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Antioxidant Activity of Schiff Bases and Their Metal Complexes: A Recent Review

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ABSTRACT

Schiff bases and their complexes are versatile compounds prepared from the condensation of primary amines with carbonyl groups. Schiff bases are very important compounds in various fields, especially in medicinal and pharmaceutical fields because of their wide spectrum of biological activities. The activity is usually increased by complexion therefore understanding the properties of both ligands and metals can lead to the synthesis of highly active compounds. Some of these compounds are identified as having high capacity in scavenging free radicals. This review summarizes the synthesis and antioxidant activities of Schiff bases and its complexes.

1. Introduction

Schiff Bases have been known since 1864 when Hugo Schiff reported the condensation of primary amines with carbonyls compounds [1]. The common structural feature of these compounds is the azomethine group with a general formula RHC=N-R1, where R and R1 are alkyl, aryl, cyclo alkyl or heterocyclic groups which may be variously substituted. These compounds are also known as anils, imines or azomethines [2].

Schiff bases are a special class of ligands with a variety of donor atoms exhibiting interesting coordination modes towards transition metals [3]. Schiff-bases have been widely used as ligands because of high stability of the coordination compound, of them and their good solubility in common solvents such as ethanol, methanol, chloroform, dimethyl formamide [2].

Schiff bases are well known for their wide applications and are useful intermediates in organic synthesis [4]. These compounds have intrinsic biological activities including anticancer [5], antitumour [6], antitubercular [7], antibacterial [8], antifungal and antifertility [9], antioxidant [4], herbicidal [10, 11] and antiproliferative [12], activities. Moreover, Schiff bases also exhibit fluorescence [13], photoluminescence [14], a potentiometric cation caring [15], aggregation [16] and anthelmintic [17] properties.

Schiff base ligands are easily synthesized and form complexes with almost all metal ions [18]. Their complexes are considered to be among the most important stereo chemical models in main group and transition metal coordination chemistry due to their preparative accessibility and structural variety [19]. However the incorporation of transition metal ions into these compounds have enormous wide applications in the field of the food industry, dye industry, analytical chemistry, catalysis, fungicidal, agrochemical along with biological activities and decrease in the cytotoxicity of both metal ion and Schiff base [20, 21].

Free radicals have been implicated in the causation of several oxidative damages diseases such as liver chirrhosis, atherosclerosis, cancer, diabetes, ageing [22]. Antioxidants are our first line to defense against free radical damage, the need for antioxidants become even more critical with increased exposure to free radicals pollution, cigarette smoke, drugs, illness, stress and even exercise can increase free radical exposure [23].

The search for metal-derived antioxidants has received much attention and effort in order to identify the compounds having high capacity in scavenging free radicals related to various disorders and diseases associated with oxidative damage, caused by reactive oxygen species (ROS). Presently, synthetic antioxidants are widely used because they are effective and cheaper than natural antioxidants. Currently a number of Schiff-base metal complexes have been investigated as effective scavengers of ROS, acting as antioxidants [18]. In view of these observations, I plan to review the antioxidant activities of Schiff bases and its metal complexes.

2. Experimental Methods

2.1 Synthesis of Schiff Bases and Its Complexes

Schiff bases have been synthesized from a variety of compounds, such as amino thiazoles, 2-hydroxy-1-naphthalaniline, amino sugars, aromatic aldehydes, ketones, isatin, triazole ring, thiosemicarbazides, amino acids, pyrazolone, etc., [24, 25].

The first preparation of imines was reported in the 19th century by Hugo Schiff (1864). Since then a variety of methods for the synthesis of imines have been described [26]. The classical synthesis reported by Schiff involves the condensation of a carbonyl compound with an amine under azeotropic distillation. Molecular sieves are then used to completely remove water formed in the system [27]. In the 1990s an *in-situ* method for water elimination was developed, using dehydrating solvents such as tetramethyl orthosilicate or trimethyl orthoformate [28]. The efficiency of these methods is dependent on the use of highly electrophilic carbonyl compounds and strongly nucleophilic amines [29].

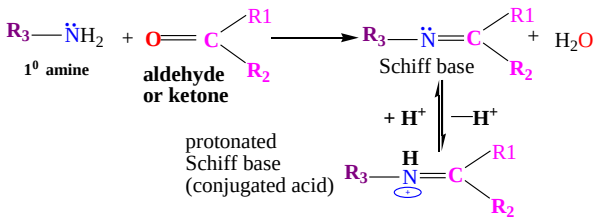

Fig. 1 General scheme for formation of Schiff bases

Formation of Schiff base generally takes place under acids or base catalysis or with heat. The common Schiff bases are crystalline solids, which are feebly basic but at least some form insoluble salts with strong acids [30]. Aromatic aldehydes especially with an effective conjugation system, form stable Schiff bases, where as those aliphatic aldehydes are unstable and readily polymerize [31]. Schiff base ligands with aldehydes are formed more readily than with ketone (Fig. 1) [32]. There are five synthetic routes to the preparation of Schiff base metal complexes (Fig. 2) [33].

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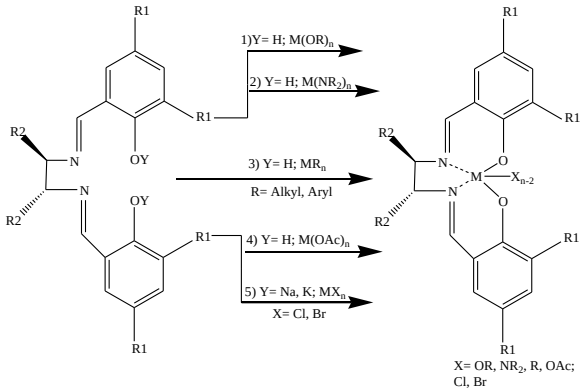


Fig. 2 Preparation of metal complexes of Schiff bases [33]

2.2 Antioxidant Activity

Free radicals are produced under certain environmental conditions and during normal cellular functions in the body. Antioxidants thus play an important role to protect the human body against damage by reactive oxygen species.

The ability of Schiff bases and their metal complexes to scavenge free radicals is an important property [34]. Presently a number of Schiff-base metal complexes have been investigated as antioxidants.

A new series of multipotent antioxidants (MPAOs), namely Schiff base-1,2,4-triazoles attached to the oxygen-derived free radical scavenging moiety butylated hydroxytoluene (BHT) (Fig. 3) were synthesized and their antioxidant activities were evaluated by 1,1-diphenyl-2-picrylhydrazyl (DPPH) method.

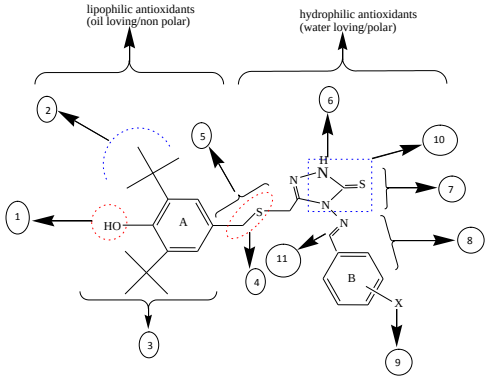


Fig. 3 Rational design of Schiff base-1,2,4-triazoles bearing BHT moieties [35]

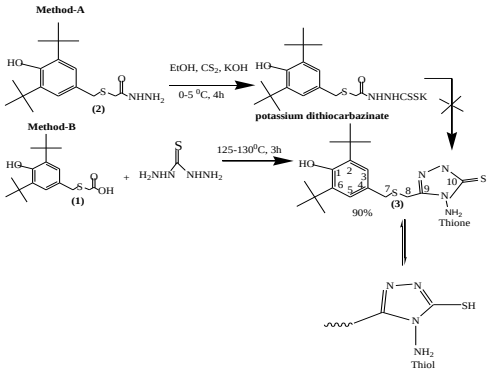


Fig. 4 Synthetic scheme for the formation of 4-amino-3-((3,5-di-tert-butyl-4-hydroxybenzylthio) methyl)-1H-1,2,4-triazole-5(4H)-thione(1) [35]

The antioxidant activities of the Schiff base-1,2,4-triazoles synthesized in this study can be divided into three classes. 4-(3,5-Di-tert-butyl-4-hydroxybenzylideneamino)-3-((3,5-di-tert-butyl-4-hydroxybenzylthio) methyl)-1H-1,2,4-triazole-5(4H)-thione(4), 4-(3,5-Di-tert-butyl-2-hydroxybenzylideneamino)-3-((3,5-di-tert-butyl-4-hydroxybenzylthio)methyl) -1H-1,2,4-triazole-5(4H)-thione(5) exhibited thrice scavenging effect of BHT on DPPH. The high activity can be explained by the resonance-based stabilizing effects of the EDG and the hydrazone on the phenoxy radical at the B ring. The higher activity of the compound 4 is due to the enhanced steric hindrance effect provided by the two ortho-tertiary butyl groups, which stabilize the phenolic antioxidant radical (Fig. 4) [35]. In compound 5, it is believed that an intramolecular hydrogen bond between the phenolic hydrogen with the imine nitrogen disfavors the DPPH scavenging activity, owing to the enhanced binding of the phenolic hydrogen atom [36]. It was found that the H-bond stabilizes phenols, therefore, the energy required to extract the hydrogen atom from the O–H is larger than in the non H-bonded phenols [37].

Thus, the OH group of compound 5 exhibited strong hydrogen bonds with the imine group the O–H, and the N atom of C=N, which could in theory increase the BDE by stabilizing the amine form, making the approach of peroxyl radicals to the O-H group more difficult for steric reasons.

3-((3,5-Di-tert-butyl-4-hydroxybenzylthio)methyl)-4-(2,3,4-trimethoxybenzylideneamino)-1H-1,2,4-triazole- 5(4H)-thione(2) and 3-((3,5-Di-tert-Butyl-4 hydroxybenzylthio)methyl)-4-(3,4,5-trimethoxy benzylideneamino)-1H-1,2,4-triazole-5(4H)-thione(3), showed significant levels of inhibition compared to BHT, yielding a DPPH inhibition of 68.13% for 2 and 74.32% for 3, while BHT resulted in a value of 25.23%[35]. Neither of these compounds contains a phenolic hydroxyl group on the B ring, but they may increase the phenyl ring stabilization, due to formation resonance of stabilized radicals. The DPPH radical scavenging activity for 4-(4-(Benzyloxy)benzylideneamino)-3-((3,5-di-tert-butyl-4 hydroxybenzylthio)methyl)-1H-1,2,4-triazole-5(4H)-thione (6),4-(Biphenyl-4-ylmethyleneamino)-3-((3,5-di-tert-butyl-4 hydroxy benzylthio)methyl)-1H-1,2,4-triazole-5(4H)-thione(7), 4-(4-Chlorobenzy lideneamino)-3-((3,5-di-tert-butyl-4-hydroxybenzylthio)methyl)-1H-1,2,4-triazole-5(4H)-thione(8) is substantially lower than that of the others, but better than the standard antioxidant (BHT), due to their resonance-based stabilizing effects [38]. All compounds showed better scavenging activity compared to the standard antioxidant (BHT). This might be due to the presence of more than one antioxidant functional group within the structure of the Schiff base-1,2,4-triazoles.The products could play a vital role in repairing cellular damage, preventing various human diseases and in medical therapeutic application[35].

Antioxidant activity of bis(N-(3-methoxy-salicylidene)-4-amino-phenyl)ether (H_2L) and its Mn(III) and Cu(II) complexes were performed by using DPPH, ABTS, superoxide and hydroxyl radical scavenging. The inhibitory effects of the tested compounds increased in dose dependent manner. Cu(II) displays a better scavenging activity of DPPH relative to those of the ligand and Mn(III) complex. $[Mn(HL)_2(H_2O)_2]_{0.5}(ClO_4)_{0.5}$ scavenged hydroxyl radical greater as compared to the ligand which may be attributed to the significant contribution of the hydroxyl units [39] and the chelating function of the organic molecules to the metal ions[40]. Simultaneously, Cu_2L_2 shows a higher antioxidant activity than H_2L, which may be due to the significant contribution of the hydroxyl units [39] and the effect of copper ion. The ABTS results indicate that Cu_2L_2 exhibits greater antioxidant properties than H_2L and $[Mn(HL)_2(H_2O)_2]_{0.5}(ClO_4)_{0.5}$[41].

A new Schiff bases [3-4(a-d)] (Fig. 5) were synthesized by reacting bis-triazole rings possessing compounds with four aromatic aldehydes and well characterized by spectroscopic data and elemental analyses. All the newly synthesized compounds were screened for their antioxidant activities by DPPH and Phosphomolydenum reducing antioxidant power (PRAP) method.

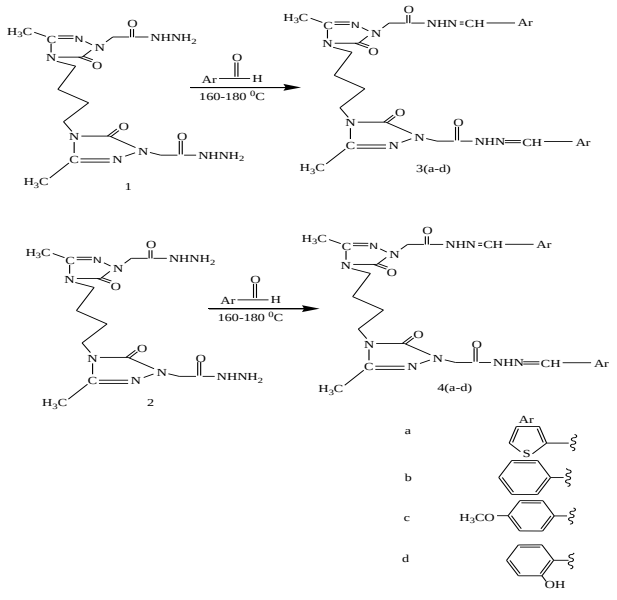


Fig. 5 Synthetic pathway for the preparation of compounds 3-4(a-d) [42]

All of the compounds exhibited moderate scavenging activities. Compound 3c showed the lowest IC50 value with 0.781 ± 0.01 mg/mL and the highest PRAP absorbance value 2.0279 ± 0.049 followed by compound 4c indicating their antioxidant potential [42].

A series of Schiff bases of 4-(methylthio)benzaldehyde derivatives were synthesized and their antoxidant activity has been evaluated by DPPH radical scavenging. The aromatic ring system with halogens like chlorine or fluorine in (E)-N-(4-(Methylthio)benzylidene)-4-bromo-2-chloro-6-methylbenzenamine, (E)-N-(4-(methylthio)benzylidene)-4-chloropyridin-2-amine, and (E)-N-(4-(Methylthio)benzylidene)-3-chloro-5-(trifluoromethyl)pyridin-2-amine, were found to be more active than other compounds in the series. Thiazole group in (E)-N-(4-(methylthio)benzylidene)thiazol-2-amine and thiadiazole group in (E)-5-(4-(methylthio)benzylideneamino)-1,3,4-thiadiazole-2-thiol, are found to be similar antioxidant activity. Compounds (E)-N-(4-(methylthio)benzylidene)-3,5-dibromopyrazin-2-amine, (E)-N1-(4-(methylthio)benzylidene)-4-methyl-N3-(4-(pyridin-4-yl)pyrimidin-2yl)benzene-1,3-Diamine, and (E)-(4-(methylthio)benzylidene)-3-(2-methyl-5-nitrophenyl)guanidine showed moderate antioxidant activity. The nature of the functional groups is crucial for biological activity [43].

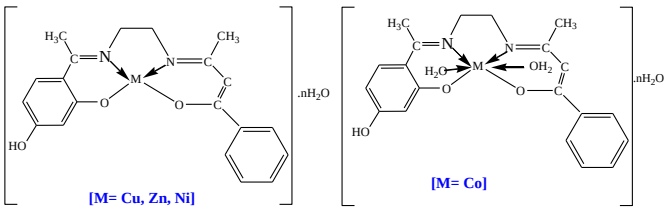
(E)-2-(4-(methylthio)benzylideneamino)-6-methylpyrimidin-4-ol showed higher radical inhibition activity due to the presence of hydroxy group in its aromatic ring [44].

Antioxidant activities of 4,8-dimethyl-2-(salicylidenethiosemicarbozone)quinoline and its Ni(II) and Co(II) complexes were studied in (DPPH). Ni(II) complex exhibited good scavenging activity whereas Co(II) complex exhibited moderate activity than the ligand. The higher scavenging activity of Ni (II) complex on comparision to ligand, could be due to the coordination of metal with azomethine nitrogen and phenolic oxygen of the ligand [45].

A Schiff base ligand derived from L-tryptophan and 2'-hydroxyacetophenone and its Co(II), Ni(II), Cu(II) and Zn(II) complexes (Fig. 6) were prepared. Their antioxidant activity was screened by DPPH method. All the complexes exhibited moderate (30-40%) scavenging activity. The order of scavenging activity is [CuL(tmen)]> [NiL(tmen)] > [ZnL(tmen)] > [CoL(tmen)] [46].

Schiff bases of carboxymethyl chitosan and 4-hydroxy benzaldehyde with its metal [Cu(II), Ni(II)] complexes have been screened for their antioxidant activities by DPPH method. The order of scavenging activity is [CMC-SB1-Ni]>[CMC-SB1-Cu]> CMC-SB1[47].

Antioxidant activity of (3E)-3-[(2-{(E)-[1-(2,4-dihydroxyphenyl)ethylidene]amino}ethyl)imino]-1-phenylbutan-1-one($DEPH_2$) and its metal[Co(II), Ni(II), Zn(II), Cu(II)] complexes were screened by DPPH and ABTS method.



Where n = 2 for Cu(II), Co(II) and Zn(II); n = 3 for Ni(II)

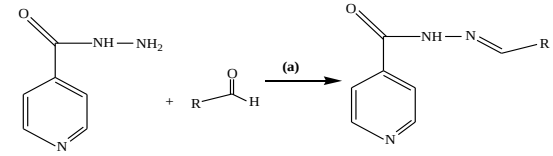
Fig. 6 Structure of Schiff base metal complexes[48]

Metal(II) complexes showed higher activity than that of the free Schiff base $DEPH_2$. The increased antioxidant activity of the complexes can be attributed to the electron withdrawing effect of the metal ions which facilitates the release of hydrogen to reduce the DPPH radical. The order of scavenging activity is Vit. C > Cu(DEP) > Ni(DEP) = Rutin > Co(DEP) > Zn(DEP) > Schiff base ($DEPH_2$) and that of the ABTS is: BHT > $DEPH_2$ > Cu(DEP) > Zn(DEP) > Rutin > Ni(DEP) > Co(DEP). The test samples exhibited moderate to higher % inhibition scavenging activity than rutin and BHT at the lowest concentration (100 µg/mL) with Cu(DEP) possessing the highest potency (IC_{50} = 2.11 + 1.69 µM). The enhanced inhibition displayed on the DPPH radical shows that the compounds are capable of donating electrons to neutralize free radicals and thus, could be promising therapeutic agents for the treatment of pathological diseases and conditions caused as a result of excessive radicals or stress [48].

Three INH Schiff bases were prepared and their antioxidant activity was studied using DPPH method.

The compounds showed significant increase in free radical scavenging activity in a dose dependent manner. INH Schiff base 1 and INH Schiff base 3 showed considerable antioxidant properties (Fig. 7) [49].

5-methylpyrazine-2-carboxylate, 5-methylpyrazine-2-carbohydrazide and a series of hydrazone Schiff bases were synthesized and tested as antioxidants employing DPPH method.



Compound	R
Schiff base 1	
Schiff base 2	
Schiff base 3	

Fig. 7 Scheme of synthesis [49]

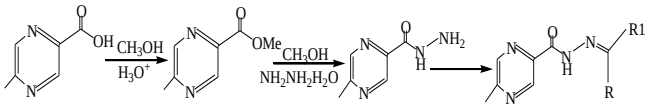


Fig. 8 General method for the synthesis of hydrazones [50]

The most active compound was found to be the 5-methylpyrazine-2-carbohydrazide (Fig. 8) but at a highly toxic level of concentration [50].

Zn(II), Fe(II) and Mn(II) complexes of (E)-ethyl-2-(2-hydroxy-3-methoxybenzylideneamino)-6-methyl-4,5,6 tetrahydrobenzo[b] thiophene-3-carboxylate(HL) were synthesized and characterized by elemental analyses, magnetic susceptibility, molar conductance, infrared, ultraviolet visible, nuclear magnetic resonance, mass techniques and thermogravimetric analyses. The antioxidant properties of the complexes were investigated using DPPH, FRAP and ABTS assays.

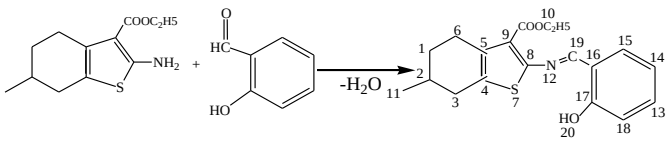


Fig. 9 Scheme synthesis of ligand [51]

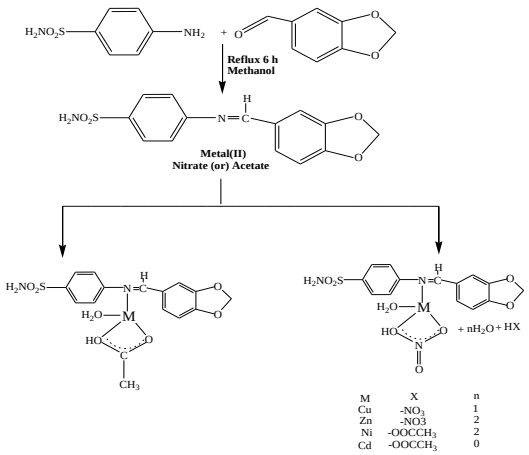


Fig. 10 Synthesis of 4-aminobenzenesulfonamide 1,3-benzodioxole-5-carbaldehyde and its metal complexes[52]

The order of scavenging activity is: ascorbic acid >BHA >BHT > $[FeL_2]\cdot H_2O$ >$[Zn_2LCl_3(H_2O)_5]\cdot 6H_2O$ > L > $[MnLCl(H_2O)_2]\cdot 2H_2O$ in 30 µg/mL of test sample. The $ABTS^{\bullet+}$ radical scavenging activity were decreased in the following order: ascorbic acid > BHT > BHA > L > $[MnLCl(H_2O)_2]\cdot 2H_2O$ > $[FeL_2]\cdot H_2O$ in 30 µg/mL of test sample. Zn(II) complex did not show significant $ABTS^{\bullet+}$ radical scavenging activity.

Only the ligand scavenged $ABTS^{\bullet+}$ radicals effectively. Reducing power of ligand and its metal complexes were increased like standard

antioxidants by increasing concentration in FRAP scavenging. The reducing power of samples and standard antioxidants decreased in the order of BHA > BHT >Ascorbic acid> L > $[FeL_2]\cdot H_2O$ > $[Zn_2LCl_3(H_2O)_5]\cdot 6H_2O$ > $[MnLCl(H_2O)_2]\cdot 2H_2O$ in presence of 30 µg/mL test sample (Fig. 9) [51]. 4-aminobenzenesulfonamide 1,3-benzodioxole-5-carbaldehyde Schiff base and its metal com Fig. 10 Synthesis of 4-aminobenzenesulfonamide 1,3-benzodioxole-5-carbaldehyde and its metal complexes [52]. Plexes have been screened for their antioxidant activities using DPPH method.

All the metal complexes showed an enhanced antioxidant activity as compared to that of free ligand. The antioxidant activity of the synthesized compounds follows in the order L < L-Cd < L-Ni < L-Zn < L-Cu [52].

The antioxidant capacities of a new Schiff base ligand N-(4-phenylthiazol-2-yl)-2-(thiophen-2-ylmethylene) hydrazinecarboxamide and its Cu(II), Co(II), Ni(II) and Zn(II) complexes were evaluated by DPPH method. The Schiff base ligand and its Cu(II), Co(II) complexes have exhibited a good antioxidant activity, whereas Ni(II) and Zn(II) complexes have shown moderate activity. The scavenging activity is concentration dependent [53].

The complexes of Tin (II) chloride with various Schiff base derivative of 2-Hydroxy-1- naphthaldehyde (HN) were synthesized and screened for their antioxidant activities by DPPH method. All the complexes showed good antioxidant activities and high antioxidant activities than their corresponding ligands [54].

A Schiff base derived from ciprofloxacin and thisemicarbazide and its Copper (II) Complex were synthesized, then tested for their antioxidant activities using DPPH.

Schiff base ligand and its copper complex showed significant free radical scavenging action, this may be due to the presence of >NH groups which may donate an electron or hydrogen atom to DPPH and form a stable free radical [55].

3-(((2-hydroxyquinolin-3-yl)methylene)hydrazono)indolin-2 one(HQMHI) Schiff base obtained by the condensation of isatin monohydrazone with 2-hydroxyquinoline-3-carbaldehyde and its metal complexes of Co(II), Ni(II), Cu(II), Zn(II), Cd(II) and Hg(II) were screened for their antioxidant activities using DPPH method. All metal complexes scavenge effectively than ligand showing excellent antioxidant properties [56].

Schiff's bases of Sulphanilamide and its copper, zinc and cadmium complexes were tested as an antioxidant. The Copper and Zinc metal complexes showed potent antioxidant activity. Whereas the metal complexes of cadmium showed moderate antioxidant activity [57]. The marked antioxidant activity of complexes could be due to the coordination of metal with the condensed ring system, increasing its capacity to stabilize unpaired electrons and, thereby, to scavenge free radicals [58, 59].

3. Conclusion

Schiff bases and their derivatives are a class of compounds with literature evident pharmacological importance and applications. These compounds and their metal complexes displayed good antioxidant properties. Although combining antioxidant functional groups is upgrading antioxidant potential, still there is a need to explore the antioxidant properties of the already synthesized one and to synthesize new antioxidant functional group complexes with more properties.

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