EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 8
Issue: 9
244-252
Year: 2021

BIOLOGICALLY ACTIVE SCHIFF BASE NANOPARTICLES: A REVIEW

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Article Received on 26/06/2021 **Article Revised on 16/07/2021** **Article Accepted on 06/08/2021**

ABSTRACT
Imine bonds containing substances called Schiff bases are known for their role in medicines apart from other fields of human interest. Their complexes with transition metals have been studied at length for their role in health of mankind. Recent awareness of climate change and harmful effect on environment attributed to fast pace of industrialization, has got the scientist community into focussing their attention on developing novel materials having same or improved qualities. One such area of attention is synthetic pathways leading to bioactive Schiffbase metal complexes. Ability of Schiff base to act as ligand to various metals to form complexes has been explored extensively due to their application in vast industrial activities such as agriculture, cosmetics, dyes, etc. Being of pharmacological importance (antifungal, antibacterial and anti-cancerous activities), synthetic procedures have been reported for nano size Schiff base metal complexes using different transition metals. Nano chitosan, graphene oxide and magnetic nanoparticles supported Schiff bases are also investigated for their biological and industrial applications. These nano size materials/hybrids not only exhibit desirable biological efficiency, additional features due to their size make them useful in other aspects of medical treatments such as drug delivery. In this review we bring together work done in this field over last five years.

KEYWORDS: Schiff base, Nanoparticles, Bioactive, antibacterial, anticancer.

INTRODUCTION
Nanomaterials (NMs) owing to their adaptable qualities enjoy prominence in technological advancements and are thus more explored compared with bigger counterparts. As a consequence of several advantages of NMs over bulk materials they find widespread application and issues related to their toxic effects are but natural.

Though categorization of NMs on the basis of their dimensions was first presented by Gleiter et al.[1] and later by Pokropivny and Skorokhod[2], depending on their size and shape, composition and on their occurrence etc., they can be characterised in many ways. As of today, with a special reference to specificity of NMs there are several legislations in place in the European Union (EU) and USA. However, a single internationally accepted definition for NM does not exist. Different organizations have a difference in opinion in defining NMs.[3] According to the Environmental Protection Agency (EPA), "NMs can exhibit unique properties dissimilar than the equivalent chemical compound in a larger dimension".[4] The US Food and Drug Administration (USFDA) also refers to NMs as "materials that have at least one dimension in the range of approximately 1 to 100 nm and exhibit dimension dependent phenomena".[5] Similarly, The International Organization for Standardization (ISO) has described NMs as a "material with any external nanoscale dimension or having internal nanoscale surface structure".[6]

Though there is no specific way of defining nano materials, whether synthesized or of natural origin having at least one dimension measuring between 1-1000 nm have been basically categorized as nanomaterials (NMs).As mentioned earlier due to lack of a single definition to summarize and describe them , NMs can be subdivided into 4 classes on basis of comprising materials.

(i) Carbon-based nanomaterials[7] (ii) Inorganic-based nanomaterials (iii) Organic-based nanomaterials (iv) Composite-based nanomaterials[8] that have multi dimensional different combinations of NMs of all the three above, but must have one dimension measuring in nanoscale. Another classification is based on occurrence:(i) Natural nanomaterials[9] and (ii) Synthetic (engineered) nanomaterials.[10]

With the aid of advancement in technology aimed at improving lifestyle, new genre of NMs, classified as NPs[11] such as carbon NPs[12], TiO_2 NPs[13] and hydroxyapatites[14] have been synthesized. These NPs find use in cosmetics, sporting goods, sunscreen and toothpaste and may cause undesirable effects on human health and environment.

A knowledge of NPs presents in living systems, humans included, has opened up newer ways of biomedical treatments as evidenced by aggressive research in field of bio nanotechnology. These are illustrated in beneficial biomedical applications such as formation of DNA-templated metal structures, DNA nanostructures, nano barcoding and DNA sensors.[15] Advances have been made in DNA-based nanoscale architectural features utilized in drug delivery, molecular electronics and logics.[16]

Based on this knowledge of NPs in humans and role of drugs to fight the abnormal biological functioning, newer less harmful yet economical ways of combating life threatening diseases have emerged as new frontiers. One such area of interest is Schiff base forming complexes with different metals synthesized as NPs. Schiff base, SB, acts as ligand through its imine group and can thus form complexes with metals. SB, named after Hugo J. Schiff[17], who first synthesized it, can be obtained by a condensation reaction between an aldehyde and a primary amine. Facile synthesis of several Schiff Base metal complexes has been reported. This synthetic ease and ready availability make these coordination complexes not only used in varied industries such as, metallurgy, photography, analytical chemistry, agrochemicals and dye industry but also in pharmaceuticals.[18,19] Antibiotic activity of SB is known since early civilization. This has led the scientist community world over to explore this aspect in SB metal complexes as well. Successful studies have shown that metals complexes like those of Fe witha variety of SB as ligands, exhibit anti-bacterial activity against *E. coli*, *P. aeruginosa*, *B. cereus*, and anti-fungal activity in cultures such as *P. purpurogenium*, *A. flavus*, and *T. rosium.*[20] Reports are shared on study of cytotoxic activity on HCT-116 cell line[21], MCF-7 (breast carcinoma), MDA-MB-231 (breast carcinoma) and CT-26 (colon carcinoma) cell lines[22], due to possible interaction of complexes with DNA. These metal Schiff base complexes, are also being used as a precursor for versatile, bioactive and commercially explored metal oxide nanoparticles.[23-25] The vibrant and miscellaneous applications of CSBs is responsible for growing interest for syntheses of new chitosan-based Schiff bases (CSBs) and their metal complexes; review articles are reported on properties of CSBs and their applications.[26-28] Therapeutically efficient Schiff base anchored nano hybrids have also been synthesized on functionalized graphene oxide and magnetic Fe_3O_4 as solid supports.[29,30] Successful syntheses of these nano Schiff base materials have paved the way for introducing green aspect of organic synthesis without compromising on their bioactivity.

This review is an attempt at collective presentation of work done over the past five years on biologically active - Schiff base-metal complex NPs, Schiff base-nanohybrids and Schiff base derived nano particles.

Nanosized Metal-Schiff base complexes (Table 1)

The science of Schiff bases and their complexation with transition metals is extensively studied and explored owing to the broad-spectrum applications of these organic-inorganic hybrids in pharmaceutical, industrial and analytical chemistry in addition to their excellent biological activity. Of the transition metal complexes with Schiff base as ligands, those with heterocyclic ligands have drawn more interest and applications in newer fields including in catalytic reactions and in organic synthesis.[20]

Three novel Schiff bases were synthesized by condensing 5-bromosalicylaldehyde with three different pyrimidine derivatives and further their nanosized complexes were prepared using Co(II), Ni(II) and Cu(II). The synthesized Schiff bases were found to behave as a tridentate chelator coordinating the metal ions by azomethine and pyrimidine ‘N’ and phenolic ‘O’ in 1: 1 (metal to ligand) ratio. To explore the ability of the prepared complexes to bind to DNA, electronic absorption and viscosity methods were employed, which indicated that binding happened through intercalation. The complexes and ligands were screened for their antifungal activity using the disc diffusion method and antibacterial activities by the well diffusion method. Complexes showed more antimicrobial activity as compared to their respective ligands. Their anticancer activity was tested on human colon and hepatic cellular cancer cell lines. Once again metal complexes performed better than the chelating ligands showing enhanced anti-proliferative action against cancer cells.[31]

Newly synthesized Oxazine Schiff base ligands, utilizing only three out of four coordinating sites reacted with Co(II), Ni(II), Cu(II), Zn(II) to provide a series of novel nano-sized complexes. The elemental analysis revealed 1:2 metal to ligand stoichiometry. The in vitro antibacterial activity of the nano hybrids against various bacterial strains was compared with the drugs such as streptomycin. Ligands, along with the hybrids showed promising antimicrobial activity against the bacterial strains. The antioxidant activity of synthesized ligand and its metal complexes was determined against DPPH. The percentage of antioxidant activities were found more for complexes than for the ligand; Copper and zinc complexes being more active. Furthermore, the antitumor activity of the synthesized compounds was evaluated using MTT method, towards human liver Carcinoma (HepG2) cell line and the results were measured in terms of percentage of cell toxicity with control. The nanometal hybrids demonstrated higher activity in comparison to their free ligands. Their DNA-binding, DNA cleavage and fluorescence properties were also studied and reported.[32]

A novel Schiff base ligand was prepared from condensation between benzoin and 2- aminothiophenol. The La (III) complex of the prepared ligands were obtained in nano size along with the Co (II), Cd (II), La (III), and Gd (III) complexes in bulk size. The examination of their cytotoxicity using MTT method revealed better possibility of Cd (II) complex to be used as an anticancer agent against tested cells with higher cell viability than the free ligand itself.[33]

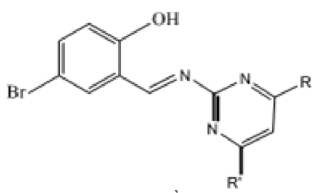
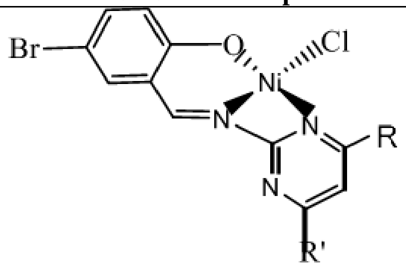
The Co(II), Ni(II), Cu(II) and Zn(II) complexes of a novel tridentate antipyrine Schiff base ligand were synthesized and dully characterized by analytical, spectral and image processing techniques. Co(II), Ni(II) and Zn(II) complexes adopted octahedral geometry whereas Cu(II) complex occupied distorted octahedral geometry. The ligand to metal ratio was found to be 1:1. XRD studies suggested the nanocrystalline nature of the synthesized complexes. The ligand and its metal (II) complexes were investigated for their bactericidal activity against Gram-positive and Gram-negative strains by Broth micro dilution method. The results proved the ligand and its complexes to be active against both type of bacterial strains but at higher concentrations. The performance of Cu(II) complex was best among all the complexes. During in vitro antifungal activity on some fungal strains, the metal Schiff base complexes performed better than the ligand in this order: Cu(II) > Co(II) > Ni(II) > Zn(II) >L. The observations were supported by chelation theory. DNA cleavage studies were also done in which formation of the reactive diffusible hydroxyl radical was predicted to be responsible for the observed cleavage activity. To check anticancer potency of the synthesized ligands and complexes were tested on Liver Bilobular cancerous cells at various and once again Cu(II) complexes responded better than the free ligand and the other complex.[34]

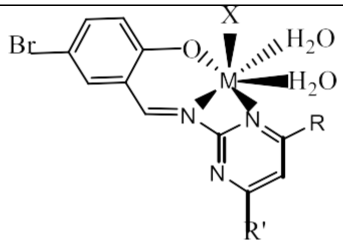
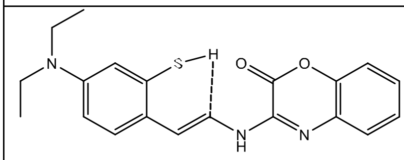
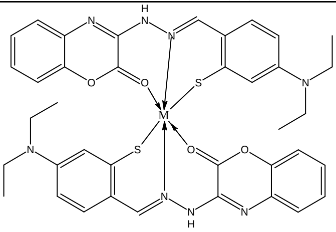
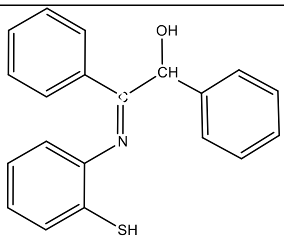
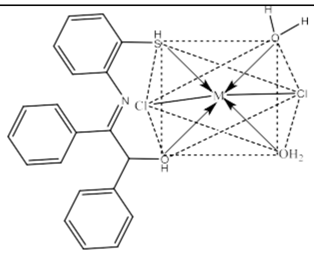
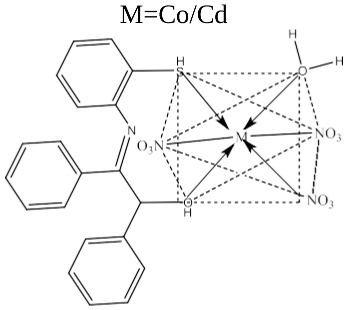
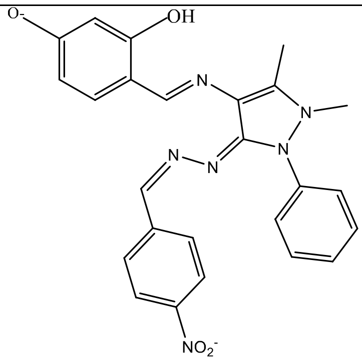
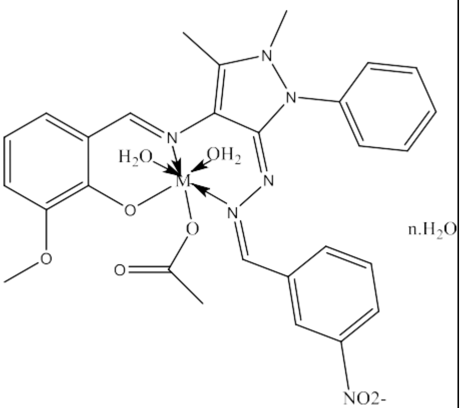
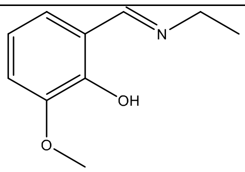
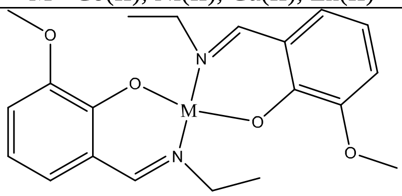
Through a one-step condensation reaction, two Schiff base ligands of 3- methoxysalicylaldehyde were obtained to synthesize three novel Cu(II) and Ni(II)-based coordination complexes. These complexes, after undergoing hand grinding technique provided nano-complexes. Biological activity studies of synthesized nanostructures, performed on MCF7 breast cancer cells, revealed the significant activity of nanoparticle having Cu(II). It was evident from these studies that the nanoparticles had sufficient anticancer activity due to mitochondrial fragmentation in MCF7 cancer cells, which in turn caused the cancer cell apoptosis.[35]

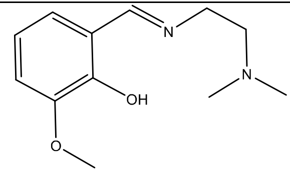
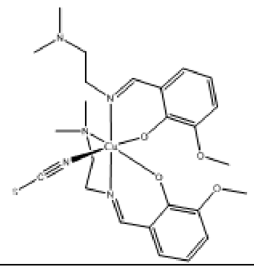
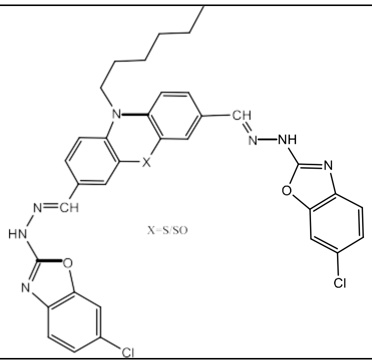
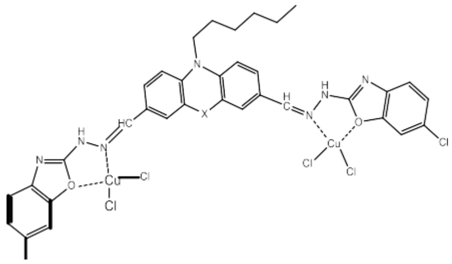
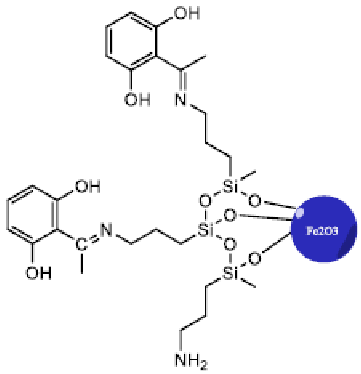
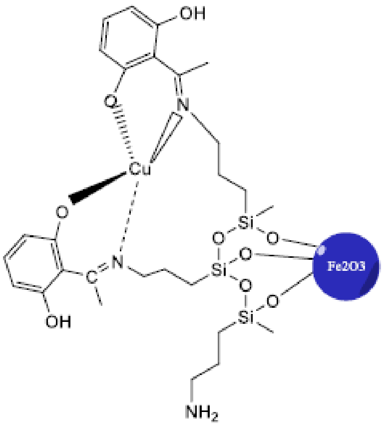
In tandem with technological advances, wider area of application of nanocomplexes and application of the green principles in synthesis, novel methods of synthesis utilizing ultrasound for N_2O_2 symmetric Schiff bases bearing phenothiazine and phenothiazine oxide and their nanosized copper(II) complexes have been reported. The antioxidant studies performed using standard procedures proved copper complexes to exhibit more scavenging action than the parent ligand. Although the action was comparable with the standard antioxidants. The complexes showed more antibacterial activity as well against the bacterial stains as compared to their ligands.[36]

Superparamagnetic $Fe_3O_4@SiO_2@APTS\text{-}NH_2$ Schiff base@Cu(II) nanoparticles have been synthesized as potential anticancer agents. First $Fe_3O_4@SiO_2$ NPs were prepared then they were made to react with (3-aminopropyl) triethoxysilane (APTS) to provide $Fe_3O_4@SiO_2@APTS\sim NH2$ which upon condensation with 2,4-dihydroxy benzaldehyde provided $Fe_3O_4@SiO_2@APTS\sim NH2$-Schiff base nanoparticles. The complexation of the later with Cu(II) yielded the final product i.e. $Fe_3O_4@SiO_2@APTS\sim NH2$ Schiff base@Cu(II) NPs. All the prepared nanoparticles were tested upon K562 (myelogenous cancer) cell lines to examine their anticancer efficacy by MTT assay test. The high toxicity of $Fe_3O_4@SiO_2@APTS\sim$Schiff base-Cu(II), with IC50: 1000 lg/mL, was attributed to their effective in situ degradation, with increased intracellular release of Fe ions, as compared to the surface passive NPs. In addition, for the first time the simulations studies of all the compounds were performed. DNA binding affinity predictions were also made using the docking methods.[37]

Table1: Nanosized metal Schiff base complexes and their biological applications.

Structure of Schiff base	Structure of Complex	Biological action	Ref
 L1; R=R'=CH_3 L2; R=OCH_3, R'=CH_3 L3; R=CH_3, R'= CH_3		**Antibacterial** *S. aureus, B. substilis* and *E. coli* **Antifungal** *C. albicans, A. flavus* and *T. rubrum* **Anticancer** Hepatic cellular (HepG- 2 cell line), human colon carcinoma cells (HCT-116 cell l Line)	[31]

	 X=NO_3, Cl M=Cu(II),Co(II)		
	 M= Co(II), Ni(II), Cu(II), Zn(II)	**Antibacterial** *P. aeriginosa*, *S. aureus*, *B. subtilis*, and *E. coli* **Anticancer** Human liver Carcinoma cell line (HepG2) **Antioxidant**	[32]
	 M=Co/Cd  M=La/Gd	**Anticancer** Colorectal cancerous cell line (Caco-2) Breast cancer (MCF-7) cells	[33]
	 M= Co(II), Ni(II), Cu(II), Zn(II)	**Anticancer** Liver Bilobular cancerous cells **Antibacterial** *S.aureus*, *S. pyogens*, *M. variance*, *E. Coli* and *K. pneumoniae* strains	[34]
		**Anticancer** MCF7 breast cancer cells	[35]

	M=Cu/Ni 		
		**Antibacterial** *S. aureus, S. faecalis, P aeruginosa,* and *E. coli* **Antioxidant**	**[36]**
	**Fe_3O_4@SiO_2@APTS-NH_2Schiff base@Cu(II)** 	**Anticancer** K562 (myelogenous leukemia cancer) cell lines	[37]

Schiff base modified nanoparticles /nanocomposites (Table2)

Ionic silver is well known since centuries for its antimicrobial properties. Though restricted to use in treatment of burns, the possible metal-organic framework has become a new favourite and found importance as pharmacophore biologically.[38,39] In view of this, a new synthetic strategy was developed to prepare Schiff base mediated silver nano particles (AgNPs). The method involved reaction between Schiff base- 2,20 -((1E,10 E)-(propane-1,3- diylbis(azanylylidene)) bis(methanylylidene))diphenol and silver nitrate. The reaction was monitored using UV–Visible spectroscopy and the resulting Schiff base -AgNPs were characterized by FT-IR and AFM techniques. Furthermore, the novel nanocomposite, in its anticancer activity, tested for the first time, induced 94% DU-145 cells lysis. which was consistent to the previously reported Schiff base nanoparticles. Additionally, the nanomaterial showed significant antibacterial action against the tested strains.[40]

To combat the problem of resistance, short half-life, limited bioavailability and adverse effects on prolonged use associated with Gentamycin, it was encapsulated on zein nanoparticles using liquid-liquid dispersion technique; further modified with Schiff base crosslinking anchored on chitosan polyvinyl alcohol gel matrix. The present nanocomposite system [GMZNP]PG-CS- PVA comprising gentamycin along with Schiff base (derived from polyallylamine hydrochloride and glutaraldehyde) presents a non-toxic and biocompatible method towards L929 cells which after application allows drug to stay intact in the dermal tissues to provide sustainable release with no need of recurrent administration. The formulation was found to have better stability, ease of application and improved penetration. Colony counting assay, performed with *E. coli* and *S. aureus*, to further confirm the efficacy of the prepared nanocomposite showed extreme decrease in colony. Authors suggest that controlled release of drug and its interaction with Schiff base are probably responsible for the observed reduction inbacterial cell growth.[41]

Organic polymeric materials like Chitosan (CS) or its derivatives are being used widely in various biomedical applications like drug delivery, wound healing, antibacterial activity etc.[42,43] As compared to free CS, metal complexes of CS reportedly have better antimicrobialactivity. Improved prospects of Schiff bases of CS compared to chitosan have also been reported.[44,45] This aspect is attributed to involvement of interface of organic-inorganic materials thereby make them non-toxic, hydrophilic, biodegradable and biocompatible.

One such biopolymeric Cs-SA Schiff base was prepared taking Salicylaldehyde (SA) as a crosslinker with chitosan. It was then made to react with TiO_2 NPs to form a hydrogel membrane having TiO_2 NPs. The nanocomposite showed excellent physical and thermal properties. The improved physical properties can be attributed to presence of either cross linkages or nano metals. The results validated that the presence of metal nanoparticles affect strength properties whereas the crosslinking affects plasticity. The prepared membranes were investigated for their antibacterial activity through CFU method and exhibited full bacterial eradication. Authors claim that all the prepared membranes can be used as antibacterial membrane for wound dressing and food backing.[46]

Iron oxide nanohybrids [Fe_3O_4@SBCTP] were prepared by condensation between amine functionalized Fe_3O_4 NPs and heterocyclic Schiff base (SBCTP). SBCTP, was synthesized by the substitution reaction between Schiff's base and aromatic aldehyde on hexachlorocyclotriphosphazene (HCCP). The nanohybrid and its constituents i.e. Fe_3O_4 NPs and SBCTP were tested for their cytotoxic activity against cancerous cells using MTT assay. Effect observed was vigorous but without the discrimination between normal and cancerous cells.[30]

A clean, economic and green synthesis of Schiff base modified Unye bentonite (UN) particle supported, Pd NPs(Pd NPs@UN) has been achieved in absence of toxic reducing agents. The prepared Pd NPs@UN demonstrated excellent catalytic efficacy, recyclability. To illustrate theantibacterial activity of the nanoparticles the disc diffusion method was adopted on Gram-negative bacteria, *E. coli* and Gram-positive, *S. aureus*, cultured in Muller Hinton (MH) agar. Antifungal activity was investigated on fungi *C. albicans*. The results revealed promising action of Pd NPs@UN against tested fungi and bacteria.[47]

Composite reaction of graphene oxide nanoparticles with isatin and guanine resulted in the formation of two novel nanocomposite material which were characterized by the FT-IR technique. The biological activity of the nanocomposites was tested on various positive and negative gram bacterial strains using Agar well diffusion method and the results had shown that the Nano Schiff base with isatin to be interestingly inhibitive against the *S. aureus* while the guanine Schiff base was found to exhibit moderate or low activity against the tested bacteria.[29]

Scientists prepared Schiff base encapsulated ZnS nanoparticles via coprecipitation method. Schiff bases used in the present study comprised salicylaldehyde nucleus (salicylaldehyde 2- methyl-3-thiosemicarbazone and salicylaldehyde triazole). Four gram-positive and gram-negative bacterial species i.e., *E. coli*, *B. subtilis*, *P. aeruginosa*, and *S. aureus* were selected for bactericidal activity of the aforesaid nanoparticles as well as their respective Schiff bases. Unfortunately, neither nanoparticle nor any of Schiff bases showed inhibition in bacterial colony under the experimental conditions. Authors expect that under the modified conditions the synthesized compounds may perform better and display substantial activity.[48]

Table 2: Various Schiff base nano particles/composites and their biological applications.

Schiff base nano particles/composite(Schiff base components)	**Biological activity**	**Ref.**
Schiff base – Ag NPs (Salicylaldehyde+diamine)	**Anticancer** DU-145 cells	[40]
[GMZNP]PG-Cs-PVA (polyallylamine.HCl + glutaraldehyde)	**Antibacterial** *E. coli* and *S. aureus* **Sustained release of drug**L929 cells	[41]
Salicylamine-chitosan/TiO_2(Salicylaldehyde + Chitosan)	**Antibacterial** *S. Auras* and *P. aeruginosa*	[46]
Fe_3O_4@SBCTP (Salicylaldehyde+ Hexachlorocyclotriphophazene)	**Anticancer** Cancer cell line	[30]
Pd NPs(Pd NPs@UN) (Pyrrole-2-carboxyaldehyde+ NH_2 modified Unye bentonite)	**Antibacterial** *E. coli* and *S.aureus* **Antifungal** *C. albicans*	[47]
Nano Schiff base-GO (Isatin/ Guanine+ Graphene oxide Np hydrazine hydrate)	**Antibacterial** *S. aureus*, *B. thyuringiensis*, and	[29]

	P. aeruginosa.	
Schiff base-ZnS (Salicylaldehyde+ 2-methylsemicarbazone/4-amino-4H-1,2,4-triazole)	**Antibacterial** *E..coli, B. subtilis, P. aeruginosa,*and *S. aureus*	[48]

Metal oxide NPs derived from Schiff base-metal complex

In recent years, metal oxide nanoparticles have become very popular amongst synthetic chemists because of their versatility, catalytic superiority and commercial applications.[49] Different methods have been reported in literature to prepare metal oxide nano particles from Schiff base metal complexes as a precursor.[50]

In this direction scientists have made attempts and successfully synthesized titanium dioxide (TiO_2) nanoparticles from titanium Schiff base complexes through direct calcination method. Synthesized nanoparticles, in their antimicrobial study showed sufficient inhibition capacity on the growth of selected plant and human pathogens in addition to their remarkable catalytic capacity for the degradation of organic dyes.[51]

Generation of CuO NPs by thermal decomposition of Cu(II)-Schiff base complex, were shown to act as reusable catalyst for reduction of 4-nitrophenol which is one of the most toxic and unmanageable pollutants in wastewater produced by industries manufacturing dyes and explosives. Activity of synthesized NPs as antimicrobials and antioxidants was also carried out.[52]

In another attempt, novel tetradentate N4 donor Schiff base ligand and its Zn(II) complexes have been synthesized which subsequently served as precursor for ZnO nanoparticles. Studieson the cytotoxic effects of the complex and photocatalytic activity of nanoparticles have been reported.[53]

CONCLUSION

Products of simple condensation reaction between an aldehyde and an amine, Schiff bases are amongst oldest known for their bioactivity along with a variety of other industry-based applications. Metal complexes derived from a variety of Schiff bases have also been found to be useful in biomedical field as well. With the recent advances in technology, nano size SB metal complexes and metal oxide from these complexes could be synthesized and studied for their bioactivity. Reports are available describing not only their potential use in waste water management, corrosion inhibitors, as catalysts, to name a few industries based application, but also as potent formulations for antifungal, anti-cancer, antibiotic and cytotoxic activity, and as drug delivery systems. Keeping in mind the fragility of environment, further research work could be designed involving study of these biocompatible NP SB metal complexes, in dose optimizations to be used as disinfectants in hospitals, activities like antimicrobial, antioxidants, etc, which would find applications in environmental, industrial, and biomedical fields.

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