymers have also shown their great aptitude in topical and ophthalmic delivery. Moreover, available literature evidences the promises of distinct Eudragit® polymers for efficient targeting of incorporated drugs to the site of interest. This review summarizes some potential researches that are being conducted by eminent scientists utilizing the distinct grades of Eudragit® polymers for efficient delivery of therapeutics at various sites of interest.

Keywords: Eudragit®; colon-specific; drug delivery; gene delivery; ophthalmic; stomach-specific

Document Type: Review Article

Publication date: July 1, 2020

This article was made available online on June 1, 2020 as a Fast Track article with title: "Expedition of Eudragit® Polymers in the Development of Novel Drug Delivery Systems".

More about this publication?

Research Article

In Silico Molecular Interaction Studies of Chitosan Polymer with Aromatase Inhibitor: Leads to Letrozole Nanoparticles for the Treatment of Breast Cancer

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Journal Name: Anti-Cancer Agents in Medicinal Chemistry
(Formerly Current Medicinal Chemistry - Anti-Cancer Agents
(https://www.eurekaselect.com/node/662/))

Volume 21 , Issue 9 , 2021

DOI : 10.2174/1871520620666200825192652 (https://doi.org/10.2174/1871520620666200825192652)

Journal of Heterocyclic Chemistry / Volume 57, Issue 9 / p. 3483-3492

ARTICLE

Design and pharmacophoric identification of flavonoid scaffold-based aromatase inhibitors

Laxmi Banjare, Sant Kumar Verma, Akhlesh Kumar Jain, Suresh Thareja ✉

First published: 04 August 2020
https://doi.org/10.1002/jhet.4068

Abstract

Aromatase is a crucial enzyme for the catalysis of aromatization reaction at the last and rate-limiting step involved in the conversion of androgenic substrates to an estrogenic substrate. A hormone-dependent breast cancer in postmenopausal woman can be cured by inhibition of estrogen biosynthesis by the help of aromatase inhibitors (AIs). The mode of interactions of flavonones with the active site of aromatase has been studied in search of potent and selective AIs as a substitute of the natural steroidal ligand. Structure-based computational approach namely, molecular docking simulations were performed to investigate the structural features of the docked complex of aromatase and flavonoid ligands. A nonsteroidal flavonoid pharmacophore showing electrostatic and steric features for selective binding within the main pocket of the catalytic active site of aromatase has been identified as an outcome of the study. The binding affinity of quercetin and isoflavone were predicted within aromatase. Isoflavone was used as a negative control to compare its binding affinities with the selected dataset. The predicted binding affinity of negative control isoflavone was in accordance with its in vitro AI efficacy. Isoflavone showed poor binding affinity and ranked last in terms of MolDock score (−86.309 kcal/molÅ) compared to dataset molecules. The generated pharmacophoric information will be helpful for the synthetic chemist to design and synthesize selective AIs with comparable binding affinity to the natural steroidal ligand.

10

Research Article

In Silico Docking of Anti Cancerous Drugs with β-Cyclodextrin polymer as a Prominent Approach to Improve the Bioavailability

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Journal Name: Anti-Cancer Agents in Medicinal Chemistry
(Formerly Current Medicinal Chemistry - Anti-Cancer Agents
(https://www.eurekaselect.com/node/662/))

Volume 21 , Issue 10 , 2021

DOI : 10.2174/1871520620666201013145725 (https://doi.org/10.2174/1871520620666201013145725)

Original Research
Published: 13 November 2020

De novo designing, assessment of target affinity and binding interactions against aromatase: Discovery of novel leads as anti-breast cancer agents

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Structural Chemistry **volume 32**, pages 847–858 (2021)Cite this article

Abstract

Aromatase inhibitors (AIs) have been emerged as promising anti-cancer agents for the treatment of hormone dependent breast cancer (HDBC) in women because of their excellent ability of inhibiting oestrogen synthesis. Here, we have implicated structure-based comprehensive approaches to discover novel drug/lead-like AIs. The molecular modelling and energy optimization were performed using Chem Office package. The e-LEA3D web server was used to design novel drug/lead-like AIs as well as generation of ADME/drug-likeness parameters. Target binding affinities and mode of binding interactions were mapped using Molegro Virtual Docker (MVD) to re-optimize the best de novo generated molecules. We have successfully designed novel AIs (compounds 1–7) using de novo technique performed on e-LEA3D. All the designed molecules were found optimum drug-like candidates based on various in silico screening parameters including 'rule of five'. The energy optimized conformers of generated molecules (1–7) were docked in the active site, corresponding to co-crystallized androstenedione (ASD), of aromatase to predict ligand-target binding affinity and their binding interactions. The molecules (1–7) showed comparable to higher binding affinity towards aromatase with MolDock Score ranges from − 134.881 to − 152.453 Kcal/mol as compared with natural substrate ASD (− 128.639 Kcal/mol) and standard letrozole (− 136.784 Kcal/mol). The de novo

IJPSR (2020), Volume 11, Issue 9 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 13 September 2019; received in revised form, 24 February 2020; accepted, 21 April 2020; published 01 September 2020

CHIA SEED IN HEALTH AND DISEASE PREVENTION: PRESENT USAGE AND FUTURE PERSPECTIVES

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Keywords:

Salvia hispanica L., Omega-3-alpha linolenic acid, CVS, Diabetes, Anticancer effects, Immune system, Obesity

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ABSTRACT: *Salvia hispanica* L. Well known as chia is gaining popularity day by day due to its nutritional value. This plant is native to Mexico, belonging to family Labiatae / Laminacea, and it was used as a superfood from ancient times. Chia is valued more due to its oil content as it consists of omega -3-alpha linolenic acid in higher amount along with various types of other nutrients, e.g., proteins, dietary fibers, antioxidants, *etc.* which is very beneficial to keep a person healthy and also it helps in prevention of many diseases like CVS, diabetes, obesity cancer and also it gives strength to our immune system. In the past few decades, we have noticed a certain growth in the market value of chia, and it is increasing day by day, not in a particular area or region but around the whole globe. In this paper, we have discussed all the important characteristics of chia (from its morphological characters to its pharmacological properties along with nutritional values and its today's marketing value) by collecting different kinds of literature and surveys.

INTRODUCTION: The exploitation of plants by human beings for the treatment of various diseases has been in practice for a very long time [1-6]. Herbal source of drugs constitutes a major part in all the traditional system of medicines. Chia (*Salvia hispanica* L.) is a well-known plant that belongs to the genus of Salvia, and it consists of approximately 900 different species of plants, shrubs, and brushes of Salvia Family [7]. The chia belongs to the Labiatae / Lamiaceae family containing the very high nutritional and therapeutic value. This species belongs to an annual plant growing mainly from western Mexico to northern Guatemala.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(9).4123-33

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(9).4123-33

S. hispanica is derived from the Spanish word "chian" which refers to oil-related substances, and it is also known as the powerhouse of omega-3 fatty acids containing other nutrition like proteins, dietary fibers, vitamins, minerals, and various polyphenolic antioxidants which is mainly used to avoid catabolism of chia seed [8]. Chia seeds are also known as functional foods or superfoods because of the fact that it consists of various and very high nutritional ingredients which protect and enhances the immune system. These days, the eye-catching fact about chia seed is the presence of high level linoleic and alpha-linolenic fatty acids because the main reason for the high content (approx. 60%) of oil is because of these omega-3 fatty acids. Therefore, the main purpose of this paper is to show the nutritional and therapeutic potential of chia seeds [9-10].

Background of Chia: After Carolus Linnaeus (1707-1778) *S. hispanica* got named who founded growing wild in the new world and disoriented with

Research Paper

Synthesis, Biological Evaluation and Molecular Docking Studies of Novel 1,8-Naphthyridine-3-carboxylic Acid Derivatives as Potential Antimicrobial Agents (Part-1)

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Synthesis and investigation of antimicrobial activity of 6 novel 1,8-naphthyridine-3-carboxylic acid derivatives are presented. Among the derivatives, compounds 4a–5b2 showed a broad-spectrum antimicrobial activity against all reference Gram-positive, Gram-negative bacteria and fungi. These compounds exhibited remarkable bactericidal activity against *Staphylococcus* and *Bacillus* sps. The tested substances 4a–5b2 were found also found to be active against *Escherichia coli*, *Salmonella* and *Shigella* sps. The chlorine substituted compounds 4a and 5a2 were found to be the most active towards the tested microorganisms. Compounds 4a–5b2 were found to be fungicidal against *Candida* sp. with a MIC values in the range of 400-2000 µg/ml. Docking studies of these compounds with *Salmonella typhi* OmpF complexed with ciprofloxacin using PDB-4KRA revealed that the compounds acted as covalent crosslinker on the DNA gyrase B of the former and intercalate the latter both with higher C score values. Thus, the antibacterial activity against tested strains suggested 1,8-naphthyridine-3-carboxylic acid derivatives warrant further evaluation as potential novel antiinfective agents. The antifungal activity of these compounds was comparable to that of griseofulvin. The drug-likeness data of synthesized compounds made them promising leads for the future development as antifungal agents.

Key words: 1,8-Naphthyridine, antimicrobial activities, antifungal action, ADMET, molecular docking

Microbes are causative agents for various types of diseases like pneumonia, amoebiasis, typhoid, malaria, common cold, cough and other infections[1]. Infectious diseases are a major health problem in the hird world countries. These diseases are treated with drugs of synthetic to natural origin including antibacterial, antiquorum sensing, antiviral, antifungal and antiparasitic agents[2,3]. Infectious diseases caused by bacterial pathogens have become the main public health problem due to extensive occurrence of drug resistance. Resistance to antimicrobial agents has increased health concerns and resulted in mortality and morbidity from treatment failures[4]. Quinolones are potent antibacterial agents used in the treatment of a wide range of bacterial infections. The history of quinolones started with the discovery of nalidixic acid in 1962. Later, first-generation quinolones such as enoxacin, lomefloxacin and norfloxacin, were discovered[5]. The second, third, and fourth-generation quinolones are called fluoroquinolones since they have a fluorine atom attached to the central ring system[6]. Although fluoroquinolones are extremely successful antibacterial agents, due to their extensive usage, fluoroquinolone-resistant bacteria have inevitably emerged. According to WHO report 2014, high rates of resistance observed in bacteria that cause common health-care-associated and community-acquired infections such as the urinary tract infection and pneumonia in all WHO regions.

Despite their success against infectious diseases, fluoroquinolone type antibacterials have some problems. Multidrug resistance, in some cases, has been attributed to mutations leading to decreased drug permeability of fluoroquinolones[7]. In addition, the effects of

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Accepted 14 November 2019
Revised 23 August 2019
Received 12 April 2019
Indian J Pharm Sci 2020;82(1):41-53

(14)

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Cite this: RSC Adv., 2020, 10, 13907

Design, *in silico* studies, and synthesis of new 1,8-naphthyridine-3-carboxylic acid analogues and evaluation of their H1R antagonism effects†

Vinod Kumar Gurjar and Dilipkumar Pal *

Received 23rd January 2020
Accepted 11th March 2020

DOI: 10.1039/d0ra00746c

rsc.li/rsc-advances

New 1,8-naphthyridine-3-carboxylic acid derivatives were designed, synthesized and evaluated for their *in vivo* antihistaminic activity on guinea pig trachea by using chlorpheniramine as the standard drug. It was found that compound 5a1 displayed a promising bronchorelaxant effect in conscious guinea pigs using the *in vivo* model. A molecular docking study was performed to understand the molecular interaction and binding mode of the compounds in the active site of the H1 receptor. Furthermore, *in silico* computational studies were also performed to predict the binding modes and pharmacokinetic parameters of these derivatives. Prior to the start of experimental lab work, PASS software was used to predict the biological activities of these compounds. An *in silico* PASS, Swiss ADME assisted docking approach was found to be suitable to derive and synthesize effective antihistaminic agents for the present study.

1 Introduction

Heterocyclic synthesis has become a powerful technique in organic synthesis for generating new molecules for drug discovery and development.[1–8] Nitrogen atom-containing heterocyclic compounds provide highly functionalized scaffolds on which pharmacophoric features can be arranged to obtain effective and selective drugs.[9–17] Histamine is one of the most important chemical mediators that influences immune regulation *via* an acute and chronic inflammatory response through 4 different types of G-protein coupled receptors, H1, H2, H3, and H4. It is involved in the pathophysiology of allergic disorders like urticaria, rhino conjunctivitis, and asthma.[18] Although antihistaminic agents belong to several chemical classes, such as ethylene-diamines, aminoethyl ethers, propyl- and propenyl-arnines, phenothiazines, piperidines and piperazines, they show remarkable chemical similarities.[19] Presently, antihistamines are widely prescribed for the management of various allergic symptoms, but these drugs show complex side effect profiles, which include sedation, light-headedness, motor incoordination, cardiovascular effects, diminished alertness, concentration difficulties, fatigue and a tendency to fall asleep.[20] A common structural feature for the classical first-generation antihistaminic drugs is an aryl group including phenyl, substituted phenyl and heteroaryl groups (2-pyridyl) linked to a terminal amino group *via* a two or three carbon chain (chlorpheniramine maleate).[21] In contrast, most of the non-sedative H1R inhibitors like azelastine, levocetirizine and fexofenadine[22] have a minimal muscarinic effect and show a better BRA (benefit-to-risk ratio). These drugs cannot diffuse through the blood–brain barrier and thus have a weaker sedating effect and possess higher receptor selectivity and affinity,[23] and they are marked as 'non-sedative' H1R inhibitors. The 'non-sedative' second-generation drugs like terfenadine and levocetirizine also have many structural features belonging to old classic antihistamines. The condensed heterocyclic ring system of the second-generation H1-antihistamines (loratadine, fexofenadine, and azelastine) does not have the above-described pharmacophoric groups of H1-antihistamines. This concept and idea have enabled the discovery of many potent antihistaminic drugs like temelastine and mangostin. The currently used antihistaminic compounds are almost completely based on modifying the structure of some old H1 antagonists (Fig. 1).

The availability of the crystal structure of H(1)R, however, can enable new ways to study the binding of histamine and its antagonists and to find the important receptor–ligand interactions. It is also possible to compare the binding affinity of the synthesized analogues to predict their possible therapeutic activity.[24,25]

Azelastine is a phthalazinone derivative and a H1R antagonist.[26] It is an antiallergic agent that inhibits the release of histamine and other mediators involved in the allergic response. It antagonizes histamine and leukotriene-induced bronchospasm in animal studies and reduces airway responsiveness to an inhaled antigen or distilled water and exercise challenges.[27] From a comprehensive literature search of 1,8-

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0ra00746c

REVIEW ARTICLE

Polysaccharides Based Novel and Controlled Released Multiparticulate Systems for Colon-specific Delivery: Contemporary Scenario and Future Prospects

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Abstract

In our noble pharmaceutical field, polysaccharides were become an indispensable part during dosage form development for the last few decades. The matrix polysaccharides that were utilizing for dosage form were mostly hydrophilic in nature that gets swell and form a viscous gel-like mass upon contact with dissolution fluids or gastrointestinal fluids. The polymeric properties were successfully exploited in the development of novel polyelectrolyte complexes based multiparticulate delivery systems based on ionic gelation techniques. These complex systems have awaken as an emerging need to deliver the drug(s) into the target site of action for possible controlling and sustaining the drug release properties and thereby affecting the pharmacological responses other than those traditional dosage forms. Site-specific deliveries to the colon were confirmed for providing enzymatic digestion of these polysaccharides. Furthermore, in the present review, an attempt was made to describe the significance of the physicochemical properties of those polysaccharides for defining its possible mechanism of actions.

Key words: Chitosan, Colon drug delivery, [illegible], Multiparticulates, Pectin, Polyelectrolyte complex, Sodium alginate

MULTIPARTICULATE (MP) SYSTEM

Development of MP systems had gained much fame over the single unit systems for oral drug delivery applications as per reports during the last few decades. It has proved to be a most preferred potential system due to numerous reasons, namely, predictable gastric emptying, reduced risk of toxicity, reduced dose dumping, reduced local irritation, reduced inter-intra subject variability, increased bioavailability, improved stability, etc. MPs mostly used for oral routes include nanoparticles, microspheres, beads, granules, and microparticles that ensure for unique release profiles, uniform drug dispersion, and absorption into the gastrointestinal tract (GI tract). These systems were mostly having particle diameter range from few micrometers to millimeter (except nanoparticles) consists of active medicaments in a multiplicity of small discrete units or typically plurality of independent subunits. It is formulated either as a reservoir or matrix type based on polysaccharides (polymer) that exhibiting some desirable novel physicochemical properties. Recently, MPs were mostly using for colon-specific targeting of medicament as compared to single-unit dosage systems, since due to its smaller particle sizes, it uniformly disperses

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Received: 3-07-2020
Revised: 18-09-2020
Accepted: 27-09-2-20

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Scanned with CamScanner

ORIGINAL ARTICLE

"Drug Release Kinetic Modeling and Gamma Scintigraphic Studies of Dual Ca^{2+} and SO_4^{2-} Cross-linked Microbeads for Colon Specific Targeting"

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Abstract

Objectives: Ionic gelation-based polyelectrolyte complexes of blend chitosan-sodium alginate polysaccharides based microbeads of methotrexate were prepared by dual cross-linkages with divalent Ca^{2+} and SO_4^{-2} ions for colon targeting. **Materials and Methods:** Those developed dual cross-linked formulations were characterized for particle size, entrapment studies, drug content, swelling degree, etc. **Results:** The surface morphology results showed that the optimized formulations were semi-spherical and rough-surfaced. The *in vitro* drug release carried out in various simulated fluids at various pH had shown lesser release profiles in acidic media as compared to alkaline media at the end of 24 h studies. A significant drug release ($P > 0.05$) was observed in colonic fluids containing 2 and 4% w/v rat cecal as compared with control. *In vivo* targeting ability for the colon-specific region was established through gamma scintigraphic imaging technique. Differential scanning calorimetry and X-ray diffraction analysis further confirms for semi-crystalline and complete cross-linking state. The release profile and mathematical kinetic modeling revealed for anomalous non-Fickian type formulations were best fitted with Higuchi and Hixson-Crowell model, respectively. **Conclusion:** It can be concluded that the optimized formulations may be effective for colon targeting and promising to achieve drug targeting for colorectal cancer.

Key words: Dual cross-linked beads, gamma scintigraphy, *in-vitro* studies, kinetic modeling, matrix polysaccharides, methotrexate, rat caecal content

INTRODUCTION

Development of polyelectrolyte and ionic gelation-based multiparticulate systems (MPs) had gained much fame over the single unit systems for oral drug delivery as per reports of the last few decades. Polyelectrolyte complexes (PEC) or "egg-box-junction" is a gel formation process which takes place when oppositely charged cationic amino groups of chitosan and anionic carboxylic acid groups of sodium alginate polysaccharides interact electrostatically in an aqueous media resulting into three-dimensional structures.[1] Beads or microparticles of these complexes were widely used for easy manipulation of mechanical properties as well as drug-releasing properties.[2]

There has been considerable research for designing of colonic drug delivery system by numerous researchers. Colon targeting has been achieved by several approaches, including prodrugs, microbial dependent, pH, and time-dependent systems. Among several polymers, those pH-sensitive sodium alginate and chitosan were also have been widely used by various researchers and proved to be promising matrix carriers in the pharmaceutical dosage forms. Chitosan is a linear cationic polyelectrolyte consisting of β-1,4-linked glucosamine (deacetylated units) and N-acetyl-D-glucosamine (acetylated units) residues. Sodium alginate contains (1,4)-linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) monomers

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Received: 10-09-2020
Revised: 28-10-2020
Accepted: 04-10-2020

JOURNAL OF MICROENCAPSULATION
2020, VOL. 37, NO. 8, 609–623
https://doi.org/10.1080/02652048.2020.1829141

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

^{99m}Tc-labelled and pH-awakened microbeads entrapping surface-modified lipid nanoparticles for the augmented effect of oxaliplatin in the therapy of colorectal cancer

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ABSTRACT

Aim: This study was aimed to develop Eudragit S100-coated, pH-awakened microbeads (MBs) encapsulating folic acid (FA)-modified tristearin solid lipid nanoparticles (SLNs) loaded with oxaliplatin (OP). Afterward, these formulations were evaluated (*in vitro* and *in vivo*) for their potential against colorectal cancer (CRC).

Methods: The SLNs were synthesised by employing the solvent diffusion technique and then they were entrapped in the MBs. The prepared uncoupled and coupled SLNs (SLN-OP and FA-SLN-OP, respectively) were examined for *in vitro* cytotoxicity effect against COLO-205. Gamma-scintigraphy study was used for determining biodistribution (*in vivo*) of drug in different organs through MBs.

Results: Outcomes for FA-SLN-OP revealed more cytotoxicity (50% inhibitory concentration [IC_{50}] = 6.8 µg/ml) against COLO-205 cells (*in vitro*) than OP solution (IC_{50} = 8.0 µg/ml) and SLN-OP (IC_{50}= 7.5 µg/ml). MBs were also investigated *in vivo* using Gamma-scintigraphy study. After 48 h study, ^{99m}Tc-EuB-FA-SLN-OP confirmed an elevated level of drug in the colonic tumour, which was found significantly ($p < 0.0001$) higher than that of ^{99m}Tc-EuB-SLN-OP.

Conclusions: In conclusion, developed MBs formulation (^{99m}Tc-EuB-FA-SLN-OP) suggested promising results against therapy of CRC using dual targeting (i.e. ligand-directed and pH-awakened) approach.

ARTICLE HISTORY
Received 17 May 2020
Accepted 22 September 2020

KEYWORDS
Colorectal cancer; Eudragit S100; microbeads; oxaliplatin; cytotoxicity study; COLO-205

1. Introduction

Worldwide, colorectal cancer (CRC) remains one of the extremely occurring cancers. Nearly 1.8 million cases of CRC were reported with 8.81 lakhs mortalities in 2018. Incidence rates for CRC may diverge by 10-times throughout the world. Countries such as Australia/New Zealand showed maximum incidence rates, while South-Central Asia exhibited the lowest (Arnold *et al.* 2020). Men are more prone (30–40% higher) to CRC than women (Siegel *et al.* 2017).

In recent times, the therapy of CRC requires more attention to design and develop innovative carrier systems that can combat not only existing issues associated with the delivery of drugs but also improve the targeting effect of the drug. The existing conventional therapies for CRC, especially in the case of chemotherapy, exhibit some shortcomings, for instance, it not only shows side effects but also kills healthy cells that reduce the efficiency of anticancer drugs in the treatment of CRC (Senapati *et al.* 2018, Pandey *et al.* 2020). To overwhelm these consequences of conventional therapies, some innovative approaches have been reported, for example, targeted therapy of drug in which carrier systems are linked with specific ligands having affinity to bind specific receptors at the surface of cancer cells in the colon. In this context, many nanocarriers have been developed for efficient delivery of anticancer molecules in the therapy of cancers, for instances, liposomes (Lujan *et al.* 2019), solid lipid nanoparticles (SLNs) (Rajpoot 2019, Rajpoot 2020a), polymeric nanoparticles (Jain *et al.* 2010, Ji *et al.* 2015), emulsion (Rajpoot and Tekade 2019, Rajpoot *et al.* 2020), etc. Briefly, active targeting strategy implicates the linking of nanocarriers with active moieties (e.g. folic acid (FA), hyaluronic acid, etc.) that possess an immense affinity to bind target cancer cells *via* exploiting overexpressed receptors on it (Rajani *et al.* 2020).

For targeting colon *via* the oral route, both gastric environments as well as motility of the stomach have

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Nanomed. J. 7(3): 211-224, Summer2020

RESEARCH PAPER

Using 5-fluorouracil-encored plga nanoparticles for the treatment of colorectal cancer: the in-vitro characterization and cytotoxicity studies

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ABSTRACT

Objective(s): Colorectal cancer (CRC) is a prevalent cancer worldwide. The present study aimed to synthesize and investigate the potential of wheat germ agglutinin (WGA) conjugated with polylactic-co-glycolic acid (PLGA) nanoparticles (NPs) incorporating 5-fluorouracil (5-FU).

Materials and Methods: The NPs were investigated in terms of various characteristics, such as the particle size, surface charge, surface morphology, entrapment efficiency rate, and in-vitro drug release profile in simulated gastric and intestinal fluids. The optimized NPs were conjugated with WGA and characterized for the WGA conjugation efficiency, mucoadhesion, and cytotoxicity studies.

Results: The zeta potential of the WGA-conjugated NPs decreased (-17.9±1.4 mV) possibly due to the conjugation of the NPs with WGA, which reduced the zeta potential. The WGA-conjugated NPs exhibited sustained drug release effects ($p<0.05$) compared to the marketed formulation containing 5-FU after 24 hours. In addition, the optimized NPs followed the Higuchi kinetics, showing diffusion-controlled drug release mechanisms. Finally, the WGA-conjugated PLGA NPs could significantly inhibit the growth of colon cancer cells (HT-29 and COLO-205) compared to the non-conjugated NPs and pure drug solution ($P<0.05$).

Conclusion: According to the results, the WGA-conjugated NPs could be potential carrier systems compared to the non-conjugated NPs for the effective management of CRC.

Keywords: Carbodiimide Linking, COLO-205, Nanoparticles, PLGA, Wheat Germ Agglutinin, 5-Fluorouracil

How to cite this article

Nath Pandey A, Rajpoot K, Jain S K. Using 5-fluorouracil-encored plga nanoparticles for the treatment of colorectal cancer: the in-vitro characterization and cytotoxicity studies. Nanomed J. 2020; 7(3): 211-224. DOI: 10.22038/nmj.2020.07.0005

INTRODUCTION

Colorectal cancer (CRC) is highly prevalent in men and women worldwide, ranked the third and second most common cancer, respectively. Similar to other cancers, the current therapies for CRC are not adequately effective due to the lower efficacy of the drug concentrations at the tumor site [1]. One of the common drugs used for this purpose is 5-fluorouracil (5-FU), which is extensively used as an anticancer agent for the inhibition of thymidylate synthetase to induce apoptosis in cancer cells [2]. However, 5-FU has several limitations, such as short biological half-life [3], erratic oral bioavailability, non-selective biodistribution, and drug resistance in malignant cells [4]. Furthermore, 5-FU has rapid degradation in the body, and high doses of drugs are required for proper efficacy [5, 6]. Therefore, the continuous infusion of the drug is required to overcome these limitations, which in turn leads to patient noncompliance and increased treatment costs [7].

A targeted drug delivery system must be applied to deliver the drug more effectively for the management of CRC. Several novel platforms have been proposed in this regard, including microspheres [8, 9], microbeads [10, 11], and nanoparticles (NPs) [12], which have been investigated for the controlled release and targeting effects of drugs in the gastrointestinal (GI) tract. In addition, the poly-lactic-co-glycolic acid (PLGA) polymer has been used for the preparation of NPs in numerous studies not only due to the biocompatible and biodegradable nature of the polymer, but also owing to its potential to control the release of drugs from NPs [13, 14].

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Note. This manuscript was submitted on February 5, 2020; approved on March 15, 2020

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Letters in Drug Design & Discovery, 2020, *17*, 000-000

RESEARCH ARTICLE

Searching for Potential HDAC2 Inhibitors: Structure-activity Relationship Studies on Indole-based Hydroxamic Acids as an Anticancer Agent

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ARTICLE HISTORY

Received: October 1, 2019
Revised: December 3, 2019
Accepted: December 16, 2019

DOI:
10.2174/1570180817666200103125701

Abstract: ***Aim*:** To predict the most potent indole based HDAC2 inhibitors from several scientific reports through the process of lead identification and SAR development.

***Background*:** The current scenario is observing Histone Deacetylase (HDAC) as an alluring molecular target for the designing and development of drugs for cancer treatment.

***Objective*:** To identify the lead and establish structure-activity correlation among indole based hydroxamic acid to find out promising HDAC2 based anticancer agent.

***Methods*:** A dataset containing 59 molecules was analyzed using structure and ligand-based integrated approach comprising atom-based 3D-QSAR (Quantitative Structure-Activity Relationship) and pharmacophore study, e-pharmacophore mapping and molecular modeling methodologies. The finest model was prepared by amalgamating the properties of electronegativity, polarizability, Vander Waals forces and other conformational aspects.

***Results*:** The result of 3D QSAR analysis, performed for 4 PLS factor, provided the following statistical information: R^2 = 0.9461, Q^2 = 0.7342 and low standard of deviation SD = 0.1744 for hypothesis ADDDH.10 and R^2 = 0.9444, Q^2= 0.7858 and again low standard of deviation SD = 0.1795 for hypothesis DDHRR.12. The XP molecular docking showed intermolecular interactions of small molecules with amino acids such as GLY154, HIP145, PHE210, HIE183, internal H_2O and Zn^{2+}.

***Conclusion*:** The interpretation of data generated as a result of this investigation clearly hints about the better biological activity of test compounds as compared to SAHA. Hence, the outcome of these structure and ligand-based integrated studies could be employed for the design of novel arylindole derivatives as a potent HDAC inhibitor.

Keywords: Hydroxamate, HDAC inhibitors, pharmacophore, 3D QSAR, docking studies.

1. INTRODUCTION

Certain genetic imperfections such as gene mutations, deletions along with chromosomal aberration are responsible for a global health issue, named cancer. Furthermore, these genetic deformities subside the function of tumor-suppressing genes and/or gain of function and encourage the hyperactivation of oncogenes, [1] ultimately leading to unregulated cell growth and proliferation due to abnormal regulation of gene expression [2-4]. The two enzymes namely, Histone Acetyl Transferases (HATs) and Histone deacetylase (HDACs), perform an essential role in maintaining the dynamic equilibrium between acetylation and deacetylation of histone protein bringing about the regulation of transcription and expression of genes in eukaryotes at DNA level [5, 6].

In the past few decades, Histone Deacetylase (HDAC) has become an alluring molecular target for the designing and development of drugs for cancer treatment [7, 8]. Basically, these are a group of zinc-dependent metalloenzymes, which catalyze the elimination of acetyl groups from lysine residues in the tails of histone proteins

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1570-1808/20 $65.00+.00

Indian Journal of Chemistry
Vol. 60B, January 2021, pp. 136-147

Exploration of anticancer potential of hydroxamate derivatives as selective HDAC8 inhibitors using integrated structure and ligand based molecular modeling approach

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Received 17 January 2020; accepted (revised) 11 November 2020

Recently, histone deacetylase inhibitors are evolving as an exhilarating new class of promising antitumor agents for the treatment of multiple malignancies. It may play a pivotal role as a therapeutic target for challenging the globally wide spread disease, cancer. At the same time, the prediction of biological activity of novel compounds, which was once a major challenge in drug design, is also pacing up its speed. This computational study has been performed in Schrodinger suite packages such as sitemap generation, grid formation, Glide for docking, Quikprop for ADME analysis, e-pharmacophore post docking script and Phase for 3D QSAR models designing, that all are available in Maestro version 9.3. Docking not only helps in predicting the preferred orientation of ligand with its target receptor, but also the binding affinity between the ligand and receptor. The application of Phase and e-pharmacophore script predicts some computational models of the provided ligands using 3D QSAR method. This decreases the cost and time of biological experiments. Glide XP reveals that compound **21** with the highest score value as the best compound from the dataset. Also, it shows good R^2=0.9834, Q^2= 0.7753, stability = 0.5407 and low standard of deviation SD=0.1085 for hypothesis ADDRR.1601, for the PLS factor 5. The outcome of these studies suggests compound **21** as a potential drug molecule for HDAC targets.

Keywords: Structure-activity relationship; molecular docking; pharmacophore; 3D-QSAR; HDAC inhibitors

Cancer is now a serious disease that endangers human health. It is the second prominent root of death globally and is appraised to interpret for 9.6 million deaths in 2018 (as per WHO report). Lung, prostrate, colorectal, stomach and liver cancer are recorded common types of cancer in men, though breast, colorectal, lung, cervix and thyroid cancer are the most common amongst women. In recent years, number of studies have shown that HDAC inhibitory drugs could inhibit the growth of tumors. There are many HDAC inhibitory drugs undergoing long research and development cycle[1-3]. The steady process of histone acetylation is balanced by histone acetyltransferases (HATs) and histone deacetylases (HDACs). HATs makes the addition of acetyl groups to lysine residues of histone tails causing relaxation of chromatin and activation of transcription of nearby genes. On the contrast, HDACs remove the acetyl groups of acetylated histones leading to transcriptional suppression. HDAC therefore plays an important role in upregulating gene transcription, cell cycle progression and apoptosis. HDACs hence can be considered as a promising targets for cancer therapy[4].

Till now, 18 mammalian HDACs have been identified and studied, which were divided into five groups: class I (HDAC1, 2, 3 and 8), class II which was further sub divided into class IIa (HDAC 4, 5, 7 and 9) and class IIb (HDAC 6 and 10), class III (SIRT 1 to 7) and finally class IV (HDAC 11)[5-7]. The enzymes of classes I, II and IV are Zn^{2+} dependent metallohydrolases[5,7]. Class I enzymes are principally confined to the nucleus and are responsible for cell proliferation and differentiation[5,8]. Class III enzymes are NAD^{2+} dependent Sir2-like deacetylases[5,7]. Mainly, this class I and IIb are found to be over expressed in most hematological and solid tumors, extremely associating with a shoddier prognosis. Consequently, class I and IIb target selective inhibitory agents turn out to be a key attention in cancer chemotherapy[5]. HDAC inhibitors are mainly recorded into few classes of hydroxamates, benzamides, aliphatic acids, cyclic tetra peptides, electrophilic ketones and some other types, suitably mentioned in table (Table I). This classification was based according to their chemical structures. At present, five HDAC inhibitors have been approved by FDA,

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Letters in Drug Design & Discovery, 2021, 18, 000-000

RESEARCH ARTICLE

Structural Investigations of Aroylindole Derivatives through 3D-QSAR and Multiple Pharmacophore Modeling for the Search of Novel Colchicines Inhibitor

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Abstract: ***Background*:** The ligand and structure based integrated strategies are being repeatedly and effectively employed for the precise search and design of novel ligands against various disease targets. Aroylindole derivative has a similar structural analogy as Combretastatin A-4, and exhibited potent anticancer activity on several cancer cell lines.

***Objective*:** To identify structural features of aroylindole derivatives through 3D-QSAR and multiple pharmacophore modelling for the search of novel colchicines inhibitor *via* virtual screening.

***Method*:** The present study utilizes ligand and structure based methodology for the establishment of structure activity correlation among trimethoxyaroylindole derivatives and the search of novel colchicines inhibitor *via* virtual screening. The 3D-QSAR studies were performed using Phase module and provided details of relationship between structure and biological activity. A single ligand based pharmacophore model was generated from Phase on compound **3** and compound **29** and three energetically optimized structure based pharmacophore models were generated from e-pharmacophore for co-crystallized ligand, compound **3** and compound **29** with protein PBD ID 1SA0, 5EYP and 5LYJ. These pharmacophoric features containing hit-like compounds were collected from commercially available ZINC database and screened using virtual screening workflow.

***Results and Discussion*:** The 3D-QSAR model studies with good PLSs statistics for factor four was characterized by the best prediction coefficient Q^2 (0.8122), regression R^2 (0.9405), SD (0.2581), F (102.7), P (1.56e-015), RMSE (0.402), Stability (0.5411) and Pearson-r (0.9397). The generated e-pharmacophores have GH scores over 0.5 and AUAC $\geq$ 0.7 indicated that all the pharmacophores were suitable for pharmacophore-based virtual screening. The virtual screened compounds ZINC12323179, ZINC01642724, and ZINC14238006 have showed similar structural alignment as co-crystallized ligand and showed the hydrogen bonding of ligand with ASN101, SER178, THR179, VAL238, CYS241 amino acid of protein.

***Conclusion*:** The study illustrates that the ligand and structure based pharmacophoric approach is beneficial for identification of structurally diverse hits, having better binding affinity on colchicines binding site as novel anticancer agents.

ARTICLE HISTORY

Received: March 19, 2020
Revised: July 27, 2020
Accepted: August 09, 2020

DOI:
10.2174/1570180817999200905092444

Keywords: Ligand and structure based, combretastatin a-4, aroylindole derivatives, 3d qsar, docking, colchicine.

1. INTRODUCTION

Computer Aided Drug Design (CADD) is an emerging technology to speed up the process of drug discovery and development using available data on current medicines and ailments, along with information supplied from other applied relevant disciplines [1-3]. Structure and ligand based drug design is the basic strategy of drug design that involves designing small molecules containing specific shape and charge to interact and bind with bimolecular target [4, 5]. The integrated strategies of structure and ligand based multiple computational approaches have been frequently and successfully applied to design the ligands more accurately. The single ligand-based or structure-based method is unable to fulfill the practical needs of drug discovery and development [6, 7].

Combretastatin A-4 (CA-4) is a low molecular weight natural product preliminarily isolated from the bark of the

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1570-1808/21 $65.00+.00

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(Dr Harish Rajak)

Turk J Pharm Sci 2021;18(2):151-156
DOI: 10.4274/tjps.galenos.2020.45556

ORIGINAL ARTICLE

QSAR Studies on Neuraminidase Inhibitors as Anti-influenza Agents

Anti-influenza Ajanları Olarak Nöraminidaz İnhibitörlerinin QSAR Çalışmaları

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ABSTRACT

Objectives: The present study aimed to establish significant and validated quantitative structure-activity relationship (QSAR) models for neuraminidase inhibitors and correlate their physicochemical, steric, and electrostatic properties with their anti-influenza activity.

Materials and Methods: We have developed and validated 2D and 3D QSAR models by using multiple linear regression, partial least square regression, and k-nearest neighbor-molecular field analysis methods.

Results: 2D QSAR models had q^2: 0.950 and pred_r^2: 0.877 and 3D QSAR models had q^2: 0.899 and pred_r^2: 0.957. These results showed that the models werere predictive.

Conclusion: Parameters such as hydrogen count and hydrophilicity were involved in 2D QSAR models. The 3D QSAR study revealed that steric and hydrophobic descriptors were negatively contributed to neuraminidase inhibitory activity. The results of this study could be used as platform for design of better anti-influenza drugs.

Key words: QSAR, neuraminidase inhibitors, thiazolidine-4-carboxylic acid derivatives, anti-influenza activity

ÖZ

Amaç: Bu çalışma nöraminidaz inhibitörlerinin belirgin ve valide nicel yapı-aktivite ilişkisi (QSAR) modellerini kurmayı ve bu bileşiklerin fizikokimyasal, sterik ve elektrostatik özelliklerini anti-influenza aktiviteleriyle korele etmeyi amaçlamıştır.

Gereç ve Yöntemler: Çoklu regresyon, parsiyel en düşük kare regresyon ve k-en yakın komşu moleküler alan analizi yöntemlerini kullanarak 2D ve 3D QSAR modellerini geliştirdik ve valide ettik.

Bulgular: Geliştirilen 2D QSAR modeli için q^2: 0,950 ve pred_r^2: 0,877 bulunurken, 3D QSAR modeli için q^2: 0,899 ve pred_r^2: 0,957 bulundu. Bu sonuçlar modellerinin tahmin gücünün olduğunu gösterdi.

Sonuç: Hidrojen sayısı ve hisrofilisite gibi parametreler 2D QSAR modellerine dahil edildi. 3D QSAR modelleri sterik ve hisrofobik tanımlayıcıların nöraminidaz inhibitör aktivitesine negatif etki ettiği belirlendi. Bu çalışmanın sonuçları influenzaya karşı ilaç tasarlamak için bir platform olarak kullanılabilir.

Anahtar kelimeler: QSAR, nöraminidaz inhibitörleri, tiyazolidin-4-karboksilik asit deriveleri, anti-influenza aktivitesi

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Received: 07.06.2019, Accepted: 12.03.2020

(Dr. Harish Rajak)

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Journal of Molecular Structure 1240 (2021) 130590

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstr

Appraisal of pyrrole as connecting unit in hydroxamic acid based histone deacetylase inhibitors: Synthesis, anticancer evaluation and molecular docking studies

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ARTICLE INFO

Article history:
Received 27 January 2020
Revised 29 March 2021
Accepted 28 April 2021
Available online 5 May 2021

Keywords:
Histone deacetylase inhibitors
Pyrrole
Synthesis
Anticancer

ABSTRACT

Pyrrole is a biologically active scaffold, which itself possess noticeable anticancer activity against several types of cancer specially leukemia, lymphoma, and myelofibrosis. SAHA and its synthetic analogs has demonstrated potent antitumor activity against numerous human cancer lines and different classes of HDACs. The HDAC inhibitor possessing pyrrole as linker moiety has been developed for anticancer property. The objective of present studies was to incorporate pyrrole as connecting unit in hydroxamic acid based HDAC inhibitors for their anticancer evaluation and molecular docking studies. A series of novel 4-substituted methyl 6-(3-acetyl-2-methyl-1*H*-pyrrol-1-yl)hexanoate **[3(a-z)]** and 4-substituted 6-(3-acetyl-2-methyl-1*H*-pyrrol-1-yl)-N-hydroxyhexanamide **[4(a-z)]** were synthesized. These analogs were evaluated for their anticancer activity using *in-vitro* method against leukemia (K-562), lung (A-549), breast (MCF-7), and cervical (HeLa) human cancer cell lines using Sulforhodamine B (SRB) assay method, HDAC1 and HDAC6 inhibitory assay and binding mode analysis using molecular docking studies. The *in-vitro* studies of **3(a-z)** indicated that substitution with electron donating groups produces active or moderately active compounds. Interestingly, *p*-nitro-substituted molecule produced a most active derivative in the series. The *in-vitro* anticancer study of **4(a-z)** indicated that the unsubstituted phenyl derivative, 6-(3-acetyl-2-methyl-4-phenyl-1*H*-pyrrol-1-yl)-N-hydroxy-hexanamide (**4a**) have moderate antitumor activity against K-562 human leukemia cell line. Substitution at 4-phenyl ring with weak and moderate electron withdrawing groups, such as fluoro, chloro, and bromo potentiated the cytotoxic activity. The **4(a-z)]** were docked against different HDAC proteins to determine the exact binding mode and orientation. These synthetic analogs have similar binding mode as SAHA on the active pocket. The pyrrole based novel SAHA analogs **3(a-z)** and **4(a-z)** displayed promising anticancer activity. These studies can be further employed for the design and development of novel SAHA analogs with promising anticancer activity.

1. Introduction

1.1. Histone deacetylase inhibitors

Histone deacetylase inhibitors (HDACi) are low molecular weight molecules increasing the acetylation of histone and non-histone proteins leading to alteration in gene expression ultimately affecting the process of angiogenesis, metastasis, and apoptosis *etc* [1-7]. USFDA has approved four drugs i.e., romidepsin, vorinostat, panobinostat, and belinostat, while one HDAC inhibitor i.e., chidamide has been approved by Chinese FDA. Apart from these drugs, a large number of HDAC inhibitors such as Abexinostat (PCI-24781), Resminostat (4SC-201 or RAS2410), Pracinostat (SB939), Givinostat (ITF2357), Quisinostat (JNJ-26481585), and Dacinostat (NVP-LAQ824) are under clinical investigation for different types of cancers [8-11]. All HDACi possess four essential pharmacophores for anticancer activity, one or more than one pharmacophores could be altered to develop newer HDACi (Fig. 1) [1-4]. Thus, there is a scope for modification in the linker, connecting unit, cap group and zinc binding group. SAR studies on HDACi shows that connecting unit is an important pharmacophore. The compounds containing heterocyclic nucleus like pyrrole itself has shown considerable anticancer activity in a vast number of human cancer cell lines via the different kind of mechanistic approaches [12-21].

1.2. Mechanism of action of histone deacetylase inhibitors

HDACs are the key enzymes liable for anomalous expression of different genes engaged in the transcriptional regulations. HDACs

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https://doi.org/10.1016/j.molstruc.2021.130590
0022-2860/

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Mini-Reviews in Medicinal Chemistry, 2021, *21*, 000-000

MINI-REVIEW ARTICLE

Synthetic and Semi-synthetic Drugs as a Promising Therapeutic Option for the Treatment of COVID-19

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ARTICLE HISTORY

Received: July 06, 2020
Revised: August 23, 2020
Accepted: October16, 2020

DOI:
10.2174/1389557520666201204162103

Abstract: The novel coronavirus disease-19 (COVID-19) is a global pandemic that emerged from Wuhan, China, and has spread all around the world, affecting 216 countries or territories with 21,732,472 people infected and 770,866 deaths globally (as per WHO COVID-19 updates of August 18, 2020). Continuous efforts are being made to repurpose the existing drugs and develop vaccines for combating this infection. Despite, to date, no certified antiviral treatment or vaccine exists. Although, few candidates have displayed their efficacy in *in vitro* studies and are being repurposed for COVID-19 treatment. This article summarizes synthetic and semi-synthetic compounds displaying potent activity in clinical uses or studies on COVID-19 and also focuses on the mode of action of drugs being repositioned against COVID-19.

Keywords: Clinical trials, coronavirus, COVID-19, pathogenesis, SARS-CoV-2, synthetic and semi-synthetic antiviral drugs.

1. INTRODUCTION

In late December 2019, numerous fatal pneumonia cases with unfamiliar etiology were reported in Wuhan, Hubei province, China [1, 2]. These subjects were epidemiologically associated with seafood and wet animal wholesale market [3]. Several research laboratories revealed coronavirus (CoV) as the causative agent behind this pandemic [4-7]. The Severe Acute Respiratory Syndrome (SARS)-CoV and Middle East Respiratory Syndrome (MERS)-CoV in the year 2002 and 2012, respectively, are previous coronavirus outbreaks in the past two decades [7]. Around 8422 people worldwide with nearly 916 fatalities were infected by SARS-CoV, depicting its fatality rate of 10%. Whereas MERS-CoV caused around 2499 confirmed cases and 816 deaths, exhibiting its mortality rate roughly 35% [8-10]. The contributory virus is known as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), and the pertinent infectious disease is called Coronavirus Disease-2019 (COVID-19) by the WHO [1] and has been announced as a global health emergency. Coronaviruses (CoVs) are positive-sense, single-stranded RNA viruses [11], belonging to the family *Coronaviridae*; subfamily *Coronavirinae* [12, 13]. To date, seven diverse strains of Human Coronaviruses (HCoVs) have been stated. 229E and NL63 strains of HCoVs belong to Alphacoronaviruses, while SARS, MERS, OC43, HKU1, and SARS-CoV-2 HCoVs belong to Betacoronaviruses [14]. As of August 18, 2020, WHO reported the spread of COVID-19 in 216 countries with a total of 21,732,472 confirmed cases, and 770,866 deaths.

The important pathogenesis (Fig. 1) visible in COVID-19 patients [15, 16] includes serious pneumonia, RNAaemia associated with the prevalence of ground-glass opacities, and intense cardiac injury [3, 17]. An increased level of cytokines and chemokines (IL1-β, IL1RA, IL7, IL8, IL9, IL10, IFNγ, IP10, MCP1, MIP1α, MIP1β, basic FGF2, GCSF, GMCSF, PDGFB, TNFα, and VEGFA) was observed in the blood sample of infected patients. Blood reports of some patients admitted to intensive care unit indicated elevated levels of pro-inflammatory cytokines, including IL2, IL7, IL10, MCP1, MIP1α, GCSF, IP10, and TNFα, that are responsible for enhancing the severity of this disease [3]. The SARS-CoV-2 infection is, day-by-day, dispersing fast with a rising number of infected patients worldwide [18].

The understanding of the mechanism of action (MOA) of drugs showing promising activity against SARS-CoV-2 would help in deciding antiviral strategies in several ways. The knowledge of MOA would allow forecasting the problems related to the clinical safety of drugs being repurposed.

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1389-5575/21 $65.00+.00

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Review

Structure–Activity Relationship Analysis of Benzimidazoles as Emerging Anti-Inflammatory Agents: An Overview

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Abstract: A significant number of the anti-inflammatory drugs currently in use are becoming obsolete. These are exceptionally hazardous for long-term use because of their possible unfavourable impacts. Subsequently, in the ebb-and-flow decade, analysts and researchers are engaged in developing new anti-inflammatory drugs, and many such agents are in the later phases of clinical trials. Molecules with heterocyclic nuclei are similar to various natural antecedents, thus acquiring immense consideration from scientific experts and researchers. The arguably most adaptable heterocyclic cores are benzimidazoles containing nitrogen in a bicyclic scaffold. Numerous benzimidazole drugs are broadly used in the treatment of numerous diseases, showing promising therapeutic potential. Benzimidazole derivatives exert anti-inflammatory effects mainly by interacting with transient receptor potential vanilloid-1, cannabinoid receptors, bradykinin receptors, specific cytokines, 5-lipoxygenase activating protein and cyclooxygenase. Literature on structure–activity relationship (SAR) and investigations of benzimidazoles highlight that the substituent's tendency and position on the benzimidazole ring significantly contribute to the anti-inflammatory activity. Reported SAR analyses indicate that substitution at the N1, C2, C5 and C6 positions of the benzimidazole scaffold greatly influence the anti-inflammatory activity. For example, benzimidazole substituted with anacardic acid on C2 inhibits COX-2, and 5-carboxamide or sulfamoyl or sulfonyl benzimidazole antagonises the cannabinoid receptor, whereas the C2 diarylamine and C3 carboxamide substitution of the benzimidazole scaffold result in antagonism of the bradykinin receptor. In this review, we examine the insights regarding the SARs of anti-inflammatory benzimidazole compounds, which will be helpful for researchers in designing and developing potential anti-inflammatory drugs to target inflammation-promoting enzymes.

Keywords: benzimidazole; cyclooxygenase; bradykinin; cannabinoid; effect of structural modification

Citation: Veerasamy, R.; Roy, A.; Karunakaran, R.; Rajak, H. Structure–Activity Relationship Analysis of Benzimidazoles as Emerging Anti-Inflammatory Agents: An Overview. *Pharmaceuticals* **2021**, *14*, 663. https://doi.org/10.3390/ph14070663

Academic Editor: Mary J. Meegan

Received: 23 May 2021
Accepted: 9 July 2021
Published: 11 July 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

Inflammation is derived from the Latin word "inflammare". The body's immune system initiates an immediate response to harmful stimuli, such as infections or any type of irritation [1]. The inflammatory responses entail several biochemical events (Figure 1). They are a defensive attempt by the body to heal infections; however, if inflammation is not controlled, it can prompt a cluster of acute, chronic and systemic inflammatory disorders [2,3]. The major symptoms of inflammation are redness, pain and swelling [4]. Some diseases, such as cardiovascular disease, autoimmune diseases, periodontal disease, Alzheimer's disease, asthma, diabetes and COPD, are related to chronic inflammation [1,2]. Steroid drugs have traditionally been used to treat inflammation, but their use has gradually

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(Dr Harish Rajak)

Review Article

Cucurbita pepo and Cucurbitacin in the Management of Anti-proliferation by JAK/STAT Pathway

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ABSTRACT

Pumpkin *(Cucurbita pepo)* is capaciously recycled similar to food and in folk medicine throughout the world. It accords to genus Cucurbita (C_{CT}) under family Cucurbitaceae. There are a plenty of important medicinal phyto-constituents belonging to cucurbitoside like triterpenoids, C^{AR}_{T} and C_{CT} glycosides. A survey of the literature demonstrates that *C. pepo*, has the capacity to improve prostatic hyperplasia, urinary dysfunction and cytotoxic properties. Many pharmacological revisions have established its role in hepatoprotection, inhibition of P_{r}^{st} gland cancer (C_{NCR}), anti (A^{n}_{t}) oxidant effects, inhibition of L_{u}^{G}, B_{R}^{st} and triple-negative B_{R}^{st} C_{NCR} by blocking JAK/STAT signaling (S_{gls}) pathway (P_{tw}). It has also A^{n}_{t} microbial, A^{n}_{t} -inflammatory, A^{n}_{t} -diabetic and A^{n}_{t} ulcer activities by supporting its traditional claims. Establishment of *C. pepo* and cucurbitacin (C_{CBT}) in the management of A^{n}_{t} -proliferation by JAK/STAT P_{tw}. Data towards writing this review are generated through exploration of different websites like MEDLINE (PubMed), Google Scholar, Science Direct, Scopus, Cochrane, SID and Magiran databases. We have selected 2016-2018 duration for the same purpose. We have found 88 papers related to this topic. C_{CBT} is found to arrest unlimited cell (C_{EL}) division and respective apoptosis (A_{ppt}) *in vitro* and *in vivo* C_{NCR} models. A plenty of molecular design targeting C_{CBT} have been invented, such as fibrous-actin, S_{gls} transducer and activator of transcription (STAT), cyclooxygenase-2, etc. This review is minded at C_{CBT} from *C. pepo* which dwindle the proliferation of human C_{NCR} C_{EL} through the JAK/STAT P_{tw}.

Key words: Anticancer activity, *Cucurbita pepo*, Cucurbitaceae family, JAK/STAT pathway, Cucurbitacin, Cyclooxygenase-2.

INTRODUCTION

C_{NCR} lies its uniqueness to the maximum normally identified diseases (D_{SEAS}) and is associated with ill health and death set up causing a health problem globally. Even though unlimited determinations have been found ready to find out a remedy, C_{NCR} remnants a very projecting cause of death in humans. Carcinogenesis (C_{CNG}) is a different step and different factorial process including the incidence of vibrant and disconnected molecular and C_{EL} modifications. There are different but thoroughly associated stages of origination, elevation and development are found in C_{NCR}.[1] Present-day C_{NCR} treatments, chemotherapy, targeted agents, radiation, surgery and immunosuppression have restrictions subsequent from the expansion of resistance to the treatment. The identification of defensive molecules starved of side effects ruins a crucial independent in the fight against C_{NCR}. The additional choices goal next to the initial finding of C_{NCR} in the preliminary stage can assist with its appropriate supervision. In the meantime, plant (P_{L})-derived products have taken a major role to inhibit numerous chronic D_{SEAS}, as well as C_{NCR}. The use of P_{Ls} substances to inhibit or defer the growth of C_{CNG} has been called for chemoprevention and there is a rapid increasing attention towards the usage of natural compounds

Submission Date: 10-01-2020,
Revision Date: 17-07-2020,
Accepted Date: 20-01-2021

DOI: 10.5530/ijper.55.1.3

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www.ijper.org

E-ISSN: 0975-8232; P-ISSN: 2320-5148

IJPSR (2021), Volume 12, Issue 3

(Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 13 March 2020; received in revised form, 19 June 2020; accepted, 28 June 2020; published 01 March 2021

ONGOING ADVANCEMENT IN THE COMPREHENSION OF MITOCHONDRIAL PROGRESSION WITH AN EXCEPTIONAL SPOTLIGHT ON ITS RELATIONSHIP WITH CANCER AND POSSIBLE THERAPEUTIC STRATEGY

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Keywords:

Mitochondria cancer, Mitochondrial fission, Mitochondrial fusion, Natural compounds, Quercetin, Aloe-emodin, Berberine, Resveratrol

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ABSTRACT: Cancer is one of the main reasons of death around the world and the quantity of new incidents keeps on rising. Despite ongoing advances in conclusion and remedial systems, many malignancy-related passes happen, demonstrating the requirement for better treatments and symptomatic methodologies. Mitochondrial morphology is dependent on continuous fusion and fission strategies that are essential for monitoring a normal mitochondrial function. Past years major discoveries have indicated that the characterization of fission and fusion is a little machinery, which is known as the physiological role of mitochondrial dynamics. Mitochondria (MND) and metabolic adjustments have been perceived as critical for growth movement. The numerous components of those organelles square measure in person connected to their morphology. Late confirmation proposes a significant association between mitochondrial (MNDL) construction and ill health, together with neurodegenerative, incendiary ailments and malignancy. Here, we scrutinize present-day movements within the perception of mitochondrial gestures with a special target with its liaison to cancer and therapeutic ways *via* synthetic and natural bioactive actives. Some notable compounds in the above class are Curcumin, Mahanine, aloe-emodin, Dioscin, Dantron, Flavo-pridiol, Xantho-humol, resveratrol, and quercetin.

INTRODUCTION: Mitochondria (MND) are double membranous organelles in which the inner membrane is larger than the outer one. For this reason, the inner membrane of the MND folds within, forming a special figure known as cristae. The inner MND membrane (IMM) contains the subunits for organic processes [1], and this inner MNDL membrane is coated by a second membrane known as the outer MNDL membrane (OMM) [2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(3).1421-32

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(3).1421-32

We tend to know the MND as the 'Powerhouse of the Cell because not only they generate adenosine triphosphate (ATP) *via* organic processes [3], but additionally participate in varied synthesis pathways (PWS) such as pyrimidine and purine biogenesis, haematin biogenesis [4] the management of N_2 equivalence in organic compounds revolution, gluconeogenesis, organic compound generation, and carboxylic acid degeneration and prolongation [5].

They additionally participate in cell signaling *via* control of the protein-protein interaction or by controlling the cellular concentration of metal ion (Ca^{2+}) and reactive atomic number 8 species [6] Throughout numerous biological diseases, MNDL morphology is altered, as in the case as once there

IJPSR (2021), Volume 12, Issue 10 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 04 August 2020; received in revised form, 11 February 2021; accepted, 24 May 2021; published 01 October 2021

GREEN SYNTHESIZED GOLD NANOPARTICLE: A NOVEL APPROACH TOWARDS BIOMEDICAL AND PHARMACEUTICAL APPLICATIONS

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Keywords:

Gold Nanoparticle, Chloroauric acid, Plant, microbial and marine sources, Recent patents, Anticancer activity, Antibacterial agent, Photo luminescent, Metal sensor

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ABSTRACT: Green synthesized gold nanoparticle is one of the most promising drug delivery approaches with biocompatibility and biodiversity. Various plant sources such as *Aegle marmelos*, *Eugenia jambolana*, Soursop, *Persea Americana*, *Terminalia chebula*, *Aloe arborescens*, *Musa paradisiacal*, *Alternanthera philoxeroides*, *Cissus quadrangularis*, *Sterculia acuminate*, *Garciniaindica choissy*, *Eucalyptus globulus*, *Rosmarinus officinalis*, *Punica granatum*, *Pistacia atlantica*, *Pistacia integerrima*, *Juglans regia*, *Curcumae kwangsiensis*; fungal sources as *Pleurotus cornucopiae* var. citrinopileatus, *Cladosporium cladosporioides*; other microbial sources as *Magnusiomyces ingens* LH-F1, *Micrococcus yunnanensis*, *Padina tetrastromatica* are used to develop biocompatible gold nanoparticle with veritable diversified particle size and applicability profile as anticancer (especially against breast cancer, liver cancer, ovarian cancer and lung cancer), antibacterial agent, photo luminescent, heavy metal sensor, *etc.* If biogenic sources are composed of a large number of hydroxyl and carboxylic acid groups, it can behave as reducing agents to develop gold nanoparticles with immense biomedical and pharmaceutical applications. This novel approach and data are very much encouraging and may be considered as one platform for searching all the important green synthesized gold nanoparticles and might be an index for evaluating drug activities.

INTRODUCTION: Since time immemorial, people in India, Europe, Egypt, Greece, and other South American countries have used plants, fungi, and moulds as traditional medicine [1-2]. Traditional herbal medicines are naturally occurring derived substances with minimal or no industrial processing that have been used to treat illness within local or regional healing practices [3-6].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(10).5208-28

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(10).5208-28

In ancient India and Himalayan regions, sages triturated medicines with gold for better efficacy, as gold was known as 'Amrita' because of its cell rejuvenating [7-8], antibacterial [9-11] and immuno-modulatory properties [12-13].

In the 17th century, Nicholas Culpepper demonstrated the use of gold elixir in the treatment of melancholy, and fever [14-15]. The composition of gold and sodium chloride [Na (Aucl4)] was effective in the treatment of syphilis. In 1890, Robert Koch developed potassium gold cyanide [K{Au(CN)2}] as bacteriostatic agent. At that time, sodium aurothiomalate and aurothioglucose were considered highly effective agents in chrysotherapy for rheumatoid arthritis.

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Current Drug Targets, 2021, *22*, 1725-1737

REVIEW ARTICLE

BENTHAM SCIENCE

GSK-3 Inhibitors: A New Class of Drugs for Alzheimer's Disease Treatment

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ARTICLE HISTORY

Received: August 28, 2020
Revised: October 26, 2020
Accepted: October 28, 2020

DOI
10.2174/1389450122666201014095207

Abstract: Alzheimer's disease (AD), a chronic neurodegenerative disease, is the most common form of dementia that causes cognitive function impairment, including memory, thinking, and behavioral changes that ultimately lead to death. The overactivation of GSK-3, an enzyme from the proline/serine K_i^{ss} family, has been associated with hyper-phosphorylation of tau proteins. The self-assembly of hyper-phosphorylated tau proteins to form tangles of straight and helical filaments is known to be involved in AD. Therefore, GSK-3 has been considered a potential target of novel drug discovery for AD treatment. Research on the development of GSK-3 inhibitors has received enormous attention from the vast scientific community because they are targeted for AD and other diseases, including type 2 diabetes, cancers, stroke, Parkinson's disease and bipolar disorder. Various drugs of both synthetic and natural origins have been designed to inhibit GSK-3 activity. However, there is a need to develop novel drug candidates that can selectively inhibit GSK-3. Hence, this review summarizes the potential of GSK-3 inhibitors for AD therapy and discusses the structure-activity relationship of current drug molecules and the potential problems associated with them.

Keywords: Alzheimer's disease, GSK-3, GSK-3 inhibitors, Tau, β-amyloid, neurodegenerative diseases, protein kinase.

1. INTRODUCTION

Neurons are the structural and functional units of the nervous system [1], and the central nervous system (CNS) is the primary system in the human body [2, 3]. The progressive loss of structure or function of neurons, including neuron death, leads to neurodegenerative diseases (NgDs), which become more prevalent as the population ages [4]. There are several NgDs, namely, amyotrophic lateral sclerosis, Parkinson's disease (PD), Alzheimer's disease (AD), fatal familial insomnia, and Huntington's disease (Fig. 1). There are a few NgD drugs available in the market (Fig. 2). Studies have shown that an aging population is prone to suffer from various incorrigible NgDs [5]. The main symptoms of NgDs are loss of memory, expressionless face, depression, akinesia, hypokinesia, rigidity, and tremor. To date, the etiology of these diseases is not clearly understood. However, there has been substantial evidence that indicates the genetics, protein misfolding (α-syncline, tau protein, and β-amyloid), DNA damage, membrane damage, and mitochondrial dysfunction responsible for the initiation and progression of NgD. AD is the most prevalent NgD. Currently, 30 million people are affected by this disease worldwide. AD alters various parts of the CNS, including the cerebral cortex, hippocampus, basal ganglia, and thalamus. It is caused by the disturbance of amyloid plaques in the brain and is characterized by progressive memory loss [6]. The treatment outcome of this disease is unpredictable; several attempts are being made to understand the etiology of the disease and identify new drug targets for the discovery of AD drugs. Various drugs have been developed to treat AD, including those that act *via* acetylcholinesterase inhibition, N-methyl-D-aspartate receptor (NMDA) receptor modulation, nicotinic acetylcholine receptor inhibition, Gamma-aminobutyric acid (GABA) receptor blockage, serotonin receptor activation, H3 receptor blockage, phosphodiesterase inhibition, and brain metabolism inhibition [7]. With the continuous efforts of the vast scientific community, glycogen synthase K_i^{ss} -3 (GSK-3) has been identified as a new target for the treatment of AD. Dysregulation of GSK-3 is the leading cause of nerve cell damage that leads to AD [8]. In this review, we describe various GSK-3 inhibitors, including synthetic and natural compounds, along with their AD treatment mechanism.

2. BRAIN CIRCUIT SYSTEMS AND AD

AD is a CNS disorder that mostly affects people over 65 years of age [9]. Approximately 60%–80% cases of dementia patients have AD [10]. AD was first discovered by Alois Alzheimer, a German psychiatrist, in 1906. According to a recent report, official death certificates recorded 121,404

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1873-5592/21 $65.00+.00

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

International Journal of Pharmacy and Pharmaceutical Sciences

Print ISSN: 2656-0097 | Online ISSN: 0975-1491

Vol 13, Issue 7, 2021

Review Article

COMPUTATIONAL APPROACHES RELATED TO DRUG DISPOSITION

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Received: 20 Mar 2021, Revised and Accepted: 28 May 2021

ABSTRACT

Drug disposition connects with the movement of drug molecules inside the body after administration irrespective with the route of administration. After entering the system, drug molecule and internal body systems comes under various pharmacokinetic interactions followed by observation of suitable biological activity. In this exhaustive process, physicochemical nature of the chemical substance and physiological nature of system makes this movement competitive. In this view, pharmacokinetic and toxic properties of the molecule regulates the destination of the molecule. Various computational processes are available for *in silico* pharmacokinetic assessment of drug molecule after absorption through biological membrane, distributed throughout the system based on the percent ionization or partition coefficient factors followed by biologically transformed into an another entity in presence of microsomal enzymes and finally excrete out from system using various cellular transport systems as well as related cellular toxicity behavior. In this chapter, we ensemble all the possible information related with the drug movement and related computational tools to understand the possible chemical and pathophysiological changes. Here detailed knowledge on database expedition, establishment of pharmacophore model, homology modelling based on sequence similarity, molecular docking study (rigid and flexible docking) and QSA_R/QSP_R study (with detailed process and available softwares) are provided. These diversely united informations actually helps a researcher to understand the factual movement of a drug molecule inside the system.

Keywords: Drug disposition, *In silico* pharmacokinetic parameter, Pharmacophore, QSA_R/QSP_R, Molecular docking, Homology modeling

DOI: https://dx.doi.org/10.22159/ijpps.2021v13i7.41531. Journal homepage: https://innovareacademics.in/journals/index.php/ijpps.

INTRODUCTION

Drug disposition means the change in the position of drug molecules after administration into the system [1, 2]. As per the pharmacological view: Drug is a substance which can cause positive or negative effect to the system. But in actual drug is a chemical substance comprised with a definite chemical structure. When a chemical substance goes into a system which itself governed by pH-partition hypothesis [3-5]. The disposition of drug molecule involves administration, distribution, metabolism, excretion and toxicity (ADMET) [6, 7]. Presence of different transporting proteins, nature of absorbing medium, pH, partition coefficient of the molecule, nature of microsomal enzyme, structural features of drug molecule, stereochemistry of the drug molecule are the directly correlated with disposition of the drug molecule [8, 9]. In the chapter, we are mainly focus on phases of drug disposition along with different computational methods/tools (molecular docking study, assessment of different databases, pharmacophore screening, *in silico* toxicity assessment, *in silico* determination of pharmacokinetic parameter) associated with disposition of drug molecule [10].

Search criteria

The keywords associated with search criteria of the manuscript were: role of ADME on drug disposition, availability of softwares for drug metabolism, availability of different active transporters related in drug disposition, exploration of different available databases related to drug distribution, pharmacophoric features development using different softwares, exploration of homology modelling softwares and standalone version, molecular docking process and its importance on drug receptor interaction and importance of QSAR/QSPR on drug disposition in different platforms such as: https://pubmed.ncbi.nlm.nih.gov/, https://www.sciencedirect.com/ with 10 y of timeline (2010-2020) as well as using different softwares such as: https://dtclab.webs.com/software-tools, https://www.click2drug.org/, http://zincpharmer.csb.pitt.edu/pharmer.html, http://bioinfo3d.cs.tau.ac.il/pharma/php.php, https://swissmodel.expasy.org/, https://blast.ncbi.nlm.nih.gov/Blast.cgi?PROGRAM=blastpandPAGE_TYPE=BlastSearchandLINK_LOC=blasthome.

Pharmacokinetic parameters associated with drug disposition

Absorption

After administration of the drug molecule, system processed the molecule through a series of biochemical reactions based on the structural features. In most of the cases, drug molecules absorb through a biological membrane following first order rate kinetics (direct correlation between increase in the drug concentration and plasma protein concentration) but when changes of drug concentration creates no positive impact on time interval, zero order chemical kinetics was followed (in saturated environment, no correlation between administrative dose increment and plasma protein concentration) [11]. Also stereoselective nature of drug molecule (R and S configuration) regulates the plasma protein concentration based on intravenous bolus dose [12]. There were two types of transporters available for transportation of drug molecules through membrane known as efflux and influx transporters, whereas efflux transporter systems belongs to ATP binding cassette and influx transporters belongs to solute linked carrier family [13]. These carrier systems were mainly found in major organs like liver, kidney, brain along with gastro-intestinal tract [14]. The permeation of drug molecule mainly depends upon solubility of the molecule in a specific environment. Initially BCS (Biopharmaceutics Classification System) was the preliminary scale to calculate the permeability of orally administered drugs (Class-I: High solubility and high permeability; Class-II: Low solubility and high permeability; Class-III: High solubility and low permeability and Class-IV: Low solubility and low permeability) [15]. In the next phase, calculation of MAD (Maximum Absorbable Dose) was developed based on solubility (S), volume of fluid (V_f), rate constant (K_a) and transition time (T_r).

$$MAD = S \times K_a \times V_f \times T_r \text{ --------- (i)}$$

$$SLAD = S_i \times V_f \times M \text{ --------- (ii)}$$

Based on the calculation of fast state simulated intestinal fluid (FaSSIF) and solubility limited absorbable dose (SLAD) values a new developability classification system (DCS) was established (Where S_i= solubility through small intestine and M = permeability factor). As per this DCS system, Class-II of BCS (good permeation in poor

Pharmaceutical Chemistry Journal, Vol. 55, No. 7, October, 2021 (Russian Original Vol. 55, No. 7, July, 2021)

NEW MERCAPTOACETAMIDE DERIVATIVES: SYNTHESIS AND ASSESSMENT AS ANTIMICROBIAL AND ANTIMYCOBACTERIAL AGENTS

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Original article submitted January 21, 2018.

During last few years, the frightening elevation of bacterial resistance was accompanied by dramatic decline in recent treatments of infectious diseases, which became a point of anxiety for healthcare industries. MDR and XDR strains of *Mycobacterium tuberculosis* (*Mtb*) result in the tuberculosis. In this regard, herein, a series of new mercaptoacetamide derivatives were synthesized via multipot synthetic pathway and the rationale was the appraisal of bioactivity in compact heteronuclei and their assessment as potential antimicrobial and antimycobacterial agents against virulent strain of *Mtb*, $H_{37}Ra$ for structure–activity relationship (SAR) studies. The inhibition zones of compounds **4c** and **4e** were found to be nearest to that of standard drug Ciprofloxacin, while compounds **4h** and **4j** were mild to moderately active against Gram positive bacteria (*Staphylococcus aureus, Streptococus pneumonia*) and Gram negative bacteria (*Pseudomonas aeruginosa, Salmonella typhimurium* and *Escherichia coli*). MIC_{90} assays indicated that new mercaptoacetamides did not exhibit *in vitro* activity against *Mtb* in contrast to Rifampicin and Streptomycin, first-line antimycobacterial chemotherapeutic agents. According to the present study, it was concluded that mercaptoacetamides of the new series succeeded as antimicrobial agents but could not develop as potential lead compounds against *Mtb* when tested in concentrations of 50, 25, 12.5 and 6.25 μg/mL.

Keywords: *Mycobacterium tuberculosis*; mercaptoacetamides; anti-tuberculosis activity; antimicrobial activity

1. INTRODUCTION

In the present milieu, tuberculosis (TB) is wild on grounds of the exposure of new cases, negative sequels of first-line anti-TB drugs rifampicin (RIF) and isoniazid (INH), emergence of MDR and XDR strains of causative pathogenic *Mycobacterium tuberculosis* (*Mtb*) and comorbidity with HIV infections [1 – 3]. These grounds gather speed by the collapsed anti-TB drug discovery efforts. Current reports designate the prompt inefficacy of Directly Observed Treatment Short-Course (DOTS) in the areas covering high prevalence of MDR-TB [4 – 7]. In this set of conditions, the sole option in prescription for *Mtb* is a combination of second line drugs with DOTS but this combination therapy is inadequate for riddance of XDR *Mtb* [8]. Consequently, necessity for the evolution of novel anti-TB drugs possessing boosted outcome such as eradication of disease quickly, diminished toxicity, elevated activity against MDR, prompt mechanism of action against *Mtb*, shortened treatment duration and host cell perforation potential is instantly required.

Various acetamides were synthesized to increase the molecular array in the series of antimicrobial agents and were subsequently shown to exhibit significant antimycobacterial activity. A series of 2-(3-fluoro-4-nitrophenoxy)-N-phenylacetamide derivatives (Fig. 1a) were synthesized and screened for anti-TB activity. It was found that all the new derivatives exerted potent or moderate activity against *M. tuberculosis* H37Rv, with MIC values ranging from 4 to 64 μg/mL. The presence of nitro group at position 2 of *N*-phenylacetamide nucleus resulted in most potent activity with an identical MIC value of 4 μg/mL for both *M. tubercu-*

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0091-150X/21/5507-0644 © 2021 Springer Science+Business Media, LLC

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Current Drug Targets, 2021, 22, 1437-1462

REVIEW ARTICLE

Recent Advances in the Discovery of GSK-3 Inhibitors from Synthetic Origin in the Treatment of Neurological Disorders

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ARTICLE HISTORY

Received: August 20, 2020
Revised: October 05, 2020
Accepted: November 19, 2020

DOI:
10.2174/1389450122666210120143953

Abstract: ***Background*:** Glycogen synthase kinase 3 (GSK-3) is a serine/threonine kinase enzyme that controls neuronal functions such as neurite outgrowth, synapse formation, neurotransmission, and neurogenesis. The enzyme has two subunits as GSK-3α and GSK-3β. 4ACC, 1Q3D, 3AFG, 1UV5, and 1Q5K are the important GSK-3 receptors isolated from Homo sapiens and Mus musculus. This enzyme mainly phosphorylates Tau protein with the increased amount in neuronal fibres together with beta-amyloid plaques that cause neuronal diseases like Alzheimer's, Parkinson's and many more.

***Objective*:** We investigated the developments of various synthetic GSK-3 inhibitors responsible for the prevention and treatment of neurological disorders, like Alzheimer's disease, bipolar disorders, acting as antidepressants, neuroprotective, *etc*.

***Results and Conclusion*:** It has been observed that structures of the GSK-3 inhibitors are comprised of benzopyridine, benzothiazole, pyrazole, pyrazine, dioxolo-benzoxazine, oxadiazole, and benzimidazole in the skeletal with cyclopropyl amide, phenyl carbamothioate, 3-[(propan-2-yl)oxy]propan-1-amine in the side chain. The molecules were evaluated against the effectivity of GSK-3, human adenosine kinase, cyclin-dependent kinase, and phosphodiesterase-4 along with tail suspension test forced swim test, percent neuronal survival and other cognitive behaviours. The observations confirmed the remarkable effects of the synthesized molecules to conquer Alzheimer, Parkinson's depression, psychosis and other forms of neurological disorders.

Keywords: GSK-3, Receptors, Alzheimer, Parkinson, Tau protein, Neuroprotective, Depression.

1. INTRODUCTION

Neurology is a study of neurons. In the body of an average person, approximately 90 billion neurons always function in a synchronized manner. A small mistake in this synchronization process turns a person into a measuring unit such as DALys (disability-adjusted life years). Recent statistics of the National Institute of Mental Health (NIMH) say that near about 5.1% of total DALys in the United States are observed with neurological disorders [https://www.nimh.nih.gov/health/statistics/personality-disorders.shtml accessed on 16.05.2020]. In the United States, almost one person out of five suffers from neurological disorders that means approximately 46.6 million people suffer from the same, amongst them the maximum number of patients are females whose ages vary between ages (18-25) years [1, 2]. According to NIMH, attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), bipolar disorder, eating disorders, depression, obsessive-compulsive disorder (OCD), Alzheimer, Parkinson's, depression, post-traumatic stress disorder (PTSD), schizophrenia and suicidal tendencies are most prevailing disorders [3, 4]. So, for conquering these devastating life and society-threatening disorders, targeting glycogen synthase kinase-3 enzyme may be one of the key weapons in this regard. So now the question is, why glycogen synthase kinase-3? In 1980, glycogen synthase kinase-3 (GSK-3) first came in the limelight. The principal activity of the enzyme is to facilitate the formation of glycogen from glucose *via* uridine diphosphate glucose molecule [5, 6]. This kinase is a serine/threonine amino acid-based enzyme found abundantly in cells. There are two types of GSK-3 enzymes, such as GSK-3α and GSK-3β. The enzyme activates the downstream process of neurons *via* phosphorylation of certain residues such as serine21 (for alpha) and serine 9 (for beta) types [7]. This downstream business inhibits the energy-dependent catalytic activity [8, 9]. GSK-3α enzyme regulates the production of beta-amyloid plaques

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1873-5592/21 $65.00+.00

Environmental Science and Pollution Research
https://doi.org/10.1007/s11356-020-11713-z

RESEARCH ARTICLE

Predictive classification-based QSTR models for toxicity study of diverse pesticides on multiple avian species

Purusottam Banjare[1] · Jagadish Singh[1] · Partha Pratim Roy[1]

Received: 30 July 2020 / Accepted: 16 November 2020

Abstract
Protection and restoration of different endangered bird species from pesticide exposure is crucial from the point of safety assessment of ecosystem. Toxicity predictions or risk assessment of pesticides by chemometric tools is one of the challenging fields in recent era. In the present study, classification-based quantitative structure toxicity relationship (QSTR) models were developed for a large dataset (516) of diverse pesticides on multiple avian species mallard duck, bobwhite quail, and zebra finch according to the Organization for Economic Co-operation and Development guidelines. The QSTR models were developed by linear discriminant analysis method with genetic algorithm for feature selection from 2D descriptors using QSAR-Co software. Different statistical metrics assured the reliability and robustness of the developed models. External compound prediction highlighted predictive nature of the models. The mechanistic interpretation suggested that presence of phosphate, halogens (Cl, Br), ether linkage, and NCOO influence the avian toxicity. Furthermore, model reliability was checked by the application of the standardization approach of the applicability domain (AD). Finally, the developed models provided a priori toxic and non-toxic classification for unknown pesticides (inside AD), with particular emphasis on organophosphate pesticides. The interspecies toxicity correlation and predictions encouraged for their further applicability for the fulfilment of data gaps in vital missing species.

Keywords Pesticides · Risk assessment · QSTR · AD · OECD · Interspecies

Introduction

Can we imagine a world without birds? Of course, the answer will be no. Birds play an important role in maintaining the ecosystem by controlling the pests, pollinating plants, cleaning up crew, spreading seeds, transforming entire landscapes, keeping coral reefs alive, and inspiring science as reported by Birdlife International (an NGO) (https://www.birdlife.org/worldwide/news/why-we-need-birds-far-more-they-need-us). About 150 avian species have been defunct from the earth since the 1500s (Saxena et al. 2015). With increasing populations, human beings continuously manipulate nature to meet their needs which may include deforestation, use of pesticides, and urbanization. The modernization of agriculture involves the extensive application of pesticides which become one of the major reasons for the destruction of different animal species including avian species (Engelman et al. 2012; https://www.paneurope.info/old/Resources/Briefings/Pesticides_and_the_loss_of_biodiversity.pdf). *The Times of India* also published 14 bird species that are under the verge of extinction due to the overuse of pesticides (https://timesofindia.indiatimes.com/home/environment/flora-fauna/14-bird-species-on-verge-of-extinction-in-India/articleshow/12416350.cms). The pesticides are designed to harm or to destroy a particular life, but the exposure of pesticides is not limited to targets but also affects non-target lives. The exposure of avian species to pesticides is very easy as the birds can freely enter everywhere in earth especially in agricultural land in search of food and habitat. Pesticides exert their toxic effects on birds by alteration in behaviour and physiological function like alteration in thermal regulation, reproductive behaviour, and food consumption as reported by different researchers (Engelman et al. 2012; Humann-Guilleminot et al. 2019; Ratcliffe 1970).

Responsible Editor: Ludek Blaha

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Published online: 06 January 2021

In Silico Pharmacology (2021) 9:28
https://doi.org/10.1007/s40203-021-00087-w

ORIGINAL RESEARCH

In silico local QSAR modeling of bioconcentration factor of organophosphate pesticides

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Received: 18 January 2021 / Accepted: 15 March 2021

Abstract
The persistent and accumulative nature of the pesticide of indiscriminate use emerged as ecotoxicological hazards. The bioconcentration factor (BCF) is one of the key elements for environmental assessments of the aquatic compartment. Limitations of prediction accuracy of global model facilitate the use of local predictive models in toxicity modeling of emerging compounds. The BCF data of diverse organophosphate (n = 55) was collected from the Pesticide Properties Database and used as a model data set in the present study to explore physicochemical properties and structural alert concerning BCF. The structures were downloaded from Pubchem, ChemSpider database. Two splitting techniques (biological sorting and structure-based) were used to divide the whole dataset into training and test set compounds. The QSAR study was carried out with two-dimensional descriptors (2D) calculated from PaDEL by applying genetic algorithm (GA) as chemometric tools using QSARINS software. The models were statistically robust enough both internally as well as externally (Q^2: 0.709–0.722, Q^2_{Ext}: 0.717–0.903, CCC: 0.857–0.880). Overall molecular mass, presence of fused, and heterocyclic ring with electron-withdrawing groups affect the BCF value. The developed models reflected extended applicability domain (AD) and reliable predictions than the reported models for the studied chemical class. Finally, predictions of unknown organophosphate pesticides and the toxic nature of unknown organophosphate pesticides were commented on. These findings may be useful for the scientific community in prioritizing high potential pesticides of organophosphate class.

Keywords BCF · QSAR · GA · Database · Aquatic · AD

Introduction

Since 1950 exponential rise in the population around the world increased the demand for food grains/crops with limited expansion of the agricultural land. Pesticides are widely used in agriculture without paying much heed to the consequences of its unregulated and indiscriminate use (Gerwick et al. 2014; Lema et al. 2014; Neve et al. 2009; Oerke 2006). Detection of pesticides and their degradations in soil, water and air at relevant levels have invoked public concern and are responsible for the adverse effects of pesticides to target and non-target organisms. The persistence, bioaccumulative, and toxic nature of agrochemical is responsible for different ecotoxicity. Some pesticides last as long as the environment (like DDT, chlordane). More specifically, the developing and agriculture-based countries like India consume much higher quantities of these chemicals (Köhler et al. 2013). Organophosphate pesticides are the most widely used as one of the cheapest pesticides. Many active ingredients (chlorpyrifos and Malathion) that are potentially dangerous to health are routinely found in food, breast milk (Gavrilescu 2005). An aquatic environment is often the final destination of many contaminants. European regulations also require the bioconcentration factor (BCF) values for registration of compounds for their safety management of concentration in water and the intern facilitates the daily intake of fish (Reach in Brief. European Commission, Environment Directorate General, 2007).

Bioconcentration is a hazard itself without acute or chronic toxicity (Grisoni et al. 2016). In environmental assessments of the aquatic compartment, the chemical property of interest in modeling fate and persistence of chemicals in the environment is bioconcentration factor (BCF) (Arnot and Gobas 2006; Wang et al. 2014). This indicates partitioning of compounds between organisms and the surrounding

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Published online: 04 April 2021

International Journal of Quantitative Structure-Property Relationships
Volume 6 • Issue 1 • January-March 2021

In silico Predictive Phytotoxicity Modeling of lactuca sativa of Personal Care Product Ingredients

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ABSTRACT

Detection and evaluation of environmental toxicity of emerging contaminants like personal care product (PCP) additives are the thrust area in the recent day risk assessment of chemical hazards. The phytotoxicity assay is usually performed to identify and quantify the environmental impact of pollutants. In this background, the authors have developed in silico predictive phytotoxicity models for 36 PCP ingredients using 2D molecular descriptors using multiple linear regression as a chemometric tool. The statistical validation parameters assured the robustness of the developed models according to OECD guidelines. The mechanistic output of the models indicated the importance of the partition coefficient (CrippenLogP) and molecular hydrophilicity. The applicability domain explicitly defines the reliability of the application of the developed models for the unknown PCP ingredients in a consensus manner. The first reported predictive phytotoxicity models for PCP ingredients can help depict the environmental impacts of these classes of emerging pollutants.

KEYWORDS

Contaminants, Partition Coefficient, PCP, Phytotoxicity, Reliability

INTRODUCTION

Detection of environmental contaminants or pollutants is one the priorities of recent days. The term "emerging contaminants" is widespread in the contemporary literature. They are the synthetic or naturally occurring substances which are not monitored in the environment but have potential to trigger adverse ecological and human health effects. They include pharmaceuticals and personal care products (PCPs), agrochemicals, endocrine disrupters, UV filters, etc. (Barel et al. 2001; Kar et al. 2020; Petrovic et al. 2013). PCPs, for their pseudo-persistence in the aquatic system and further accumulation in plants, vegetables, food chains, and finally to human populations, have got unprecedented attention from regulatory agencies and scientific communities at the global level (Houtman et al. 2004; Hyland et al. 2015).

DOI: 10.4018/IJQSPR.2021010103

(36)

Aromatase Inhibitors for the Treatment of Breast Cancer: A Journey from the Scratch

Authors: Ratre, Pooja; Mishra, Keerti; Dubey, Amit; Vyas, Amber; Jain, Akhlesh; Thareja, Suresh
Source: Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry - Anti-Cancer Agents), Volume 20, Number 17, 2020, pp. 1994-2004(11)
Publisher: Bentham Science Publishers
DOI: https://doi.org/10.2174/1871520620666200627204105

Background: Estrogens are essential for the growth of breast cancer in the case of premenopausal as well as in postmenopausal women. However, most of the breast cancer incidences are reported in postmenopausal women and the concurrent risk surges with an increase in age. Since the enzyme aromatase catalyses essential steps in estrogen biosynthesis, Aromatase Inhibitors (AIs) are effective targeted therapy in patients with Estrogen Receptor positive (ER+) breast cancer. AIs are more effective than Selective Estrogen Receptor Modulators (SERMs) because they block both the genomic and nongenomic activities of ER. Till date, first, second and third-generation AIs have been approved by the FDA. The third-generation AIs, viz. Letrozole, Anastrozole, Exemestane, are currently used in the standard treatment for postmenopausal breast cancer.

Methods: Data were collected from Medline, PubMed, Google Scholar, Science Direct through searching of keywords: 'aromatase', 'aromatase inhibitors', 'breast cancer', 'steroidal aromatase inhibitors', 'non-steroidal inhibitors' and 'generations of aromatase inhibitors'.

Results: In the current scenario of breast cancer chemotherapy, AIs are the most widely used agents which reveal optimum efficacy along with the least side effects. Keeping in view the prominence of AIs in breast cancer therapy, this review covered the detailed description of aromatase including its role in the biosynthesis of estrogen, biochemistry, gene expression, 3D-structure, and information of reported AIs along with their role in breast cancer treatment.

Conclusion: AIs are the mainstream solution of the ER+ breast cancer treatment regimen with the continuous

Mini Rev Med Chem. 2021 Jan 19. doi: 10.2174/1389557521666210119123840.
Online ahead of print.

Dual Aromatase-Sulphatase Inhibitors (DASIs) for the Treatment of Hormone Dependent Breast Cancer

Laxmi Banjare [1], Akhlesh Kumar Jain [1], Suresh Thareja [2]

Affiliations
PMID: 33463462 DOI: 10.2174/1389557521666210119123840

Abstract

Breast cancer is the most frequent diagnosed cancer in women and the second most common form of cancer, causing death after lung cancer, all across the globe at an alarming rate. The level of estrogens, in breast cancer tissues of postmenopausal women is 10-40 folds higher than the non-carcinogenic breast tissues. As a result of this greater level of estrogen, breast tissue becomes more prone to develop breast cancer; mainly estradiol plays a significant role in the initiation and development of hormone dependent breast cancer. Androstenedione, Adrenal dehydroepiandrosterone sulfate and estrone-sulfate also plays an important role of precursor for estrogen biosynthesis. Estrogens deprivation exhibits an attractive phenomena in the advancement of most ideal therapeutics for the treatment of breast cancer. Inhibition of aromatase and sulphatase emerged as attractive therapy for the treatment of hormone dependent breast cancer via deprivation of estrogen by different pathways. The cocktail of aromatase and sulphatase inhibitors known as dual aromatase-sulphatase inhibitors (DASIs) emerged as an attractive approach for the effective estrogen deprivation. The present review article focused on the journey of dual aromatase-sulphatase inhibitors from the beginning to till date (2020). Keeping in view the key observations, this review may be helpful for medicinal chemists to design and develop new and efficient dual aromatase-sulphatase inhibitors for the possible treatment of hormone-related breast cancer.

Keywords: Anticancer agents; Aromatase inhibitors; Dual inhibitors.; Estrogen; Hormone dependent breast cancer; Sulphatase inhibitors.

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