

## Versatile Importance of Schiff Bases

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### ABSTRACT

Schiff bases are condensation products of primary amines with carbonyl compounds gaining importance day by day in present scenario. Schiff bases are the compounds carrying imine or azomethine ( $-C=N-$ ) functional group and are found to be a versatile pharmacophore for design and development of various bioactive lead compounds. Schiff bases exhibit useful biological activities such as anti-inflammatory, analgesic, antimicrobial, anticonvulsant, antitubercular, anticancer, antioxidant, anthelmintic, antiglycation, and antidepressant activities. Schiff bases are also used as catalysts, pigments and dyes, intermediates in organic synthesis, polymer stabilizers, and corrosion inhibitors. Furthermore, the coordinating ability of the metal within the polymer-based macromolecules permits these materials to act as sensors. Schiff bases have N atoms as their basic elements. Schiff base derivatives containing donor atom can act as good chelating agents for the transition of metal ions.

Schiff bases are formed when any primary amine reacts with an aldehyde or a ketone under specific conditions. Structurally, a Schiff base (also known as imine or azomethine) is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group (CO) has been replaced by an imine or azomethine group

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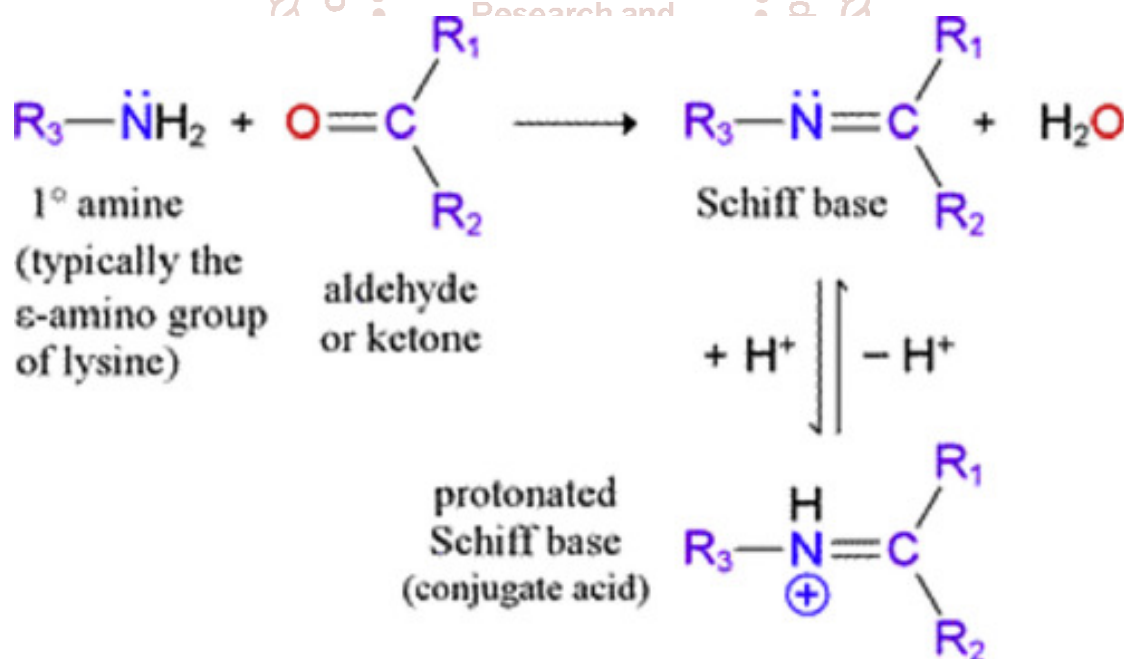
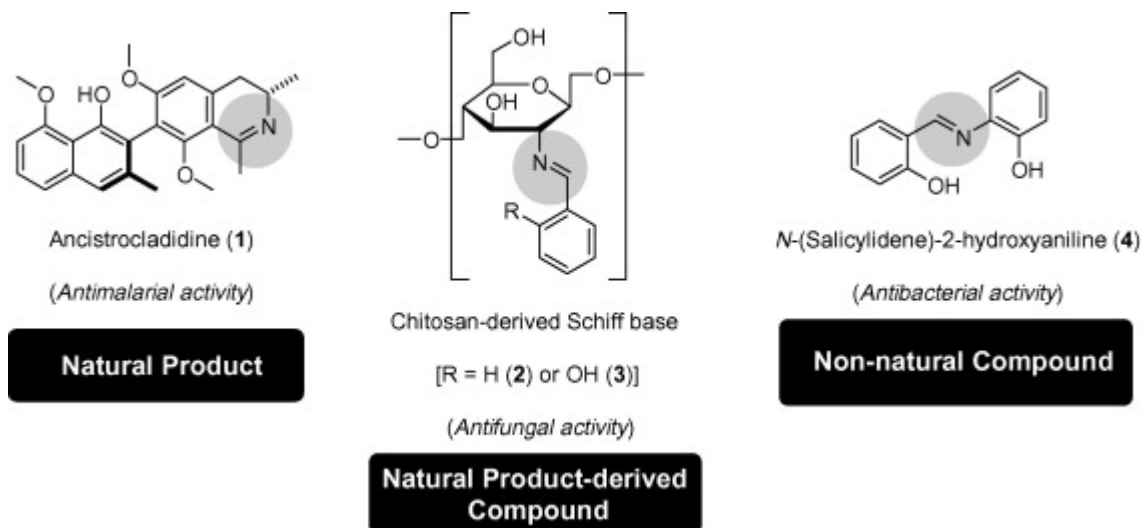


Fig. 1 General scheme for formation of Schiff bases

Schiff bases are some of the most widely used organic compounds. They are used as pigments and dyes, catalysts, intermediates in organic synthesis, and as polymer stabilisers. Schiff bases have also been shown to exhibit a broad range of biological activities, including antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral, and antipyretic properties. Imine or azomethine groups are present in various natural, natural-derived, and non-natural compounds. The imine group present in such compounds has been shown to be critical to their biological activities.



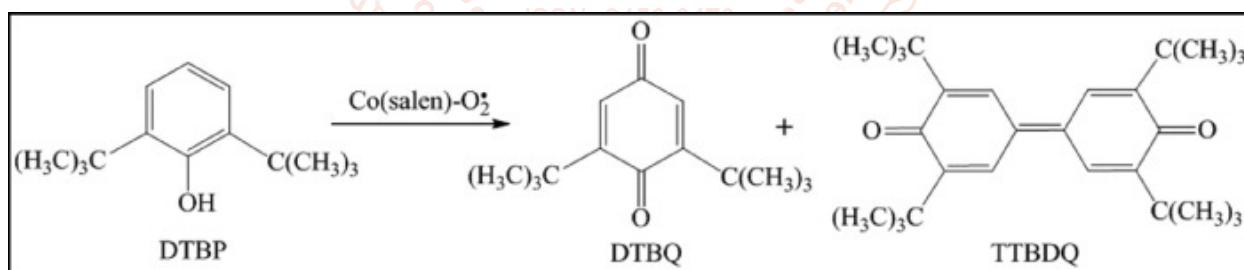
**Fig. 2** Examples of bioactive Schiff bases. The imine or azomethine group present in each molecular structure is shaded.

Applications of Schiff bases and their metal complexes as catalysts, in various biological systems, polymers and dyes are described. Their use in birth control, food packages and as an O<sub>2</sub> detector is also outlined. Introduction Metal complexes play an essential role in agriculture, pharmaceutical and industrial chemistry. Ligand, a metal surrounded by a cluster of ions or molecule, is used for preparation of complex compounds named as Schiff bases 1, which are condensation products of primary amines and aldehydes or ketones (RCH=NR', where R & R' represents alkyl and / or aryl substituents).

## INTRODUCTION

Many researchers have investigated a large number of Schiff base ligands as chelating compounds, e.g. metal chelates of copper, cobalt, etc. for a variety of interesting catalytic application. Co (II) salen complex of N,N-bis(3,5-di-*tert*-butyl-salicylidene-1,2-cyclohexane diaminato) was used as catalyst in oxidation of 2,6-di-*tert*-butylphenol (DTBP) and 3,5-di-*tert*-butylphenol (35-DTBP) in super-critical carbon dioxide (scCO<sub>2</sub>)

The oxidation of DTBP resulted into 2,6-di-*tert*-butyl-4,4'-benzoquinone(DTBQ) along with the side product of radical coupling, i.e. 3,5,3',5'-tetra-*tert*-butyl-4,4'-diphenoquinone (TTBDQ) [1]



**Typical aerobic oxidation of DTBP by Co (salen). DTBP, 2,6-di-*tert*-butylphenol.**

## Biological Applications

### Antimalarial activity

Malaria is a chronic disease which was neglected for many years. Every year, nearly 500 million people are affected by this disease and approximately 1-3 million people die among them. Schiff's bases are proved to be a very good source for the design of antimalarial agents. Schiff Base 5 was the most effective antimalarial agent among the other synthesized bases.[2]

### Antibacterial Activity

Bacteria is the root cause of many infectious diseases and responsible for an increase in the mortality rate. There are different kinds of bacteria, and they exhibit a lot of resistance to antibiotics. Schiff's bases have emerged as promising antibacterial agents. For example, Mycobacterium can be effectively treated with N- (salicylidene) -2-hydroxyaniline.[3]

### Antifungal activity

Schiff bases with a 2,4-dichloro-5-fluorophenyl moiety have been proven to restrict the growth of fungi like *Aspergillus flavus*, *Aspergillus fumigatus*, *Trichophyton mentagrophytes*, and *Penicillium marneffeii*.

## Conjugated Schiff Bases

Conjugated Schiff Bases possess some interesting optoelectronic properties and have been used in electronics such as the organic field-effect transistor, Perovskite solar cells, and electrochromic devices. These are also used in the manufacturing of Covalent Organic Framework that is used for gas storage.[4]

When two equivalents of salicylaldehyde are combined with a diamine, a particular chelating Schiff base is produced. The so-called Salen ligands with four coordinating sites and two axial sites open to ancillary ligands. Although the term Salen was used originally only to describe the tetradentate Schiff bases derived from ethylenediamine, the more general term Salen-type is used in literature to describe the class of [O,N,N,O] tetradentate Schiff base ligands. **Salen compounds** are insoluble in aqueous solutions and they decompose easily in acidic solutions, limiting their use to basic condition.

**Salophen** or acetylparamidophenyl salicylate is a Schiff's base with non-toxic properties, which is an effective substitute for salicylic acid.

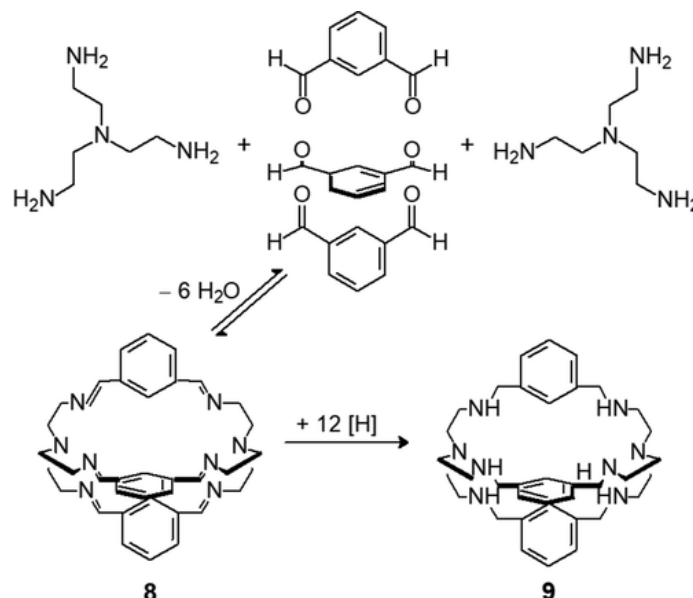
**Hydrazones** are a class of organic compounds with the general structure of  $R_2C=NNR_2$  which are related to ketones and aldehydes by the replacement of the oxygen with the  $NNR_2$  functional group. These compounds are commonly formed through the reaction of hydrazine with ketones or aldehydes. Schiff's bases are able to coordinate metals through imine nitrogen, and there is a wide use of these metal complexes as catalysts. In the last few years, various Schiff's base complexes of transition metals including Mn(III), Fe(II), Ni(II), Cr(III), Ru(III) etc. have been used as the catalysts for epoxidation of olefins and as mono oxygen sources for catalyst to carry out oxygen transfer to the olefins. They are easy to synthesize (simply and cheaply) and multidentate. Substitution at the aromatic ring can modify the electronic and steric properties of the resulting complexes (fine-tuning) as it can form metal complexes of various sizes because of its open structure.[5]

Schiff bases tend to isomerize because of the imine group ( $C=N$ ) to yield two stereoisomers *E* and *Z* (or *cis* and *trans*) isomers, and the formation of these stereoisomers can be controlled either kinetically or thermodynamically. Azobenzenes—common organic dyes—have been studied extensively owing to their potential applications in materials, medical, molecular switches, and other devices. Azobenzenes are photosensitive materials which undergo rapid reverse photoisomerization from the more stable *E* isomer to the less stable *Z* isomer. The exact mechanism of the *cis-trans* isomerization is not clear yet even after several decades of research. Reverse photoisomerization largely depends on the synthetic conditions like polarity of the medium; viscosity of the solvent used; and molecular substitutions on the azobenzene skeleton as these have very dramatic effects on the spectra of the molecules and the kinetics of isomerization.[6]

UV–Visible spectroscopy is a very useful analytical tool for studying the spectral properties of Schiff bases generally obtained as mixture of geometrical isomers, their sensitivity to the solvent properties, effect of substitution, pH, ambient temperature, etc. Absorbance spectra are generally recorded in the range of 300–450 nm; and the spectra are strongly solvent dependent and the corresponding *E* or *Z* isomer. With isatin Schiff bases under consideration, *Z(cis)* isomer appeared at higher wavelengths, that is, of lower energy when compared with *E(trans)* at lower wavelengths (higher energy); solvent-dependent electron density transfer was also observed, and the role of the position of substituent affected the appearance of frequency bands. Excited state was stabilized with a directional  $\pi$ -conjugative electron density shift in the molecule which might be a consequence of the long-range transmission of substituent effects, which supports the larger polarization of carbonyl group and thereby enhancing H-bonding capability of carbonyl oxygen and separation of electronic charges. Solvent affects are very complex phenomena, and the absorbance maxima altered inconsistently with respect to solvent and the position/type of the substituent(s) and geometrical features. In addition, other molecular properties like dipole moments, difference of electronegativity, partial charges, and chemical reactivity also significantly affected electronic spectra. In the IR spectra,  $C=N$  is most commonly reported in the  $1690\text{--}1640\text{ cm}^{-1}$  region as a strong and a sharp band at somewhat lower frequencies than the bands of  $C=O$  groups and close to  $C=C$  stretching frequencies. Angle strain, steric repulsion, and other complicated local factors and solution concentration and nature of solvent, in neutral solvents, the stretching frequency of  $C=N$  is found to be at  $1670\text{ cm}^{-1}$ , and the corresponding force constant,  $10.6\text{ dynes cm}^{-1}$ , is in the harmonic oscillator approximation. The frequency is usually lowered in the absence of one or more groups in conjugation with the  $C=N$ . Generally, there is no difference between IR and Raman frequencies and between the spectra of pure liquids and solids and their solutions in common organic solvents  $CCl_4$  or other not very associative solvents. Generally, water of crystallization appeared at  $3300\text{ cm}^{-1}$  plus range. [7]

## DISCUSSION

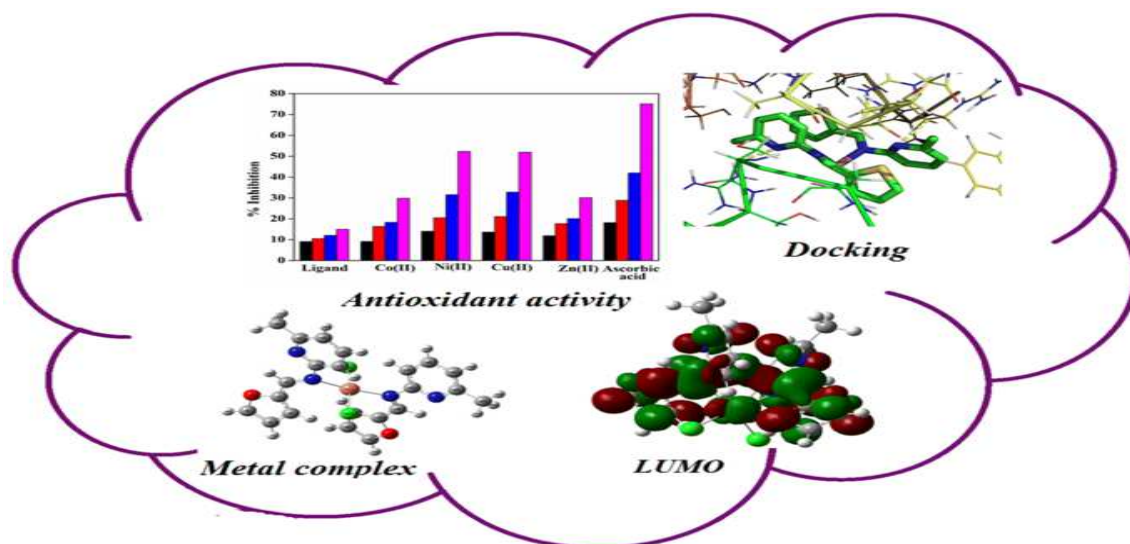
Metal complexes of Schiff bases synthesized from condensation of an amine with carbonyl compounds are widely used for industrial purposes such as catalysts, pigments and dyes, intermediates in organic synthesis, polymer stabilizers, and corrosion inhibitors. For design and development of various bioactive compounds, Schiff bases carrying imine or azomethine ( $-C=N-$ ) functional group, are versatile pharmacophores. Medicinal chemists give attention toward new chemotherapeutic Schiff bases and their metal complexes owing to numerous applications in pharmacology as antiviral, antibacterial, antifungal, antimalarial, antituberculosis, anticancer, anti-HIV, anti-inflammatory, and antipyretic agents. [8]



**Schiff base condensation of two molecules of branched tetramine tren with three molecules of 1, 3-benzene-dicarbaldehyde, to give unsaturated cage-shaped molecule 8, whose six C=N bonds are subject to hydrolysis. Imine bonds are then hydrogenated to give kinetically stable octamine 9, bistren.**

**Anil compounds** are Schiff bases derived from aniline moiety containing phenyl or substituted phenyl group, which sometimes called Azo dyes. These Schiff bases can be directly prepared from aromatic amine with aromatic carbonyl groups, which are stable and can be manipulated under different and suitable conditions. The phenomena of coordination of Schiff bases with metal ions give the Schiff bases the good advantages to be introduced in the dyes synthesis. The classification of dyes is based on the chemical structure or on the basis of the chromophoric system. The **metal complex dyes** are combinations of dyestuff and metal ions, in which the coordination complex can be applied or used to be improvement factors in dye techniques. The investigation and the characterization of the resulted dyes were performed by using different physical techniques. The produced dyes were applied to different fibres, such as sheep wool and goat hair with two Schiff bases synthesised from salicylaldehyde either with 2-aminophenol or 2-aminobenzyl alcohol. Also the investigation includes the effect of mordant type on the dyeing process.[9]

In many cases, the cofactors of biologically important proteins are linked to their apoproteins by Schiff bases. First, we focus on **retinylidene proteins**, in which the cofactor retinal is fixed to the apoprotein by a protonated Schiff base. Light induced retinal isomerization triggers a photocycle or a cascade of structural changes in which deprotonation of the Schiff base is a crucial step. We compare the photocycles of archaeal type rhodopsins, channelrhodopsins and the light induced cascades of **visual rhodopsins**. Pyridoxal phosphate (PLP) dependent enzymes are summarized in the second section. In these proteins, the cofactor PLP is linked via a Schiff base to the side chain of a lysine. In most cases, hydrolysis of this linkage is critical for substrate binding. Finally, aldolases, that catalyze aldol cleavage during glycolysis, contain a lysine residue at their active center. Formation of a protonated Schiff base linkage to a carbonyl group of the substrate is the first step of the catalytic mechanism.[10]



### Biomedical Phenomenon

## RESULTS

Transition metal complexes with different ligand systems have been developed. Majority of them are derived from heteroaromatic cycles and Schiff bases of variety of aromatic aldehydes, diketones with amino acids, polyamines, N-aromatic cycles and ethylenediamines. Metal complexes of Schiff bases are used as polymers, dyes and in various biological systems. They show antimicrobial activity and can be used as suitable drug to treat bacterial and fungal infections. Most of the Cu, Ni and Co complexes are also capable of binding and cleaving DNA.[11]

In nature, an imine group ( $-C=N$ ) is present in the molecular chain of Ancistrocladidine that is produced as a secondary metabolite in plants of family Dioncophyllaceae and Ancistrocladaceae. This linkage of carbon and nitrogen is also similar to protein opsin that is present in the retina of eye. Due to the presence of lone pair of electrons on nitrogen and the nucleophilic character of double bond, Schiff bases are basic in nature. These are crystalline form insoluble salts by reaction with strong acids. Formation of Schiff base is a reversible reaction. These are sensitive to moisture and decompose when exposed to air. Schiff Bases containing alkyl substituents are generally unstable because in aliphatic aldehydes polymerization occurs readily. Schiff bases that possess aryl substituents are stable due to conjugation and can easily be isolated. The nature of amine as well as carbonyl compounds tells about the mechanism and the position of equilibrium. At room temperature, aromatic aldehydes are very reactive towards amine to form a stable Schiff base even without the removal of water.[12]

Schiff bases act as an intermediate in chemical analysis and synthesis. These are used in the synthesis of different organic compounds by the acylation of

Schiff bases from acid chlorides, acid anhydrides and acyl cyanides. In Strecker synthesis, Schiff bases react with HCN forming an amino acid precursor. These are also utilized in the preparation of Ruhemann's purple used for identifying fingerprints. In inorganic chemistry, Schiff bases are used in the synthesis of pigments, dyes, lubricating oils, heat resistant polymers, photographic emulsions, antiknocking agents, high temperature stabilizers and liquid crystals. These bases act as ligands with transition metals to form complexes. Substituted Schiff bases are bidentate ligands. These bases also act as corrosion inhibitors. In gas chromatography, Schiff bases are used as a stationary phase.[13]

## Biological Aspects

**1. Urease Inhibitory Activity** The urease enzyme (EC 3.5.1.5) is present in bacteria, yeast, higher plants and exceptional in *Helicobacter pylori* and is basically a protein. Urease is also produced by various pathogens in gastrointestinal and urinary tract. The enzyme possesses nickel metal and is involved in the formation of carbamate and ammonia by hydrolysis of urea. The carbamate further decomposes to carbonic acid and ammonia, which causes an increase in pH [14]

**2. The Breakdown of Urea to Ammonia and Carbamate.** Urease inhibitors the new drug targets and antiulcer agent to treat urinary and some hepatic diseases can be obtained by urease inhibitors. Hp induced pathologies are a major cause. The first line of treatment for prevention from infections caused by urease producing bacterium like *Helicobacter pylori* (Hp) therefore, include strategies based on urease inhibition which are being considered now. The colonies of gram-negative bacterium are developed in gastric mucosa of ~50 % of all humans. The bacterial persistence is by Hp which contributes to the treatment failure occupies and protected intra-cellular

environment. The infections by various organisms may be developed by broad spectrum of diseases, which include gastric cancer, gastritis and peptic ulceration. Hp survival is one of the major factors for urease in the stomach which is also involved in the formation of infectious stones and adds to the pathogenesis of hepatic encephalopathy, urolithiasis, urinary catheter encrustation and hepatic coma. The important class of urease inhibitor is hydroxamic acid and some of its derivatives. The binding of metal ions to the active site of enzyme is involved in the mechanism of inhibition and they serve as good metal chelators. AHA causes rapid and complete inhibition of urease inhibitor and acetohydroxamic acid (AHA) is the best studied hydroxamate which is the best inhibitor at 25 °C with Ki value of 5 µM. [15]

**3. Lipoxygenases Inhibitory Activity** The hydroperoxidation of lipids is catalyzed by a class of iron-containing dioxygenases known as lipoxygenases possessing structure of cis-1, 4-pentadiene. They are very much wide spread in animals and plants. The metabolism of leukotrienes and prostaglandins is carried out by a number of lipoxygenases isozymes in animals. The formation of hydroperoxides is catalyzed by hydroperoxides as the biosynthesis of several inflammatory mediators in first step, which leads to leukotriene synthesis. The large non-haeme iron-containing enzymes like lipoxygenases use molecular oxygen for the dioxygenation of arachidonic acid for the formation of hydroperoxides due to significance of such compounds, in a number of diseases, the extensive study has been conducted on lipoxygenase. The broad range of cardiac, inflammatory diseases and human cancers involve the implication of such enzymes. These enzymes are actually peroxidases. The conversion of procarcinogen into carcinogens is catalyzed by these catalysts. The precursors of hormones, such as lipoxins and leukotriensleukotriens, are produced by human lipoxygenases (HLO) which have implications in critical signaling in a number of cancers and inflammatory diseases.

**4. Alpha-Glucosidase Inhibitory Activity** The easily absorbing sugars are obtained upon break down of complex carbohydrates by alphasglucosidase. Inhibition of leukotriene biosynthesis has been extensively studied as a potential for the development of inhibition of leukotriene biosynthesis has been extensively studied as a potential for the development of blood sugar levels in diabetic people. The drugs which are used to block alpha-glucosidase (alpha-glucosidase inhibitors) are also beneficial for people suffering from diabetes. [16]

**5. Chymotrypsin Inhibitory Activity** The proteolysis of chymotrypsinogen is carried out by trypsin which is also involved in the activation of chymotrypsin. The chymotrypsin is produced in acinar cells of the pancreas. The enzyme inhibitors are the substances which intercede natural substrates of enzymes especially in their conversion. The enzyme inhibition study of reported compounds is involved in the investigation of the choice of drugs in the pharmaceutical research area. The hyperactivity of enzymes is debilitated due to physiological abnormalities and enzyme inhibitors are the urgent need in such circumstances. The decimation of cellular proteins and peptides along with replication of viruses is brought about the proteases in the enzyme mundane. The targets of anti HCV and anti-HIV drugs are the proteases of HCV (NS3 protease) and HIV which are involved in the replication of viruses. The declared inhibitors in genetically engineered plants are also targets of plant pathogens. [17]

**6. Antioxidant Activity** The free radicals and reactive oxygen species (ROS) are involved in complete damage of our tissues and such type of damage can be avoided by employing antioxidants. The amount of ROS which is removed is detoxified by mitochondria and at the same time, ROS is generated at mitochondrial site. The capacity of removal of ROS from mitochondria could be very much different from that of generated ROS. The difference in ROS removal and generation leads to the emission of ROS outside mitochondria. The rate of emission of ROS and the production of ROS by extra mitochondrial resources determines the steady state ROS concentration.

**7. DNA Cleavage Activity** The importance of certain compounds in medical diagnosis and genomic research is based on the ability of such compounds to bind and cleave double stranded DNA under physiological conditions. The hydrolytic and oxidative cleavage pathways are involved in DNA cleavage reactions. The formation of fragments may be considered to take place through enzymatic processes which occurs due to hydrolysis of phosphodiester. The nucleobase oxidation and/or degradation of sugar by abstraction of sugar hydrogen atoms take place during oxidative process. The oxidative cleavage of DNA is brought about by various methodologies and the methodology which involves irradiation with visible light of long wavelength, has achieved significant importance for their major use in photodynamic therapy (PDT) of cancer. The binding ability of DNA is the main source for making comparison in cleavage efficiency

of the complexes to that of the control. The open circular DNA is obtained from supercoiled DNA by complexes. The account of DNA cleavage by hydroxyl radicals abstraction of a hydrogen atom from sugar units and proposed general mechanisms that predicts the release of specific residues which arise from transformation of sugars, which also depends on the position of hydrogen atom removal. The hydroxyl radical mediated cleavage reactions and cleavage of peroxy derivatives is inhibited by free radical scavengers. [18]

**8. Brine Shrimp Activity** The shrimp lava are often destroyed by employing bioactive compounds and new bioactive synthetic products can be preliminary monitored by in vivo lethality test of the shrimp larvae. The in vivo animal experiment on large scale can be carried out by making use of this is rapid, inexpensive, in-house general bioassay.

**9. Anti-Bacterial Activity** The microorganisms adsorb metal ions on their cell walls and as a result respiration processes of cells are disturbed and protein synthesis is blocked which is the requirement for further growth of organisms. The growth inhibition effects of metal ions are considerable. The only passage of lipid soluble material is favored by the lipid membrane that surrounds the cell in accordance with the overtone's concept of cell permeability, as the antifungal activity is controlled by lipophilicity factor. The overlap of ligand orbitals and the behavior of metal ions to share charge with the donor groups is reduced upon chelation. Besides this, the delocalization of  $\pi$  electrons over the whole ring is due to chelation and lipophilicity of complexes is enhanced. The proliferation of microorganisms is further restricted because the penetration of complexes in lipid membranes is facilitated by increased lipophilicity. The impermeability of microbial cells and differences in ribosomes of cells are the major reason for variations in the effectiveness of different compounds against a variety of organisms. In most of the cases, ligands are less effective antifungal agents than their metal complexes.[19]

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