

eISBN: 978-1-68108-558-6

ISBN: 978-1-68108-559-3

eISSN: 2210-2698

ISSN: 2467-9615

Anti-Obesity Drug Discovery and Development **Volume 4**



Editors:

Atta-ur-Rahman, *FRS*

M. Iqbal Choudhary

Bentham  Books

Anti-Obesity Drug Discovery and Development

(Volume 4)

Edited by

Atta-ur-Rahman, FRS

Honorary Life Fellow, Kings College, University of Cambridge, Cambridge, UK

&

M. Iqbal Choudhary

*H.E.J. Research Institute of Chemistry, International Center for Chemical
and Biological Sciences, University of Karachi, Karachi, Pakistan*

Anti-Obesity Drug Discovery and Development

Volume # 4

Editors: Atta-ur-Rahman and M. Iqbal Choudhary

ISSN (Online): 2210-2698

ISSN (Print): 2467-9615

ISBN (Online): 978-1-68108-558-6

ISBN (Print): 978-1-68108-559-3

©2018, Bentham eBooks imprint.

Published by Bentham Science Publishers – Sharjah, UAE. All Rights Reserved.

Author's Copy
Not for Sale or Distribution

CONTENTS

PREFACE	i
LIST OF CONTRIBUTORS	iii
CHAPTER 1 DIETARY MODULATION, OBESITY AND CANCER PREVENTION	1
<i>Jennifer Man Fan Wan and Hiu Yee Kwan</i>	
INTRODUCTION	2
HOW DIET RELATES TO CANCERS?	3
Dietary Factors that Promote the Cancer Initiation	3
Ingestion of Powerful, Direct-Acting Carcinogens or their Precursors	4
Ingestion of Carcinogens that are Produced <i>via</i> Food Processing	4
Ingestion of Carcinogens Produced in Stored Food	5
Formation of Carcinogens in the Body	5
DIETARY FACTORS THAT PROMOTE THE CANCER DEVELOPMENT	5
GENERAL MECHANISM OF HOW OBESITY CAN CAUSE AND PROMOTE CANCER	6
DIETARY COMPONENTS WITH CANCER PREVENTION POTENTIAL	9
DIETARY COMPONENTS THAT AFFECT BODY WEIGHT	12
PROSPECTIVE FOR THE ANTI-CANCER STUDY	14
SUMMARY	15
ABBREVIATIONS	16
CONSENT FOR PUBLICATION	18
CONFLICT OF INTEREST	18
ACKNOWLEDGEMENTS	18
REFERENCES	18
CHAPTER 2 THE ROLE OF ANTI-OBESITY MEDICATIONS IN POLYCYSTIC OVARY SYNDROME	25
<i>Ilgın Turkuoğlu and Rauf Melekoglu</i>	
INTRODUCTION	26
Orlistat, Sibutramine, and Rimonabant	31
Insulin-sensitizing Drugs (Metformin, Rosiglitazone, Pioglitazone, and D-chiro-inositol) ...	34
<i>GLP-1 Agonists (Exenatide, Liraglutide), Phentermine and Topiramate</i>	38
<i>Other drugs</i>	45
CONSENT FOR PUBLICATION	45
CONFLICT OF INTEREST	45
ACKNOWLEDGEMENTS	46
REFERENCES	46
CHAPTER 3 SIRTUINS AND BILE ACIDS: POTENTIAL ANTI-OBESITY STRATEGIES TARGETING MITOCHONDRIA	57
<i>João Alves Amorim, João Soeiro Teodoro, Carlos Marques Palmeira and Anabela Pinto Rolo</i>	
INTRODUCTION	57
SIRTUIN ACTIVATORS AS A NOVEL ANTI-OBESITY STRATEGY	59
Sirtuins	59
Physiological Role of Sirtuins in Metabolism	61
Physiological Role of Sirtuins and Obesity and Metabolic Syndrome	62
Sirtuins Activators For Therapy	67
Sirtuin Activators For Therapy in Obesity	68
NAD ⁺ -boosting Compounds	72
BILE ACIDS, OBESITY AND MITOCHONDRIA	74

Bile Acid Receptors Discovery and Properties	74
BA Effects and Mitochondria	76
CONCLUDING REMARKS	78
CONSENT FOR PUBLICATION	78
CONFLICT OF INTEREST	79
ACKNOWLEDGEMENTS	79
REFERENCES	79
CHAPTER 4 DEVELOPMENT AND CHARACTERIZATION OF CALCIUM SILICATE BASED FORMULATIONS FOR ANTI-OBESITY THERAPY: ORLISTAT	98
<i>Sunil K. Jain</i>	
INTRODUCTION	98
FLOATING MICROSPHERES	103
Preparation of OT Absorbed CS	103
Preparation of Floating Microspheres	103
Characterization of Floating Microspheres	104
<i>Micromeritic Properties and Morphology</i>	<i>104</i>
<i>Percentage Buoyancy and Drug Entrapment</i>	<i>105</i>
<i>In vivo Drug Release of Floating Microspheres</i>	<i>106</i>
<i>Gamma Scintigraphy</i>	<i>108</i>
<i>Pharmacokinetic Studies</i>	<i>110</i>
FLOATING GRANULES	112
Preparation of Floating Granules	112
Characterization of Floating Granules	112
<i>Drug Content and Floating Ability</i>	<i>112</i>
<i>In vitro Drug Release of Floating Granules</i>	<i>114</i>
CONCLUSION	117
CONSENT FOR PUBLICATION	117
CONFLICT OF INTEREST	117
ACKNOWLEDGEMENTS	117
REFERENCES	117
CHAPTER 5 MULTI TARGETED STRATEGIES TOWARDS IDENTIFICATION OF POTENTIAL DRUG CANDIDATES FROM NATURAL PRODUCTS IN THE MANAGEMENT OF OBESITY	121
<i>Baddireddi Subhadra Lakshmi and Gopal Thiyagarajan</i>	
INTRODUCTION	122
CURRENT TREATMENT STRATEGIES FOR OBESITY	123
MEDICINAL PLANTS AS A SOURCE FOR NOVEL DRUGS	123
MECHANISM AND MOLECULAR TARGETS OF OBESITY	125
INHIBITION OF LIPID ABSORPTION	125
Pancreatic Lipase Inhibitors	125
SUPPRESSION OF APPETITE	128
Glucagon Like Peptide 1 Analogues and Dipeptidyl Peptidase 4 Inhibitors	129
Cholecystokinin Agonists	131
Neuropeptide Y Antagonist	132
Leptin	133
Protein Tyrosine Phosphatase 1B Inhibitors	135
INHIBITION OF ADIPOGENESIS	139
Peroxisome Proliferator Activated Receptor γ (PPAR γ)	140
Adiponectin	142
Partial PPAR γ Agonists	149

ENERGY EXPENDITURE	153
Thermogenesis	153
MODULATION OF LIPID METABOLISM	155
Lipolysis	155
β -Oxidation	157
Adenosine Monophosphate (AMP) Kinase Activators	158
Sirtuin 1 as a Novel Target of Obesity	161
MULTIFUNCTIONAL ROLE OF NATURAL ANTI-OBESITY COMPOUNDS	162
CLINICAL TRIALS STUDY	169
CONCLUSION	172
CONSENT FOR PUBLICATION	173
CONFLICT OF INTEREST	173
ACKNOWLEDGEMENTS	173
REFERENCES	173

CHAPTER 6 ANTI-OBESITY MOLECULES FROM PLANTS AND THEIR MODE OF

ACTION	197
<i>Megha Valsaraj, Navaneetha Saseendran, Arun Subash Koorapally and Anu Augustine</i>	
GENERAL INTRODUCTION	197
Obesity	198
<i>Definition and Assessment of Obesity</i>	198
<i>Genetic and Environmental Factors Causing Obesity</i>	200
<i>Endocrine and Metabolic Factors</i>	200
<i>Psychological Factors</i>	200
<i>Control of Appetite and Energy Expenditure</i>	201
Obesity Management	201
Role of Medicinal Plants in Obesity Treatment	201
Mechanism of Action of Anti obesity Agents from Plants	202
<i>Modifying Serum Lipoprotein</i>	202
<i>Modifying Serum Apolipoproteins</i>	203
<i>Enzyme Inhibition</i>	203
<i>Inhibitors of Adipogenesis and Adipogenic Factors</i>	204
<i>Blocking Intestinal Absorption</i>	205
<i>Appetite Suppressants</i>	205
Details of Plants Selected for Study	205
<i>Holoptelea Integrifolia</i>	205
<i>Averrhoa bilimbi Linn.</i>	205
<i>Terminalia chebula Retz.</i>	206
<i>Acorus calamus Linn.</i>	206
<i>Picrorhiza kurroa Royle ex Benth</i>	207
Experimental Model and Findings	207
<i>Methodology</i>	207
<i>Animals</i>	207
<i>Acute Oral Toxicity</i>	208
<i>Establishment of Experimental Model</i>	208
<i>Drug Treatment</i>	209
<i>Effect of Plant Extracts on Serum Lipids</i>	209
<i>Effect of Plant Extracts on HDL Cholesterol Levels</i>	209
<i>Effect of Plant Extracts on LDL Cholesterol Levels</i>	211
<i>Effect of Plant Extracts on Apolipoproteins</i>	211
Effect of Different Plant Extracts on Enzymes Involved in Cholesterol Pathway	213

<i>HMG-CoA Reductase</i>	213
<i>Lecithin-Cholesterol Acyltransferase</i>	214
<i>Lipoprotein Lipase</i>	215
<i>Effect of Different Plant Extracts on Intestinal Fat Absorption</i>	216
<i>Effect of Different Plant Extracts on Inhibition of Adipogenesis and Adipogenic Factors</i>	216
CONCLUDING REMARKS	219
CONSENT FOR PUBLICATION	220
CONFLICT OF INTEREST	220
ACKNOWLEDGEMENTS	220
REFERENCES	220
SUBJECT INDEX	225

Author's Copy
Not for Sale or Distribution

Development and Characterization of Calcium Silicate Based Formulations for Anti-Obesity Therapy: Orlistat

Sunil K. Jain*

Institute of Pharmaceutical Sciences, Guru Ghasidas Vishwavidyalaya, Bilaspur, Chhattisgarh, India

Abstract: On health front, today's generation is struggling with increasing rate of obesity which is undisputedly reckoned as a leading cause for a number of pathological conditions *e.g.* coronary heart disease (CHD), high blood pressure, stroke, abnormal blood fats, metabolic syndrome, cancer, osteoarthritis, sleep apnea, obesity hypoventilation syndrome, reproductive problems, gallstones, and type 2 diabetes *etc.* In recent research, calcium silicate based two formulations *i.e.*, floating microspheres and floating granules have been developed for anti-obesity drug *i.e.*, orlistat, to deliver the incorporated therapeutic agent in effective concentrations and extended therapeutic course of time. Floating characteristic over the gastric content of such formulations is capable to provide prolonged retention in gastric region. Formulation of microspheres with incorporation of calcium silicate increases the effectiveness of this granular formulation to matchup the desired release pattern with buoyancy. The developed formulations of orlistat are found to be safer and more effective which is the need of day in pharmaceutical industry as an alternative drug delivery system for a highly prevalent and chronic disease like obesity.

Keywords: BMI, Buoyancy, Calcium silicate, Floating granules, Floating microspheres, Gamma scintigraphy, Gastro-retention, *In vitro* drug release, Obesity, Orlistat, Pharmacokinetics.

INTRODUCTION

Obesity is a disorder related to the accumulation of extra body fat to an extent which triggers health risks in terms of different diseases. It also leads to the reduction in life expectancy with or without stimulating any health complications [1]. Body mass index (BMI) is generally used for the assessment of obesity. BMI is first introduced by Belgian statistician and anthropometrist, Adolphe Quetelet

* **Corresponding author Sunil K. Jain:** Institute of Pharmaceutical Sciences, Guru Ghasidas Vishwavidyalaya, Bilaspur, Chhattisgarh, India; Tel: +91 9425452174; E-mail: suniljain25in@yahoo.com