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Role of Enzymes and Enzyme Modulators in the Treatment of Diseases

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Abstract: The enzymes are mostly proteins and are natural biocatalysts; they catalyze many anabolic and catabolic specific chemical reactions without itself undergoing any change in overall reaction. The temperature, pH, concentration of substrates and enzymes can affect their actions. The enzymes are useful in digestion, coagulation, tissue repair and numerous other life essential processes. The enzyme modulators are groups in two i.e. enzyme inhibitors and enzyme activators, bounds to enzymes either reversibly or irreversibly. The enzyme inhibitors are the molecules that correct a metabolic imbalance by reducing enzymatic activity, like selegiline inhibit MAO_B enzyme, decreases the metabolism of dopamine in brain and useful in the treatment of depression and other panic disorders. However, the enzyme activators enhance enzymatic activity, such as tissue plasminogens activators activate the conversion of plasminogen to plasmin that digests fibrin, fibrinogen and other proteins and equally important to treat complicated diseases of heart.

Key words: Biocatalysts · Biological Polymers · Enzyme Inhibitors · Enzyme Enhancers.

INTRODUCTION

Enzymes are the vital body substances they catalyze the specific chemical reactions that make life [1]. More than 3000 enzymes catalyzing a wide array of reactions are known to exist. They are colloidal-proteins and can be extracted from living tissues, purified and even crystallized. The enzymes are also known as biological polymers or biocatalysts. They are the catalysts for many anabolic and catabolic reactions. A catalyst means a substance that enhances the velocity or rate of a chemical reaction without itself undergoing any change in overall process [2]. Human intracellular enzymes work best at 37°C and pH 7. They get denatured by high temperature, pH, chemicals, X-rays and gamma-rays. They are basically classified into six classes based on the type of reaction catalyzed such as oxidoreductases, transferases, hydrolases, lyases, isomerases and ligases. Recombinant technology was only possible after the discovery of restriction endonucleases, the enzymes used as cutters for a desired segment [3] of genes known as recognition sequences. There are various other enzymes that have great value in recombinant technology such as DNA polymerases, ligases, kinases, alkaline phosphatases and nucleases [4]. They acts as drug or many drugs produces their actions by modulating the enzymes or enzymatic systems. Dr. Edward Howell's [5] worked on enzyme therapy and proposed that enzymes from foods help to pre-digest the food in the stomach. The plant enzymes such as protease, amylase, lipase and cellulase are obtained from pineapple and papaya; animal enzymes such as pepsin obtained from organs of cows and pigs are used as enzyme supplement for the treatment of non-digestive ailments. This article provides information on vital role of enzymes and their modulators in the management of disease free life.

A. Classification of Various Enzymes Necessary for Various Vital Functions of the Daily Life:

1. *Enzymes useful in digestion:* Bromelain, Chymopapain, Diastase, Pancreatin, Papain, Pepsin.
2. *Enzymes useful in coagulation:* Fibrinolysin, Streptokinase, Thromboplastin, Urokinase.
3. *Enzymes useful in tissue damage:* Chymotrypsin, Collagenase, Serratiopeptidase, Trypsin.
4. *Thrombolytic enzymes:* Alteplase, Anistreplase, Duteplase, Reteplase, Saruplase, Streptase or streptokinase, Tenecteplase, Tissue plasminogen activator, Urokinase.

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5. *Therapeutic enzymes:* Aeromonas aminopeptidase, Agalsidase beta, Alpha-glactosidase-A, Dornase alpha, Galsulfase or *N*-acetylgalactosamine-4-sulfatase, Imiglucerase or glucocerebrosidase or alglucerase, Laronidase or alpha-L-iduronidase.
6. *Enzymes for miscellaneous use:* Adenylyl cyclase, Aldehyde dehaydrogenase, Alpha chymotrypsin, Aminopeptidase, Amylase, Angiotensinogenase, Aromatase, Asparaginase, Synthase, Carbonic anhydase, Cephalosporinase, Cholesterase, Co-enzyme Q10, Cyclo-oxygenase, Cytochrome-P, Decarboxylase, Dihydrofolate, Eductase, DNA Polymerase, Dnase or Streptodornase, Esterases, Flavin enzymes, Folate synthetase, Gluco-6-phosphate dehydrogenase, Guanyl cyclase, HMG-CoA reductase, Hyaluronidase, Kininase-II-ACEIs, L-asparaginase, Lipase, Monoamino-oxidase-A andB, Na^+ K^+ ATPase, Na Ħ ƒK+ATPase, Penicillinase, Peptidase, Peroxidase, Phosphodiesterase, Phospholipase-A andC, Protein kinase, Streptokinase, Transcriptase, Tyrosine kinase, Urokinase, Xanthine oxidase, Zymase, β-lactamase.

B.classification of Various Agents That Inhibiting Enzymes:

1. *Aldehyde dehydrogenase inhibitors:* Acamprosate, Citrated calcium carbimide, Disulfiram, Few cephalosporins, Griseofulbin, Metronidazole, Naltrexone, Topiramate, Certain oral hypoglycemic agents.

2. *Mono amino oxidase inhibitors:*

i. *Non selective*

a. *Hydrazines:* Iproniazide, Isocarboxazide, Phenelzine.
b. *Non-hydrazines:* Tranylcypromine.

ii. *Isoenzyme selective*

a. MAO_A*:* Brofaromine, Clorgiline, Moclobemide, Nialamide, Toxoxatone.
b. MAO_B*:* Selegiline.

3. *Angiotensin converting enzyme inhibitors:* Benazepril, Captopril, Cilazopril, Enalapril, Enalaprilat, Fosinopril, Imidapril, Lisinopril, Moexipril, Perindopril, Quinapril, Ramipril, Spirapril, Trandolapril, Zofenopril.
4. *Renin-angiotensin antagonists:* Candesartan, Eprosartan, Irbesartan, Losartan, Olmesartan, Saralasin, Telmisartan, Valsartan, Zolasartan.
5. *HMG-CoA-reductase inhibitors or fungal metabolites or statins:* Atorvastatin, Cerivastatins, Fluvastatin, Lovastatin, Mevastatin, Pravastatin, Rosuvastatin, Simvastatin.
6. *β-lactamase inhibitors:* Clavulanic acid, Tazobactam, Sulbactam.
7. *Na^+K+ATPase inhibitors:* Acetyl digoxin, Acetyl strophanthidin, Amrinone, Bufotoxin, Convallotoxin, Deslanoside, Digitoxin, Digoxin, Gitalin, Gitoxin, Milrinone, Proscillaridin-A, Strophanthin-G (Ouabain), Strophanthin-K, Theventin, β-methyl digoxin.
8. *Na^+H^+ATPase inhibitors:* Esomeprazole, Lanzoprazole, Omeprazole, Pantoprazole, Rabeprazole.
9. *Penicillinase inhibitors:* Cloxacillin, Dicloxacillin, Methicillin, Nafcillin, Oxacillin.
10. *Phosphodiesterase-inhibitors:* Amrinone, Benzimidazoline, Caffeine, Ibopamine, Inamrinone, Milrinone, Pimobendan, Theophylline, Vesnarinone.
11. *Miscellaneous drugs that inhibit drug metabolizing enzymes:* Allopurinol, Amiodarone, Chloramphenicol, Cimetidine, Ciprofloxacin, Diltiazem, Disulfiram, Erythromycin, Isoniazid, Ketokonazole, Metronidazole, Omeprazole, Phenylbutazone, Propoxyphene, Quinidine, Sulfonamides, Verapamil.

C. Classification of Various Agents That Activates Various Enzymes: These are the agents which activate plasminogen and convert insoluble clot to soluble. They are effectively useful in the treatment of myocardial complications, thrombosis and angina pectoris like-Streptokinase, Urokinase,

Tissue Plasminogen Activators: Alteplase, Anistreplase, Duteplase, Reteplase, Retiplase, Saruplase, Tenecteplase. *Miscellaneous agents:* ASVIN (an enzyme from snake venom).

Therapeutic Impact of Selected Enzymes

Co-enzyme Q10: It is a solid waxy, fat soluble vitamin like co-factor required for the mitochondrial electron-transport chain. It is found in foods and synthesized in almost all body tissues. It is also obtained from tobacco leaf extracts, fermented sugar cane and beets. Its level decreases due to excessive exertion, hypermetabolism and acute shock. It is used in cardiovascular complications. *Pharmacological actions:* it protects cells of skin from oxidative damage by UVR. It involved in electron

transport and energy production in mitochondria. *Mechanism of action:* it acts as co-factor and enhance ATP production, antioxidant prevent against peroxidation of lipid membranes and also inhibiting the oxidation of LDL-cholesterol. *ADME:* well absorbed from small intestine after oral administration, when taken with high lipid food, excreted in bile and faces. *Interactions*: HMG-CoA reductase inhibitors suppressed the biosynthesis of Q10. *Dose:* 150-300mg/orally/day. *Uses*: it is preferred in congestive heart failure, angina pectoris, ischemia and reperfusion injury [6], atherosclerosis, amyotrophic lateral sclerosis, Parkinson disease, Huntington's chorea, mitochondrial disorders, periodontal diseases, muscular dystrophy, immune dysfunctions, obesity, aging disorders, cancer, to enhance athletic performance and as cellular antioxidant [7].

Alteplase: It is an enzyme that catalyzes tissue plasminogen to plasmin and is commonly used to prevent clot-related myocardial disorders. *Mechanism of action*: it dissolves blood clots by converting plasminogen into plasmin that digests fibrin, fibrinogen and other proteins. *Interactions*: its action accelerates in combination with heparin. *Contraindicated in*: bleeding, defective homeostasis, trauma, surgical procedures, stroke, acute pericarditis, hypoglycemia and hyperglycemia. *Dose*: 100 mg/*i.v.* infusion. *Adverse effects*: Alteplase may cause nausea, vomiting, fever, arrhythmias, allergy, hypotension, intracranial hemorrhage and GIT bleeding. *Uses*: it is preferred in cases of angina pectoris, as an anticoagulant, intravascular thrombosis, ischemic diseases, myocardial infarction, pulmonary embolism and to dissolve thrombi [8].

Streptase or Streptokinase: It is obtained from β-hemolytic streptococci group-C. It combines with circulating plasminogen to form an activation complex, which then causes limited proteolysis of other plasminogen molecules to plasmin. Antistreptococcal antibodies present due to the initial dose of streptokinase make a loading dose necessary in the beginning. *Mechanism of action*: streptokinase activates the conversion of plasminogen (profibrinolysin) into plasmin (fibrinolysin), which stimulates the conversion of fibrin (insoluble) into fibrin fragments (soluble). *Dose*: 250,000 units followed by 100,000 units/hour for 1-3 days/*i.v*. *Contraindicated in*: active internal bleeding, bleeding diathesis, cerebral tumor. If hemostasis is important, pregnancy, previous cerebrovascular accident, recent cranial trauma, surgery within ten days and uncontrolled hypertension. *Adverse effects*: streptokinase may cause anaphylaxis, bronchospasm, hypersensitivity, fever, hypotension and arrhythmias. *Uses*: it is preferred in cases of acute arterial thromboembolism, acute myocardial infarction, acute thrombotic stroke, deep venous thrombosis, local thrombolysis in the anterior chamber of the eye, myocardial infarction and unstable angina [9].

Urokinase: It is a proteolytic but not antigenic, fibrin-selective, thrombolytic, or fibrinolytic agent. It is developed by recombinant technology as pro-urokinase and is also derived from the human kidney (present in urine). It is converted to urokinase from pro-urokinase upon its binding to fibrin. *Mechanism of action*: it directly converts plasminogen into plasmin. *Contraindicated in*: bleeding risks, vascular aneurysm, endocardial thrombi and allergy to streptokinase. *Dose*: 3,00,000 units/hour for 12 hours/*i.v*. *Adverse effects*: urokinase may cause fever, bleeding, GIT bleeding and hemolytic stroke. *Uses*: it is preferred in cases like central deep vein thrombosis such as superior vena cava syndrome and ascending thrombophlebitis. It is also effective in acute coronary thrombosis, myocardial infarction and multiple pulmonary emboli [10].

Anistreplase: Anistreplse or anisoylated plasmino gen-streptokinase activator complex is a human plasminogen and streptokinase. The anisoyl group is removed in blood by a hydrolytic deacylation process. *Dose*: 30 units/*i.v*. infusion over 2-5 minutes. *Adverse effects*: anistreplase may cause hypotension and allergy [11].

Tenecteplase: It is developed by the recombinant technique and is a mutant of alteplase containing 527 amino acids. It is more fibrin-selective and more resistant to plasminogen activator inhibitor-1. It is given as a single bolus injection of 30-50 mg. It has a longer $t_{1/2}$ and greater efficacy [12].

Saruplase: It is a full-length, human, unglycosylated, single-chain polypeptide containing 411 amino acids, urokinase type plasminogen activator and also known as prourokinase. It is obtained by recombinant technology from *E. coli*. It is a fibrin-specific fibrinolytic agent and is effectively used for the treatment of thrombotic disorders such as acute myocardial infarction. *Dose*: 20 mg/*i.v*. bolus followed by a 60 mg infusion for 60 minutes. *Uses*: it is preferred in thrombotic disorders and myocardial infarction [13].

Imiglucerase: It is administered as enzyme replacement therapy in Gaucher's disease, a familial disorder affecting mainly the liver, spleen, bone marrow and lymph nodes due to the deficiency of beta-glucocerebrosidase activity, leading to the accumulation of glucocerebrosidase in many body tissues. It improves hematological abnormalities, hepatosplenomegalia and quality of life in patients of Gaucher's disease. *Mechanism of action*: it catalyzes the hydrolysis of glucocerebrosidase to glucose and ceramide. *Dose*: 60 units/kg/*i.v*. infusion/two weeks. *Adverse effects*: imiglucerase may cause abdominal cramps, angioedema, diarrhea, dizziness, fatigue, fever, flushing, headache, hypotension, nausea, vomiting, tachycardia and urticaria. *Uses*: it is preferred in the treatment of Gaucher's disease [14].

Agalsidase Beta: It is an enzyme used for the treatment of Fabry's disease; a lysosomal storage disorder caused by a deficiency of alpha-galactosidase, leading to progressive accumulation of glycosphingolipids, particularly GL-3 in many body tissues. *Mechanism of action*: it provides an exogenous alpha-galactosidase-A and catalyzes the hydrolysis of glycosphingolipids including GL-3. *Dose*: 1 mg/kg/*i.v*. infusion/two weeks for 20 weeks. *Adverse effects*: agalsidase beta may cause nausea, vomiting, abdominal pain, abnormal tear secretion, anemia, bradycardia, dizziness, drowsiness, edema, fatigue, fever, headache, hypersensitivity reactions, hypertension, injection site pain, myalgia, palpitation, paraesthesia, proteinuria, tachycardia, tremors and visual disturbances. *Uses*: it is preferred in the treatment of Fabry's disease [15].

Laronidase: It is an enzyme used for the treatment of non-neurological manifestations of mucopolysaccharidosis-I, a lysosomal storage disorder caused by the deficiency of alpha-L-iduronidase. *Dose*: 0.58 mg/kg/*i.v*. infusion/once a week. *Adverse effects*: laronidase may cause flushing, musculoskeletal pain, rashes, headache and abdominal pain. *Uses*: it is preferred in non-neurological manifestations of mucopolysaccharidosis-I and to improve pulmonary functions [16].

Dornase Alpha: It is an enzyme prepared from Chinese hamster ovary cells. It is a 260 amino acid, phosphorylated, glycosylated, recombinant human deoxyribonuclease-1 (rhDNase) or is a genetically engineered product of a naturally occurring human enzyme that breaks extracellular deoxyribonucleic acid or DNA. It is useful in the treatment of cystic fibrosis. *Pharmacological actions*: it reduces mucous viscosity in cystic fibrotic patients. *Mechanism of action*: cleaves extracellular DNA and reduces sputum viscosity. *Precautions*: breast feeding mothers. *Dose*: 2.5 mg/OD or BD/inhaled by nebulizer. *Adverse effects*: dornase alpha may cause chest pain, conjunctivitis, laryngitis, pharyngitis, rashes, urticaria and changes in voice. *Uses*: it is preferred in the treatment of cystic fibrosis [17].

Serratiopeptidase: It is a natural protein breaking enzyme. *Pharmacological actions:* It exerts anti-inflammatory, proteolytic, fibrinolytic and mucoprotease actions by hydrolyzing bradykinin, histamine and 5HT. It controls permeability and reduces dilatation of blood capillaries. Enhances fibrinolytic activity of plasmin by inhibition of plasmin inhibitors. It reduces swelling and improves microcirculation by preventing clogging of microcapillaries due to fibrin. Improving clearance and drainage by reducing viscosity and elasticity of mucus. *Mechanism of action:* it exerts anti-inflammatory, proteolytic, fibrinolytic and mucoprotease actions by hydrolyzing bradykinin, histamine and 5HT. It also masking of antigenicity of α_2-macroglobulin. *Dose:* 2.5-20mg/TDS. *Uses:* it is preferred in case of inflammatory conditions like arthritis, atherosclerosis, fibrocystic breast cancer and carpal tunnel symdrome. It dissolves ovarian breast cysts, no living tissues, blood cysts and arterial plaques. It speed the healing of torn ligaments, sports injures and post operative healing [18].

Trypsin: It is obtained from ox pancreas, destroys proteins and removes dead tissues and promoting wound healing. *ADME*: administered intravenously. *Contra-indicated in* Asthma, Allergic conditions, hepatic disorders and renal failure. *Adverse effects:* burning sensation and pain at injection site. *Uses:* it is preferred in chronic wound treatment [19].

Chymotrypsin: It is a proteolytic enzyme, obtained from pancreas of bovine, speed up healing of damaged tissues and other complication. *ADME:* applied locally or administered orally. *Uses:* it is preferred in inflammatory conditions [20].

Alpha Chymotrypsin: It is used during surgery for extraction of dislocated lens of eye. It dissolved suspensory ligament of the lens. *Adverse effects:* raise intraocular tension, vitreous loss and retinal damage. *Uses*: it is preferred in to dissolve suspensory ligaments of dislocated lens of eye [21].

Hyaluronidase: It depolymerizes hyaluronate which forms a protective barrier in the tissues. Hyaluronidase prepared from mammalian testis can be used therapeutically to enhance dispersion of drugs like local anaesthetics in various parts of the body [22]. It enhances spreading of drug fluids in intracellular spaces, administered through the subcutaneously or intramuscularly and known as spreading factor. *Mechanism of action:* enhances spreading and absorption of drugs by breaking ground substances. *Dose:* 150 units. *Adverse effects:* allergic reactions, anaphylaxis, enhances infections and spreading of malignant cells. *Uses:* it is preferred to enhances the fluid diffusion of subcutaneously or intramuscular injection and to reducing ganglion cyst [23].

Collagenase: It is an exotoxin (a virulence factor) and helps to facilitate the spread of gas gangrene. It normally targets the connective tissue in muscle cells and other body organs [24]. Collagen, a key component of the animal extracellular matrix, is made through cleavage of pro-collagen by collagenase once it has been secreted from the cell. This stops large structures from forming inside the cell itself. Collagenase production can be induced during an immune response, by cytokines that stimulate cells such as fibroblasts and osteoblasts and cause indirect tissue damage. *Mechanism of action:* it breaks the peptide bonds in collagen and assist in destroying extracellular structures in pathogenesis of bacteria such as *Clostridium*. *Adverse effects:* erythema and hypersensitivity reactions. *Uses:* it is preferred in removal of dead tissues and promotes wounds and burns healing [25].

L-asparaginase: L-asparaginase is required for the protein synthesis. While most normal tissues are able to synthesize L-asparaginase in amounts sufficient for the protein synthesis, some types of lymphoid malignancies derive the required amino acid from plasma. Asparaginase is an enzyme that catalyzes the hydrolysis of asparagine to aspartic acid, deprives malignant cells of the asparagine and leading to cell death [26]. *Uses:* it is preferred in acute lymphoblastic leukemia, chronic lymphocytic leukemia, Hodgkin's lymphoma, multiple myeloma, non-Hodgkin's lymphoma, plasma cell leukemia and to reduced immunogenicity [27].

Dnase or Streptodornase: It is produced by hemolytic streptococci that are used medically, often in combination with streptokinase to dissolve purulent or fibrinous secretions from infections [28].

α_1- Antitrypsin: It is a proteolytic enzyme that hydrolyse and destroy proteins. It has a very vital function in lungs. In normal lung the alveoli are chronically exposed to low level of neutrophil elastase released from activated and degenerating neutrophils. This proteolytic activity can destroy the elastin in the alveolar walls if unopposed by the inhibitory action of α_1-antitrypsin. Deficiency of α_{1}-antitrypsin results in emphysema. The deficiency of α_{1}-antitrypsin can be reversed by intravenous administration of α_1-antitrypsin [29].

Papain: It is dried and purified latex of the fruit of carica papaya belonging to the caricaceae family. It contains several proteolytic enzymes such as peptidase, renin, amylolytic, clotting and an enzyme with mild activity on fats. *Uses*: it digest proteins, helps in wound and minor cuts, acts as ant-inflammatory agent and along with antibiotics to treat skin diseases. It is an important ingredient of solutions used in cleaning contact lenses. It is used in tenderizing meat, clarifying beverages, making cheese, softening textiles and tanning leather. It is also used to raise platelet count in dengue fever [30], effective in chikungunya, alcohol induced acute gastric damage and blood oxidative stress [31].

Chymopapain: It is protein, chemically related to papain, comparing 218 amino acids. *Adverse effects*: risk of anaphylactic shock. *Uses*: it is injected into the intervertebral disc for the treatment of sciatica due to herniated lumbar disc [32].

Bromelain: It is a protein digesting and milk clotting enzyme. It consists of a mixture of proteolytic enzymes obtained from the stem and ripened fruits of the pineapple plant and ananas comsus, belonging to the bromeliaceae family. *Uses*: it is use as anti-inflammatory agent for soft tissues and in case of oedema caused by surgery or injury, because it blocks pro-inflammatory agents and also reduces migration of neutrophils to sites of acute inflammation. It is investigated for the treatment of traveler's diarrhea, bruising, gout, arthritis, haemorrhoids, menstrual pain, autoimmune disorders and AIDS. It is also used for the commercial production of protein hydrolyzates, as a meat tenderizer and in leather industry [33].

Therapeutic Impact of Selected Enzymes Modulators

Disulfiram: Their active metabolite irreversibly inhibits *aldehyde dehydrogenase* and ultimately increases the concentration of acetaldehyde in tissue and blood that causes aldehyde syndrome. *Symptoms*: Flushing, burning

sensation, throbbing headache, perspiration, uneasiness, tightness in chest, dizziness, vomiting, visual disturbances, mental confusion, postural fainting and circulatory collapse and thirst. *Dose pattern*: Treatment is start after abstaining the patient or person or drinker from alcohol overnight. Then disulfiram given 1gm on 1st day, 0.75gm on 2nd day, 0.5gm on 3rd day, 0.25or 0.5gm daily for 1-2 weeks followed by 0.125-0.25gm/day. Sensitization to alcohol develops after 2-3 hours of first dose and lasts for 7-14 days after stopping it. *Contra-indicated in*: physically dependent, cardiovascular disorders, epilepsy and cirrhosis. *Adverse effects*: rashes, metallic taste, nervousness, malaise and abdominal pain. *Uses*: it is preferred in the following cases to reduce cravings for alcohol, to prevent alcohol drinking and in the treatment of chronic alcoholism [34].

Selegiline: It is a MAO_B enzyme inhibitor, decreases the metabolism of dopamine in brain. *Mechanism of action*: it acts by inhibiting the breakdown of dopamine in brain and also interferes with reuptake of dopamine at synapses. *Dose*: 5mg/BD/orally. *Adverse effects*: nausea and confusion. *Uses*: it is preferred in depression, panic disorders, chronic pain, Parkinsonism and Alzheimer's disease [35].

Captopril: It is a dipeptide, sulphyhydral containing proline surrogate, angiotensin converting enzyme inhibitors hypotensive agent. *Mechanism of action*: inhibition of vasoendothelial kininase-II enzyme and prevent the conversion of angiotensin-I to angiotensin-II or decreasing peripheral resistance. *ADME*: well absorbed orally, converted into active forms in liver and excreted through kidney. *Interactions*: NSAIDs inhibits hypotensive action, hyperkalemia with potassium sparing diuretics, Antacids reduce bioavailability and lithium clearance inhibited. *Contraindicated in*: pregnancy due to teratogenic effect. *Dose*: 25-50mg/BD/TDS/1 hour before or 2 hours after a meal. *Adverse effects*: acidosis, angioedema, bronchospasm, dizziness, dysguesia, fetal damage, flushing, GIT upsets, granulocytopenia, headache, hyperkalemia, hypotension, maculopapular rash, nausea, non-productive cough, photosensitivity, proteinurea, renal failure, skin rashes, stomatitis, tachycardia, vertigo, vomiting and weight loss. *Uses*: it is preferred in hypertension, cardiac failure, myocardial infarction, diabetic neuropathy and progressive renal insufficiency [36].

Losartan: It is a vasoconstrictor, AT_1 angiotensin-II antagonist and also have some ACE inhibiting properties. It is useful in the treatment of hypertension. *Pharmacological actions*: relaxes vascular smooth muscles, reduces peripheral vascular resistance, blocks vasoconstrictor and secretary effects of angiotensin-II and enhances excretion of water, salts and uric acid. *Mechanism of action*: binds and antagonized the actions of angiotensin-II mediated through AT_1 receptors. *ADME*: well absorbed after oral administration, bounds to plasma proteins metabolized in liver into a more active carboxylic acid metabolite and excreted in urine. *Contraindicated in:* pregnancy and breast feeding. *Dose*: 50mg/OD. *Adverse effects*: anaemia, angioedema, asthenia, cough, dizziness, fatigue, hepatitis, hyperkalaemia, hypotension, light headedness, migraine, myalgia, pruritis, rashes, taste disturbance, urticaria, vasculitis and vertigo. *Uses*: it is preferred in essential hypertension and hyperuricaemia [37].

Cardiac Glycosides: They are the drugs having cardiac inotropic property, increase myocardial contractility and output of a hypodynamic heart without increasing O_2 consumption. *Mechanism of action*: Inhibition of Na^+K^+ATPase enzyme and produce positive inotropic effect. *Pharmacological actions*: increased the force of contraction of myocardium. Decreased the heart rate by increasing circulation (positive inotropic effect), increasing vagal tone, decreasing sympathetic over activity, Direct action on SA and AV nodes, digitalis decreased the conduction (so increase the P-R interval in ECG). In CHF patient it decreases vasoconstriction and peripheral resistance. In CHF patients it increases diuresis but ineffective in other renal problems like edema state. Higher doses may cause nausea and vomiting, hyperapnoea, mental confusion, psychosis, visual disturbances and central sympathetic stimulation. *Adverse effects*: Abdominal, pain, anorexia, arrhythmias, diarrhea, disorientation psychosis, fatigue, gynaecomastia, headache, hyperapnoea, malaise, mental confusion, nausea, restlessness, skin rashes, visual disturbances and vomiting. *Uses*: they are preferred in congestive heart failure and cardiac arrhythmias [38].

Caffeine: It is a purine derivative alkaloid methylxanthine, stimulate CNS. *Pharmacological actions*: it stimulates the higher centers of CNS and produces insomnia. It stimulates respiration by acting on medullary centre and produces wakefulness. It removes fatigue and drowsiness. It improves performance and motor activities. It produces feeling of wellbeing, alertness and reduces fatigue. It enhances the contractile capacity of skeletal muscles and it enhancing the secretion of HCl and pepsin in stomach. *Mechanism of action*: facilitate neurotransmission by increasing the release of

acetylcholine. *ADME*: well absorbed after oral administration from the GIT, widely distributed, $t_{1/2}$ is 3-6 hours, rapidly metabolized by demethylation and oxidation in liver and excreted by kidneys. *Interactions*: enhancing the absorption of ergotamine and Neurotoxicity with antihistaminics and amantadine. *Contraindicated in: p*eptic ulceration. *Dose*: 200-500mg/day. *Adverse effects*: nausea, vomiting, gastric irritation, agitation, convulsions, delirium, excitement, insomnia, muscular twitching, nervousness, panic, palpitation, restlessness, rigidity, rise in body temperature, tolerance and tremors. *Uses*: it is preferred in narcolepsy, algesia, tiredness, migraine and apnoea in neonates [39].

Allopurinol: It is a purine compound, structurally similar to hypoxanthine, converted to alloxanthine and inhibits biosynthesis of uric acid. It is used to treat hyperuricaemia. *Mechanism of action*: suppressed oxidation of purine to uric acid by inhibiting xanthine oxidase enzyme. *ADME*: well absorbed after oral administration, $t_{1/2}$ is 2 hours, excreted in urine, as such or as alloxanthine. *Interactions*: suppressed metabolism of 6-mercaptopurine, azathioprine, warfarin, theophylline, cyclophosphamide and oral anticoagulants, rise skin reactions with ampicillin and interfere with mobilization of iron. *Contraindicated in:* kidney and liver diseases, pregnancy and lactation. *Dose*: 50mg/day gradually increased upto 300-600mg/day. *Adverse effects*: nausea, vomiting, diarrhea, alopecia, aplastic anaemia, arthralgia, drowsiness, eosinophilia, exfoliation, fever, haemolytic anaemia, headache, hepatitis, hepatotoxicity, hypertension, leucopenia, leukocytosis, liver damage, lymphadenopathy, malaise, myalgia, neuropathy, paraesthesia, rashes, renal impairment, taste alteration, thrombocytopenia, urticaria, vasculitis, vertigo and visual disturbances. *Uses*: it is preferred in chronic gout, hyperuricemia, nephropathy, tophi or uric acid stones and given with cytotoxic agents to excrete out uric acid produce by cytotoxic agents [40].

Clavulanic Acid: Produced by streptomycin clavuligeru, poor antimicrobial activity irreversibly inhibits β-lactamases produces by gram+ve and gram-ve bacterias. *Mechanism of action:* prevent breakdown of lactam ring by irreversibly inhibiting lactamase or penicillinase enzyme. *Dose*: 125mg with 250mg amoxicillin/TDS or QID/orally. *Adverse effects:* diarrhoea and nausea when combined with amoxicillin. *Uses:* with penicillins against penicillin resistance organisms [41].

Tissue Plasminogen Activator: It is fibrin-selective but does not activate systemic plasminogen. It is synthesized by recombinant technology and is also obtained from cultured human melanoma cells. *Mechanism of action*: it induces fibrinolysis of the formed thrombus by preferentially activating plasminogen bound to fibrin. *Dose*: 100 mg/*i.v.*/3 hours. *Uses*: it is preferred in the treatment of deep vein thrombosis [42].

CONCLUSION

The enzymes are the biocatalysts; they catalyze many anabolic and catabolic specific chemical reactions without itself undergoing any change in overall reaction. The enzymes are useful in digestion, coagulation, tissue repair and numerous other life essential processes. The enzyme modulators i.e. enzyme inhibitors like MAO inhibitors in depression, ACEIs and renin antagonists in hypertension, statins in hyperlipidimia, Na^+K^+ATPase inhibitors in congestive heart failure, Na^+H^+ATPase inhibitors in ulceration, aldehyde dehydrogenase inhibitors in alcohol withdrawal and many others may help to treat life threatening disorders. The enzyme activators such as tissue plasminogens activators also equally important to treat complicated diseases of heart. The information regarding the enzymes and their modulators may have a great value in proper disease management.

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