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REVIEW

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# A review on the anti-parasitic activity of ruthenium compounds

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## Abstract

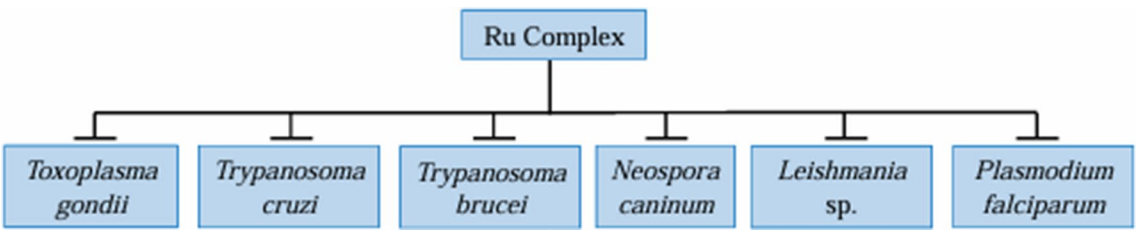
**Background** There are many infectious diseases in the world caused by parasites. Among them, toxoplasmosis, American trypanosomiasis, African trypanosomiasis, leishmaniasis, neosporosis and malaria are more common and contribute to a majority of the affected individuals.

**Main body** Due to extensive use of antibiotics, antibiotic resistant strain of the parasites has developed. So, we need to develop a new metal ligand complexes which have many configurations, can overcome this drug resistance and also show significant results in elimination of the parasites. A series of anti-parasitic drugs have been formulated and tested for its activity. In this review, we have tried to see the interaction of different ruthenium drugs (arene ruthenium complex, ruthenium clotrimazole complex, etc.) on different parasites associated with the aforementioned diseases.

**Conclusion** Combination of ruthenium to any organic ligand shows synergistic effects against parasite either by overcoming the drug resistance of the parasite or by binding with new targets due to the presence of ruthenium ion. The multiple modes of action generate an effective drug exhibiting anti-parasitic activity at low concentration.

**Keywords** Ruthenium, Cytotoxicity, Stress, Apoptosis, Parasite

### Graphical abstract

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## Background

World is facing a major problem due to various parasitic diseases. A large sum of population dies due to such diseases but there is little economic investment for the search of new drugs to counter such diseases. It is more challenging to produce new drugs due to multi-drug resistance of the parasite (Li et al., 2015). Metallic compounds can be used for the treatment of diseases as they have structural diversity in their 3D configuration due to the presence of different geometry, metal ion, ligands, etc. (Morrison et al., 2020). The problem with organic compounds is their planar or linear structures which cannot be easily modified for recognition by a biomolecule. This is solved by the use of metal complex due to their complex 3D structure which results in strong interaction with the intercellular target (Morrison et al., 2020). Metal complexes have unique properties which are absent in organic compounds, like redox activation, production of reactive oxygen species (ROS) and targeting vital processes (Anthony et al., 2020; Claudel et al., 2020).

Synergism of a metal ion with a drug with anti-proliferative property leads to the formation of a complex with enhanced anti-proliferative property and decreases the cytotoxicity toward normal cells, thereby leading to inhibition of parasitic growth (Hess et al., 2015; Iniguez et al., 2013). For example, bismuth-based compounds are used for therapeutic purposes (Keogan et al., 2014). In this review, we are going to discuss the anti-parasitic potential of ruthenium compounds.

## Methodology

The data presented in this review have been procured and summarized on the basis of the following principles.

### Search strategy and inclusion criteria

This review consists of several literature survey of the anti-parasitic activity of ruthenium compounds against *Toxoplasma gondii, Neospora caninum, Trypanosoma sp., Leishmania sp.* and *Plasmodium sp.* Those compounds exhibiting optimum anti-parasitic effects have been enlisted and the corresponding mechanisms of action have been discussed briefly. The literature survey stressed on scientific research papers and review articles published from 1984 to 2022. The following keywords were included as part of the search strategy: ruthenium, *Toxoplasma, Neospora, Trypanosoma, Leishmania, Plasmodium*, anti-parasitic activity, malaria, toxicity, in vitro study, ER stress, clotrimazole, etc. Google Scholar and PubMed were the main databases used for searching relevant information.

### Data extraction and analysis

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist was consulted because this review bears some characteristics of an overview, which in turn, is partially synonymous to a systematic review (Grant & Booth, 2009). The PRISMA flow diagram shows how the relevant data have been extracted and analyzed (Fig. 1) (Liberati et al., 2009).

### Quality assessment

The quality of the studies included for quantitative analyses was assessed using the Critical Appraisals Skills Program (CASP) checklist with slight modifications (Table 1) (Critical Appraisal Skills Program (2018). CASP (Systematic Review) Checklist. [online] Available at: https://casp-uk.net/casp-tools-checklists/. Accessed: 20th July, 2023). A summary of the data obtained from such studies has been included in Table 2. During quality assessment of 18 short-listed literatures, it was observed that the contents of 9 articles had already been summarized in a previously published scientific review. Therefore, the single scientific review (Munteanu et al., 2021) was considered for quality assessment instead of the concerned 9 articles to avoid unnecessary complexity.

## Main text

### Chemical properties of ruthenium

Of the two redox potentials of ruthenium, Ru(III) is more inert than Ru(II) oxidation state. Ru(III) and Ru(II) usually form compounds with octahedral geometry that lead to interconversion of oxidation states without the requirement of large amount of energy for the associated structural rearrangement (Gasser et al., 2011; Zeng et al., 2017). Some enzymes like ascorbate reduce Ru(III) to its more reactive Ru(II) form. There are also some enzyme like cytochrome oxidase which can reverse the reaction and convert Ru(II) back to Ru(III) (Allardyce et al., 2005). The kinetic stability of the ruthenium drug depends on the ligand to which it binds. Different ruthenium drug complexes (Ru complexes) can be made which show high cytotoxicity against parasites (Munteanu et al., 2021). Ruthenium drugs have been mostly used to treat cancer. Simultaneously, they are found to be effective against helminth infections (Han Ang & Dyson, 2006; Hess et al., 2015; Küster et al., 2012).

### Mechanism of action of ruthenium

Existing literature lacks a detailed understanding of the mechanism of action of ruthenium compounds, especially against parasitic diseases. However, the

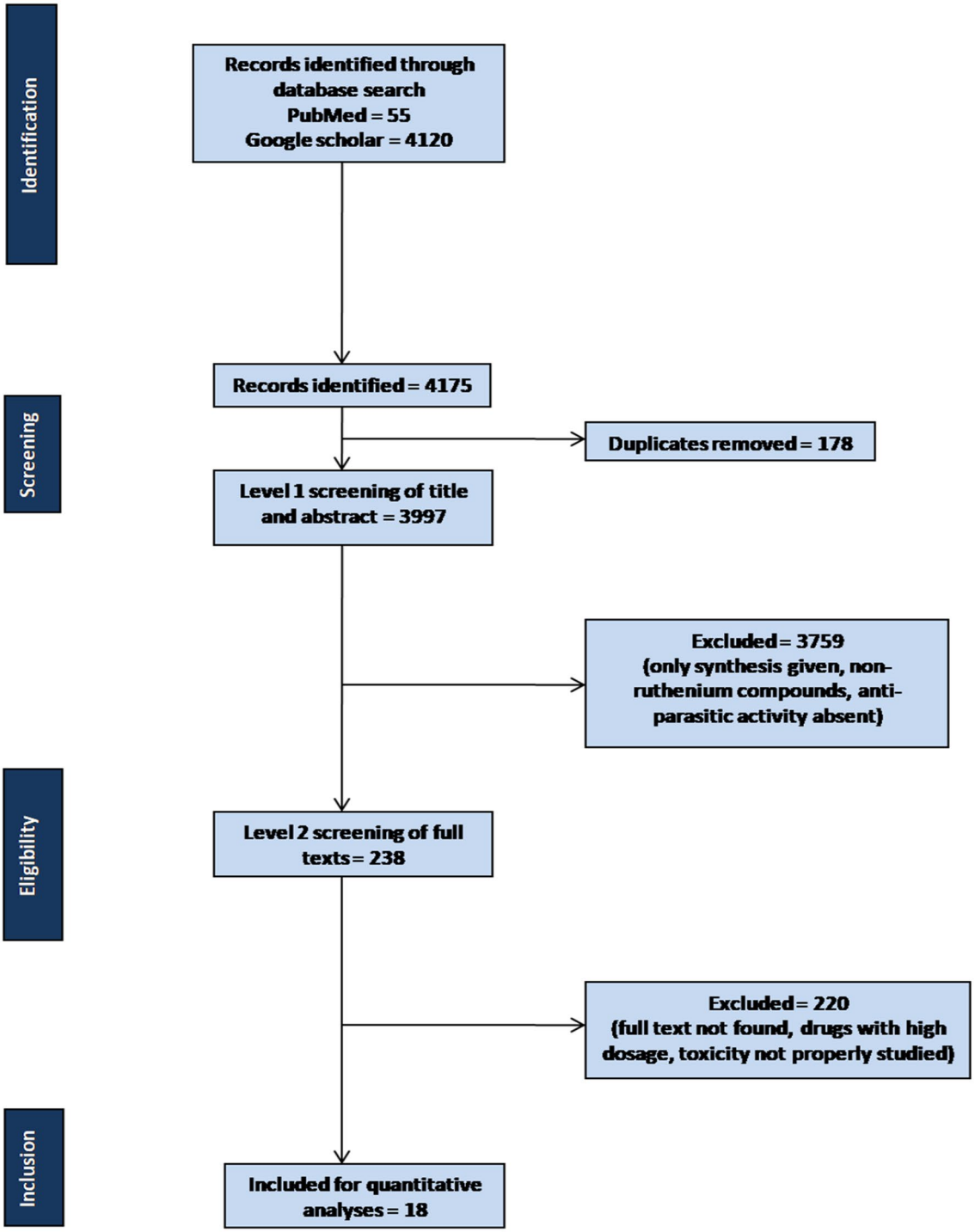


**Fig. 1** PRISMA flow diagram

following discussion may provide insights into their possible routes of interaction and inspire further extensive research.

***Ruthenium-DNA interaction***

The diamine groups, the hydrophobic arene and the chloride leaving group of ruthenium arene complexes have

**Table 1** Modified CASP Checklist

| Question | Anghel et al., (2021) | Basto et al., (2017) | Barna et al., (2013) | Basto et al., (2019) | Munteanu et al. (2021) | Demoro et al. (2013) | Jelk et al., (2019) | Rodriguez Arce et al. (2015) | Martinez et al. (2012) | Costa et al., (2019) |
|---|---|---|---|---|---|---|---|---|---|---|
| *Did the study address a clearly focused question?* | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| *In course of a literature survey, did the authors/reviewers look for the right type of papers?* | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| *Was the exposure accurately measured to minimize bias?* | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| *Was the outcome accurately measured to minimize bias?* | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| *Are the results of the study reasonable?* | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| *Are the results quite precise?* | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| *Do you believe the results?* | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| *Can the results be applied to the local population?* | Can't Tell | May be | Can't Tell | May be | May be | Can't Tell | May be | May be | Yes | Can't Tell |
| *Were all important outcomes considered?* | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| *Overall quality* | High | High | High | High | High | High | High | High | High | High |

**Table 2** Summary of key findings in this review

| Author, Year, Country | Compound | Parasite | $IC_{50}$ value |
|---|---|---|---|
| Anghel et al. (2021); Switzerland | Trithiolato bridged dinuclear Ru(II) arene conjugated with 9–(2–oxy-ethyl)–adenine unit | *Toxoplasma gondii* | 59 nM |
| Basto et al. (2017); Switzerland | Dinuclear thiolato bridged arene ruthenium complex | *Toxoplasma gondii* | 1.2 nM |
| Barna et al. (2013); Switzerland | $\eta^6$-areneruthenium(II) phosphite complex | *Toxoplasma gondii* | 18.7 nM |
| | | *Neospora caninum* | 6.7 nM |
| Basto et al. (2019); Switzerland | $[(\eta^6\text{-p-MeC}_6\text{H}_4\text{Pr}^i)_2\text{Ru}_2(\mu_2\text{-SC}_6\text{H}_4\text{-p-CH}_3)_3]\text{Cl}$, | *Neospora caninum* | 15 nM |
| | $[(\eta^6\text{-p-MeC}_6\text{H}_4\text{Pr}^i)_2\text{Ru}_2(\mu_2\text{-SC}_6\text{H}_4\text{-p-Bu}^t)_3]\text{Cl}$, | | 5 nM |
| | $[(\eta^6\text{-p-MeC}_6\text{H}_4\text{Pr}^i)_2\text{Ru}_2(\mu_2\text{-SCH}_2\text{C}_6\text{H}_4\text{-p-Bu}^t)_2\text{-}(\mu_2\text{-SC}_6\text{H}_4\text{-p-OH})]\text{BF}_4$ | | 1 nM |
| Munteanu et al. (2021); Romania (Review) | | | |
| Silva et al. (2007, 2009) | trans-$[\text{Ru(NO)(NH}_3)_4\text{(isn)}]^{3+}$ and trans-$[\text{Ru(NO)(NH}_3)_4\text{(imN)}]^{3+}$ complexes forming trans-$[\text{Ru(NO)(NH}_3)_4\text{(isn)}](\text{BF}_4)$ and trans-$[\text{Ru(NO)(NH}_3)_4\text{(imN)}](\text{BF}_4)_3$ | *Trypanosoma cruzi* | – |
| Silva et al. (2010) | cis-$[\text{Ru(NO)(bpy)}_2\text{(imN)}](\text{PF}_6)_3$ | *Trypanosoma cruzi* | 89 µM |
| | cis-$[\text{Ru(NO)(bpy)}_2\text{SO}_3]\text{PF}_6$ | | 153 µM |
| Bastos et al. (2014) | *cis,trans*-$[\text{RuCl(NO)(dppb)(5,5'-mebipy)}](\text{PF}_6)_2$ | *Trypanosoma cruzi* | 2.1 µM (acute stage) |
| | | *Trypanosoma cruzi* | 1.3 µM (chronic stage) |
| Martinez et al. (2012) | $[\text{RuII(p-cymene)(bpy)(CTZ)}][\text{BF}_4]_2$ | | 15 nM |
| | $[\text{RuCl}_2\text{(Lap)(dppb)}]$ | | – |
| Barbosa et al. (2014) | | *Leishmania major* | |
| | $[\text{RuCl(OH}_2)_3\text{(CQ)}]_2[\text{Cl}]_2$ | | – |
| Martinez et al. (2008) | | *Leishmania amazonenis* | |
| | $[\text{RuCQ}(\eta^6\text{-C}_{10}\text{H}_{14})\text{(N–H)}]^{2+}$ | | – |
| Macedo et al. (2016) | | *Plasmodium falciparum* | |
| Chellan et al. (2013) | TrinuclearRu(II)-$\eta^6$-p-cymene complexes where ruthenium center is linked by pyridyl aromatic ether ligands | | 240 nM |
| | | *Plasmodium falciparum* | |
| | | *Plasmodium falciparum* | |
| Demoro et al. (2013); Uruguay | $[\text{Ru}_2\text{(p-cymene)}_2\text{(L)}_2]\text{X}_2$ | *Trypanosoma brucei* *Trypanosoma cruzi* | – |
| Jelk et al. (2019); Switzerland | $[(\eta 6\text{ -p-MeC}_6\text{H}_4\text{Pr}^i)_2\text{Ru}_2(\mu_2\text{-SC}_6\text{H}_4\text{-o-Pr}^i)_3]\text{Cl}$ | *Trypanosoma brucei* | 4 nM |
| Rodriguez Arce et al. (2015); Uruguay | $[\text{RuCp(PPh}_3)_2\text{(CTZ)}](\text{CF}_3\text{SO}_3)$ | *Trypanosoma brucei* | 0.6 µM |
| Martinez et al. (2012); USA | $[\text{Ru(II)}(\eta^6\text{ -p-cymene})\text{Cl}_2\text{(CTZ)}]$ | *Leishmania major* | – |
| Costa et al. (2019); Brazil | cis-$[\text{RuII}(\eta^2\text{-O}_2\text{CC}_{10}\text{H}_{13})\text{(dppm)}_2]\text{PF}_6$ (bbato), | *Leishmania amazonenis* | – |
| | cis-$[\text{RuII}(\eta^2\text{-O}_2\text{CC}_7\text{H}_7\text{S})\text{(dppm)}_2]\text{PF}_6$ (mtbato), | | |
| | cis-$[\text{RuII}(\eta^2\text{-O}_2\text{CC}_7\text{H}_7\text{O}_2)\text{(dppm)}_2]\text{PF}_6$ (hmxbato) | | |

important role in their mechanism of recognition of nucleic acids (Chen et al., 2003). Some ruthenium complexes intercalate with the DNA by non-covalent stacking interactions with DNA base pairs (Chen et al., 2003; Mishra & Mukherjee, 2006; Nyawade et al., 2014).

#### *Inhibition of membrane sterol biosynthesis*

Ruthenium clotrimazole complex shows anti-parasitic effects against *Leishmania major*. It easily passes the parasite's membrane and upon hydrolysis liberates clotrimazole. This azole derivative then inhibits the cytochrome

P-450 dependent C(14)-demethylation of lanosterol to ergosterol (Iniguez et al., 2016).

#### *Effect on ultrastructure and membrane potential of mitochondria*

Dinuclear thiolato bridged arene ruthenium complexes have been reported to cause alterations in the ultrastructure and membrane potential of mitochondria in bloodstream forms of *Trypanosoma brucei*. Such alterations include distortion of mitochondrial membrane with transformation of the mitochondrial matrix into an amorphous moiety having varying degrees of electron density or filling of the organellar interior with unknown filamentous structures, and the dose and time dependent effects of the complexes on the mitochondrial membrane potential (Jelk et al., 2019).

#### *Modulation of endoplasmic reticulum (ER) stress pathway*

Sodium *trans*-[tetrachloridobis(1*H*-indazole) ruthenate(III)] (NKP-1339), a ruthenium compound metal complex, has been reported to generate reactive oxygen species (ROS) in colon cancer cell lines. ROS leads to activation of Nrf2 and the subsequent transcription of antioxidant response gene. ROS generation also leads to accumulation of misfolded proteins in the ER and subsequent ER stress. At low concentrations of NKP-1339 in HCT116 cells, GRP78, a key regulator of ER stress, is upregulated. GRP78 releases PERK, a transmembrane receptor of ER, which is then phosphorylated. Then, phosphorylation of eIF2α ensues, which leads to the inhibition of CAP-dependent translation. Consequently, the CAP-independent transcription factor ATF4 is upregulated. It translocates to the nucleus and induces expression of CHOP. CHOP downregulates Bcl-2 and activates death receptor 5 (DR5), thereby promoting apoptosis. (Fig. 2) (Flocke et al., 2016).

### Anti-parasitic activity against *Toxoplasma gondii*

*Toxoplasma gondii* belongs to the clades Alveolata and Diaphoretickes (Smith et al., 2021). It is life threatening to immune suppressed hosts like humans and other animals (Dubey, 2021). Its seroprevalence is found to be quite high in some African and European populations (Milne et al., 2020). Many such parasites follow auxotrophic pathway, and we can conjugate ruthenium with purines which can increase the uptake of drug by the parasite (Coppens, 2014). Such drugs can modulate the cell death machinery (Klinkert & Heussler, 2006).

A trithiolato bridged dinuclear Ru(II) arene conjugated with 9–(2–oxyethyl)–adenine unit inhibits proliferation of T. *gondii* tachyzoites at $IC_{50}$ of 59 nM (Fig. 3A). When T. *gondii* is treated with this complex, the YOU2 family C2C2 zinc finger protein of the parasite binds to this compound (Anghel et al., 2021).

A dinuclear thiolato bridged arene ruthenium complex (Fig. 3B) exhibits an $IC_{50}$ value of 1.2 nM against T. *gondii*. It affects the extracellular parasites and prevents them from adhesion, invasion and establishment in the host cell. It mainly binds to the T. *gondii* elongation factor 1α (TgEF1-α), affects the mitochondria and results in death of most of the tachyzoites within 48 h of treatment. It targets the cytochrome $b/c_1$complex of mitochondria (Basto et al., 2017).

An $\eta^6$-areneruthenium(II) phosphite complex (Fig. 3C) has been shown to exhibit an $IC_{50}$ value of 18.7 nM against T. *gondii* parasite. 12 h after treating with the drug, lipid inclusions are found in the cytoplasm, the nuclear membrane appears fuzzy in appearance and chromatin threads are mostly located at the periphery of the nucleus of the tachyzoites when observed under TEM. After 36 h of treatment, the cytoplasm is completely disorganized and the organelles of the tachyzoites are hardly detectable (Barna et al., 2013).

### Anti-parasitic effect on *Neospora caninum*

*Neospora caninum* is an apicomplexan parasite which exhibits the rapidly proliferating tachyzoite stage and the cyst forming bradyzoite stage which remains in the host for a longer period of time without showing any symptoms. They live in the immune compromised tissue, affect the immune system of the host and modulate it for their own benefit. The parasite causes neosporosis leading to abortion and maternal infertility in cattle and neurological disorder in dogs (Dubey & Lindsay, 1996; Innes et al., 2007; Lüder et al., 2009).

An $\eta^6$-areneruthenium(II) phosphite complex (Fig. 3C) showed the $IC_{50}$ value of 6.7 nM against N. *caninum* (Barna et al., 2013). The drug severely impaired the proliferation of the parasite.

Dinuclear trithialato bridged arene ruthenium complexes $[(\eta^6\text{-p-MeC}_6\text{H}_4\text{Pr}^i)_2\text{Ru}_2(\mu_2\text{-SC}_6\text{H}_4\text{-p-CH}_3)_3]\text{Cl}$ (Fig. 3D), $[(\eta^6\text{-p-MeC}_6\text{H}_4\text{Pr}^i)_2\text{Ru}_2(\mu_2\text{-SC}_6\text{H}_4\text{-p-Bu}^t)_3]\text{Cl}$ (Fig. 3E) and $[(\eta^6\text{-p-MeC}_6\text{H}_4\text{Pr}^i)_2\text{Ru}_2(\mu_2\text{-SCH}_2\text{C}_6\text{H}_4\text{-p-Bu}^t)_2\text{-}(\mu_2\text{-SC}_6\text{H}_4\text{-p-OH})]\text{BF}_4$ have shown an $IC_{50}$ value of 15, 5& 1 nM against N. *caninum*, respectively. After the delivery of the drug, changes in the structure of parasite mitochondria was observed rapidly. After the delivery of the three drugs, within 6 h, large vacuoles appeared in the mitochondrial matrix. All the 3 compounds showed high lipophilicity and prompted toward their easy cellular uptake (Basto et al., 2019).

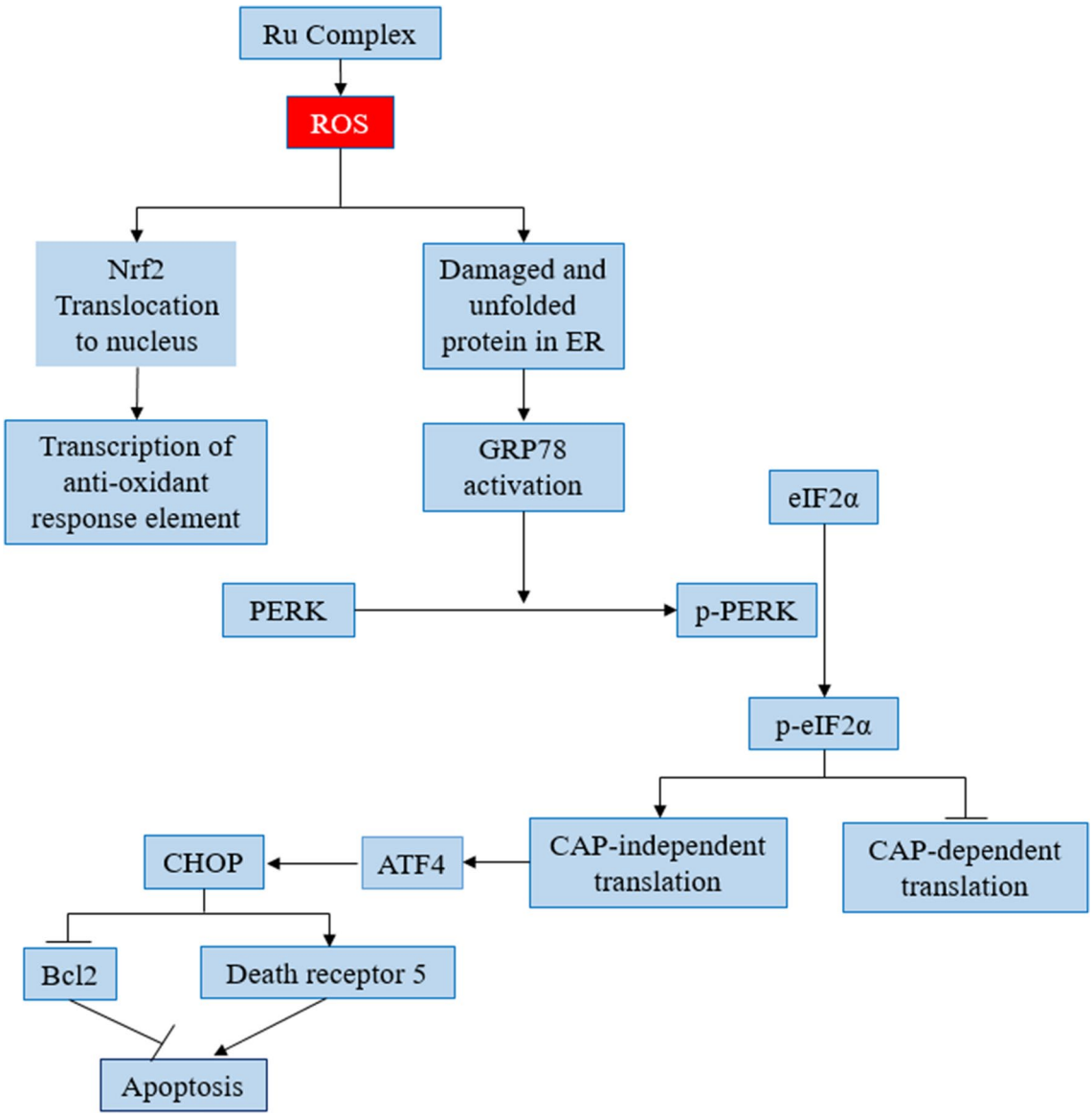


**Fig. 2** Modulation of pathway of ER stress mediated apoptosis by NKP-1339 in colon cancer cell. ATF4: Activating transcription factor 4; CHOP: C/EBP-homologous protein; DR5: Death receptor 5; eIF2α: Eukaryotic initiation factor 2 alpha; GRP78: Glucose regulated protein 78 kD

***Anti-parasitic effect against Trypanosoma sp.***

*Trypanosoma sp.* is a parasite of class kinetoplastida. This parasite is extracellular in nature and lives in the body fluids. They feed on blood and lymph of the host. *Trypanosoma cruzi* causes the Chagas disease (American trypanosomiasis) in humans. *Trypanosoma brucei* is a parasite which is mostly found in Africa (Cavalli & Bolognesi, 2009; Le Loup et al., 2011; Rivera et al., 2009). They show high proliferating power which resembles the proliferation of the cancer cells, and so, we can use anti-cancer drugs for treating such parasite infections (Gambino & Otero, 2012).

*Trypanosoma cruzi* This disease affects more than 20 million people per year and result to death of approximately 50,000 people per year in South and Central America (Hotez et al., 2008; Kirchhoff, 2011; WHO Report, 2002). It affects humans in trypomastigote stage through its vector, the reduviid bugs, which suck blood from the host and help in transmitting the parasite by the deposition of the parasite loaded faeces on the host body surface. It can also be transmitted blood transfusion and organ transfusion (Bern et al., 2011; Schmunis, 2007).

trans-$[Ru(NO)(NH_3)_4(isn)]^{3+}$ (Fig. 3F) and trans-$[Ru(NO)(NH_3)_4(imN)]^{3+}$ (Fig. 3G) complexes forming

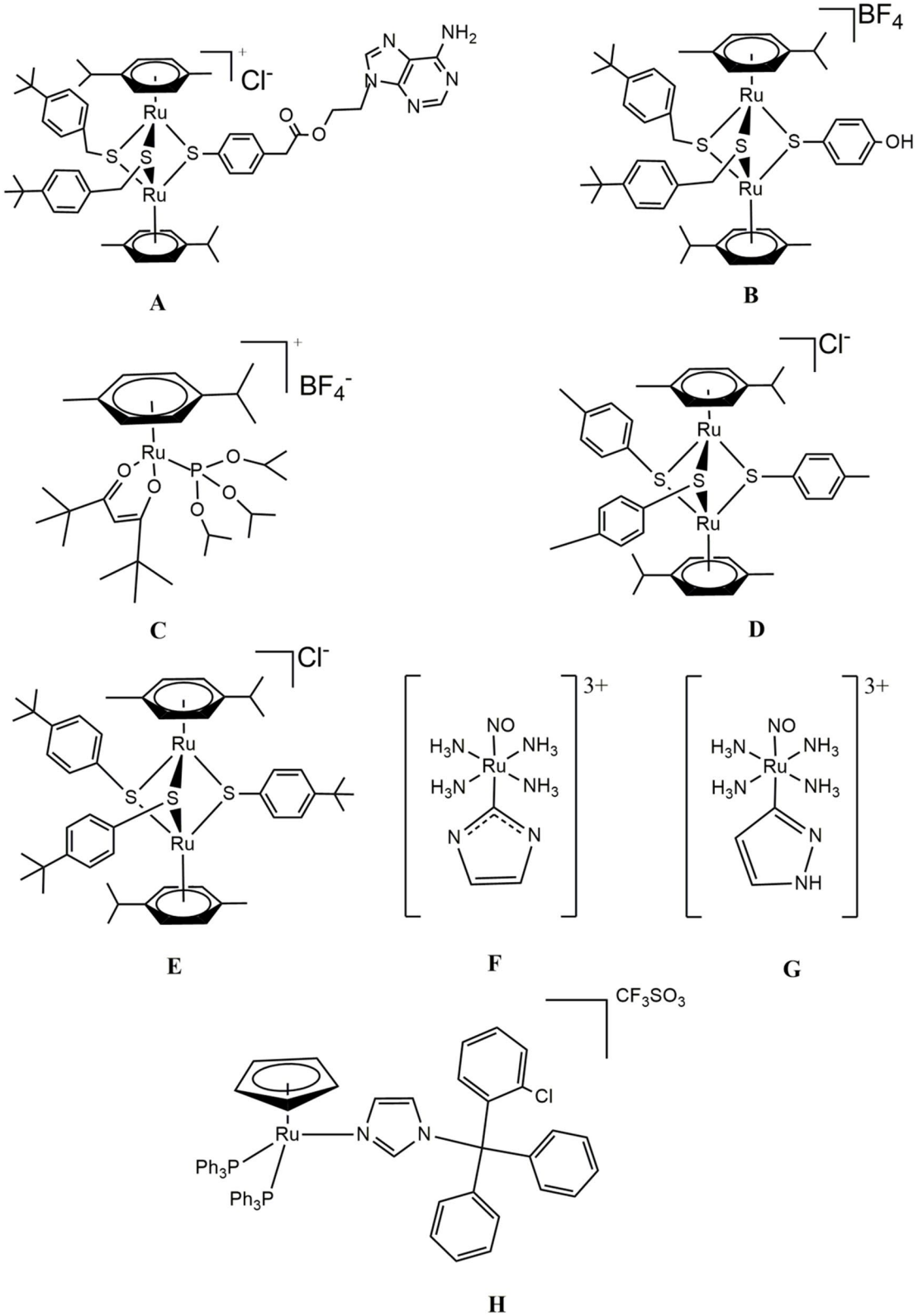


**Fig. 3** Ruthenium compounds exhibiting anti-parasitic activity against *Toxoplasma gondii* (**A**–**C**), *Neosporacaninum* (**C**–**E**) and *Trypanosoma sp.* (**F**–**H**). **A**–**E** arene ruthenium complexes; **F**, **G** ruthenium nitrosyls; **H** ruthenium-based clotrimazole drug. *(The structures have been constructed using ChemDraw Pro 8.0)*

trans-$[Ru(NO)(NH_3)_4(isn)](BF_4)_3$ (where isn stands for isonicotinamide) and trans-$[Ru(NO)(NH_3)_4(imN)](BF_4)_3$ (where imN stands for imidazole), are found to be effective against the parasite (Munteanu et al., 2021; Silva et al., 2007, 2009). Ruthenium nitrosyls on reduction result in release of trypanosomicidal NO.

cis-$[Ru(NO)(bpy)_2(imN)](PF_6)_3$ and cis-$[Ru(NO)(bpy)_2SO_3]PF_6$ show inhibitory effects on the *T. cruzi* glyceraldehyde 3-phosphate dehydrogenase through $IC_{50}$ of 89 and 153 μM, respectively (Munteanu et al., 2021; Silva et al., 2010).

*cis,trans*-$[RuCl(NO)(dppb)(5,5'\text{-mebipy})](PF_6)_2$ (where dppb stands for 1,4-bis(diphenylphosphino)butane and mebipy stands for 5,5'-dimethyl-2,2'-bipyridine) shows an $IC_{50}$ value of 2.1 μM against the acute stage of the disease, i.e., trypomastigote and $IC_{50}$ value of 1.3 μM against the chronic stage of the disease, i.e., amastigotes (Munteanu et al., 2021; Bastos et al., 2014).

Organoruthenium(II) compounds $[Ru_2(p\text{-cymene})_2(L)_2]X_2$ (where L are bioactive 5-nitrofuryl-containing thiosemicarbazones and X = Cl or PF6 show anti-parasitic activity against both T. *cruzi* and T. *brucei* (Demoro et al., 2013).

*Trypanosoma brucei* *Trypanosoma brucei* is a flagellated parasite and its subspecies T.b. *rhodesiense* and T.b. *gambiense* cause human African trypanosomiasis of which T.b. *gambiense* contributes to 80% cases of the disease (Giordani et al., 2016). They use tsetse fly as the vector. They live in the blood stream of the host (Priest & Hadjuk, 1994).

$[(\eta6\text{-}p\text{-}MeC_6H_4Pr^i)_2Ru_2(\mu_2\text{-}SC_6H_4\text{-}o\text{-}Pr^i)_3]Cl$ is a dinuclear thiolato bridged arene ruthenium complex showing $IC_{50}$ value of 4 nM against T. *brucei* (Jelk et al., 2019).

A ruthenium-based clotrimazole drug, $[RuCp(PPh_3)_2(CTZ)](CF_3SO_3)$ (where Cp stands for cyclopentadienyl and CTZ stands for clotrimazole) (Fig. 3H) affects the trypomastigotes stage of the parasite with an $IC_{50}$ value of 0.6 μM (Rodriguez Arce et al., 2015).

### Anti-parasitic activity against *Leishmania sp.*

Leishmaniasis is a protozoan disease caused by a parasite belonging to the class kinetopastida and genus *Leishmania*. It is mostly present in the subtropical and tropical part of the world. It is transmitted by a sand fly which belongs to the phlebotominae subfamily. It causes three types of leshmaniasis which are cutaneous leishmaniasis which accounts for one third of the total affected individuals, visceral leishmaniasis which is also known as kala azar and mucocutaneous leishmaniasis. It affects around 2 million people every year (Den Boer et al., 2011). So, ruthenium complex drugs can be used for its treatment.

A ruthenium clotrimazole complex, $[Ru(II)(\eta^6\text{-}p\text{-cymene})Cl_2(CTZ)]$, (Fig. 4A) shows an $IC_{70}$ value of 29 nM against the amastigote stage of L. *major* (Martinez et al., 2012). It is also effective against epimastigotes of T. *cruzi*.

A ruthenium clotrimazole complex, [RuII(p-cymene)(bpy)(CTZ)][$BF_4$]$_2$ (Fig. 4B) shows $IC_{50}$ of 15 nM against L. *major* (Martinez et al., 2012; Munteanu et al., 2021).

$[RuCl_2(Lap)(dppb)]$ shows anti-parasitic activity against L. *amazonensis* promastigote stage (Munteanu et al., 2021; Barbosa et al., 2014).

cis-$[RuII(\eta^2\text{-}O_2CC_{10}H_{13})(dppm)_2]PF_6$ (bbato), cis-$[RuII(\eta^2\text{-}O_2CC_7H_7S)(dppm)_2]PF_6$ (mtbato), cis-$[RuII(\eta^2\text{-}O_2CC_7H_7O_2)(dppm)_2]PF_6$ (hmxbato) (where dppm stands for bis(diphenylphosphino)methane) are effective against various leishmanial species (Costa et al., 2019).

### Anti-parasitic activity of ruthenium compounds against *Plasmodium sp.*

Malaria is caused by a plasmodium parasite belonging to order haemosporida. Of the various species of plasmodium, *Plasmodium falciparum* is quite dangerous and accounts for 90% of global malarial mortality (Snow, 2015).

$[RuCl_2(CQ)]_2$ is an organometallic complex where CQ is chloroquine which itself has anti-malarial property (Fig. 4C). It is five times more active than CQ due to the more lipophilic character of the drug than free CQ (Munteanu et al., 2021). The drug binds to hematinand prevents haemozoin accumulation. In the aqueous solution, the drug is converted to $[RuCl(OH_2)_3(CQ)]_2[Cl]_2$ which is the active drug resulting in anti-malarial activity (Martinez et al., 2008; Munteanu et al., 2021).

$[RuCQ(\eta^6\text{-}C_{10}H_{14})(N\text{–}H)]^{2+}$ is also an organoruthenium complex where $\eta^6\text{-}C_{10}H_{14}$ stands for α-phellandrene group and N–H represents either 5,5'-dimethyl-2,2'-bipyridine, 2'-bipyridine, 4,7-diphenyl-1,10-phenanthroline or 1,10-phenanthroline group. This drug shows anti-malarial activity against the sexual stage and also against stages of the parasite which target the liver. It produces ROS leading to death of the parasite (Macedo et al., 2016; Munteanu et al., 2021).

Trinuclear Ru(II)-$\eta^6$-p-cymene complexes where ruthenium centre is linked by pyridyl aromatic ether ligands have been found to show an $IC_{50}$ of 240 nM against CQ sensitive and 670 nM against CQ resistant P. *falciparum* strains (Chellan et al., 2013; Munteanu et al., 2021).

### Clinical trials

Various anti-tumour drugs have been used for the treatment of parasitic infections (Farrell et al., 1984; Gambino, 2011). Similarly, this review demonstrates the use of ruthenium complexes as anti-parasitic drugs.

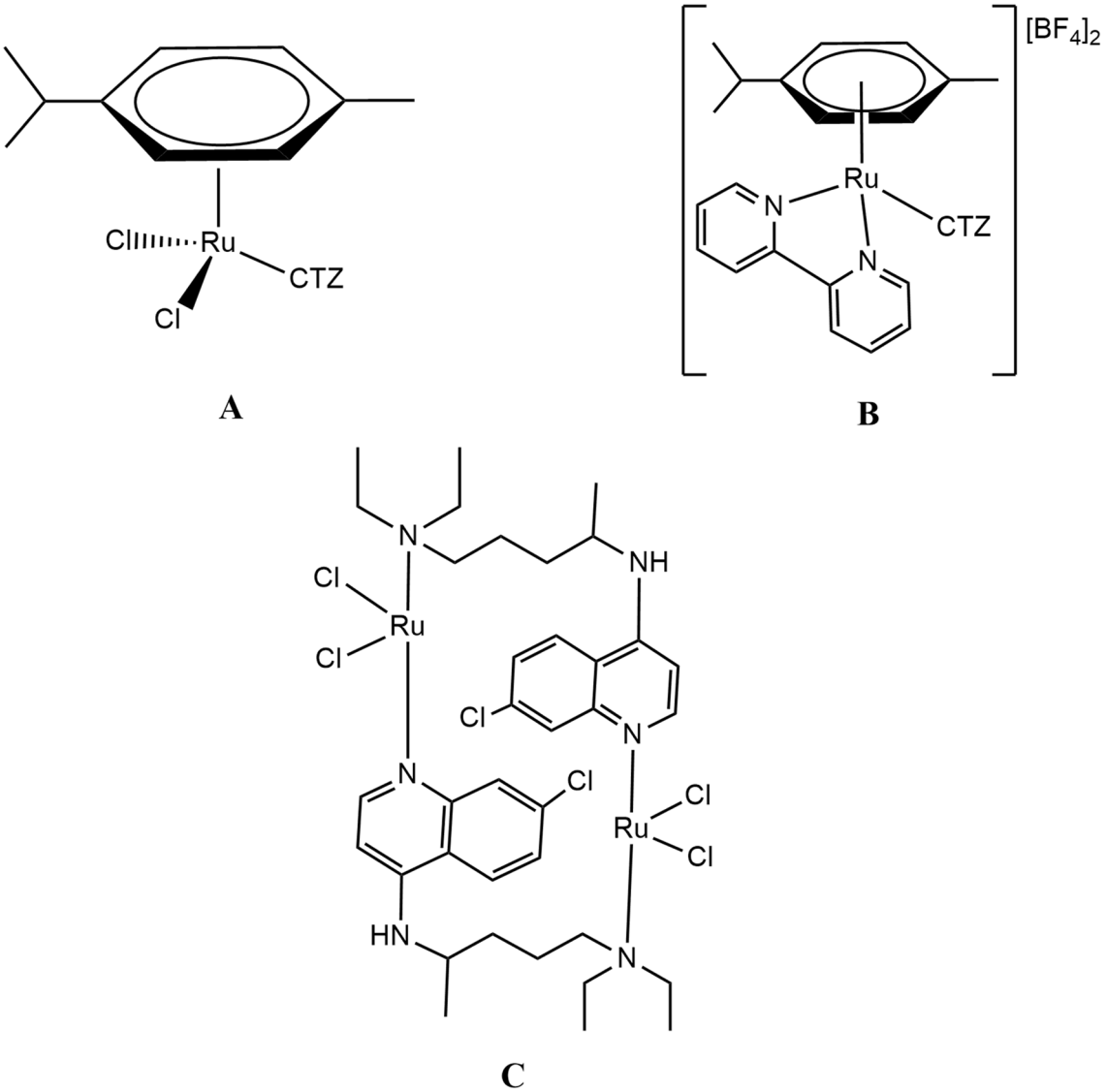


**Fig. 4** Ruthenium compounds exhibiting anti-parasitic activity against *Leishmania sp.* (**A**, **B**) and *Plasmodium sp.* (**C**). **A**–**C** ruthenium clotrimazole and chloroquine complexes. *(The structures have been constructed using ChemDraw Pro 8.0)*

Till date, no ruthenium drug has been put up for clinical trial with respect to treatment of parasitic diseases. However, there are drugs like NAMI-A, NKP-1339, KP1019, which have reached the phase of human clinical trials for ruthenotherapy against cancer (Hartinger et al., 2008; Rademaker-Lakhai et al., 2004; Trondl et al., 2014). Extensive research is necessary for various ruthenium compounds to reach the stage of human clinical trials for the treatment of parasitic diseases.

## Conclusion

From the data we have received, we are able to conclude that the combination of ruthenium to any organic ligand shows synergistic effects against parasite either by overcoming the drug resistance of the parasite or by binding to new targets due to the presence of ruthenium ion. The drug interaction with DNA produces ROS. The concerned drugs bind to different proteins and damage the process of cell membrane synthesis. This multiple mode of action adds up to generate an effective drug exhibiting anti-parasitic activity at low concentration. Ruthenium has two oxidation states, and it binds

to different bioactive ligands. So, ruthenium drugs with selective activity can be developed using different ligands depending on the nature of the parasite. We should focus in developing new organometallic drugs that show considerable activity against parasites owing to their lipophilic character which results in their easy cellular uptake.

### Limitation of current research

Existing literature on anti-parasitic activity of ruthenium compounds exhibit the limitations of poor solubility of the compounds in water, lack of proper understanding of their mechanisms of action and the lack of clinical research (Munteanu et al., 2021; Serrano-Ruiz et al., 2017).

### Future perspectives

Ruthenium drugs have immense potential in exhibiting anti-viral, anti-bacterial, anti-cancer and anti-parasitic effects in vitro. However, in vivo studies are necessary to validate such claims. To achieve therapeutic victory, proper understanding of the mechanism of action and studies on the targeted delivery of such drugs is essential. In this review, we have investigated about anti-parasitic activity of different ruthenium conjugated drugs. Developing countries are facing loss of human resource due to parasitic diseases but still we keep a blind eye toward it. Focus on investment for the development of many ruthenium conjugated drugs and testing their toxicity toward the parasite can help in generating effective drugs against various parasitic diseases.

#### Abbreviations

| | |
|---|---|
| Acac | Acetylacetone |
| ASK1 | Apoptosis signaling regulating kinase |
| Bpy | 2,2′-Bipyridine; Cp, cyclopentadienyl group |
| CQ | Chloroquine |
| CTZ | Clotrimazole |
| DAPK1 | Death associated protein kinase 1 |
| DHA | Dihydroartemisinin |
| Dppb | 1,4-Bis(diphenylphosphino)butane |
| Dppm | Bis(diphenylphosphino) methane |
| DR5 | Death receptor 5 |
| ER | Endoplasmic reticulum |
| 9-ETG | 9-Ethylguanine |
| ImN | Imidazole |
| Lap | Lapachol |
| Mebipy | 5,5-Dimethyl-2,20–bipyridine |
| PERK | Protein kinase RNA-like endoplasmic reticulum kinase |
| $Ph_3P$ | Triphenylphosphine |
| TEM | Transmission electron microscopy |
| TgEF1-α | *T. gondii* Elongation factor 1α |
| TNF | Tumor necrosis factor |
| TRAF2 | TNF receptor associated factor 2 |

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#### Author contributions

SC was contributed to conceptualization, methodology, data curation, writing—original draft, visualization, investigation, validation, writing—review and editing, formal analysis. SG was contributed to visualization, investigation, data curation, validation, writing—review and editing, formal analysis. SD was contributed to visualization, investigation, data curation, validation, writing—review and editing. AD was contributed to conceptualization, methodology, data curation, writing—original draft, supervision, writing—review and editing.

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Not applicable.

#### Consent for publication

Not applicable.

#### Competing interests

The authors share no conflict of interest.

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