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SOME DRUGS IN ACTION: METAL IONS DO INFLUENCE THE ACTIVITY!

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ABSTRACT: A large no of synthetic and natural compounds behave as very effective drugs. All these compounds have a wide range of biological activities like anti-bacterial, anti-fungal, anti-cancer, anti-viral, anti-inflammatory, anti-neoplastic, anti-tumorigenic, anti-HIV and so on. On the other hand, metals have played an important role in medicine for years. Many are essential in our diets in varying quantities. In addition to the metalloantibiotics, a number of drugs and potential pharmaceutical agents also contain metal-binding or metal-recognition sites, which can bind or interact with metal ions and potentially influence (increase or decrease) their bioactivities. In this review changes in drug potentiality upon interaction of metal ions with some natural and synthetic drugs have been discussed. Different metal ions which are toxic at higher concentrations are also useful for maintaining life processes at lower concentrations and are even effective in the modification of some well established drug molecules towards their better action. The alkaline earths and transition metal ions are the most thoroughly studied amongst all.

INTRODUCTION: Different synthetic drugs like quinolones, fluoroquinolones, piroxicam, triazole compounds, trimethoprims, verliprides have potential applications as antimicrobial, anti-inflammatory, anticancer and antipsychotic agents. These drugs are widely prescribed and used for their respective actions in human body. However, there is also over-usage of these drugs which result in their excess concentration in the body which is many times undesirable. Metal ion complexation may affect the drug activity of these compounds either in positive or negative way[1]. Humans are also exposed to different metal ions either through diet or through different environmental factors.

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Some of which are directly essential for our well being and others are toxic above certain concentrations. Many of the pharmaceutical agents contain metal ions which are in current clinical use, and new areas of application are rapidly emerging[2]. Some of these are used for targeting and bio-transformation.

Targeting is important to reduce the toxicity associated with metal compounds. If the drug is delivered directly to the tissues, cells and receptors where they are required, the toxicity may be reduced. The ease with which, many metal complexes undergo ligand substitution and redox reactions decide the activity and possibility of bio-transformation of the administered complex. Identification of these active species will lead to the more effective use of metal compounds as drugs. When dealing with the interaction between drugs and metal ions in living systems, a particular interest has been given to the interaction of metal ions with antibiotics. Many drugs possess modified

pharmacological and toxicological properties when administered in the form of metallic complexes. Probably the most widely studied cations in this respect are transition metals, since they have been proven beneficial against several diseases such as tuberculosis, rheumatoid, gastric ulcers, and cancers[3-6]. There has been a tremendous growth of drugs from quinolone family, which began with the discovery of nalidixic acid over 40 years ago. Since then, the exponential growth of this family has produced more than ten thousand analogues[7].

Complexation of drug molecules with metal ions may affect the fate of chemical reaction as their pharmacokinetics may get altered upon metal ion complexation. This may occur in the body in a number of ways

- Changes in absorption properties: Some drugs are acidic and are dissolved in acidic pH or in full stomach. Metal binding may change the pK_a and absorption profile, e.g., griseofulvin in acidic pH and quinine in basic pH[8, 9].
- Changes in distribution: Some drugs are bound to plasma proteins and hence are distributed mainly in the vascular compartment. These are easily dialyzable. On the other hand few don't bind with plasma proteins, they diffuse to tissues and cause toxicity at low doses and have low therapeutic index, e.g., Digoxin[10]. Metal binding may change their plasma protein (albumin/globulin) binding profile.
- Change in allergenicity and potency: Metal binding may alter potency and allergenicity of antibiotics. Some are notorious for side effects, e.g., water retention and heart failure upon sodium penicillin administration[11]
- Changes in excretion: Glomerular filtration depends on the change of molecules – metal binding by altering change may enhance filtration even in chronic renal failure, e.g. streptomycin with metals have enhanced filtration rate[12].
- Drug interactions: Metal binding may enhance activity of enzymes which have important actions in metabolism of potentially toxic drugs/bilirubin, e.g., effect of thiopurine-s methyl transferase in drug action of 6MP, an anticancer drug[13], effect of N-acetyl transferase in drug action of isoniazid (INH) [14]. There has been large number of evidences which support this fact and here in this review we summarize the effect of metal ion complexation on the drug action of some well established drugs. **Table 1** summarizes the evidences observed. We classify the drugs on the basis of their natural occurrence and synthetic preparation while discussing their action upon metal ion complexation.

TABLE 1: DIFFERENT DRUG MOLECULES AND THEIR DRUG ACTIONS UPON METAL ION COMPLEXATION

Metal	Ligand	Drug action with respect to parent ligand
Magnesium	Dihydrazone (DASHZ)[29]	+
	Sparfloxacin (Hsf)[46]	+
Calcium	Dihydrazone (DASHZ)[29]	+
	Sparfloxacin (Hsf)[46]	+
Vanadium	Isatin (1H-indole-2,3-dione)[19]	+
	Sparfloxacin (Hsf)[38]	-
Chromium	(E)-2-(2-(2-hydroxybenzylidene)hydrazinyl)-2-oxo-N-phenylacetamide[30]	+
	Sparfloxacin (Hsf)[46]	+
	Verlipride (VER)[52]	-
Manganese	H_1L_1 (O,O′,O″,O‴- diaryldithioimidophonates) and H_1L_2 (O,O′,O″,O‴- tetra aryldithioimidophonates)[21]	+
	(E)-2-(2-(2-hydroxybenzylidene)hydrazinyl)-2-oxo-N-phenylacetamide[30]	+
	dihydrazone (DASHZ)[29]	+
	Di-2-pyridylketone thiosemicarbazone[32]	+

	Sparfloxacin (Hsf)[38]	-
	Sparfloxacin (Hsf)[46]	+
	Verlipride (VER)[52]	*
Iron	Chromones[15]	+
	Isatin (1H-indole-2,3-dione)[19]	+
	dihydrazone (DASHZ)[29]	+
	(E)-2-(2-(2-hydroxybenzylidene)hydrazinyl)-2-oxo-N-phenylacetamide[30]	+
	Di-2-pyridylketone thiosemicarbazone[32]	+
	Sparfloxacin (Hsf)[38]	-
	Nalidixic acid (nalH)[39]	+
	Sparfloxacin (Hsf)[46]	+
	Trimethoprim (TMP)[51]	+
Cobalt	Isatin (1H-indole-2,3-dione)[19]	+
	H_1L_1 (O,O′,O″,O‴- diaryldithioimidophonates) and H_1L_2 (O,O′,O″,O‴- tetra aryldithioimidophonates)[21]	*
	4,6-di-tert-butyl-3-[(2-hydroxyethyl)thio]benzene-1,2-diol[23]	+
	dihydrazone (DASHZ)[29]	+
	(E)-2-(2-(2-hydroxybenzylidene)hydrazinyl)-2-oxo-N-phenylacetamide[30]	+
	bis(3-acetylcoumarin)thiocarbohydrazone[31]	+
	Di-2-pyridylketone thiosemicarbazone[32]	+
	Furazolidone (Fu)[35]	*
	Quinolino [3,2-b]benzodiazepine (QBD) and quinolino[3,2-b]benzoxazepine (QBO)[42]	+
	Sparfloxacin (Hsf)[46]	+
	Sulfonamides[49]	+
	3-mercapto-4-phenyl(cyclohexyl)-4H-1,2,4-triazoles[50]	-
	Verlipride (VER)[52]	+
Nickel	Isatin (1H-indole-2,3-dione)[19]	+
	H_1L_1 (O,O′,O″,O‴- diaryldithioimidophonates) and H_1L_2 (O,O′,O″,O‴- tetra aryldithioimidophonates)[21]	*
	4,6-di-tert-butyl-3-[(2-hydroxyethyl)thio]benzene-1,2-diol[23]	+
	dihydrazone (DASHZ)[29]	+
	(E)-2-(2-(2-hydroxybenzylidene)hydrazinyl)-2-oxo-N-phenylacetamide[30]	+
	bis(3-acetylcoumarin)thiocarbohydrazone[31]	+
	Di-2-pyridylketone thiosemicarbazone[32]	+
	Sparfloxacin (Hsf)[38]	-
	Quinolino [3,2-b]benzodiazepine (QBD) and quinolino[3,2-b]benzoxazepine (QBO)[42]	+
	Sparfloxacin (Hsf)[46]	+
	Isonicotinoylhydrazones (ISNE)[47]	-
	Sulfonamides[49]	*
	3-mercapto-4-phenyl(cyclohexyl)-4H-1,2,4-triazoles[50]	-
	Verlipride (VER)[52]	+
Copper	Chromones[15]	+
	Quercetin (3',3,4',5,7-flavine)[16]	+
	Isatin (1H-indole-2,3-dione)[19]	+
	O-methyl-(2-thiophenomethylene) aryloxyacetic acid hydrazide[20]	+
	H_1L_1 (O,O′,O″,O‴- diaryldithioimidophonates) and H_1L_2 (O,O′,O″,O‴- tetra aryldithioimidophonates)[21]	+
	4,6-di-tert-butyl-3-[(2-hydroxyethyl)thio]benzene-1,2-diol[23]	+
	NSAID drugs, salicin, aspirin, diflunisal, salsalate, phenoprofen, naproxen, tolmetin, diclofenac, tenoxicam, piroxicam, mefenamic acid[28]	+
	dihydrazone (DASHZ)[29]	+
	(E)-2-(2-(2-hydroxybenzylidene)hydrazinyl)-2-oxo-N-	+

	phenylacetamide[30]	
	bis(3-acetylcoumarin)thiocarbohydrazone[31]	+
	Di-2-pyridylketone thiosemicarbazone[32]	+
	Furazolidone (Fu)[35]	+
	nalidixic acid (nalH)[39]	+
	Clioquinol (5-chloro-7-iodo-8-hydroxyuinoline, CQ)[43]	+
	1-ethyl-6-fluoro-1,4dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid[45]	+,-
	Sparfloxacin (Hsf)[46]	+
	Isonicotinoylhydrazones (ISNE)[47]	-
	Sulfonamides[49]	+
	Trimethoprim (TMP)[51]	+
	Verlipride (VER)[52]	+
Zinc	O-methyl-(2-thiophenomethylene) aryloxyacetic acid hydrazide[20]	+
	H_1L_1 (O,O′,O″,O‴- diaryldithioimidophonates) and H_1L_2 (O,O′,O″,O‴- tetra aryldithioimidophonates)[21]	No effect
	dihydrazone (DASHZ)[29]	+
	nalidixic acid (nalH)[39]	+
	Di-2-pyridylketone thiosemicarbazone[32]	+
	Quinolino [3,2-b]benzodiazepine (QBD) and quinolino[3,2-b]benzoxazepine (QBO)[42]	+
	Sparfloxacin (Hsf)[46]	+
	2,6-bis(2-benzimidazolyl)pyridin[48]	+
	Sulfonamides[49]	+
	3-mercapto-4-phenyl(cyclohexyl)-4H-1,2,4-triazoles[50]	-
	Trimethoprim (TMP)[51]	+
	Verlipride (VER)[52]	+
Ruthenium	Trimethoprim (TMP)[51]	+
Palladium	Isatin (1H-indole-2,3-dione)[19]	+
Silver	1-ethyl-6-fluoro-1,4dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid[45]	+,-
Cadmium	dihydrazone (DASHZ)[29]	+
	Quinolino [3,2-b]benzodiazepine (QBD) and quinolino[3,2-b]benzoxazepine (QBO)[42]	+
	Sparfloxacin (Hsf)[46]	+
	2,6-bis(2-benzimidazolyl)pyridin[48]	+
	3-mercapto-4-phenyl(cyclohexyl)-4H-1,2,4-triazoles[50]	+
Platinum	Trimethoprim (TMP)[51]	+
Gold	1-ethyl-6-fluoro-1,4dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid[45]	+,-
Lead	dihydrazone (DASHZ)[29]	+
Uranium	Sparfloxacin (Hsf)[38]	-

Natural Drugs and Their Metal Complexes

Naturally occurring compounds such as chromones, flavonoids and coumarins have been well known for their medicinal properties towards diabetes mellitus, some bacterial infections or even cancers, neurodegenerative diseases, like Huntington's disease, or in preventing conditions like heavy metal poisoning, Friedreich ataxia and β-thalassemia, HIV, viral infection, spasmolytic, *Wilson's disease, Menkes' disease* lymphocytic leukemia HL-60 promyelocytic leukemia cell lines.

They can act as anti-inflammatory, antioxidant, antiallergic, hepatoprotective, antithrombotic, antiviral, antimicrobial and anti-carcinogenic agents. All these chromones, flavonoids and coumarins have a good chelation affinity towards metals like copper (II) or iron (III). The fact that metal complexes are more effective than the compounds alone has been well established in a review by Grazul and Budzisz[15].

Flavonoids are non-nutritive compounds present in plants, and have broad pharmacological activity. Quercetin (3', 3, 4', 5, 7-flavine), one of the most abundant natural flavonoid, is present in various vegetables and fruits, and its average human daily intake is estimated to be 16–25 mg/person. It is also

one of the main active components of many natural Chinese traditional medicines (CTM).

This flavonoid forms coordination complexes with some essential trace metals, and it is the active form of the compound, which is medicinally beneficial. Quercetin has several biological activities as antibacterial and anti-tumour agents. Some metal ions, especially transition metals, not only play vital roles in a vast number of widely differing biological processes, but also may be potentially toxic in their free state. However upon interaction between with flavonoids, the complexes modify the drug action to enhance their effectiveness. The quercetin-Cu (II) complex has considerably higher activity towards bacteria and tumour cell than that of free quercetin. The possibility for targeting the DNA by these complexes was proved using some spectral studies. Neutral Red (NR) was used as a spectral probe to study the interaction capacity of quercetin-Cu (II) complex with double helix of the calf thymus DNA. The quercetin–Cu (II) complex got intercalated into the double helix of the DNA by exchanging with the NR fluorophoric dye probe from NR–DNA complex[16].

Isatin (1H-indole-2, 3-Dione) is a member of quinolyl hydrazones group which occurs in jasmine flowers and orange blossoms. The importance of the isatinic quinolyl hydrazones arises from incorporating the quinoline ring with the indole ring in the same compound. Quinoline ring has therapeutic and biological activities[17, 18]. On the other hand, isatin (1H-indole-2, 3-Dione) and its derivatives exhibit a wide range of biological activities as anti-malaria, antimicrobial activity etc. The physiological and biological activities of quinolyl hydrazones arise from their tendency to form metal chelates with transition metal ions.

Isatin forms mono- and binuclear as well as dimeric chelates with Fe(III), Co(II), Ni(II), Cu(II), VO(II) and Pd(II) ions. The antimicrobial activity of the ligand is less than that of its metal complexes. Inspection of the data revealed the following:

i. The ligand lacks the antimicrobial activity.

ii. Fe, Co, and Cu-complexes lack the antimicrobial activity towards Gram negative bacteria.

iii. Superior antibacterial activity of the binuclear Pd (II) - complex against *S. pyogenes* bacteria.

iv. Antimicrobial activity towards Gram positive bacteria is highly influenced by the nature of the metal ion. The chelation increases the lipophilic character of the metal chelate and favors its permeation through the lipid layer of the bacterial membranes.

v. The degree of inhibition is influenced by the type of the coordinated anion as well as their concentration.

vi. All the investigated complexes exhibit lower to moderately higher activities against the studied organisms relative to the standard reference. The metal- isatinic complexes gave a fair inhibitory effect on growth of the microorganisms and were more potent as bacteriostatic agents which were found to have the following trend Ni (II) > V (II) > Co (II) > Cu (II) ≈ Pd (II) >> Fe (III)> Ligand (Isatin) [19].

Novel Synthetic Drugs and Their Metal Complexes

Organic ligands containing nitrogen, oxygen, or sulphur are reported to possess a wide range of biological activities possibly due to their involvement in the donor sites of bioactive drugs. Acid hydrazides having nitrogen and oxygen as donor sites are known to have antimicrobial, antitubercular, and antiinflammatory activities.

O-methyl-(2-thiophenomethylene) aryloxyacetic acid hydrazide is a ligand, which forms a conjugated O-N-S tridenate system, thus coordinating with metal through oxygen of the carbonyl group, nitrogen of azomethine, and sulphur of thiophene moiety. This ligand forms complexes with Cu (II) and Zn (II) metal ions.

Antibacterial activity of different derivatives of the ligand and their metal complexes were tested against *E. coli.* and *B. subtilis,* and the antifungal activity was tested against various plant pathogenic fungi viz. *Alternaria alternata, Rhizoctonia solani, Colletotrichum capsici,* and *Giomeralla cingulata.* Biological activity of the ligands increased upon coordination with metal in terms of minimum inhibitory concentration (MIC) values[20].

Substituted-thioimidophonate derivatives H_1L_1 (O, O′, O″, O‴- diaryldithioimidophonates) and H_1L_2 (O, O′, O″, O‴- tetra aryldithioimidophonates) were found to have antibacterial and antifungal properties. Both the ligands form complexes with Mn(II), Co(II), Ni(II), Cu(II), and Zn(II) metal ions. Antibacterial activity of the prepared compounds was reported against the standard strains: *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus* and the antifungal activity against the standard strains: *Aspergillus flavus*, *Aspergillus niger*, and *Candida albicans*. All the complexes were found to exhibit improved antimicrobial activity than their parent ligands.

The ligands exhibited MICs in the range of 0.75-1.5 mg/mL. The Mn(II) complex of H_1L_2 showed effective antibacterial activity against *B. subtilis* (MIC, 0.09 mg/ml). Complexes of Mn(II) and Cu(II) showed moderate inhibitory activity against the pathogens (MIC 0.18-0.37 mg/mL)[21]. Several studies reported that the metal complexes of divalent cations are more toxic than their metallic forms, particularly when compared to their own inorganic equivalents[22]. It may be due to chelation of metal because chelation reduces the polarity of the central metal ion by partial sharing of its positive charge with the donor groups. This increases the lipophilic nature of the metal ion, which in turn favors its migration into the lipid layer of the membrane.

A substituted diol, 4, 6-di-tert-butyl-3-[(2-hydroxyethyl) thio] benzene-1, 2-diol (L) is reported to have antifungal and anti-HIV activities. This compound forms complexes with several bivalent transition metals like Co (II), Ni (II) and Cu (II).The complexation was characterized by means of elemental analysis, TG/DTA, FT-IR, ESR, UV-vis, XRD, magnetic susceptibility, cyclic voltammetry, and conductance measurements and has a stoichiometry of ML_2.

Antifungal activities of the compounds were tested against yeasts (*Pichia pastoris, Lypomyces lipofer, Saccharomyces cerevisiae, Cryptococcus laurentiive, Candida utilis, Candida boidinii*) and fungi (*Aspergillus niger, Fusarium spp., Mucor spp., Penicillium lividum, Botrytis cinerea, Alternaria alternata, Sclerotinia sclerotiorum, Monilia spp.*). For both the antifungal and anti-HIV, the activity changes from the ligand to metal (II) complexes were found to have the sequence $CuL_2 > CoL_2 \approx NiL_2 > HL$[23].

Non-steroidal anti-inflammatory drugs (NSAIDs) present in nature are renowned for their anti-inflammatory activity and gastrointestinal (GI) toxicity. Some NSAID drugs are salicin, aspirin, diflunisal, salsalate, phenoprofen, naproxen, tolmetin, diclofenac, tenoxicam, piroxicam, mefenamic acid, etc. Additional interest in NSAIDs lies in their possible therapeutic benefits in the prevention of various cancers including colorectal and lung cancers and even in the treatment of Alzheimer's disease, Ulcerogenic activity, SOD activities[24-27].

There is a wide and expanding clinical use of NSAIDs, particularly in chronic diseases of the elderly, in whom the GI, renal and cardiovascular side-effects lead to significant morbidity and mortality. Copper was first shown to be an essential biological element in the 1920s when anemia was found to result from Cu-deficient diets in animals and addition of Cu salts corrected this affliction. It is now recognized as an essential trace element for many biological functions. This NSAID drugs can lead to development of numerous Cu (II) complexes with enhanced anti-inflammatory activity and reduced gastrointestinal (GI) toxicity[28].

Several hydrazones have exhibited specific pharmacological activities that have prompted researchers to fit them in the role of antineoplastic, antiviral, anti-inflammatory, and antibactericidal activities. A dialdehyde starch (32%) can be obtained from periodate oxidized potato starch and which can also get converted into its dihydrazone (DASHZ).

This dihydrazone (DASHZ) was found to coordinate with Ca (II), Cd(II), Co(II), Cu(II), Fe(II), Mg(II), Mn(II), Ni (II), Pb(II), and Zn(II) ions. Hydrazones coordinated to metal ions were found to have increased and even changed the kind of their biological activity. Several metal complexes of hydrazones have been used as antitumour agents. Transition metal complexes of hydrazone compounds have also been screened for their bactericidal activity[29]. Hydrazones also play an important role in improving the antitumor

selectivity and toxicity profile of antitumor agents by forming drug carrier systems employing suitable carrier proteins. (E)-2-(2-(2- hydroxybenzylidene) hydrazinyl) - 2 - oxo - N - phenylacetamide is a derivative of hydrazone which play an important role in improving the antitumor selectivity and toxicity profile of antitumor agents.

The ligand chelate with Mn(II), Fe(II), Co(II), Ni(II), Cu(II), and Cr(III). Minimum inhibitory concentration (MIC) was determined for each of the active compounds along with ampicillin and nystatin as standard controls. The screening was performed against the Gram negative *Escherechia coli* and the Gram positive *Staphylococcus aureus*, in addition to the pathogenic fungi *C. albicans*. Most of the metal chelates have a higher antibacterial activity than the free ligand[30].

Another type of hydrazone, bis(3-acetylcoumarin)thiocarbohydrazone, which is a derivative of coumarin contains several types of pharmacological activities such as antibacterial, antifungal, anticancer, anti-HIV, anticoagulant, spasmolytic antioxidant and antiproliferative. The bis(3-acetylcoumarin)thiocarbohydrazone ligand complexes with Co(II), Ni(II) and Cu(II).

The strains chosen for antibacterial and antifungal activity were *E. coli, S. aureus, B. aureus* and *A. niger* and *C. albicans*. The ligand (L) was found to be active against bacteria and promising results were observed for the complexes $[Cu(L)Cl_2].2H_2O$, $[Cu(L)(NO_3)_2]$ against all bacterial and fungal strains. For the study of antitumor activity, the brine shrimp lethality test was used to predict the presence of cytotoxic activity. MIC of the ligand is 19.22 mg/mL and for the complexes are in between 3.17 and 7.62 mg/mL and hence it can be concluded that the activity of metal complexes is higher than that of the parent ligand[31].

The search for novel compounds that are able to prevent cancer cell proliferation is vehemently ongoing work. Much current chemotherapy remains ineffective against common and aggressive tumors, e.g., malignant melanoma and breast, prostate, lung, and brain cancer. A series of di-2-pyridylketone thiosemicarbazone (HDpT) chelators showed marked and selective antitumor, anticancer activity. Di-2-pyridylketone thiosemicarbazone forms complexes with Fe(II), Mn(II), Co(III), Ni(II), Cu(II), and Zn(II) metal ions. Iron is crucial for many metabolic reactions including the rate-limiting step of DNA synthesis involving the Fe-dependent enzyme, ribonucleotide reductase (RR*a*), which converts ribonucleotides to deoxyribonucleotides. Copper has also much biological activity and hence Fe(II) and Cu(II) complexes of HDpT show redox activity within cells. But at the same time the divalent Mn(II), Ni(II), Cu(II), and Zn(II) complexes of the HDpT analogues are equally active in preventing proliferation as their ligands, suggesting the complexes behave as lipophilic vehicles facilitating intracellular delivery of the free ligand upon dissociation[32].

Conventional drugs and Their Metal Complexes

Nitrofuran derivatives have been used for more than 30 years in medicine for the treatment of gastrointestinal infections in animals and humans. The main pharmaceutical uses of nitro aromatic compounds (RNO_2) are as antibacterial and anticancer agents. It has been reported that nitro compounds generate a reversible one electron process due to the formation of the nitro radical anion ($RNO_2^{\cdot-}$) and an irreversible three electrons process corresponding to the formation of the hydroxylamine (RNHOH) in aprotic media[33, 34].

Furazolidone (Fu) is a nitrofuran derivative which has all the above activities. As we know, redox properties control most biological responses of nitro compounds, the reduction of Fu is a reversible one-electron process, forming $Fu^{\cdot-}$ which is complexed by metal ions which could be delivered to DNA. Cu(II) complex of Fu shows acceleration in the rate of streptonigrin-mediated DNA cleavage in the presence of NADH.

In contrast, Co (II) complex has no effect on the streptonigrin-mediated DNA cleavage, and Co (II) complex has been reported to act as radical inhibitor. So it is clear that divalent transition metals increase the accessibility of the nitro redox chemistry to biological reductants. Although many nitro radical anions with anticancer drug activity have been studied in details, the relationship between the rate of DNA cleavage and anticancer activity is unknown. Nevertheless, it could be observed that, metal complexes of Fu with several

metal ions accelerate the rate of DNA cleavage compared to the free drug[35].

Quinolones (quinolonecarboxylic acids or 4-quinolones) are a group of synthetic antibacterial agents containing a 4-oxo-1, 4-dihydroquinoline skeleton. Quinolones are compounds of great interest because of their broad antibacterial spectrum both towards Gram-positive and Gram-negative bacteria and their *in-vivo* chemotherapeutic efficacy. They are extremely useful for the treatment of various infections, such as urinary tract infections, soft -tissue infections, respiratory infections, bone-joint infections, typhoid fever, sexually transmitted diseases, prostatitis, community-acquired pneumonia, acute bronchitis and sinusitis[36, 37].

Sparfloxacin (Hsf), is the first marketed aminodifluoroquinolone. Several complexes of this third generation quinolone were prepared upon interaction with Fe (III), VO (II), Mn (II), Ni (II) and UO (II). The efficiencies of the ligand, the metal salts and the complexes have been tested against three microorganisms; two Gram negative, *E. coli*, ATCC 25922 and *P. aeruginosa* ATCC 27853, and one Gram positive, *S. aureus* ATCC 29213. The result reveal that the MIC value of the ligand sparfloxacin lies in between 0.5–8 µg/L whereas for the complexes are in between 16–128 µg/L which reveals the antimicrobial activity of the complexes exhibit lower value than free sparfloxacin[38].

Nalidixic acid (nalH), pefloxacin (pfH) methanesulfonate, cinoxacin (cxH), nfH, cfH hexahydrate,cfH lactate, norfloxacin dihydrochloride, 5- aminooxolinic acid, oxolinic acid, lomefloxacin, rosoxacin, piromidic acid and sparfloxacin are several free quinolones. Activity of this series of drugs in presence of different metal ions can be found in a typical review[39].

The fluoroquinolones are highly active against aerobic Gram negative microorganisms but less active against Gram positive microorganisms. They are extremely useful for the treatment of a variety of infections, including urinary tract infections, soft tissue infections, respiratory infections, bone-joint infections, typhoid fever, sexually transmitted diseases, prostatitis, community acquired pneumonia, acute bronchitis and sinusitis. The absorption of quinolone drugs is lowered when they are consumed simultaneously with magnesium or aluminium antacids. Many other ions found in pharmaceuticals cause similar effect. Antacids not only contain magnesium or aluminium, but can also contain calcium or bismuth ions.

In the treatment of anaemia, iron is orally administered while zinc is present in multivitamin mixtures. Iron (III), zinc (II) complexes of nalidixic acid (nalH), were tested in vitro against the Gram negative microorganisms *E. coli* and *Bacillus dysenteria* bacteria. The complexes showed stronger activity than nalH. The biological activity of the Cu- phen- nal complex and its individual components were tested against *Entamoeba histolytica* (HM 1), *E. coli* and *Clostridium symbiosum*.

The complex showed the highest inhibitory activity on axenic and monoxenic amobease. *E. coli* showed high susceptibility to the Cu- phen-nal complex, whereas *C. symbiosum* did not, which implies Cu-phen-nal could have a potential use as an alternative drug in chemotherapy of some bacterial infections in disease caused by *E. histolytica*. In contrast, the iron and magnesium complex of nalH showed significantly less active than the parent quinolone drugs. Bismuth- cfH, copper- cx were screened for activity against several bacteria (minimal inhibitory concentration (MIC) values) showing the same antimicrobial activity as the corresponding ligand[39].

Quinolino [3, 2-b] benzodiazepine (QBD) and quinolino[3,2-b]benzoxazepine (QBO) are the derivatives of quinoline groups and have antibacterial, antifungal effects. These QBD and QBO form complexes with several transition metals such as Co (II), Ni (II), Zn (II), Cd(II). The ligands and their Co (II), Ni (II), Cd(II) and Zn(II) complexes were tested for the in vitro antibacterial activity against *P. aerugenosa* (Gram-negative) and *S. aureus* (Gram-positive) and the antifungal studies of the ligands and their metal complexes were tested on fungal strains namely, *C. albicans*, *A. flavus* and *A. niger* in growth media by using Batemann poisoned food technique[40,41]. The antibacterial and antifungal activity of the metal

complexes was found to have higher antimicrobial activity than the parent ligands[42].

Clioquinol (5-chloro-7-iodo-8-hydroxyuinoline, CQ) is a compound in the hydroxyquinoline family and has been shown to reduce or prevent the formation of amyloid plaques in the brains of Alzheimer's disease in transgenic mice. CQ is currently in use clinically for the treatment of Alzheimer's and Huntington's diseases. Prior to the discovery of its efficacy in treating Alzheimer's disease, CQ was used successfully to treat and prevent *Shigella* and *Entamoeba histolytica* infections. It also has anticancer activity. Clioquinol forms a stable complex with Cu (II) metal ion and the Ic_{50} value of the complex is 2.5 microGram[43, 44].

Norfloxacin, a fluoroquinolone, is 1-ethyl-6-fluoro-1, 4dihydro – 4 – oxo - 7 - (1-piperazinyl) – 3 - quinolinecarboxylic acid. Norfloxacin belongs to the family of molecules known as the fluoroquinolones, and is a wide-ranging drug used in treating bacterial infections of the urinary tract, the respiratory tract, and the skin, amongst others. It is also known to be effective in treating diarrhea and can in addition treat conjunctivitis when it is administered in the form of eye drops.

Probably the most widely studied metal ion for complexation with this compound is Cu (II), since a host of low-molecular-weight copper complexes have been proven beneficial against several diseases such as tuberculosis, rheumatoid, gastric ulcers, and cancer. Norfloxacin is considered the best of the third generation quinolone family.

The antibacterial activities of the compound were investigated against *Escherichia Coli*, *Bacillus subtilis*, and *Pseudomonas aerruginosa* as well as some kinds of fungi *Aspergillus flavus*, *Fusarium solani*, and *Penicillium verrcosum*. The antibacterial and antifungal investigations of the Ag(I), Cu(II), and Au(III) complexes of the ligand were also tested, as well as the pure compound. The Ag (I), Cu (II), and Au (III) complexes of norfloxacin are more active than the ligand for *P. aeruginosa* bacteria and *Penicillium verrcosum* fungi, and less active than ligand for *Bacillus subtilis* bacteria[45].

Sparfloxacin (SPFX) or 5-amino-1-cyclopropyl-7-(cis-3, 5-dimethyl-1-piperazinyl)-6, 8, di-fluoro-1-4-dihydro-4-oxo-3-quinocarboxylic acid is well known for its antifungal, antibacterial, antiproliferative activities. Mg(II), Ca(II), Cr(III), Mn(II), Fe(II) , Fe(III), Co(II), Ni(II), Cu(II), Zn(II), Cd(II) metal ions form stable complexes with sparfloxacin (SPFX).

The formed complexes of sparfloxacin were screened for their antimicrobial activity against a series of Gram-positive (*Bacillus subtilis, Micrococcus luteus, Staphylococcus aureus, and Streptococcus features*) and Gram-negative (*Salmonella typhi, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Escherichia coli, Citrobacter and Shigella flexneri*) organisms by the conventional cylinder-plate method.

Antifungal activity was also tested against series of fungi *Candida albican, Fusarium solani, Trichophyton rubrum, Aspergillus purasiticus, Aspergillus effuses and Saccharomyces cerevisiae.* All the synthesized complexes were found to be more potent as compared to the parent drug as well as some of them were more potent than other advanced fluroquinolones. Among all the metal ions, Fe and Cd complexes showed higher activities and these two complexes may be recommended for possible therapeutic purposes as antibacterial and antifungal agents[46].

The recurrence of tuberculosis (TB) coincident with the spread of AIDS is nowadays a challenging health problem all over the world. Isoniazid (INH) is a primary anti-TB drug which is also a novel agent against AIDS-associated pathologies. The binary neutral Cu (II) and Ni (II) complexes of INH have been obtained in methanol solution by reaction of isonicotinoylhydrazones (ISNE) with the metal acetate or chloride. The substitution position was changed with several substituents and hence several compounds were prepared with Cu (II) and Ni(II) metal ions. Among all the compounds Cu (II) complexes were more potent drug than that of Ni (II) complexes.

The MIC values of ligand (ISNE) ranges from 0.025 to 0.2 µg/mL, reveal very significant activity, equal or higher than that of rifampin used as reference drug; the potency of several substituted

ligands are similar to that of the parent-drug INH. All tested hydrazones, ISNE and its metal complexes showed 99 to 100% growth inhibition.

ISNE shows similar or more potency than their Cu (II) and Ni (II) complexes, suggesting that the antitubercular activity of the metal complexes could be mainly due to slow release of the ligands, inside the mycobacterial cell. In fact bioactivity was never revealed in complexes of inactive ligands such as hydrazones isosteres of ISNEs. Thus the active principle of these compounds should be ultimately the same ligand, while the metal should play a role mainly connected with their enhanced capacity to cross the mycobacterial cell wall so providing the inhibitory agent for a long period[47].

Benzimidazole is a typical heterocyclic ligand with nitrogen as the donor atom. Due to their privileged structure and properties, benzimidazole and its derivatives exhibit various remarkable biological activities in the field of drugs and pharmaceuticals such as antitumor, antiviral, anticancer, antimicrobial, antiprotozoal, antihistaminic, and anti-inflammatory or analgesic activities. Transition metal complexes have attracted considerable attention due to their useful functions, including stabilizing protein structure, affecting enzymatic activity and controlling cell metabolism.

In addition, transition metal complexes are being used to bind and react at specific sequences of DNA in a search for novel chemotherapeutics and for probing DNA. 2, 6-bis (2-benzimidazolyl) pyridine (bbp) is a V-shaped ligand, and is a derivative of benzimidazole which shows similar biological activity as benzimidazole.

2, 6-bis (2-benzimidazolyl) pyridine forms complexes with zinc (II) and cadmium (II). The complexes bind to DNA in an intercalation mode, and DNA-binding affinity of the Zn (II) complex is stronger than that of the Cd(II) complex owing to the different V shaped angles (α_V).

The IC_{50} value of Zn and Cd complexes are 1.43 and 1.32 µM respectively. In view of the observed IC_{50} values, two complexes can be considered as a potential drug to eliminate the hydroxyl radical than that of the ligand. Superoxide radical $O_2^{-\cdot}$ Scavenging activity of these two complexes has been investigated. The Zn complex has good superoxide radical scavenging activity, but Cd complex does not have the activity. The results indicate that the Zn complex may be acted as an inhibitor (or a drug) to scavenge superoxide radical *In- vivo*[48].

Sulfonamides is an well known drug and has been recently known as synthons in the preparation of various valuable biologically active compounds used as antibacterial, antitumor, diuretic, anti-carbonic anhydrase, hypoglycaemic, anti-thyroid and protease inhibitor.

Two derivatives of sulfonamide, pyrimidinyl sulphonamides, 4 - {[(E) - (5-bromo-2-hydroxyphenyl) - methylidene] amino}-N- (4, 6 – dimethyl – pyrimidin – 2 - yl) benzenesulfonamide (L^1) and 4-{[(E)-(5-bromo-2 hydroxyphenyl) methylidene] amino} - N - (pyri-midin-2-yl)benzenesulfonamide (L^2) was derived from the reaction of sulfamethazine and sulfadiazine with 5-bromosalicylaldehyde respectively.

These synthesized sulfonamides and their Cu(II), Ni(II), Co(II) and Zn(II) complexes have been investigated for their in vitro antibacterial activity against four Gram-negative *(Escherichia coli*, *Shigella flexenari*, *Pseudomonas aeruginosa* and *Salmonella typhi*) and two Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) bacterial strains and for in vitro antifungal activity against *Trichophyton longifusus*, *Candida albican*, *Aspergillus flavus*, *Microscopum canis*, *Fusarium solani* and *Candida glaberata* fungal strains.

All the compounds showed moderate to significant antibacterial activity against one or more bacterial strains and good antifungal activity against various fungal strains. L^1 and L^2 form compounds with Cu (II), Ni (II), Co (II) and Zn (II) respectively. Zn-L^2 showed excellent antifungal activities against *T. longifusus*. Similarly compounds Co-L^1 and Co-L^2 against *C. albican*. Cu-L^1, Zn-$L^1$and Zn-L^2 were the most active towards antibacterial response. The MIC of these most active compounds was in the range of $3.204x10^{-8}$ to $1.341x10^{-7}$ M while Zn-L^1 proved to be the most active one. It inhibited the growth of *B. subtilis* at $6.65x10^{-8}$ M [49].

The aromatic triazole nucleus is associated with a variety of pharmacologic actions. Metal complexes of substituted triazoles have also demonstrated efficacy in inhibiting tumor growth. 3-mercapto-4-phenyl (cyclohexyl)-4H-1, 2, 4-triazoles is a derivative of aromatic triazole. Ni(II), Co(II), Zn(II) and Cd(II) complexes of 3-mercapto-4-phenyl(cyclohexyl)-4H-1,2,4-triazoles were prepared via cyclization of 1 -benzoyl-4 substituted thiosemicarbazides under alkaline condition.

Complexes were assayed *in-vitro* for their ability to inhibit the growth of representative Gram-positive and Gram-negative bacteria and various fungal species. Most of the complexes were proved inactive as antibacterial agents. The aromatic Cd complex is significantly more active against the bacteria studied than triazoles complexed with other metals. The complex was however always a less active antibacterial than either its saturated analog or the reference compound streptomycin. In terms of MIC, the aromatic compound of Cd demonstrated significantly greater activity against *S. aureus* and *S. typhimurium* than *E. coli*. The aromatic Cd complex is most active anifungal also. The antimicrobial activity of the complexs were in order as CdL>HL>NiL>CoL>ZnL[50].

Trimethoprim (TMP), chemically 5-(3, 4, 5-trimethoxybenzyl) pyrimidine-2, 4-diamine, belongs to the class of chemotherapeutic agents known as dihydrofolate reductase inhibitors. It is used in prophylaxis treatment and urinary tract infections. Cu (II), Zn (II), Pt (II), Ru (III) and Fe (III) forms several stable complexes with trimethoprim which has antibacterial, antifungal activities and ability to bind to calf-thymus DNA (CT DNA).

The complexes can bind to CT DNA by both the intercalative and the electrostatic binding mode. The antimicrobial activity of these complexes has been evaluated against three Gram-positive and four Gram-negative bacteria. Antifungal activity against two different fungi has been evaluated and compared with the reference drug TMP. Almost all types of complexes show excellent activity against all type of bacteria and fungi than TMP[51].

Verlipride (VER) (L) is an anti-psychotic drug, used in treatment of cardiovascular and psychological symptoms associated with the menopause. It is N-[(1-allyl-2-pyrrolidinyl) methyl]-5-sulfamoyl-2-veretramide.

Mn(II), Cr(III), Co(II), Ni(II), Cu(II) and Zn(II) transition metal ions form solid chelates with VER drug molecule. The VER drug, in comparison to its metal complexes is also screened for its biological activity against Gram positive bacterial (*Staphylococcus aureus*) and Gram negative bacteria (*Escherichia coli*) and fungi (*Candida albicans* and *Aspergillus flavus*) *in-vitro*. Biological activity against Gram-positive bacteria follow the order as ZnL_2 > NiL_2>CoL_2> CuL_2 >MnL_2 = CrL_2> VER drug.

It is obvious that the biological activity of the metal complexes is more than the parent VER drug. For Gram-negative bacteria the order is CoL_2 > ZnL_2 =NiL_2 > CuL_2 > VER =MnL_2 > CrL_2. The biological activity of the VER drug and its complexes are lower than tetracycline standard. The Co (II), Ni (II), Cu (II) and Zn (II) complexes also show antifungal activities against *Candida albicans* fungus while the parent VER drug has no such activity which makes these complexes of interest. The importance of this lies in the fact that these complexes could be applied fairly in the treatment of some common diseases caused by *Escherichia coli*, e.g., septicemia, gastroenteritis, urinary tract infections, and hospital-acquired infections[52].

CONCLUSIONS: Pharmaceutical compounds play important roles in our day to day lives. Modification in the mechanism of their action is desirable with lesser side effects and keeping the cost low. Metal ion complexation has proved this time and again with a few exceptions. A judicious method of metal complexation with the already existing drugs may turn out in fashionable smart operating better drug formulations. The present review will encourage the pharmaceutical researchers to adopt new metal complexes to achieve better generation of drug action.

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