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SCHIFF BASES AS ANTI-INFLAMMATORY AGENTS - A COMPREHENSIVE REVIEW

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ABSTRACT
Organic chelating ligands can form a large number of complexes with metal ions, which imparts the complexes academic, commercial and medicinal importance.[1] As a result, their study attracts chemists in the world. Bioinorganic chemistry involving presence of metal ions in the biological system and their importance, organometallic chemistry and biomedical sciences are the fields of study gaining continuous importance as a result of this. Schiff bases along with their various derivatives belong to the category of these organic chelating ligands. The formation of Schiff bases is a result of reaction between a primary amine and an aldehyde or a ketone. They are considered as imines(C=N). Metal ion complexes of Schiff bases and their derivatives have been studied for a number of biological activities including antimicrobial, antifungal, antitumor, antianxiety and anti-inflammatory. This review focusses on the anti-inflammatory activity of metal ion -Schiff base complexes and their various derivatives and also focusses on the need to prepare new derivatives of Schiff bases with various metal ions and organic chelating ligands.

INTRODUCTION
Schiff bases get their name from the German chemist Hugo Schiff who won the noble prize for his work.[1] Schiff bases are stable and can have varied denticity. Metal ion complexes of Schiff bases have been known since early times. Stable complexes of Schiff bases with metal ions can be designed by Schiff base ligands.[2] This is a significant concept of coordination chemistry. Many Schiff bases in presence of moisture show catalytic activity in biological systems, polymers and dyes. One of the valuable uses of Schiff bases is as the starting materials for the synthesis of items having pharmaceutical and industrial value.[3] Since they act as biological catalysts so they can be labelled as showing enzymatic activity.[4] There are many Schiff bases which act as homogeneous and heterogeneous catalysts.[5,6] Studies have shown that Schiff bases behave as catalysts in the reaction of hydrogenation of olefins. They are also used as corrosion inhibitors.[7] Chemists all over the world have a lot of interest in Schiff bases because they have numerous applications including catalysis, synthesis, medicine and many new technologies.[8]

Transition metal complexes of linear or cyclic Schiff bases[9] together with their derivatives have a variety of biological activities.[10-12] As a result, these have gained interest in recent times. They have been studied for their anti-inflammatory, antitumor, antimicrobial, antifungal and antioxidant activities due to the presence of azo methine group (-CH=N-).[13,14] Hydroxyl radicals are highly reactive and are the cause of many pathological conditions because they have the ability to attack any component of the living system, including DNA, protein chains, enzymes etc. Anti- inflammatory activities are possessed by those antioxidants which exhibit free radical scavenging activity. They are more potent than NISAIDs (3). Apart from this they also exhibit anti-ageing and antitumor activities, because ageing and tumor growth are a result of formation of free radicals. Hence the compounds which have antioxidant properties can prevent diseases due to inflammation of joints (rheumatoid arthritis) and other kinds of inflammation. Many complexes of various Schiff bases with copper ions have been studied for their anti – inflammatory activities.[15-24] Many other compounds with heterocyclic ligands are similar in structure to some biological proteins.[25]

Anti- Inflammatory activity of various Schiff base complexes
Studies on the antioxidant and anti-inflammatory activities of Cu (II) Schiff base coordination compounds of dien with heterocyclic aldehydes and 2-amino-5-methyl-thiazole have been reported by F. Ponitki et al.[9] Schiff bases of dipropylenetriamine with 2-thiophene carboxyaldehyde have also been assessed for their anti-inflammatory activity. These compounds have been reported to show inhibition of carrageenin induced rat

paw edema hence depicting the activity of Schiff bases as radical scavengers. DPPH is a stable radical which was used to assess biological activities.

Shahzad et al[26] have discussed the Schiff bases of 4 aminophenazone, which have lesser amount of side effects as compared to NSAIDs. This has pyrazol-3-one fragment and compounds containing this fragment have antibacterial[27], anti-inflammatory[28], anti-hypertensive[29], anti-fungal[30], anti- HIV[31], antitumor[32], and anticonvulsant activities.[33] Inflammation is a type of syndrome that can trigger a number of diseases, which can have drastic effects on human beings and animals. Inflammation is a result of body's defence against microbial infection. However, if inflammation is in excess, it may leadto chronic diseases. Common diseases linked to inflammation are asthma, chronic prostriatis, rheumatoid arthritis and acne vulgaris.[34,35] Myocardial infarction[36] is a side effect of NISAID, which may lead to renal failure also. NISAIDs have been used to treat management of edema and tissue damage due to arthritis. The mechanism of action of any anti- inflammatory drug is by the inhibition of COX (cyclooxygenase) pathway of arachiodonic acid metabolism, resulting in the production of prostaglandins which are hyperalgesic and can cause edema, erythema and pain. Hence for the treatment of rheumatic diseases, which cause pain, certain analgesic and anti-inflammatory drugs are required.[37] Shahzad et al, used the CIPO method for studying anti-inflammatory activity of drugs[38] in mice, and observed the potent anti-inflammatory activity of the Schiff base ligand they chose in their study, which was comparable to NISAIDs. Mizushima[39] had established that the mechanism of action of NISAIDs is their defence against protein denaturation which could be contributing its anti-inflammatory activity.

Some copper complexes of Schiff bases have photodynamic anti -inflammatory and antimicrobial activities as reported by Furkan Ayaz et al.[40] They have prepared a number of derivatives of Schiff bases to get photoluminescence capacity and observed that these newcopper containing Schiff bases exerted strong photodynamic anti-inflammatory activity. They also showed anti-microbial activity on gram- positive and gram- negative bacteria.

Sameh et al[41] in their article, have discussed the anti-inflammatory, antioxidant and antibacterial properties of Chitosan derivative of Schiff bases by testing its antibacterial activity against gram-positive and gram-negative bacteria which were observed to show multidrug resistance, by agar well diffusion method whereas anti-inflammatory activity was testedby albumin denaturation, membrane stabilisation and proteinase inhibition methods. They observed that the Chitosan derivative (MACSpNBA) Schiff base behaved as an effective antibacterial, anti-inflammatory biomaterial, with no cytotoxicity observed, hence indicating that these could be used for the treatment of skin burn infections because of its antibacterial,anti-inflammatory activity and also its hemocompatibility along with absence of cytotoxicity.

Ahmed et al[42] in their article have described the synthesis of Schiff bases based on pyrrolizine along with thiazolidinone moiety along with studies on their anti-cancer and anti-inflammatory activities. They found that this derivative of Schiff base exhibited cytotoxicity against cancer cell lines. Also, these exhibited anti-inflammatory activity which further improved in the presence of a heteroaromatic species.

Schiff bases synthesised from 3-phenylpropenal (cinnamaldehyde) with tryptophan /histidine as ligands and complexes formed with Cu ions were reported by Huda S. Abood et al.[43] Their anti-inflammatory activities were reported in mice by the complex, where tryptophan was used as a ligand. The Schiff base derivatives can form numerous complexes with several metal ions and can form mono, di, polynuclear complexes, depending upon their denticity. As stated earlier, inflammation is defence mechanism of the body to protect itself from infectionor response of tissue to injury caused by a pathogen. Uncontrolled inflammation, however, may lead to chronic illness.

Usama H. Ramadhan et al[44] reported the synthesis of transition metal salicylaldehyde derived Schiff base of aromatic substituted aniline and also studies on their anti-inflammatory activities by using egg albumin induced inflammation. They observed that Fe containing Schiff base complexes showed high anti-inflammatory activity. Cobalt complexes on the other hand showed very high toxicity which they observed and reported in mice. Nickel complexes showed moderate activity. Although Cobalt complexes showed high anti-inflammatory activity but were toxic. Since Fe is more widely present in the biological system hence its anti- inflammatory activities are more. Ni and Co are trace. The mechanism of action of Fe is that it easily gets oxidised and thus can destroy free radicals and H_2O_2 which are produced in inflammation.

Novel 4-aminophenazone Schiff bases have been synthesised using the technique of grinding and further, by docking studies with PDE7, they have been studied as anti-inflammatory agents by Rashmi et al.[45] NISAIDs have therapeutic potentials and are used for the treatment of gout, arthritis and bronchitis, but their long term used can lead to gastrointestinal ulcers. Thus arises the need for alternatives to NISAIDs. Molecular docking studies have helped the authors to predict the stability of the synthesised compounds and expect that these could act as potential inhibitors of PDE7 protein.

Anti-inflammatory property of a Vanadyl Schiff base complex has been studied and reportedby Jieunki et al.[46] When the transfer of glucose transporter 4 to plasma

membrane occurs, glucose is taken up and absorbed by biological cells. This reaction is triggered by insulin. The major cause of Diabetes type 2 is inflammation. As reported, the Vanadium oxo complexes show insulin imitative activities and the tryptamine moiety in the complex has anti- inflammatory properties. The authors found that Vanadyl Schiff base complex could restore insulin signalling in diabetic patients during IR. This was established using quantum dot studies. The prepared complex was found to be effective in nanomolar concentration, indicative of low toxicity.

Aqsa Gulzar et al (3) have reported the anti-inflammatory and antitumor activities of Novel Schiff base derived from 2-[(1,3-benzothiazol-2-yl) sulfanyl] -N- [4-(hydrazine carbonyl) phenyl]acetamide.

Schiff bases of 2-(4-Aminophenyl) benzimidazole have been studied for their anti- inflammatory, antioxidant and analgesic properties by Asma et al.[48] DPPH radical was used to evaluate the antioxidant activity of the Schiff base. DPPH is widely used to test free radicalscavenging ability of the Schiff base. This is a test done on laboratory animals. Since ROS are produced during inflammation and antioxidants can conquer free radicals so antioxidants could reduce inflammation also. Hence it was concluded that benzimidazole Schiff bases could act as anti-inflammatory agents.

Pandey et al[49] have reported the anti-inflammatory behaviour of novel thiadiazole derivatives in-vitro, wherein the test compounds were synthesised and checked for the inhibition of protein denaturation, inhibition of RBC hemolysis and proteinase (trypsin) inhibition assay. Since inflammation is a result of denaturation of proteins, so the ability of the Schiff base complex to inhibit protein denaturation has been reported in the article by the authors. It was observed that as the concentration of the Schiff base compound increases, the percentage inhibition of protein denaturation increases. The compound also reported tosuppress RBC hemolysis. Membrane stabilisation effect of the Schiff base compound was reported as an additional mechanism for their anti-inflammatory action. These compounds were found to behave as proteinase inhibitors as proteinase is involved in arthritis (inflammation of joints).

A review has been written by Md. Saddam Hossain et al[50] on the microbial application of coordination complexes. Many a literature is available regarding interaction of a variety of metal ions complexes with DNA. These metal ions are V (IV), Ni (II), Co (II), Cu (II), and Zn (II). Cu (II) is an important biological element responsible for redox reactions, growth and chemistry of the body. Many enzymatic and biological reactions are carried out in the presence if Cu (II). Copper Schiff bases are found to bind to DNA and prevent its replication.

The anti-inflammatory and anti-tubercular activity of Schiff base of Isatin with 2- thiopheneethylamine and its Mannich bases have been studied by Bhushan D. Varpe et al.[51] This study was done by analysing percentage inhibition of denaturation of the protein Bovine Serum Albumin. The authors reported the effectiveness of 3-(2-thiophen-2-yl) ethylimino) indolin -2-ones (Mannich bases of 2-thiopheneethylamine) as an effective anti-inflammatory drug.

The derivatives of Indomethacin with Schiff bases as anti-inflammatory and anti- cancer agents have been studied by Jessica Shlimoon Alawad et al.[52] They reported that inflammation is a series of responses exhibited by the body to eliminate the source of infection. Untreated acute inflammation can lead to chronic inflammation which can cause acute inflammation. Anti-inflammatory medicines have been found to be effective in preventing cancer and reducing mortalities due to cancer. NISAIDs help in the reduction of risks due to cancer. The COX (cyclooxygenase) enzyme family is the target of NISAID, and NISAIDs reduce the activity of COX-1 and COX-2. The authors have reported the modification of one of the NISAID – Indomethacin, using molecular docking to increase the effectiveness of the drug. By using ADME studies, the effectiveness of the prepared compounds has been reported. The Schiff bases have been described to exhibit anti-inflammatory activities by reporting the molecular docking studies for ligand interactions with COX-2 protein.

T.J.Saritha et al[53] have reported the anti-inflammatory activity of transition metal complexes with Schiff base which has been derived from curcumin and semicarbazide. By various spectral techniques like FT-IR, UV-Vis, NMR, Mass, TG-DTA and ESR, the structures ofthe Schiff base ligand were established and confirmed. By evaluating the Schiff base ligand and its metal complexes, for their anti-inflammatory and antimicrobial action, it was reported that the metal complexes of the Schiff base ligand were more active than the ligand itself. Moreover, Zn (II) complexes with Schiff base were found to be the most active in terms of anti-inflammatory activity. This study was carried out by the protein denaturation method.

Betriz et al[54] synthesised and studied a nitro Schiff base compound for its anti- inflammatory activity. The synthesis and characterisation were done by ^{1}HNMR and ^{13}CNMR. The anti-inflammatory activity was studied in vivo, using models causing inflammation like the neutrophil migration assay, paw edema and exudiation assay along with studying the production of NO in vivo and in vitro, since NO caused inflammation. It was observed the compound did not induce hemolysis or cytotoxicity or genotoxicity in cells. The neutrophil migration assay showed reduction in the number of neutrophils. Paw edema model showed reduction in paw volume of mice, and the production of NO was found to

decrease in vivo and in vitro. By these results the authors came to the conclusion that nitro Schiff base compound effectively inhibited inflammation.

A Schiff base was formed by 4-aminoantipyrine and its derivatives. It was then condensed with different types of carbonyl compounds and their metal complexes. The metal chelates which resulted are used in anti-inflammatory, antioxidant and antimicrobial activities. Thesestudies have been reported by Sakthivel et al.[55]

Antibacterial and antifungal effects of a thiazolyl-triazole Schiff base were studied against Gram positive and Gram negative bacteria by Cristian Cezar Login et al[56] The Schiff base showed more efficiency as an antibacterial agent against L. Monocytogenes and P.Aeruginosa**.** Apart from this, the Schiff base also showed anti-inflammatory activities. As mentioned, ROS play an important role in causing inflammation, by attracting more cells to the inflamed site. Nitric Oxide produced by the bacteria protects Gram positive and Gram negative bacteria against oxidative stress and increases bacterial resistance towards antibiotics. Bioactive substances like thiazoles, triazoles and their derivatives are found in antibacterial and anti-inflammatory drugs, can reduce nitric oxide synthesis in bacteria, as reported by the authors.

Quinazolinone Schiff bases can behave as biotherapeutics as studied and reported by B.J. Ullas et al.[57] They synthesised and characterised two series of quinazolinone derived Schiff bases by analytical and spectroscopic techniques. The in-vitro biological studies were carriedout for all compounds. Electron withdrawing groups like (F, Cl, Br, NO_2) favour the anti-inflammatory activity whereas electron donating groups (-OH, $-OCH_3$) favour antioxidant activity and both electron withdrawing and electron donating groups favour antimicrobial activity of Schiff base ligand in the above.

Silibinin (SIL) is a flavonoid -lignan used to treat fatty liver disease. However, its use is limited because of its insolubility in lipids. Hence Rong Xu et al[58] have synthesised SIL derivatives with greater biosafety and solubility. The authors have prepared two SIL derivatives by Schiff base reaction and the solubility of these derivatives is greater. The two derivatives also showed lower toxicity and higher anti-inflammatory activity. SIL extracted from silibinin seeds shows many bioactivities, including antioxidant, anti-inflammatory, anti-cancer and anti-viral activities. To overcome the limitations of insolubility in lipids, Xu et al chose the carbonyl side of SIL for the reaction with Schiff bases and sulphur containing amino acids were chosen as hydrophilic ligands. The solubility of SIL in biological fluids is found to improve due to the hydrophilic nature of the ligand. The authors studied acute liver injury caused by CCl_4 in an animal model to observe behaviour of the two Schiff base derivatives. This enabled Xou et al to understand and detect the hepatoprotective activity of the drugs, pathology related to inflammation and liver apoptosis. Several SIL derivatives were formed with Schiff bases by condensation reaction of SIL with sulphur containing hydrophilic ligands. They were tested for physiochemical properties, in vivo biosafety and bioactivity. S-allyl-L-cysteine/taurine and NaOH were reacted with SIL to obtain SS and ST. They were further analysed by Powder X- Ray Diffraction method, in vitro solubility test, cytotoxicity, oral toxicity, liver toxicity, hematology, serum biochemistry, histopathology etc. It was reported that SS and ST's improved the in vitro solubility of SIL, along with improved safety, reduced CCl_4 induced hepatocyte and necrosis. SIL is a hepatoprotective drug and is used in the treatment of clinical toxicity. Experiments were carried out to show the low toxicity of SS and ST's.

R.V. Sakthivel et al[59] have synthesised Co, Ni and Cu metal complexes from Schiff base ligand 2,2'-(1E,1E') (4 nitro-1,2-phenylene) bis (azanylylidene) bis (methanylylidene) diphenol. The structure was analysed by FT-IR, NMR, UV-VIS spectrum, elemental analysis and Powder X-Ray diffraction. Biological activities like antioxidant and anti-inflammatory have been studied and their complexes synthesised were found to have good anti-inflammatoryproperties.

Mn (II), Ni (II) and Cu (II) are the transition metal ions which have been used to synthesise metal chelates with Schiff bases of diacetyl monoxime with o-phenylenediamine, by Abdulsalam et al.[60] They have studied the antibacterial activities of these complexes. Schiff bases are also known as imines or azomethines. After their synthesis, their antibacterial activity was studied where the bacteria species suspension was prepared in a sterile distilled water and spread on agar medium surface. All the compounds synthesised were allowed to interact with these. Then various analysis methods including IR, NMR, mass spectra were used to study the characterisation of the compounds, on the basis of which, the authors deduced the ratio of transition metal ion -Schiff Base chelates to be 1:1 (M:L). These compounds showed good activity against all types of bacteria.

Bicyclic derivatives of Schiff Bases having 1,3,4 thiadiazole moiety have been studied in a review by Sherin A. Hameed et al.[61] 1,3,4 thiadiazole is having a heterocyclic nucleus which forms a part of medicinal agents. Schiff Bases with 1,3,4 thiadiazole exhibit antifungal, antibacterial, antitubercular, antioxidant, anti-inflammatory analgesic, anticonvulsant, antidiabetic and anticancer activities. They reported the studies of Alok Pandey et al wherein the compound showed good anti-inflammatoryactivity.

Rabiha et al[62] synthesised some new thiazolidinone compounds which were derived from Schiff base compounds and were evaluated for their biological

activities. 6-flouro -2- aminobenzothazol compound was prepared by reacting aniline with KSCN in the presence of cool CH3COOH. Benzothiazoles are heterocyclic compounds behaving as anti-inflammatory agents. Schiff bases also have different uses. The thiazolidine-4-onering is reported to have anti-inflammatory, antifungal, antitumor and antimicrobial activities. The authors have synthesised 2-amino-6-flouro benzothiazoles using substituted anilines and KSCN in Schiff base compounds with the help of a mixture 2- hedruzeno-6-sub benzothiazole and aromatic benzaldehyde in ethanol was done. From this, thiazolidine-4-one derivatives were synthesised using Schiff base and thioglycolic acid. After this, their biological activities were studied against Gram positive and Gram negative bacteria. By the results, it was observed that the compounds prepared showed effective anti -inflammatory activity.

P.N. Balaji et al[63] in their studies, have established the in vitro anti-inflammatory activity for novel imine derivatives from acetyl coumarin. In this study, they have used glycerol as a solvent for synthetic uses. The imine derivative coumarins were subjected to in vitro anti-inflammatory activity screening by studying their potency to inhibit bovine albumin denaturation by thermal induction technique. Upon analysis, it was found that the synthesised compound showed anti-inflammatory activity.

Similarly, K.P. Rakesh et al[64] have synthesised Schiff bases of quinazoline derivatives, which are potential anti-inflammatory agents. These derivatives were checked for in vitro anti-inflammatory activities and were also found to be good anti-inflammatory agents.

CONCLUSION

Schiff base derivatives and their complexes with metal ions have gained importance in recent years because of their varied applications. They are a class of versatile complexes having applications in the field of medicine, catalysis and material science. The present review focusses on the synthesis of metal ion-Schiff Base complexes and their anti-inflammatory applications over the past six years. Their advantages over NSAIDs have also been discussed. Along with this, the growing interest in Schiff base complexes as antimicrobial, antifungal and anticancer agents, has also been described. Since the Schiff base complexes have abundance of potential uses, this review therefore aims to provide a collective summary of the anti-inflammatory drugs from Schiff base derivatives and tends to pave the way for research on the synthesis of new Schiff bases having anti-inflammatory and other therapeutic applications.

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