SUBJECT CODE: AS-2534
SUBJECT: PHARMACOLOGY-IV
SECTION: A
All questions are compulsory. Each question carries 2 marks

1. i. **Duration, no of animals used and parameters observed in acute toxicity study?**

Ans. Duration: For at least 14 days after dosing or longer if positive sign are produce. Several species of animals, one of which must be either sex rodent classes of animals (such as mice/ rat). No. of animals: 05(Minimum), Parameters: changes in skin and fur, eyes and mucous membranes, respiratory, circulatory,autonomic and central nervous systems, and somatomotor activity and behavior pattern. Attention should be given to tremors, convulsions, salivation, diarrhoea, lethargy, sleep and coma.

ii. **Explain the term mutagenicity?**

Ans. Mutagenicity is capability to induce mutation. Mutagenicity refers to the induction of permanent transmissible changes in the structure of the genetic material of cells or organisms.

iii. **What is poison management center?**

Ans. Provide information about drug/ chemical poisoning nature, collect information from various sources, diagnosis and management.

iv. **Specific locus test is used for which activity?**

Ans. Measures the frequency of transmitted gene mutation in mouse/ mice spermatogonia. i.e. Mutagenicity study. Or Screens for newly occurring mutants allels in offsprings form the parentral cross.

v. **Mention antidotes used for barbiturate poisoning?**

Ans. No specific antidote is available but, but aid can be provided by:

a. Gastric lavage: by activated charcoal.
b. Alkaline dieresis: by sodium bicarbonate
c. Haemodialusis and Haemoperfusion
d. Supportive measures for respiration

However antidotes such as Methyl gluterimide, Ethyl Gluterimide, Mikedimide.

vi. **Antidotes used for cadmium poisoning?**

Ans. No specific chelating agent/ antidotes for cadmium toxicity so

i. DMSA (Di merkepto succinic acid)
ii. EDTA (Ethylene diamine tetra acetic acid)
iii. BAL (2,3- dimerkepto propanol)

However antidote such as Calcium disodium edetate ($CaNa_2EDTA$) can be use.

vii. **Function of Glutathione peroxidase.**

Ans. Glutathione peroxidase is an erythrocyte enzyme which protects the haemoglobin from oxidative breakdown.

1. Free radicals scavengers.
2. Prevention from various diseases like cancer, cardiovascular diseases.
3. Neurological disorder like e.g. Alzheimer's disease and Parkinson's disease.

viii. **Define the term "Circaseptan".**

Ans.-Circaseptan – It is a type of biological rhythm, which changed in 7 days. A cycle of 7 days in which many biological processes of life resolves.

ix**. Why HMG-CoA-reducutase inhibitor antagonists are given in the evening?**

Ans. HMG-CoA reductase inhibitors are given at evening because they show maximum effect at mid night. The evening timing of HMG-CoA reductase antagonists, taking intoaccount the evening increase of cholesterol synthesis in the liver, and increases cholestyrogenesis in the liver and muscles, so HMG-CoA-reductase given at evening time by chronopharmatherapeutis treatment.

x. **What is satellite group used in toxicity study?**

Ans. Satellite groups- groups of animals included in the design and conduct of a toxicity study, treated and housed under conditions identical to those of the main study animals, but used primarily for toxicokinetics.

x. What is Infradian rhythm?

Ans. Infradian rhythms cycles with period longer than 1day and shorter than 6 days.

xi. **Name two in-vitro genotoxicity assays.**

Ans. In-vitro test-

i. Micronucleus chromosomal test.
ii. Common bacterial test (*Salmonella typhimurium*- reverse mutation assay).
iii. *E. coli* test.
iv. Other *S. typhimurium.* mutants.
v. HGPRT gene mutation.
vi. Metaphase analysis.

Section B
(Descriptive type questions)
4x14= 56

2. Discuss three main stages of reproductive toxicity studies in detail.

Ans. Reproductive toxicity is a hazard associated with some chemical substances, that they will interfere in some way with normal reproduction. It includes adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring. It is usual to take a practical definition, including several different effects which are unrelated to each other except in their outcome of lowered effective fertility. The Globally Harmonized System of Classification and Labeling of Chemicals (GHS) separates reproductive toxicity from germ cell mutagencity and carcinogenicity, even though both these hazards may also affect fertility.

One well known group of substances which are toxic for reproduction are teratogens – substances which cause birth defects of which (*S*)-thalidomide is possibly the most notorious. Another group of substances which has received much attention (and some controversy) as possibly toxic for reproduction are the so-called endocrine disruptors. However many substances which are toxic for reproduction do not fall into either of these groups: lead compounds, for example, are considered to be toxic for reproduction given their adverse effects on the normal intellectual and psychomotor development of human babies and children.

Many drugs have effects on the human reproductive system: these may be desired (hormonal contraception), a minor unwanted side effect (many antidepressants) or a major public health problem (thalidomide). However most studies of reproductive toxicity has focused on occupational or environmental exposure to chemicals and their effects on reproduction. It may be noted that both consumption of alcohol and tobacco smoking are known to be toxic for reproduction in the sense that the term is used here.

Reproductive toxicity refers to a wide variety of toxicological effects that may occur in different phases within the reproductive cycle. This includes effects on fertility, sexual behaviour, embryo implantation, embryonic/foetal development, parturition, postnatal adaptation, and subsequent growth and development into sexual maturity.

The U.S. Environmental Protection Agency (EPA) is publishing in final form a document entitled Guidelines for Reproductive Toxicity Risk Assessment (hereafter “Guidelines”).

These Guidelines were developed as part of an interoffice guidelines development program by a Technical Panel of the Risk Assessment Forum. They were proposed initially in 1988 as separate guidelines for the female and male reproductive systems. Subsequently, based upon the public comments and Science Advisory Board (SAB) recommendations, changes made included combining those two guidelines, integrating the hazard identification and dose-response sections, assuming as a default that an agent for which sufficient data were available on only one sex may also affect reproductive function in the other sex, expansion of the section on interpretation of female endpoints, and consideration of the benchmark dose approach for quantitative risk assessment. These Guidelines were made available again for public comment and SAB review in 1994. This notice describes the scientific basis for concern about exposure to agents that cause reproductive toxicity, outlines the general process for assessing potential risk to humans from exposure to environmental agents, and addresses Science Advisory Board and public comments on the 1994 Proposed Guidelines for Reproductive Toxicity Risk Assessment. Subsequent reviews have included the Agency's Risk Assessment Forum and interagency comment by members of subcommittees of the Committee on the Environment and Natural Resources of the Office of Science and Technology Policy. The EPA appreciates the efforts of all participants in the process and has tried to address their recommendations in these Guidelines

3. Write short notes on:

(i) Iron toxicity
(ii) Mercury poisoning

Ans. Iron toxicity

ILarge amounts of ferrous salts are toxic, but fatalities are rare in adults. Most deaths occur in children, particularly between the ages of 12 and 24 months. As little as 1 to 2 g of iron may cause death, but 2 to 10 g usually is ingested in fatal cases.

Sources- Iron is rapidly absorbed from GIT and corrosive nature may increase absorption. The over doses of iron may occurs due to ingestion of FeSO4 or multivitamins preparation mistaken taken in children.

Other sources-drinking water, iron pipes and cook wares.

Symptoms- Symptoms of severe poisoning may occur within 30 minutes after ingestion or may be delayed for several hours. They include abdominal pain, diarrhea, or vomiting of brown or bloody stomach contents containing pills. Of particular concern are pallor or cyanosis, lassitude, drowsiness, hyperventilation due to acidosis, and cardiovascular collapse. And stomach pain may be due to ulceration.

Target organs- it includes Liver, Kidney and CVS.

Treatment's- chelation Therapy- Chelation with deferoxamine is usually useful but BALL or DMSO is contraindicated.

Supportive therapy- However, vomiting should be induced when there is iron in the stomach, and an x-ray should be taken to evaluate the number of pills remaining in the small bowel (iron tablets are radiopaque).

GIT contamination- Iron in the upper GI tract can be precipitated by lavage with sodium bicarbonate or phosphate solution, although the clinical benefit is questionable. When the plasma concentration of iron is greater than the total iron-binding capacity (63 milimol; 3.5 mg per liter), deferoxamine should be administered; dosage and routes of administration are detailed in Chapter 65. Shock, dehydration, and acid-base abnormalities should be treated in the conventional manner. Most important is the speed of diagnosis and therapy. With early effective treatment, the mortality from iron poisoning can be reduced from as high as 45% to about 1%.

II. Mercury Poisoning-

Absorption-(I) GI inorganic salts are variably absorbed (10%) but may be converted to organic (methyl and ethyl in gut by bacteria) , inorganic compounds are well absorbed > 90%

(ii) Inhalational- elemental Hg completely absorbed, in bones and respiratory system.

Distribution depends upon source of exposure - Elemental Hg (vapour) crocess membranes well and rapidly moves from lungs to CNS . Organic salts (lipid soluble) are evently distributed, intestinal (intracellular)-fecal elimination. Inorganic salts concentrate in blood, plasma and kidney (renal elimination). Half life is 60 to 70 days.

Source of exposure – (1) Environmental from electronics and plastics industry,

(i) Mining operation,
(ii) Color alkali paints,
(iii) Paper industries
(iv) Dental amalgam

(2) Seed fungicide treatment, dentistry/ dental alloy
(3) Rainfall, food chains and fishes.
(4) Thermometer and thermostat etc.

Three types of mercury was harmful –

(1) Alimental
(2) Inorganic
(3) Organic

Organic Hg readily absorbed as compared to inorganic. The target organs are kidney and brain

Symptoms-

Acute toxicity- cough, sour through, shortness of breath, metallic test, abdominal pain, common nausea and vomiting and sometime diarrhea, common headache, common weakness, visual disturbances, bradycardia etc .

Chronic symptoms- Permanent damage to CNS and kidney.

Symptomatically tremor, anxiety, forgetfulness, emotional instability, insomnia, fatigue, weakness, anorexia, cognitive and motor dysfunction and kidney damage.

Diagnosis-(1) Generally urine seminal fluid is observed for Hg.
(2) chest and abdominal X-ray
(3) Pulmonary embolism's.

Treatment-

Chelation Therapy - Chelation therapy with dimercaprol (for high-level exposures or symptomatic patients) or penicillamine (for low-level exposures or asymptomatic patients) is used routinely to treat poisoning with either inorganic or elemental mercury. Recommended treatment includes dimercaprol 5 mg/kg intramuscularly initially, followed by 2.5 mg/kg intramuscularly every 12 to 24 hours for 10 days. Penicillamine (250 mg orally every 6 hours) may be used alone or following treatment with dimercaprol. The duration of chelation therapy will vary, and progress can be monitored by following concentrations of mercury in urine and blood. The orally effective chelator succimer appears to be an effective chelator for mercury, although it has not been approved by the FDA for this purpose.

The dimercaprol-mercury chelate is excreted into both bile and urine, whereas the penicillamine-mercury chelate is excreted only into urine. Thus penicillamine should be used with extreme caution when renal function is impaired. In fact, hemodialysis may be necessary in the poisoned patient whose renal function declines. Chelators still may be used because the dimercaprol-mercury complex is removed by dialysis.

Pathophysiology- Hg is highly reactive with Selenium(Se) special with seleno enzyme. It prevents oxidative damage in brain and other organs.

Hg irreversibly inhibit the activity of seleno enzyme eg Thioredoxin reductase, Thioredoxin reductase restore the vitamin C and vitamin E .bake into the reduced form dose high level of Hg duplets the thioredoxin.

In particular myelin formation and other cellular developments

4. Explain pharmacokinetic and pharmacodynamics drug intractions with suitable examples.

Ans. Pharmacokinetic interactions- Those interaction in which the ADME of the object drug is altered by the precipitant also called ADME INTERACTION.The resultant effect is altered plasma concentration of the object drug. Pharmkokinetic interaction can be classified as Faster or slower absorption or More or less complete absorption.

Absorption-

These interactions alter the concentration of the object drug at its site of action (and consequently the intensity of response) by affecting its absorption, distribution, metabolism or excretion Absorption of an orally administered drug can be affected by other concurrently ingested drugs. This is mostly due to formation of insoluble and poorly absorbed complexes in the gut lumen, as occurs between tetracyclines and calcium/iron salts, antacids or sucralfate. Phenytoin absorption is decreased by sucralfatedue to binding in the g.i.lumen. Such interactionscan be minimized by adminstering the two drugs with a gap of 2-3 hours so that they do not come in contact witheach other in the g.i.t. Ketoconazole absorption is reduced by H2 blockers and proton pump inhibitors because they reduce gastric acidity which promotes dissolution and absorption of ketoconazole. Antibiotics like ampicillin, tetracyclines, cotrimoxazole markedly reduce gut flora that normally deconjugates oral contraceptive steroids secreted in the bile as glucuronidesand permits their enterohepatic circulation.

Interactions Based on Distribution and Binding- Distribution of a drug can be altered by other drugs that compete for binding sites on plasma proteins. For example, antibacterial sulfonamides can displace methotrexate, phenytoin, sulfonylureas, and warfarin from binding sites on albumin. However, it is difficult to document many clinically significant interactions of this type, and they seem to be the exception rather than the rule. Changes in drug distribution can occur if one agent alters the size of the physical compartment in which another drug distributes. For example, diuretics, by reducing total body water, can increase plasma levels of aminoglycosides and lithium, possibly enhancing drug toxicities.

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Interactions Based on Excretion- Excretion Interaction involving excretion are important mostly in case of drugs actively secreted by tubular transport mechanisms, e.g. probenecidinhibits tubular secretion of penicillins and cephalosporins and prolongs their plasma t7z. This is particularly utilized in the single dose treatment ofgonorrhoea. Aspirin blocks the uricosuric action of probenecid and decreases tubular secretion of methotrexate. Change in the pH of urine can also affect excretion of weakly acidic or weakly basic drugs.utilized in the treatment of poisonings. Diuretics and to some extent tetracyclines, ACE inhibitors and certain NSAIDs have been found to raise steady-state blood levels of lithium by promoting its tubular reabsorption.

Pharmacodynamic interactions-

These interactions derive from modification of the action of one drug at the target site by another drug, independent of a change in its concentration. This may result in an enhanced response(synergism), an attenuated response (antagonism) or an abnormal response. The phenomena of synergism and antagonism are described in Chapter 4, and are deliberately utilized in therapeutics for various purposes. Of clinical significance are the in-advertent concurrent administration of synergistic or antagonistic pair of drugs with adverse consequences. Some examples are:

1. Excessive sedation, respiratory depression, motor incoordination due to concurrent administration of a benzodiazepine(diazepam), a sedating antihistaminic (promethazine), a neuroleptic (chlorpromazine), an opioid (morphine) or drinking alcoholic beverage while taking any of the above drugs.

2. Excessive fall in BP and fainting due to concurrent administration of a1 adrenergic blockers, vasodilators, ACE inhibitors, high ceiling diuretics and cardiac depressants.

3. Pronounced and asymptomatic hypoglycaemia can occur when propranolol is administered to diabetics receiving insulin/ sulfonylureas, due to blockade of adrenoceptors which contribute to recovery from hypoglycaemia as well as some hypoglycaemic symptoms.

4. Additive prolongation of prothrombin time and bleeding by administration of ceftriaxone or cefoperazone to a patient on oral anticoagulants.

5. Excessive platelet inhibition resulting in bleeding due to simultaneous use of aspirin I ticlopidine I clopidogrel and carbenicillin.

6. Increased risk of bleeding due to concurrent use of antiplatelet drugs (aspirin, clopidogrel) with anticoagulants (warfarin).

7. Marked bradycardia due to administration of propranolol in digitalized patients.

8. Precipitous fall in BP and myocardial ischaemia due to use of sildenafil by patients receiving organic nitrates, because nitrates increase generation of cGMP, whilesildenafil prevents its degradation by inhibiting PDE 5.

9. Severe hyperkalaemia by concurrent use of ACE inhibitors and K+ sparing diuretics.

10. Additive ototoxicity due to use of an aminoglycoside antibiotic in a patient receiving furosemide.

5. Describe carcinogenicity studies in reference to OECD guidelines.

Ans. Carcinogenicity studies in reference to OECD guidelines

1. Identification of the carcinogenic properties of a chemical, namely its potential to induce neoplastic lesions, resulting in an increased incidence of malignant neoplasms or an appropriate combination of benign and malignant neoplasms, and its chronic toxicity,

2. Identification of target organs,
3. Characterisation of the dose:response relationship,
4. Identification of a no-observed-adverse-effect level (NOAEL) or departure point for establishment of a Benchmark Dose (BMD),
5. Prediction of the health effects of a chemical at human exposure levels,
6. Provision of data to test hypotheses regarding mode of action

The three main routes of administration are oral, dermal and inhalation.

The choice of the route of administration depends on the physical and chemical characteristics of the test substance and the predominant route of exposure of humans. Additional information on choice of route of exposure is provided in guidance.

This Test Guideline focuses on exposure via the oral route, the route most commonly used in carcinogenicity studies.

While long–term carcinogenicity studies involving exposure via the dermal or inhalation routes may also be necessary for human health risk assessment and/or may be required under certain regulatory regimes, both routes of exposure involve considerable technical complexity.

The majority of chronic toxicity/carcinogenicity studies are carried out in rodent species.

In order to reduce the number of animals used, consideration should be given to carrying out this combined chronic toxicity and carcinogenicity study, rather than separate execution of a chronic toxicity study (TG 452) and carcinogenicity study (TG 451).
The study design consists of two parallel phases, a chronic phase, normally of one year duration, and a carcinogenicity phase, normally of two years duration.

DESCRIPTION OF THE METHOD

Selection of animal species

1. This Guideline primarily covers assessment and evaluation of carcinogenicity in rodents. The use of non-rodent species may be considered when available data suggest that they are more relevant for the prediction of health effects in humans

2. In this Test Guideline, the preferred rodent species is the rat, although other rodent species, e.g., the mouse, may be used.

Housing and feeding conditions

1. Animals may be housed individually, or be caged in small groups of the same sex; individual housing should be considered only if scientifically justified. Cages should be arranged in such a way that possible effects due to cage placement are minimised. The temperature in the experimental animal room should be 22°C (± 3°C). Although the relative humidity should be at least 30% and preferably not exceed 70% other than during room cleaning, the aim should be 50-60%. Lighting should be artificial, the sequence being 12 hours light, 12 hours dark

Dose groups and dosage

1. At least three dose levels and a concurrent control should be used. Preparation of doses and administration of test substance
2. The test substance is normally administered orally, by gavage or via the diet or drinking water.
3. Where necessary, the test substance is dissolved or suspended in a suitable vehicle.

Consideration should be given to the following characteristics of the vehicle and other additives, as appropriate: effects on the absorption, distribution, metabolism, or retention of the test substance; effects on the chemical properties of the test substance which may alter its toxic characteristics;

Duration of study

1. The period of dosing and duration of the chronic phase of this study is normally 12 months.

2. The duration of the carcinogenicity phase of the study will normally be 24 months for both rats and mice, representing the majority of the normal life span of the animals to be used.

3. In order for a negative carcinogenicity study to be considered acceptable, it should meet the following criteria:
   (a) No more than 10 per cent of any group should be lost due to autolysis, cannibalism, or management problems.
(b) Survival in each group in the study should be no less than 50 per cent at 24 months.

OBSERVATIONS (CARCINOGENICITY PHASE)

All animals should be checked for morbidity or mortality, usually at the beginning and the end of each day. Additionally, animals should be checked at least once each weekend day and holiday. Particular attention should be paid to tumour development; the time of onset, location,

dimensions, appearance, and progression of each grossly visible or palpable tumour should be recorded. Animals should be checked routinely for specific signs of toxicological relevance.

Test report

The test report should include the following information:

• Test substance:

a. physical nature, purity and physicochemical properties
b. identification data;
c. source of substance
d. batch number.

• Vehicle (if appropriate): Justification for choice of vehicle (if other than water).

• Test animals:

a. species/strain used and justification for choice made
b. number, age, and sex of animals at start of test
c. source, housing conditions, diet etc.
d. individual weights of animals at the start of the test.

• Test conditions:

rationale for route of administration and dose selection;

when applicable, the statistical methods used to analyse the data; details of test substance formulation/diet preparation, achieved concentration, stability and homogeneity of the preparation, route of administration and details of the administration of the test substance;

for inhalation studies, whether nose only or whole body, actual doses (mg/kg body weight/day), and conversion factor from diet/drinking water test substance concentration (mg/kg or ppm) to the actual dose, if applicable, details of food and water quality.

Results: General

survival data;

a. body weight/body weight changes;
b. food consumption, and water consumption if applicable;
c. toxicokinetic data if available;

Clinical findings

a. Include signs of toxicity;
b. Incidence and severity of any abnormality;
c. Nature, severity, and duration of clinical observations (whether reversible or not);

Necropsy data

a. Terminal body weight;
b. Organ weights and their ratios, if applicable;
c. Necropsy findings; Incidence and severity of abnormalities.

Histopathology

a. Non neoplastic histopathological findings,

b. Neoplastic histopathological findings,
c. Correlation between gross and microscopic findings
d. Detailed description of all treatment-related histopathological findings

including severity gradings;
Statistical treatment of results, where appropriate.
Tumour incidences

Discussion of results including:
a. Discussion of any modelling approaches
b. Dose:response relationships
c. Consideration of any mode of action information
d. Relevance for humans

Conclusions

6. Give applications of isolated hearts, lung and liver techniques in toxicology.

Ans. a) heart

(i) Study of effect of toxic substances on metabolism of muscle.

(ii) Anoxia, lack of substrates uptake in muscle.

(iii) Linearity of oxygen and substrate uptake in an additional means of assessing function in this along with assay of observed abnormalities of cardiac rhythm.

(iv) Drugs effects on myocardial contractile function

(iv) Interference in liberation of energy of the metabolic fuels utilized by the myocardial tissue.

(v) Study of drug induced heart diseases

(vii) Appearance and disappearance kinetic of the possible metabolites of the test toxin

(b) Liver

(i) Study and evaluation of toxic substances

(ii) Evaluation of effect of CCl4 as fatal to haepatic cells along with increase in vascular resistance and enhanced response to noradrenaline.

(iii)study of ungal toxin like sporidesmin and icterogenin on the mechanism of bile secretion

(iv) effect of hyperoxia on lysomal enzyme

(v) uptake and metabolism of hepatocorcinogen, vinyl chloride

(vi) examine the effect of hypoxia on metabolism of halothane

(vii) mainly evaluating the haepatobiliary action due various possible toxins

(viii) study of cholrocarbon pesticides, imipramine, p-nitronisole

(ix) effect on NADPH concentration by various chemicals.

(c) Lungs

(i) uptake, metabolism, disposition of various pharmacological and toxicological agents.

(ii) study of toxic gases

(iii) study on pulmonary uptake and disposition of aldrine and dieldrin uptake of the herbicides

(iv) paraquat uptake and metabolism of trichloroethylene and benzo(a)-pyrene

study of effect of carcinogenic agents

7. Explain the role of endogenous and exogenous antioxidants with suitable examples.

Ans.-**Role of endogenous and exogenous antioxidants** –

Damage to cells caused by free radicals is believed to play a central role in the aging process and in disease progression. Antioxidants are our first line of defense against free radical damage, and are critical for maintaining optimum health and wellbeing. Antioxidants are capable of stabilizing, or deactivating, free radicals before they attack cells. Antioxidants are absolutely critical for maintaining optimal cellular and systemic health and well-being.

Mechanism: An antioxidant is a molecule that inhibits the oxidation of other molecules. Oxidation is a chemical reaction that transfers electrons or hydrogen from a substance to an oxidizing agent. Oxidation reactions can produce free radicals. In turn, these radicals can start chain reactions. When the chain reaction occurs in a cell, it can cause damage or death to the cell. Antioxidants terminate these chain reactions by removing free radical intermediates, and inhibit other oxidation reactions. They do this by being oxidized themselves, so antioxidants are often reducing agents such asthiols, ascorbic acid, or polyphenols.

ENDOGENOUS ANTIOXIDANTS:

In addition to dietary antioxidants, the body relies on several endogenous defense mechanisms to help protect against free radical-induced cell damage. The antioxidant enzymes – glutathione peroxidase, catalase, and superoxide dismutase (SOD) – metabolize oxidative toxic intermediates

and require micronutrient cofactors such as selenium, iron, copper, zinc, and manganese for optimum catalytic activity. Glutathione, an important water-soluble antioxidant, is synthesized from the amino acids glycine, glutamate, and cysteine. Glutathione directly quenches ROS such as lipid peroxides, and also plays a major role in xenobiotic metabolism. Lipoic acid and its reduced form, dihydrolipoic acid (DHLA), are capable of quenching free radicals in both lipid and aqueous domains and as such has been called a "universal antioxidant."12 Lipoic acid may also exert its antioxidant effect by chelating with pro-oxidant metals. Eg.

• Bilirubin
• Thiols, e.g., glutathione, lipoic acid, N-acetyl cysteine
• NADPH and NADH
• Ubiquinone (coenzyme Q10)
• Uric acid
• Enzymes:
– copper/zinc and manganese-dependent superoxide
dismutase (SOD)
– iron-dependent catalase
– selenium-dependent glutathione peroxidase

EXOGENOUS ANTIOXIDANTS:

Vitamin C, vitamin E, and beta carotene are among the most widely studied dietary antioxidants. Vitamin C is considered the most important water-soluble antioxidant in extracellular fluids. It is capable of neutralizing ROS in the aqueous phase before lipid peroxidation is initiated. Vitamin E, a major lipid-soluble antioxidant, is the most effective chain-breaking antioxidant within the cell membrane where it protects membrane fatty acids from lipid peroxidation. Vitamin C has been cited as being capable of regenerating vitamin E.1 Beta carotene and other carotenoids are also believed to provide antioxidant protection to lipid-rich tissues.

Eg.

• Vitamin C
• Vitamin E
• Beta carotene and other carotenoids and oxycarotenoids,e.g., lycopene and lutein
• Polyphenols, e.g., flavonoids, flavones, flavonols, and proanthocyanidins