INTRODUCTION

Intestinal sickness, a tropical parasitic illness that now remains universally stretched out to over 40% population and is one of the real reasons for grime and demise from irresistible ailments around the world (after respiratory contaminations, HIV/AIDS, diarrheal infections, and tuberculosis) and the second in Africa, after HIV/AIDS [1,2]. It began from Italian word "aria male" which means awful air, brought about by an erythrocytic protozoan initially identified by Alfonse Laveran in 1880 [3]. The term was abbreviated to "intestinal sickness" in the twentieth century and in 1889, R. Ross found that mosquitoes transmitted intestinal sickness. There are five recognized types of this parasite, to be specific, Plasmodium vivax, P. falciparum, P. ovale, P. malariae and P. knowlesi. P. falciparum is more typical in sub Saharan Africa and Melanesia (Papua New Guinea, Solomon Islands)[4]; P. vivax in Central and South America, India, North Africa and Middle East; P. ovale in Western Africa and P. malariae is sporadic around the world [5].

Of the four normal species that cause intestinal sickness, the most destructive sort is P. falciparum that can bring about cerebral jungle fever. Be that as it may, another generally new species P. knowlesi is additionally a risky animal category that is normally found in since a long time ago followed in pigtailed macaque monkeys. The other three regular types of intestinal sickness (P. vivax, P. ovale, P. malariae) were less deadly and are not life debilitating. It is conceivable to be tainted with more than one types of Plasmodium in the meantime [6]. Jungle fever is transmitted by the female anopheles mosquito that can be dealt with in only 48 h, if left untreated, they may create extreme intricacies. As indicated by the WHO, jungle fever is pervasive in 108 nations of the tropical and semitropical world (Africa; Amazon, focal and southern America; focal, south and SE Asia; Pacific) that are home to the greater part of the world's people. Jungle fever is predominant in tropical area on the grounds that are critical measures of precipitation, warm temperature and dormant waters give living spaces perfect to mosquito larvae [7,8]. Endeavours have likewise been made on blend of antimalarial medications for compelling control of the infection [9]. The development of medication resistance parasites prompted new methodologies including alteration of existing operators, disclosure of new characteristic mixes and ID of new targets. New antimalarial drugs and combinations are being considered however there is not yet adequate data on their viability. In the present review we discussed the antimalarial potential of metal complexes of antimalarial drug (primaquine). It may help the researchers for further investigation.

Keywords: Plasmodial resistance, Metal complexes, Antimalarial activity
indicated more significant action against intestinal sickness parasite, when contrasted with the parent mixes. The metal buildings were intended to conquer the resistance in intestinal sickness parasite and to treat the infection in better consistence. The two ligands introduce potential restricting destinations, when these were chosen to concentrate their coordination propensities, characterisation in the wake of complexing with metals and their natural exercises.

\[-LL’L''−LL''+MM+2L’,−LL’L''−LL"\]

MCL\(_n\) + L\(_1\) + L\(_2\) > [ML\(_1\)L\(_2\)]Cl\(_n\)\(\times\)H\(_2\)O [9]

Metal complexes as antimalarial potential:
Adediji et al., synthesized the Nickel (II) chloride hexahydrate complex of mefloquine and pyrimethamine. The antimalarial activities of metal complex were studied using mice infected with P. berghei. The chelate so formed do not show any toxicity against alkaline phosphate activities of enzymes from the homogenates of serum, liver and kidney homogenates of experimental rats. The metal chloride salt were reacted with the parent compounds according to the equation-

\[M+L1+L2=ML1L2\]

The synthesized complex was found to be non-hygroscopic solids with lemon green colour. The results showed that the metal chelate exhibited higher activity against malaria with high percentage inhibition of 70.3% at 25mg/kg dosage and hence overall metal complexes exhibited better properties as compared with that of parent compounds [13].

Wasi and Singh synthesized the metal complexes of two well known antimalarial drugs amodiaquine and primaquine with different metal salts. Amodiaquine hydrochloride and primaquine diphosphate were complexed with Oxovanadium(II), Chromium(III), Iron(III), Copper(II), Cobalt(II), Nickel(II), Zinc(II), Cadmium(II), Mercury(II), Rhodium(III), Palladium(II), Gold(II), Silver(I), Manganese(II), Tin(II). The synthesized metal complexes had been characterized and screened by an in-vitro microtechnique for their schizonticidal activity.

The inhibitory activity of drug was studied against P. falciparum strain of malaria parasite. The antimalarial activity of synthesized metal complexes was found to be shown same activity as that of parent compound. The minimum inhibitory activity of amodiaquine and its metal complex were found to be 10\(^{-7}\) M while of primaquie was found to be 10\(^{-6}\) M. However metal salts of Mercuric complex showed minimum inhibitory activity of 10\(^{-10}\) M, cadmium exhibited 10\(^{-10}\) M inhibitory activity while the Tin and Silver Complex exhibited minimum inhibitory activity of 10\(^{-8}\) M [12].

Machura et al., synthesized the molecular structure of 5,8-quinolinedione derivatives in complexation with rhenium chloride Re(Co)\(_2\)Cl\(_2\). The two novel tricarbonyl complexes of 7-acetamido-2-methyl-quinoline-5,8-dione and 6-acetamido-2-methyl-quinoline-5,8-dione has been synthesized and their structure was determined [14].

Khanye et al., synthesized the Gold(III) thiosemicarbazon complexes by complexing dimethylaminoethylphenyl with gold to increase their activity. The complexes were studied for their in-vitro antimalarial and antituberculor activity. The
activity was performed on *P. falciparum* for antimalarial studies and on *Mycobacterium tuberculosis* virulent strain H₃,₇Rv for antibacterial activity. The incorporation of gold centre to the thiosemicarbazone showed selective antimalarial activity [15].

Bjelosevic *et al.*, synthesized the Platinum (II) and Gold (I) complexes based on 1,1′-bis(diphenylphosphino) metallocene derivatives. The three gold(I) complexes synthesized were {1-[1-(dimethylamino)ethyl]-1,2-bis(diphenylphosphino) ruthenocene-κ^P,P′}bis[chlorogold(I)] with inhibitory concentration of 1.40 μM (IC₅₀ = 1.40 μM), {1-[1-(acetoxyethyl)]-1′,2-bis(diphenylphosphino) ferrocene-κ^P,P′}bis[chlorogold(I)] with inhibitory concentration of 0.50 μM (IC₅₀ = 0.51 μM), {1-[1-(3-carboxypropanamido)ethyl]-1′,2-bis(diphenylphosphino) ruthenoceneκ^P,P′}bis[chlorogold(I)] with inhibitory concentration of 1.784 μM (IC₅₀ = 1.784 μM), have the best activities against cancer, HIV and malaria respectively. The antimalarial activity was performed on *P. falciparum* strains W2 by culturing in human erythrocytes. Cytotoxic activity i.e. anticancer activity were performed on a cervical carcinoma cell line(Hela)(CCL-2) and antiviral activity were performed on T-lymphoblastoid cell line CEM-SS[16].

Lam and Geiger synthesized and studied anodic electrochemistry of cymanquein and related compounds. Cymaquein is the analogue of ferroquine in which the FeCP group is replaced by a Mn(CO)₆ group. Three compounds of 4-aminochloroquinolines were prepared by covalent linkage to a cyclopentadienyl manganese tricarbonyl moiety. The new compounds exhibited a rich set of oxidative electrochemical reactions [17].

Patti *et al.*, synthesized the 2-ferrocenylquinoline derivatives and their antimalarial activity was evaluated. Quinoline based compounds bearing a ferrocenyl unit in the 2-position of the heterocyclic system were synthesized from ferrocenyl-o-nitrochalcones through a simple hydrogenation. The antimalarial activity of ferrocenyl derivatives were *in vitro* evaluated for the chloroquine-resistant W2 strains of *P. falciparum*. The ferrocenyl derivatives showed increased potency of antimalarial drugs [18].

Khanye *et al.*, synthesized and performed *in vitro* evaluation of gold(I) thiosemicarbazone complexes. The antimalarial activity of complex was studied on malaria parasite *P. falciparum*. The complex shows enhanced efficacy by inhibition of parasite cystine protease falcipain-2. Hence these complexes exhibited antimalarial activity through the inhibition of more than one target [19].

Glans *et al.*, synthesized, characterized and performed antimalarial activity of new chromium arene quinoline half sandwich complexes. Organometallic analogs of chloroquine are of great importance to overcome the resistance of chloroquine by malaria parasite. Two new chromium arene CQ-analogs: [η^6-N-(7-chloroquinolin-4-yl)-N'-dime thylamino-methylbenzyl]-ethane-1,2-diamine]tricarbonylchromium and [η^6-N-(7-chloroquinolin-4-yl)-N'-dime thylamino-methylbenzyl]-ethane-1,2-diamine]tricarbonylchromium have been synthesized, characterized and their *in vitro* antimalarial activity against chloroquine resistant strains were studied. The chromium complex Cr(CO)₅ complexes showed high activity against chloroquine sensitive and chloroquine resistant strains of *P. falciparum* [20].

Quirante *et al.*, synthesized Platinum (II) and Palladium(II) complexes with (N,N') and (C,N,N') ligands from pyrazole and their *in vitro* activities were performed for anticancer and antimalarial activities. Platinum drugs have played a key role among the metal based anticancer drugs. The *in vitro* antimalarial activities were performed against *P. falciparum* strains and the cytotoxic activities were performed against a human lung carcinoma cell line (A549) and two human breast cancer cell lines. The complex of anticancer drugs showed higher cytotoxic activity than cisplatin in the three human cell lines [21].

Hemmert *et al.*, synthesized silver (I), gold(I), and gold(III) complexes involving N-heterocyclic carbine ligands. A series of mono and dinuclear silver(I) complexes containing bis(N-heterocyclic carbene) or non functionalised NHC were synthesised and characterised. The *in vitro* antimalarial and antifungal activities of a family of N-functinalized bis(imidazolium) proligands and their corresponding complexes were investigated against chloroquine-resistant strain of *P. falciparum* and against two *Candida* strains. Antifungal tests were performed against *Candida albicans* and *Candida glabrata* of molecules [22].

The metal complexes showed an increase in antimalarial activity with IC₅₀ values of 330nM.

Pandey *et al.*, synthesized and bioevaluated novel 4-aminoquinoline-tetrazole derivatives as potent antimalarial agents. These derivatives were screened for their antimalarial activities against both chloroquine-sensitive (3D7) and chloroquine-resistant (K1) strains of *P. falciparum* as well as cytotoxic activity against VERO cell lines Compounds with significant *in vitro* antimalarial activity were evaluated for their *in vivo* efficacy in Swiss mice against *P. yoelii* by both intraperitoneal as well as oral administration [23].

Chellan *et al.*, synthesized the cyclopalladated complexes containing tridentate thiosemicarbazone and their antimalarial activity was performed. The C-H activation reaction of two aryl-derived thiosemicarbazones with K₂[PdCl₄] forms a cyclopalladated complexes where thiosemicarbazone act as a tridentate donor coordinated to palladium via the ortho-carbon of the aryl ring, imine nitrogen and thiolate sulfur.

Different
palladium complexes were \([\text{Pd}(3,4\text{-dichloroacetophenone thiosemicarbazone})]_n\), \([\text{Pd}(3,4\text{-dichloroacetophenone thiosemicarbazone})]_n\), \([\text{Pd}(3,4\text{-dichloroacetophenone thiosemicarbazone})]_n\), \([\text{Pd}(3,4\text{-dichloropropiophenone thiosemicarbazone})]_n\). These palladium complexes along with their free ligands were evaluated as bioorganometallic antimalarial agents against two \(P. falciparum\) strains, 3D7 (chloroquine sensitive) and K1 (chloroquine and pyrimethamine resistant) [24].

Belloti de souza et al., synthesized the 4-aminoquinoline metal complexes and their antimalarial activities were performed. 4-aminoquinolines derivatives were the most potential sources of antimalarial drugs. 1,2,4-aminoquinoline derived drugs were obtained and some of them were used to form platinum complexes. These compounds were tested \emph{in-vivo} in murine model and showed remarkable inhibition of parasite multiplication. These drugs act by the inhibition of \emph{in-vivo} protoporphyrin IX (FP-IX). The 25 mg/kg dose of platinum complex showed greater activity than ligands against antimalarials. It showed 50-80\% inhibition of parasite multiplication and in addition they showed no cytotoxic effects [25].

Mohamed and Gad-Elkreem synthesized, characterized and performed thermal studies on metal complexes of new azo compounds derived from sulfa drugs. Four new azo compounds of sulfa drugs have been prepared and characterized. These azo ligands coordinate via the azo N, carbonyl O, enolic sulphonamide OH, and pyrazole or thiodiazole \(N\) groups forming two binding chelating agents. The ligands were \([\text{MX},(\text{L1})\text{(H}_2\text{O}),_n\text{nH}_2\text{O}, [(\text{MX}),_3\text{(HL}\_2\text{ or \text{HL}_2})\text{(H}_2\text{O}),_n\text{nH}_2\text{O and }[\text{M,X,(L1)}\text{(H}_2\text{O})],\text{nH}_2\text{O. Metal salts used for ligands formation were Cobalt (II), Nickel(II), Copper(II) and Zinc(II)}] [26].

Hemmert et al., synthesized gold (I) complexes involving functionalized N-heterocyclic carbene which were evaluated for their antimalarial activity. The gold complexes were evaluated for chloroquine-resistant \(P. falciparum\ in-vitro\) and then on Vero cells to determine their selectivity. The drugs showed good antiplasmodial activity and with \(IC_{50}\) in the micro and submicromolar range [27].

Arancibia et al., synthesized the rhenium bioorganometallics based on the 4-aminoquinoline structure and evaluated for their antimalarial activity against CQ-resistant strains (W2) and on CQ-susceptible strains of \(P. falciparum\). It indicates that cyretrene conjugates are less active compared to their organic analogues. The \emph{in-vitro} assays were performed on \(P. falciparum\) strains and the drug concentration able to inhibit 50\% of the parasite growth was found to be effective [28].

Niculescu et al., synthesized the Novel 2,3-disubstituted 1,4-naphthoquinone derivatives and their metal complexes. The potential cytotoxic activity of novel 2,3-disubstituted 1,4-naphthoquinone and their metal complexes were studied against L929 mouse fibroblasts cells grown \emph{in-vitro}. The two new naphthoquinonic ligands containing S, N as donor atoms were: 2-acetamino-3-mercaptop-1,4-naphthoquinone (AMNQ) and 2-mercaptop-3-(5-nitrobarbituro)-1,4-naphthoquinone (MNBQN). The \(IC_{50}\) of ligands were 0.0088mg/ml for AMNQ and 0.0022 mg/ml for MNBQN. It has been showed that steric interactions of the substituent at either position-2 or position-6 also important for cytotoxic effect [29].

Chopin et al., synthesized novel 1,4-disubstituted-[1,2,3]-triazole-derived β-aminovinyl trifluoromethylated ketones and their copper (II) complexes. The copper catalyzed cyclodehydration reaction of N-Boc propargyl amine with benzylazide (1,3-dipole) was found to proceed smoothly in t-BuOH/H\(_2\)O at room temperature to provide corresponding 1,4-disubstituted-[1,2,3]-triazole derived N-Boc amine in good yield. (Z)-4-(((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)amino)-1,1,1-trifluorobut-3-en-2-one and (Z)-4-(((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)amino)-1,1,1-trifluoro-4-phenylbut-3-en-2-onewere synthesized and their copper complexes were formed by methanolic addition of ethaminone and by stirring for 2hrs and then filtered. They had been screened for as potential antifungal agents and the antimalarial activity against two \(P. falciparum\) strains (3D7 and W2) [30].

Gokhale et al., synthesized and characterized copper (II) complexes of pyridine-2-carboxamidrazones as potent antimalarial agents. Copper (II) complex of pyridine-2-carboxamidrazones is cis-[dichloro(N\(^2\)-acetylthiophene-pyridine-2-carboxamidrazones)copper(II)]. The \emph{in-vitro} activities of the synthesized compounds were tested against the 3D7 strains of malarial parasite \(P. falciparum\). The compound showed enhanced lipid solubilities and \(ED_{50}\) of copper complex were found to be 0.13 µg/ml [31].

Lei et al., synthesized and studied structure and properties of Cd (II) complexes generated from 2-phenylquinoline derivatives. Cadmium complexes of 2-phenylquinoline derivatives were 2-(4-fluorophenyl) quinoline-4-carboxylic acid and 2-(4-methoxyphenyl)quinoline-4-carboxylic acid. The two complexes show good activity [32].

Chilbale et al., synthesized new amine and urea analogs of ferrochloroquine and their in \emph{vivo} antimalarial activity and electrochemical studies were performed. The compounds were evaluating \emph{in-vitro} against the sensitive D10 and resistant K1 strain of \(P. falciparum\). Most analogs were found to be active than chloroquine in both strains. In D10 ureas were found to be more active than the amines [33].

Ocheskey et al., synthesized, characterized and studied molecular structure of a gallium (III) complex of an amine-phenol ligand with activity against chloroquine-sensitive \(P. falciparum\) strains. Gallium complex, \([(1,12-bis(2-hydroxy-5-methoxybenzyl)-1,5,8,12-tetraazaazadecane)-gallium(III)]\) was synthesised and its antimalarial efficacy was studied against chloroquine- sensitive HB3 \(Plasmodium\) lines. The slight variations in the position of methoxy functionalities on the aromatic rings of the organic scaffold dramatically altered
specificity and thereby possess targeted drug delivery. The complex was found to possess modest antimalarial efficacy against a chloroquine sensitive line and low efficacy against chloroquine resistant line[34].

Hubin et al., synthesized the metal complexes and antimalarial activity of metal complexes of cross-bridged tetraazamacrocyclic ligands were performed. Metal complexes of magnesium(II), cobalt (II), nickel(II), copper(II) and zinc(II) with tetraazamacrocyclic were synthesized and their antimalarial activity was evaluated against chloroquine-resistant W2 and chloroquine-sensitive D6 strains of P. falciparum. The magnesium complex of this ligand shows antimalarial activity with IC50 of 0.127 and 0.157µm Copper and Iron complexes also showed improvement in activity but Nickel, Cobalt and Zinc complexes did not show any improvement in activity upon the metal free ligands for antimalarial activity[35].

**CONCLUSION**

General well being has for some time been influenced by intestinal sickness in the creating scene with more than one million clinical scenes and 3000 passing's consistently. Tranquilize treatment confronts significant difficulties because of advancement of parasite imperviousness to first line antimalarials and inaccessibility of an antibody. This has animated a pursuit of new characteristic and manufactured antimalarials to balance resistance. In this manner, the pharmacophores of these medication hopefuls to overcome the antimalarials to balance resistance. In this manner, the animation a pursuit of new characteristic and manufactured line antimalarials and inaccessibility of an antibody. This has because of advancement of parasite imperviousness to first line antimalaria and low efficacy against Plasmodium falciparum in-vitro, Exp Parasito, 80, 373-381(1995).


