REVIEW ARTICLE

The Antiparasitic Potential of Flavonols: A Systematic Review

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ABSTRACT

Background: Parasites represent a significant global health burden, especially in tropical and subtropical regions. Despite the availability of different types of antiparasitic drugs, their harmful side effects and limited treatment options highlight the urgent need for new therapeutic alternatives. Additionally, the development of resistance to existing medications complicates treatment efficacy. Consequently, researchers are focusing on compounds found in medicinal plants, particularly flavonols, due to their potential to inhibit parasite growth effectively. This review aims to establish an evidence-based foundation for developing novel flavonol-based antiparasitic drugs that can effectively combat parasites. **Method:** The review adhered to the methodological rigor outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. Specific keywords related to flavonols and antiparasitic activity were used in a systematic search of databases, including PubMed, Web of Science, ProQuest, and Science Direct. The methodological quality of the included papers was judged using the QuADS criteria. **Results:** The systematic review included 44 studies after screening 1,629 papers based on eligibility criteria. The study compiles 43 compounds and several plant extracts containing flavonols, all of which have demonstrated antiparasitic properties. **Conclusion:** This review summarizes various flavonols with differing levels of potential to combat a wide range of protozoan parasites, along with their mechanisms of action. However, more in-depth and detailed research is still needed to fully explore the potential of flavonols as future safe antiparasitic agents.

INTRODUCTION

Parasites are major contributors to human diseases globally, affecting regions such as Africa, Southeast Asia, and the Americas (Torgerson et al., 2015). They significantly impact tropical and subtropical countries like Brazil, Myanmar, Indonesia, Thailand, and Malaysia, where prevalence rates are high (Kim et al., 2016; Sahimin et al., 2016; Zanetti et al., 2021). Globally, parasitic infections are highly prevalent. For instance, the Centers for Disease Control and Prevention reported approximately 241 million cases of malaria worldwide in 2020, resulting in 627,000 deaths, mostly in sub-Saharan Africa (Global Health & Division of Parasitic Diseases, 2020). Given the global burden of parasitic diseases, the need for effective treatment options is paramount. Antiparasitic drugs play a vital role in managing these infections; however, the current market provides only a limited selection of efficacious agents (Peña-Espinoza et al., 2022), highlighting a significant gap between therapeutic availability and clinical demand. Additionally, these medications are associated with several adverse reactions, including skin rashes, gastrointestinal issues, and elevated liver enzyme levels (Starkey & Blagburn, 2022). Moreover, cases of drug resistance have been reported in certain parasites (Jain et al., 2022), further reducing the effectiveness of existing medications. This situation underscores the urgent need to discover new potential antiparasitic drugs to control parasitic infections. Researchers have investigated many plants for their biologically active compounds, known as natural products, which exhibit antiparasitic activity. These include *Cytisus villosus* Pourr, *Raillietina echinobothrida*, *Allium sativum*, and *Lippia graveolens* Kunth (Chetia & Das, 2018; Hamad, 2023; Larit et al., 2019; Quintanilla-Licea et al., 2020). Among natural products, alkaloids, flavonoids, and

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terpenoids have been studied for their antiparasitic properties, with positive outcomes (Baldim et al., 2017; Kumatia et al., 2023; Lam et al., 2020). Research has shown that flavonoids effectively inhibit multiple types of parasites. Furthermore, flavonols, a subclass of flavonoids, have demonstrated antiparasitic activities against various parasites in numerous studies. This review aims to provide an evidence-based foundation for the development of novel drugs by compiling the results of the antiparasitic actions of flavonols, serving as a reference for further research on their biological activity and clinical applications.

Parasites and parasitic diseases

Malaria is one of the most widespread parasitic infections, caused by *Plasmodium* species such as *Plasmodium knowlesi* (*P. knowlesi*), *Plasmodium vivax* (*P. vivax*), *Plasmodium falciparum* (*P. falciparum*), *Plasmodium malariae* (*P. malariae*), and *Plasmodium ovale* (*P. ovale*) (Milner, 2018). There are over 200 officially recognized *Plasmodium* species, each affecting specific host groups. However, only the five aforementioned species typically infect humans and cause malaria worldwide (Sato, 2021). Between 2013 and 2017, Malaysia documented 16,500 malaria cases, with the majority occurring in Sarawak (34.4%) and Sabah (43.3%) (Hussin et al., 2020). Currently, the predominant species in Malaysia is *P. knowlesi*, responsible for simian malaria (Chin et al., 2020).

African sleeping sickness, also known as Trypanosomiasis, is an infectious disease transmitted by tsetse flies and caused by the parasite *Trypanosoma* species (Hollingshead & Bermudez, 2024). Conversely, *Trypanosoma cruzi* (*T. cruzi*) causes Chagas disease, also known as American trypanosomiasis, which affects thousands of people. The parasite spreads through the bitten area or mucous membranes of a mammalian host when contaminated vector feces gain entry. Additional transmission routes include blood transfusions, organ transplants, ingestion of contaminated food or drink, and transmission from mother to fetus during pregnancy (Bern et al., 2019).

Protozoans belonging to the genus *Leishmania* cause the vector-borne disease leishmaniasis, which primarily affects tropical and subtropical regions. According to the World Health Organization (WHO), an estimated 700,000 to 1 million individuals become infected each year. However, only a small proportion of those infected develop the illness, with 20,000–30,000 eventually succumbing to it (Steverding, 2017).

Entamoeba histolytica (*E. histolytica*), the causative agent of amoebiasis, is one of the most lethal parasitic infections worldwide. It is estimated to affect up to 50 million people, predominantly in impoverished regions, leading to over 100,000 deaths annually (Kantor et al., 2018). Due to its resistance to environmental changes and ease of transmission, the cyst form ensures the survival of the species. The immune system or antibiotic therapy cannot eradicate the infection from cysts because of their extreme resistance. Amoebic infection arises when water, sanitation, and hygiene practices are inadequate. Mature cysts are excreted in the host's feces and spread to others through fecal-oral transmission via contaminated food or drink or direct contact (Guillén, 2023).

Toxoplasma gondii (*T. gondii*) causes toxoplasmosis, a neglected parasitic illness that affects people worldwide. This parasite can be transmitted through the consumption of raw or undercooked meat, polluted soil, tainted water, or contaminated food (Abugri et al., 2023).

Flavonoids

Flavonoids, naturally occuring polyphenolic compounds, are byproducts of plant extraction found in various plant sections. Vegetables utilize flavonoids to thrive and protect themselves against pathogens (Panche et al., 2016). While flavonoids are present in a variety of foods and drinks, including beer, wine, and tea, the highest natural flavonoid content is generally found in vegetables, flowers, fruits, and seeds (Dias et al., 2021). Flavonoids are water-soluble phenylpropanoids with a C6-C3-C6 carbon skeleton, consisting of a 3-carbon heterocyclic ring connected to two 6-carbon benzene rings (A and B). These compounds are categorized into six main groups based on their chemical structure: flavones, flavonols, isoflavones, flavanones, flavan-3-ols, and anthocyanins (Dias et al., 2021) (Figure 1).

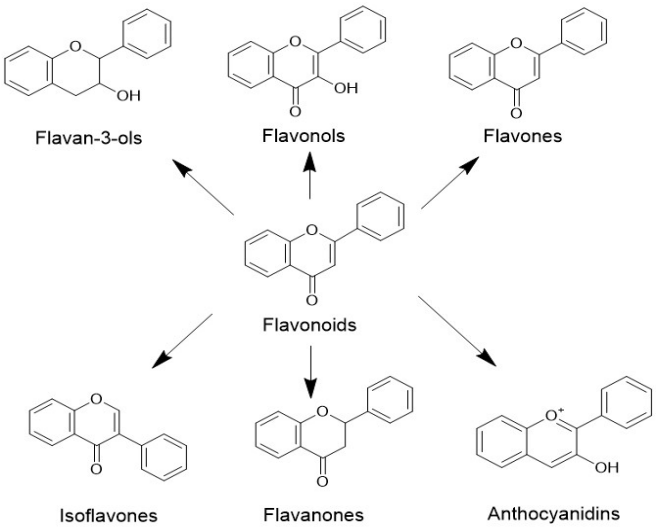

Figure 1: Flavonoids and their subclasses

However, Tsuchiya (2015) suggested that isoflavones should be classified under isoflavonoids instead of flavonoids. Flavonoids are further classified into six subclasses, with specific compounds listed under each. For example, phloretin and arbutin are grouped under the chalcone subclass; apigenin and tangeretin under flavones; quercetin and rutin under flavonols; genistein and daidzein under isoflavonoids; and cyanidin and malvidin under anthocyanins (Panche et al., 2016). Researchers have long been interested in developing flavonoids as therapeutic agents, leading to numerous studies aimed at increasing their use in clinical trials. Flavonoids have been identified to possess various beneficial properties, including neuroprotective, anti-inflammatory, analgesic, anti-cancer, anti-microbial, antiviral, and antiparasitic effects (Ullah et al., 2020). Due to their antiparasitic activities, extensive research has been carried out to explore flavonoids as potential new antiparasitic drug candidates.

Flavonols

Flavonols are a subclass of flavonoids distinguished by the presence of a hydroxyl group at the C3 position and a double bond between C2 and C3 in the heterocyclic ring (ring C), which contributes to their structural stability and biological activity. These compounds are commonly glycosylated, appearing as mono-, di-, or triglycosides, primarily at the C3 position, which influences their solubility, bioavailability, and physiological effects. Rutinosides, which are flavonol glycosides with at least two sugar moieties, are commonly observed. Flavonols are widely distributed in plant-based foods, with significant variations in their concentrations. Foods such as berries, broccoli, onions, apples, and tomatoes are known to contain high levels of flavonols (Murkovic, 2015). The most commonly studied flavonols include myricetin, kaempferol, and quercetin, along with their derivatives. These compounds have demonstrated various biological activities, including antitumor, antiparasitic, antibacterial, and antifungal effects, as confirmed by numerous research studies (Argüello-García et al., 2020; Martins et al., 2019; Periferakis et al., 2022; da Silva, 2021).

MATERIALS AND METHODS

This review was conducted in alignment with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure methodological rigor and transparency. All checklist items were strictly adhered to according to the PRISMA 2020 framework, guaranteeing consistency and completeness in reporting (Page et al., 2021).

Search strategy

The systematic review was conducted using four major academic databases: ProQuest, Web of Science, Science Direct, and PubMed. The primary search terms employed were “Flavonols AND antiparasitic” and “Flavonoids AND antiparasitic”, applied specifically to the [Title/Abstract] fields. Additionally, to ensure relevance and accessibility, the search was limited to full-text open-access articles published between 2013 and 2023.

Eligibility criteria

Irrelevant data were systematically excluded by screening academic paper titles and abstracts. Inclusion criteria for this review were defined through a detailed evaluation of relevant studies. Inclusion Criteria: Studies were selected based on the following parameters: 1. Articles published in English or Malay; 2. Research discussing the antiparasitic effects of flavonoids; 3. Studies with full-text access; 4. Papers addressing the biology of parasites; 5. Publications from 2013 to 2023; 5. Data sourced from PubMed, ScienceDirect, ProQuest, and Web of Science. Exclusion Criteria: The following studies were excluded: 1. Articles published in languages other than English or Malay; 2. Research with uncertain methods, data, or outcomes; 3. Letters, conference papers, posters, editorials, and review articles; 4. Studies from disputed or predatory journals.

Risk of bias assessment

The Quality Assessment with Diverse Studies (QuADS) criteria were applied to systematically evaluate the methodological rigor of the studies included in the final data synthesis. This framework ensured a comprehensive, standardized assessment, allowing for consistency in identifying strengths and limitations across diverse research designs (Harrison et al., 2021). This 13-criteria instrument assesses the quality of various research designs, including mixed-methods, quantitative, and qualitative studies. Each criterion is scored from 0 (no mention) to 3 (full information), with a maximum possible score of 39.

Each study was assigned a QuADS score, which was then used to create an overall quality evaluation by summing all the item scores and dividing the result by the highest possible score. Studies were categorized based on their scores as follows: less than 50% (poor methodological quality), between 50% and 70% (moderate methodological quality), and more than 70% (high methodological quality) (Medlinskiene et al., 2021).

Study selection

The articles were selected based on their relevance to the antiparasitic effects of flavonoid compounds, including studies on flavonoid biosynthesis, molecular modification to enhance antiparasitic activity, parasite biology, and the epidemiology of parasitic diseases.

Data collection process

Mendeley Reference Manager was used as the primary storage for all results obtained from the search strategy, as it provides a folder for managing and checking for duplicate articles. Redundant research was removed from this folder. The data were then tabulated using Microsoft Word and organized into columns for number, name of the compounds, source of the compounds, name of the tested parasites, study design, results of the selected research, and their references.

RESULTS

Data collection was conducted between October and December 2023, focusing on academic papers published in English and Malay. The screening process was carried out by the supervisor and co-supervisors, with any discrepancies resolved by the first author. From a total of 1,629 papers identified through a systematic search of digital databases, 180 met the eligibility criteria. Additionally, four articles were retrieved from the reference lists of included studies, one of which was incorporated into the final review.

This systematic review ultimately included 42 studies after applying exclusion criteria. Articles published in languages other than English and Malay, studies with unclear methods, data, or outcomes, as well as letters, conference papers, posters, editorials, and publications from disputed or predatory journals were omitted. The results have been summarized in the PRISMA 2020 flow diagram (Figure 2).

Quality Assessment

As mentioned earlier, the studies were evaluated using the QuADS tool to assess their quality and risk of bias. The methodological quality of the examined research ranged from 54% to 82%. Specifically, 18 studies were classified as having high-quality methodologies, with scores ranging from 72% to 82%. Conversely, 24 studies displayed moderate-quality methodologies, earning scores between 54% and 69%. No studies were found to have low scores. The table of risk of bias assessment is provided in the supplementary document (Appendix 1).

Antiparasitic activity of flavonols

Table 1 summarizes the findings on the antiparasitic activity of flavonol compounds. The antiparasitic activity of flavonol derivatives is compiled in Table S1 (Supplementary file- Appendix 2), and the antiparasitic activity of plant extracts containing flavonols as major compounds is discussed in Table S2 (Supplementary file- Appendix 2).

Mechanism of action of flavonols as antiparasitic agent

Several studies have been conducted to elucidate the mechanisms by which flavonols contribute to antiparasitic properties. Conserva et al. (2021) observed a persistent increase in intracellular parasite Ca^{2+} levels. The death of *T. cruzi* might be due to a Ca^{2+} imbalance triggered by compound **21**. Following a two-hour incubation period, the trypomastigotes exhibited an increase in mitochondrial membrane potential, which was followed by depolarization after four hours. Additionally, ATP levels were reduced after four hours. Furthermore, compound **1** has been documented to demonstrate several methods of inhibiting parasites, as supported by numerous research findings. Compound **1** (Figure 3) was shown to interfere with the mitochondrial membrane potential of parasites, leading to impaired mitochondrial function (Abugri et al., 2023; Larit et al., 2021; Yang et al., 2020).

Furthermore, it has been demonstrated that quercetin induces an increase in the formation of reactive oxygen species (ROS) within parasites (Abugri et al., 2023; Cataneo et al., 2019), primarily causing either necrosis or apoptosis. Compound 1 has also been reported to stimulate the activation of nuclear factor erythroid 2-related factor (Nrf2), functioning as an antioxidant. When administered to L. braziliensis-infected macrophages, it was found that Nrf2 and heme oxygenase 1 (HO-1) expression levels increased. Additionally, flavonols have been verified to repress parasitic enzymes, thereby enhancing their antiparasitic activity. Yang et al. (2020) and Larit et al. (2021) demonstrated that compounds **1** and **3** can inhibit crucial parasite enzymes, such as acetylcholinesterase, DNA topoisomerase, kinase, and heat-shock protein (HSP), specifically the *T. brucei* Hexokinase 1 (TbHK1) enzymes.

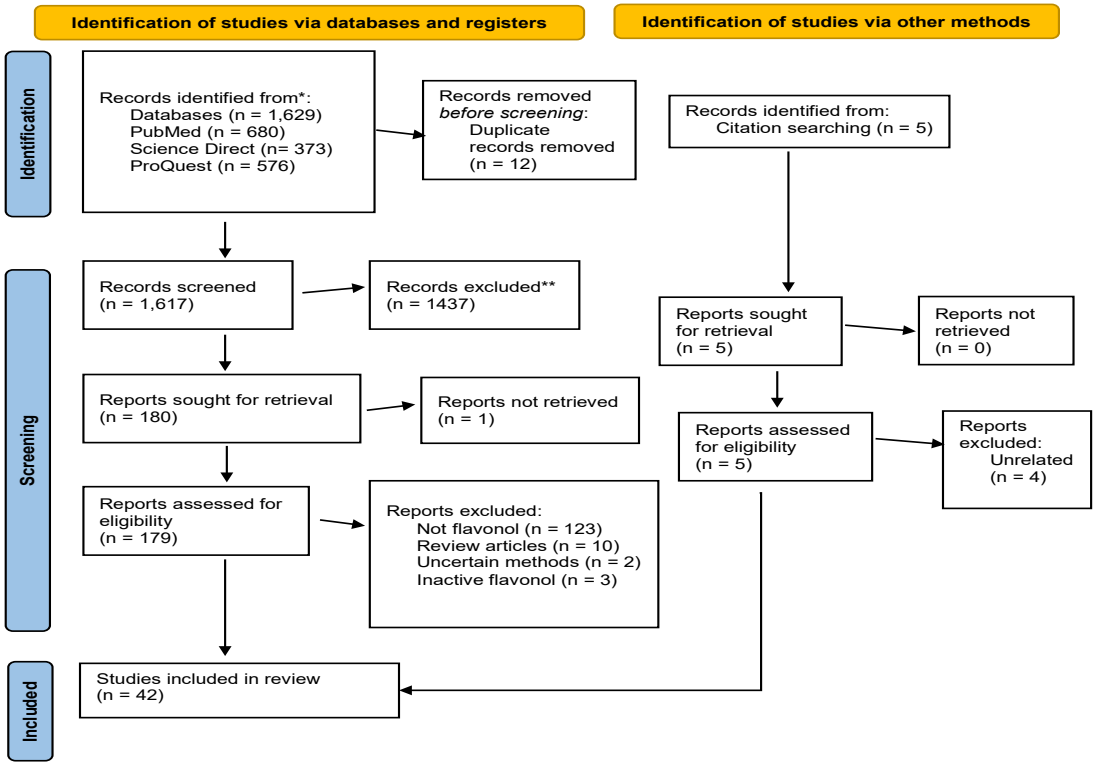

Figure 2: PRISMA 2020 flow diagram summarising systematic search and study selection

Compound **4** inhibits the functioning of arginase (ARG), decreases glutathione (GSH) levels, and reduces nitric oxide (NO) production. These effects collectively impede the proliferation of promastigotes (Adinehbeigi et al., 2017). Mehwish et al. (2021) verified that trypanothione reductase (Try-R) and trypanothione synthetase (Try-S) enzymes were inhibited in *L. donovani* after compounds **1** and **27** were applied for 24 hours. Additionally, it has been shown that both compounds can directly attach to DNA by intercalation, causing damage to double-stranded DNA at its original location. Transmission electron microscopy (TEM) analysis demonstrated that both compounds induced significant changes in the ultrastructure of parasite cells. These changes included nuclear condensation, deformation of the flagellar pocket, disruption of the mitochondria-kinetoplast complex, and an increase in lipid droplets. These alterations ultimately resulted in the mortality of *Leishmania* parasites.

Additionally, compound **8** triggered significant mitochondrial morphological changes, including the formation of cytoplasmic lipid bodies, enlarged and swollen mitochondria compared to the untreated control, and an increase in plasma membrane blebs (surface blebbing) in *L. amaz*/tc3 promastigotes. Moreover, this compound enhanced the production of Th1 cytokines in infected cultured macrophages, surpassing levels observed in infected but non-stimulated controls. Notably, cells treated with compound 8 exhibited a higher production of IL-12 p70 (García-Bustos et al., 2021).

Additionally, *Leishmania* species contain arginase, the initial enzyme in the polyamine (PA) pathway. Inhibiting this enzyme can enhance oxidative stress and facilitate infection management. Compound **4** has demonstrated strong inhibitory activity on arginase. This inhibitory activity is closely linked to the presence or absence of a sugar moiety at position 3 in the flavonoid molecule. Noncompetitive inhibition was identified for the C-glucoside, while mixed inhibition was observed for the O-glucoside. These hydrogen bonds function as 'molecular anchors' to assist the binding of molecules to the enzyme's active site (Manjolin et al., 2013).

Nwodo et al. (2015) explained the inhibitory mechanism of compound 7, which appears to be related to the extent of methylation of the hydroxyl groups and its effectiveness against trypanosomes. The increased lipophilicity of the compound enhances its permeability through the parasite membranes. Additionally, Gupta et al. (2022) determined that the mechanism through which DHDM-Zn inhibits *L. donovani* is attributed to cell cycle arrest at the G1/S checkpoint. This arrest prolongs the G1 phase and increases the cell population, preventing the targeted parasite from initiating nuclear division due to DNA arrest.

Table 1: Antiparasitic activity of flavonols

Compounds	Source	Parasites	Study design	Results	Reference
Quercetin **(1)**	Santa Cruz Bio-technology Inc.	*T. gondii*	*In vitro*	IC_{50} 0.50 µM	(Abugri et al., 2023)
	Acros (Fair Lawn, NJ, USA)	*L. braziliensis*		48 and 70 µM showed leishmanicidal activity	(Cataneo et al., 2019)
	Sigma Aldrich	*E. histolytica*, *T. vaginalis*		IC_{50} 44.48 µg/mL (*E. histolytica*) 21.17 µg/mL (*T. vaginalis*)	(Elizondo-Luévano et al., 2021)
	Pelliciera rhizophorae	*L. donovani*, *P. falciparum*, *T. cruzi*	*In vitro* *In silico*	IC_{50} 12.6 ± 0.2 µM (*L. donovani*), 9.7 ± 0.3 µM (*P. falciparum*), 13.0 ± 0.4 µM (*T. cruzi*)	(López et al., 2015)
	Hypericum afrum	*T. brucei*	*In vitro*	IC_{50} 7.52 µM, IC_{90} 9.76 µM	(Larit et al., 2021)
	Dioscorea bulbifera	*P. falciparum K1*, *P. falciparum 3D7*		IC_{50} 28.47 µM (*P. falciparum K*1), IC_{50} 50.99 µM (*P. falciparum 3D7*)	(Chaniad et al., 2021)
	Merck KGaA	*L. major*, *P. falciparum*	*In vitro*	Effective in all concentrations (100, 200 & 400 µg/ml) against *L. major*. 400 µg/ml was the most effective dose for antiplasmodial activity	(Hanif et al., 2023)
	Sigma-Aldrich	*L. donovani*		IC_{50} 84.65 µg/mL	(Mehwish et al., 2021)
	Sigma–Aldrich	*L. amazonensis*	*In vitro* *In silico*	IC_{50} 4.3 µM	(Manjolin et al., 2013)
	Persea americana	*P. berghei*	*In vivo*	Chemosuppression of parasitemia (>50%)	(Uzor et al., 2021)
Kaempferol **(2)**	*Nectandra oppositifolia*	*T. cruzi*	*In vitro*	IC_{50} 32.0 µM	(Conserva et al., 2021)
	Annona cherimola	*G. duodenalis*	*In vitro* *In silico*	Proapoptotic effect on *G. duodenalis* trophozoites	(Argüello-García et al., 2020)
	Helianthemum glomeratum	*E. histolytica*	*In vitro*	Decreased the viability of *E. histolytica* to 44.5% at concentration of 150 µM	(Levaro-Loquio et al., 2023)
	Pelliciera rhizophorae	*L. donovani*	*In vitro* *In silico*	IC_{50} 22.9 ± 0.2 µM	(López et al., 2015)
	Dioscorea bulbifera	*P. falciparum K1*, *P. falciparum 3D7*	*In vitro*	IC_{50} 62.45 µM (*P. falciparum K*1), IC_{50} > 80 µM (*P. falciparum 3D7*)	(Chaniad et al., 2021)
	Temperate Propolis	*T. brucei*, *L. mexicana*		*T. brucei* IC_{50} 24 µM (TbS427WT), IC_{50} 30.2 µM (B48), IC_{50} 28.4 µM (ISMR1), *L. mexicana* IC_{50} 414 µM (WT)	(Alotaibi et al., 2021)
	Senna surattensis	*T. b. rhodesiense*	*In vitro*	IC_{50} 10.35 ± 0.38 µM	(Dawurung et al., 2021)
	Sigma–Aldrich	*L. amazonensis*	*In vitro* *In silico*	IC_{50} 50 µM	(Manjolin et al., 2013)
Myricetin **(3)**	*Hypericum afrum*	*T. brucei*		IC_{50} 5.71 µM, IC_{90} 7.97 µM	(Larit et al., 2021)
Fisetin **(4)**	Sigma-Aldrich	*L. amazonensis*		IC_{50} 1.4 µM.	(Manjolin et al., 2013)
		L. infantum	*In vitro*	IC_{50} 0.283 µM against promastigotes and 0.102 µM against amastigotes	(Adinehbeigi et al., 2017)
Morin **(5)**		*L. amaz/tc*	*In vitro* *In vivo*	IC_{50} 122.4 ± 2.55 µM	(García-Bustos et al., 2021)
Penduletin **(6)**	*Vitex simplicifolia*	*T. b. rhodesiense*	*In vitro*	IC_{50} 13.8 µg/ml	(Nwodo et al., 2015)
Artemetin **(7)**				IC_{50} 4.7 µg/ml	
Galangin **(8)**	Temperate Propolis	*T. brucei*, *L. mexicana*		*T. brucei* IC_{50} 28.2 µM (TbS427WT), IC_{50} 32.2 µM (B48) IC_{50} 26.3 µM (ISMR1) *L. mexicana* IC_{50} 20.2 µM (WT), IC_{50} 54.4 µM (C12Rx)	(Alotaibi et al., 2021)
	Sigma-Aldrich	*L. amaz/tc3*	*In vitro* *In vivo*	IC_{50} 20.59 ± 4.47 µM	(García-Bustos et al., 2021)
		L. amazonensis	*In vitro* *In silico*	IC_{50} 100 µM	(Manjolin et al., 2013)
6,5'-dihydroxyflavonol **(9)**	Sigma-Aldrich	*T. brucei* pteridine reductase 1 *(Tb*PTR1*)* *L. major* pteridine reductase *1 (Lm*PTR1*)*	*In vitro* *In silico*	IC_{50} 4.3 Mm (*Tb*PTR1), IC_{50} 12.5 µM (*Lm*PTR1)	(Di Pisa et al., 2017)
6,4',5'-trihydroxyflavonol **(10)**				IC_{50} 38.0 µM (*Tb*PTR1), IC_{50} 35.0 µM (*Lm*PTR1)	

Levaro-Loquio et al. (2023) conducted an extensive analysis of the amoebicidal properties of compound 2 against *E. histolytica*. The compound stimulates excessive protein production in *E. histolytica* while suppressing the activity of enzymes such as thioredoxin reductase (TrxR), peroxiredoxin (Prx), and rubrerythrin (Rr). It also lowers

the activity of myeloperoxidase (MPO) and reduces interactions between neutrophils and *E. histolytica*. Furthermore, compound **2** causes a low release of ROS and reduces NO production in *E. histolytica*, affecting the functioning of detoxifying enzymes and interactions between the parasite and neutrophils.

The inhibitory action of flavonol glycosides has also been documented by Martín-Escolano et al. (2021). Compound **38** induced structural modifications in *Acanthamoeba* trophozoites, leading to the formation of spherical trophozoites lacking acanthopodia and containing substantial vacuoles. Upon exposure to compounds **39**, **40**, and **41**, a significant number of trophozoites detached and subsequently died. Additionally, certain trophozoites exhibited distinct structural alterations, including decreased size, absence of acanthopodia, and a more rounded shape.

Recent research suggests several molecular modifications that could enhance the antiparasitic effects of flavonols. For example, compound **21** highlights the importance of incorporating a p-coumaroyl group into the rhamnoside moiety to boost antiparasitic activity and reduce mammalian toxicity compared to kaempferol (Conserva et al., 2021). Abdeyazdan et al. (2022) demonstrated that the increased lipophilicity of compound **24**, relative to amphotericin B and antimony complexes, led to superior anti-promastigote activity against *L. major*. Although flavonol antimony complexes showed limited effectiveness against promastigotes, they exhibited stronger anti-amastigote effects compared to meglumine antimonate, with IC_{50} values ranging from 0.5 to 15 µM.

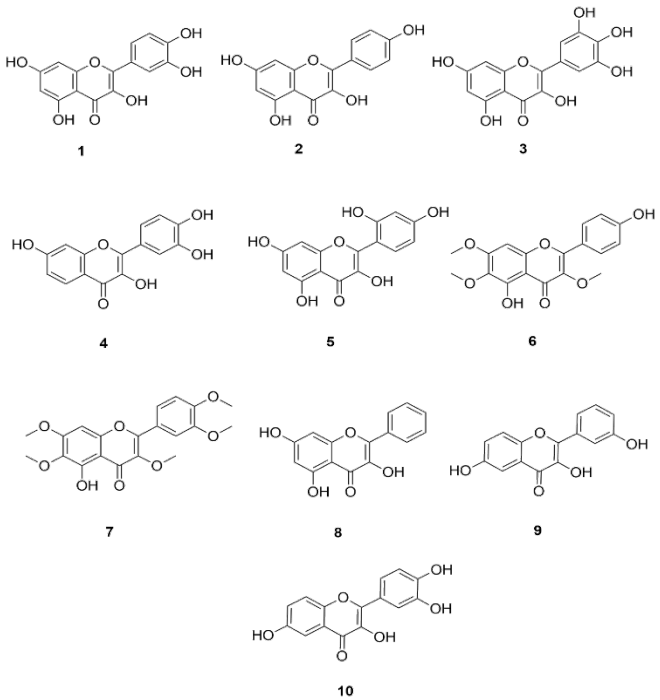

Figure 3: Chemical structure of antiparasitic flavonols (refer Table 1).

Molecular modification of flavonols to increase antiparasitic activity

These findings suggest that modifications to the molecular structure or the introduction of specific functional groups can markedly enhance the antiparasitic efficacy of flavonols. To understand the superior IC_{50} and IC_{90} values of compound **3** compared to compound **1**, Larit et al. (2021) conducted a molecular docking study. Compound **3** had a docking score of -8.31 kcal/mol, while compound **1** scored -6.62 kcal/mol. The additional hydroxyl group on compound **3** did not result in significant new interactions with neighbouring amino acids. However, some chemical bonds were disrupted, likely due to the rearrangement of interacting functional groups to accommodate the extra hydroxyl group within the binding site. During molecular dynamics (MD) simulations, myricetin maintained a stable position in the binding pocket, with a root mean square deviation (RMSD) of approximately 3.0 Å. In contrast, compound 1 had a much higher RMSD value of around 15.0 Å.

A study revealed that compound **1**, a flavonol known for its potent antimalarial properties against *Plasmodium falciparum*, is more effective in inhibition compared to quercetin glycosides, which showed lesser effects. Compound **1**, with five hydroxyl groups at positions 3, 5, 7, 3', and 4', exhibited significant interactions with *Plasmodium falciparum* lactate dehydrogenase (PfLDH), similar to those of artesunate. The binding configurations of this compound differ from those of other flavonoids, forming a hydrogen bond with ASP53 through direct interaction. Its strong activity may be attributed to the substantial number of hydrogen bonds and the variability in binding patterns (Chaniad et al., 2021).

Nwodo et al. (2015) suggested that methylation of the hydroxyl groups might enhance the trypanocidal effect of compound **7**, supporting its antiparasitic properties. The concomitant increase in lipophilicity improves the compound's ability to penetrate parasite membranes, explaining the observed effect. The presence of a methoxy group at position C-3 may be responsible for the activity of active molecules in this context. Additionally, the absence of an OH group in ring B might contribute to the compound's effect.

Furthermore, the interaction between compound **4** and the *Leishmania amazonensis* arginase enzyme (ARG-L) is strengthened through an inversion of the interaction, facilitating hydrophobic interactions between the flavone group of compound **4** and His154 and His139. The presence of the catechol group is crucial for inhibitory action, as its absence results in minimal inhibition. The

hydroxyl group at position 3 plays a crucial role in the inhibitory action of arginase, whereas the hydroxyl group at position 5 has minimal impact. These compounds bind to the enzyme's active site via hydrogen bonding, serving as molecular anchors that stabilize interactions. Manjolin et al. (2013) reported that ARG-L inhibition is significantly enhanced when the phenyl group is hydroxylated at positions 3, 5, and 7, suggesting that specific hydroxylation patterns influence binding efficiency and enzymatic suppression.

DISCUSSION

Antiparasitic activity of flavonols

Flavonols have demonstrated antiparasitic activity against a broad spectrum of protozoan species. Notably, several studies have reported that specific flavonols possess the ability to inhibit multiple protozoan types, highlighting their potential as versatile antiparasitic agents. A study by Abugri et al. (2023) confirmed the potent antitoxoplasma activity of compound **1,** which exhibited an IC_{50} of 0.50 µM against *T. gondii*. Compound **1,** when mixed with azithromycin at a 2:1 ratio, the mixture demonstrated a synergistic effect, yielding an IC_{50} of 0.08 µM against *T. gondii,* substantially lower than the IC_{50} values of compound **1** and azithromycin (0.66 µM) alone.

Several studies have evaluated the antileishmanial effects of compound **1**. Remarkably, Cataneo et al. (2019) revealed that compound **1** exhibited leishmanicidal action at 48 and 70 µM concentrations. Both doses significantly decreased the average number of *L. braziliensis* amastigotes per macrophage. López et al. (2015) documented an IC_{50} value of 12.6 ± 0.2 µM, though Mehwish et al. (2021) discovered an IC_{50} value of 84.65 µg/mL against *L. donovani.* The latter investigation revealed a noteworthy occurrence of DNA damage, as indicated by a Total Comet Score (TCS) of 57. In addition, Hanif et al. (2023) confirmed the effectiveness of compound **1** at all tested concentrations (100, 200 and 400 µg/mL) against *L. major*. Manjolin et al. (2013) conducted a distinct *in vitro* study and found that the IC_{50} against *L. amazonensis* was 4.3 µM. The compound demonstrated inhibitory effects on *P. falciparum*, with IC_{50} 9.7, 28.47 and 50.99 µM, as reported by Chaniad et al. (2021) and López et al. (2015). According to Hanif et al. (2023) again, compound **1** achieved more than 50% chemosuppression of parasitemia against *P. berghei* in an *in vivo* study, while Uzor et al. (2021) found that 400 µg/mL was the most effective dose for antiplasmodial action. Conversely, Elizondo-Luévano et al. (2021) assessed the effectiveness of the same compound against *E. histolytica* and *T. vaginalis* and found IC_{50} 44.48 and 21.17 µg/mL, respectively. Concurrently, favourable results were obtained from studies on effectiveness against *Trypanosoma* sp. A study by López et al. (2015) reported the IC_{50} 13.0 µM against *T. cruzi* whereas Larit et al. (2021) found the IC_{50} against *T. brucei* was 7.52 µM, and the IC_{90} was 9.76 µM. Also, Dawurung et al. (2021) observed an IC_{50} 8.44 µM against *T. b. rhodesiense*.

Apart from compound **1**, compound 2 has also demonstrated a broad spectrum of antiparasitic activities. Conserva et al. (2021) reported an IC_{50} of 32.0 µM against *T. cruzi*, while Dawurung et al. (2021) found an IC_{50} of 10.35 ± 0.38 µM against *T. b. rhodesiense*. Further testing on *T. brucei* strains TbS427WT, B48, and ISMR1 revealed IC_{50} values of 24, 30.2, and 28.4 µM, respectively (Alotaibi et al., 2021). In a combined *in vitro* and *in silico* study, compound **2** exhibited a proapoptotic effect on *G. duodenalis* (Argüello-García et al., 2020). Levaro-Loquio et al. (2023) found that compound **2** showed amoebicidal activity against *E. histolytica* at a concentration of 150 µM, significantly reducing viability to 44.5%, a notable difference from the effect of metronidazole.

Compound **2** also targeted *L. donovani*, resulting in an IC_{50} of 22.9 ± 0.2 µM (López et al., 2015). Alotaibi et al. (2021) discovered antileishmanial activity against *L. mexicana* strain WT, with an IC_{50} of 414 µM, while Manjolin et al. (2013) reported a lower IC_{50} of 50 µM against *L. amazonensis*. Chaniad et al. (2021) determined IC_{50} values of 62.45 µM and >80 µM for *P. falciparum* strains K1 and 3D7, respectively. Compound **3** exhibited IC_{50} and IC_{90} values of 5.71 µM and 7.97 µM, respectively, against *T. brucei* (Larit et al., 2021). Compound **4** showed leishmanicidal activity against *L. amazonensis* with an IC_{50} of 1.4 µM (Manjolin et al., 2013) and also exhibited IC_{50} values of 0.283 µM against promastigotes and 0.102 µM against amastigotes of *L. infantum* (Adinehbeigi et al., 2017).

Compound **5** had an IC_{50} of 122.4 ± 2.55 µM against the *L. (L.) amazonensis* clone (*L. amaz/tc3*) (García-Bustos et al., 2021). Compounds **6** and **7**, extracted from *V. simplicifolia*, showed trypanocidal activity against *T. b. rhodesiense* with IC_{50} values of 13.8 µg/mL and 4.7 µg/mL, respectively (Nwodo et al., 2015). The antiparasitic properties of compound **8** have been extensively studied. Alotaibi et al. (2021) identified IC_{50} values of 28.2, 32.2, and 26.3 µM against *T. brucei* strains TbS427WT, B48, and ISMR1, respectively. The IC_{50} for inhibiting the growth of *L. mexicana* strains Leish WT and C12Rx were 20.2 and 54.4 µM, respectively. García-Bustos et al. (2021) recorded an IC_{50} of 20.59 ± 4.47 µM against *L. amaz/tc3*, while Manjolin et al. (2013) documented a higher IC_{50} of 100 µM against *L. amazonensis*.

Compounds **9** and **10** were tested against the parasite enzymes TbPTR1 and LmPTR1 by Di Pisa et al. (2017). Compound **9** had significant inhibitory effects on both enzymes, with IC_{50} values of 4.3 µM against TbPTR1 and 12.5 µM against LmPTR1. Conversely, compound **10** showed moderate inhibition with IC_{50} values of 38.0 and 35.0 µM against TbPTR1 and LmPTR1, respectively.

Antiparasitic activity of flavonol glycosides

Flavonol glycosides are a type of flavonoid compound found in various plants, particularly medicinal herbs. They consist of two primary components: a sugar molecule called glycoside, which is bound to the basic structural component of the flavonoid, the flavonol aglycone. Several studies have been conducted to determine the antiparasitic activities of flavonol glycosides. Tajuddeen et al. (2021) revealed that compound **11** (Figure S1) significantly inhibited the growth of *P. falciparum*, reducing its viability to 16.2 ± 2.2% at a dose of 50 µg/mL, while compound **12** reduced viability to 18.4 ± 2.9%. Additionally, compound **13** showed potential by reducing parasite viability to 19.1 ± 0.5%. López et al. (2015) verified the antileishmanial activity of compound **11**, with an IC_{50} of 3.4 ± 0.1 µM against *L. donovani*. Manjolin et al. (2013) reported IC_{50} values of 10 µM and 3.8 µM for compounds **11** and **12**, respectively, against *L. amazonensis*. Koagne et al. (2020) obtained an IC_{50} value of 25.1 ± 0.25 µM against the *P. falciparum* 3D7 strain.

Compound **14**, synthesized via a penta-acetylation process, exhibited leishmanicidal activity with an IC_{50} of 75.1 ± 4.7 µM against *L. amazonensis* (da Silva et al., 2021). Compound **15** was discovered by Kikowska et al. (2020) to produce a strong amoebicidal effect on *Acanthamoeba trophozoites* with an IC_{50} of 0.35 mg/mL. Chaniad et al. (2021) revealed that compounds **16** and **17** exhibited moderate antiplasmodial activity against *P. falciparum* strains K1 and 3D7. Compound **16** had IC_{50} values of 44.03 µM and 70.79 µM against K1 and 3D7, respectively, while compound **17** displayed IC_{50} values of 48.33 µM and 68.93 µM against the same strains.

Mahmoud et al. (2020) reported that compound **18** showed IC_{50} values of 4.5 µM against *L. donovani* and 7.3 µM against *P. falciparum*. Tajuddeen et al. (2022) found that compound **19** effectively reduced the viability of *P. falciparum* to 21.9 ± 1.5% at a concentration of 50 µg/mL. Koagne et al. (2020) documented an antimalarial effect of compound **20** with an IC_{50} of 19.0 ± 0.25 µM. Conserva et al. (2021) observed a more potent antiparasitic activity of compound **21** against *T. cruzi*, with an IC_{50} of 6.7 µM. Hammi et al. (2020) identified an IC_{50} of 206.40 ± 1.63 µg/mL for compound **22** (Figure S2) against *L. major.*

Tajuddeen et al. (2021) revealed that compound **23** had significant antiplasmodial activity at a dose of 50 µg/mL, reducing parasite viability to 18.1 ± 1.0%. In leishmanicidal testing on compound **24**, Abdeyazdan et al. (2022) obtained an IC_{50} of 14.93 ± 2.21 µM against *L. major*. Alotaibi et al. (2021) performed a comprehensive *in vitro* study on the effects of compounds **25** and **26** against three strains of *T. brucei* (TbS427WT, B48, and ISMR1) and two strains of *L. major* (WT and C12Rx). Compound **25** demonstrated trypanocidal activity against TbS427WT, B48, and ISMR1, with IC_{50} values of 15.2, 22.4, and 21.1 µM, respectively, and leishmanicidal action with IC_{50} values of 41.4 and 10.4 µM, respectively. Compound **26** exhibited trypanocidal abilities, with IC_{50} values of 95.2, 103, and 94.1 µM against the corresponding strains, but its leishmanicidal action was only evaluated against the WT strain, yielding an IC_{50} of 12.9 µM.

Compound **27** has been determined to exert antileishmanial effects in several studies. Hammi et al. (2020) reported an IC_{50} of 78.51 ± 1.09 µg/mL against *L. major*, while Mehwish et al. (2021) documented a slightly higher IC_{50} of 98 µg/mL against *L. donovani*. Kant et al. (2022) used a combined *in silico* and *in vivo* approach to assess the efficacy of compound **27** against *L. donovani*, finding IC_{50} values of 40.95 µM against promastigote forms and 90.09 µM against amastigote forms. García-Bustos et al. (2021) obtained a higher IC_{50} of 133 ± 8.25 µM against L. amaz/tc3 via *in vitro* and *in vivo* studies. Chepkirui et al. (2021) conducted antileishmanial research on compounds **28** and **29** against *L. donovani* antimony-sensitive and resistant strains, yielding potent IC_{50} values of 9.0 µM against the sensitive strain and 5.0 µM against the resistant strain. Compound **30** was shown to have leishmanicidal activity in a study by Gupta et al. (2022), with an IC_{50} of 63 ± 0.73 µM against *L. donovani*. Compound **31**, obtained from Saudi propolis, exhibited a minimum inhibitory concentration (MIC) of 14.7 µg/mL against *T. brucei* (Alanazi et al., 2021).

Nwodo et al. (2015) tested compounds **32–36** for their ability to inhibit *T. b. rhodesiense*, finding IC_{50} values of 10.2, 12.3, 19.4, 23.7, and 10.8 µg/mL, respectively. Compound **37**, synthesized by Olías-Molero et al. (2018), showed antileishmanial effects against *L. infantum* and *L. donovani*, with an estimated IC_{50} of 90.23 µM. Compounds 38-41 (Figure S4) were evaluated for their amoebicidal effects against *A. castellanii*, showing significant antiparasitic effects with IC_{50} values of 3.5 ± 3.0, 1.4 ± 1.2, 1.4 ± 0.4, and 2.3 ± 0.4 for compounds **38**, **39**, **40**, and **41**, respectively (Martín-escolano et al., 2021). Koagne et al. (2020) examined the antimalarial efficacy of compounds **42** and **43** against the *P. falciparum* 3D7 strain, finding strong antimalarial activity with IC_{50} values of 7.5 ± 0.25

and 6.8 ± 0.25 µM, respectively.

Antiparasitic activity of plant extracts

Plant extracts are concentrated preparations obtained from various parts of plants including leaves, flowers, stems, roots, and fruits, using specialized extraction techniques. These extracts contain a diverse array of secondary metabolites, particularly flavonols, which are known for their siginificant biological functions and therapeutic potential. Identifying specific flavonol compounds within these extracts enables researchers to better understand their mechanisms of action and explore their potential applications in promoting human health and well-being.

A study on the ethanolic extract of *E. uniflora* demonstrated significant leishmanicidal activity, with EC_{50} values of 47.0 µg/mL and 22.1 µg/mL against the promastigote and amastigote forms of *L. amazonensis*, respectively. Chemical analysis identified myricitrin (**44**) and compound **11** as the major constituents (Santos et al., 2019). Ferreira et al. (2021) further evaluated the antileishmanial properties of extracts from *M. pungens*, *A. muricata*, *N. megapotamica*, and *B. uniflora* on *L. amazonensis* and *L. braziliensis*. The *M. pungens* extract exhibited IC_{50} values of 180 µg/mL for *L. amazonensis* and 210 µg/mL for *L. braziliensis*. Similarly, the *A. muricata* extract showed IC_{50} values of 270 µg/mL and 210 µg/mL, respectively. The *N. megapotamica* extract demonstrated IC_{50} values of 200 µg/mL for *L. amazonensis* and 760 µg/mL for *L. braziliensis*. Lastly, the *B. uniflora* extract presented IC_{50} values of 220 µg/mL against *L. amazonensis* and 460 µg/mL against *L. braziliensis*.

Rama et al. (2021) developed two distinct patent-protected extracts from white grape marc, denoted as HOP and HOL. The antiparasitic investigation revealed that HOP, containing higher concentrations of compounds **2** and **27**, had superior antimalarial (IC_{50} 0.26 µg/mL) and antitoxoplasma (IC_{50} 0.57 µg/mL) effects against *P. falciparum* and *T. gondii* compared to HOL. Conversely, HOL, with a higher concentration of isoquercetin (**45**), demonstrated six times better antimalarial activity than HOP (IC_{50} 3.17 µg/mL).

In another study, the ethyl acetate extract of *C. citrinus* showed a total flavonoid content of 438.38 ± 11.73 mg RE/100 g, with IC_{50} values of 9.7 µg/mL against *T. brucei* and 13 µg/mL against *P. falciparum*. The methanol extract, with a higher total flavonoid content of 512.90 ± 11.00 mg RE/100 g, showed IC_{50} values of 8.4 µg/mL against *P. falciparum* and 6.6 µg/mL against *T. brucei* (Larayetan et al., 2019). Brito et al. (2015) evaluated the effectiveness of a hydroethanolic extract from *Z. joazeiro* in eliminating parasites such as *L. braziliensis*, *L. infantum*, and *T. cruzi*. HPLC analysis detected compounds **27** (9.72 mg/g), **12** (15.24 mg/g), **1** (21.30 mg/g), and **2** (5.17 mg/g) in the extract. The IC_{50} values were 612.06 µg/mL against *T. cruzi* and 693.67 µg/mL against *L. infantum*, but the extract was not significantly effective against *L. braziliensis* (IC_{50} > 5000 µg/mL). Bitu et al. (2017) observed effective trypanocidal activity (IC_{50} 10.6 µg/mL) against *T. cruzi*, but lower leishmanicidal efficacy (IC_{50} 236.93 µg/mL against *L. braziliensis* and 342.90 µg/mL against *L. infantum*), possibly due to the presence of compound **1** in *O. hamiltonii* leaf infusion. Kikowska et al. (2022) documented IC_{50} values of 0.25 mg/mL and 3.70 mg/mL against *Acanthamoeba* sp. strain Ac55 using *E. planum* and *E. maritimum* shoot cultures, respectively. The extract from *P. cauliflora* showed strong trypanocidal activity against *T. cruzi*, with EC_{50} values of 9.94 ± 2.25 µg/mL after two hours and 6.84 ± 2.54 µg/mL after 24 hours (Galvão et al., 2021).

The antiparasitic efficacy of pepper peel ethanolic extract (PPEE) against *T. gondii* was less potent in an *in vitro* study by Menezes et al. (2022), with the extract suppressing parasite growth at doses of 256 µg/mL and 512 µg/mL. LC-ESI-MS analysis revealed the presence of flavonol glycosides, specifically compound **11** and isorhamnetin 3-O-rhamnoside (**46**), which might be responsible for its antiparasitic properties. Using an *in vivo* method, Uzor et al. (2021) reported a chemosuppressive impact on parasitemia above 50% from the crude extract of *P. americana*. Calixto Júnior et al. (2016) provided evidence of the antiparasitic effects of *G. ulmifolia* extract, observing activity of 92.20%, 95.23%, and 61.15% against *L. braziliensis*, *L. infantum*, and *T. cruzi*, respectively.

CONCLUSION

This review highlights the broad-spectrum antiparasitic activity of various flavonol compounds against multiple protozoan species. Although some treatments have demonstrated efficacy, many exhibit limited or inconsistent results. To date, no flavonol compounds have advanced to clinical trials as antiparasitic drugs. While current findings shed light on proposed mechanisms of action and the impact of structural modifications on biological activity, further research is essential to fully elucidate their therapeutic potential and support the development of flavonols as future antiparasitic agents.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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Supplementary Material

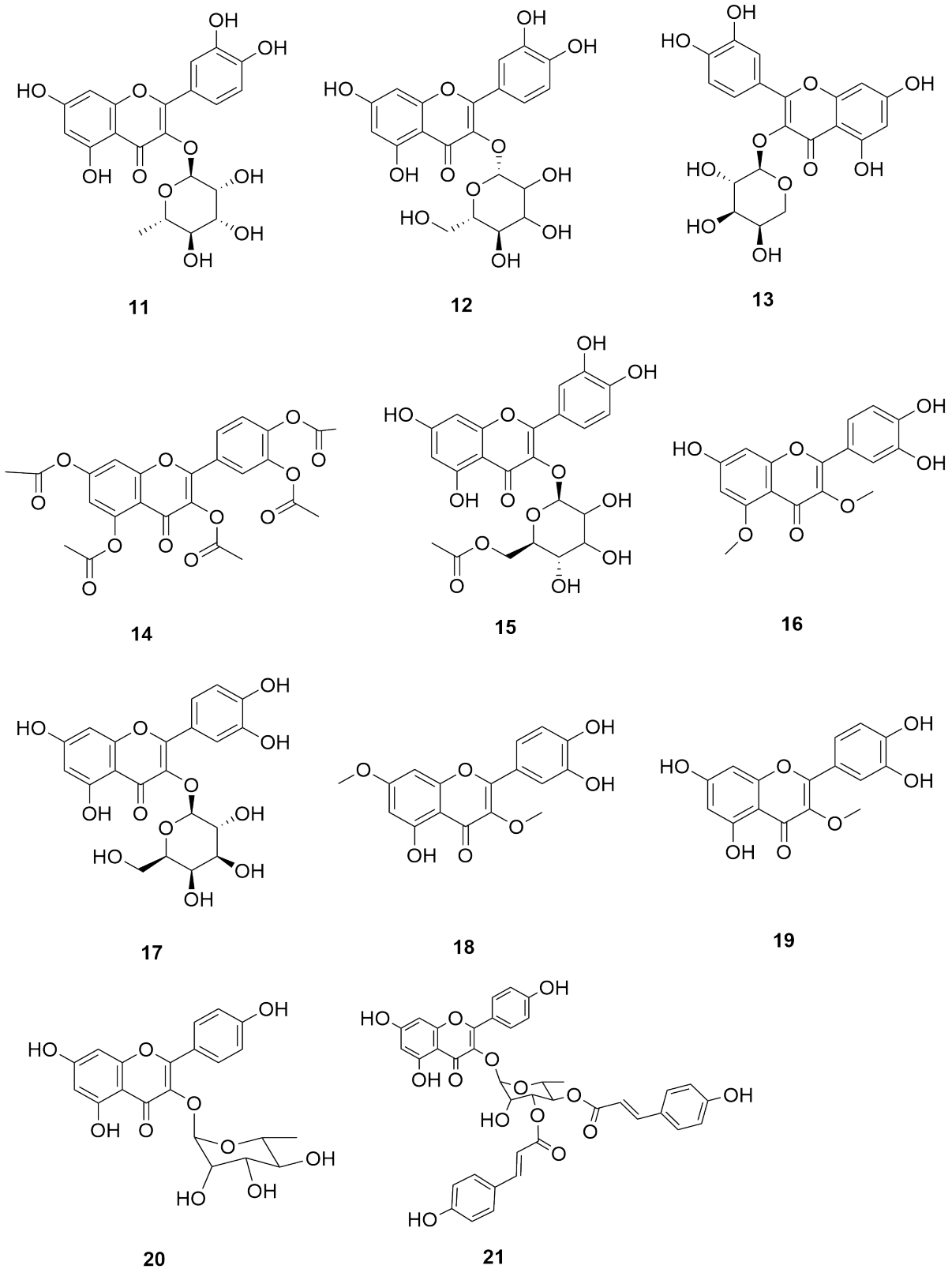


Figure S1: Chemical structure of flavonol derivatives (refer Table S1)

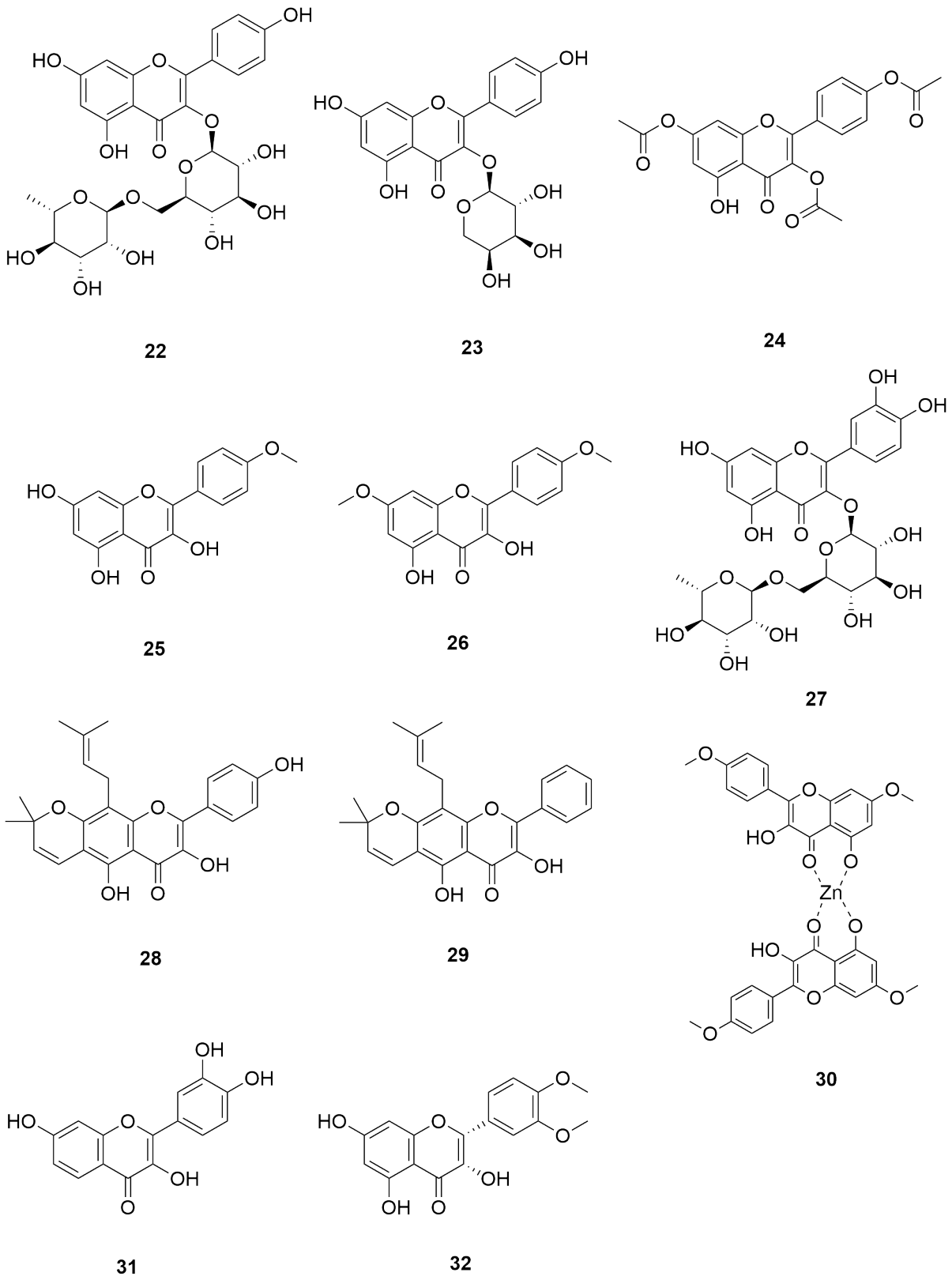
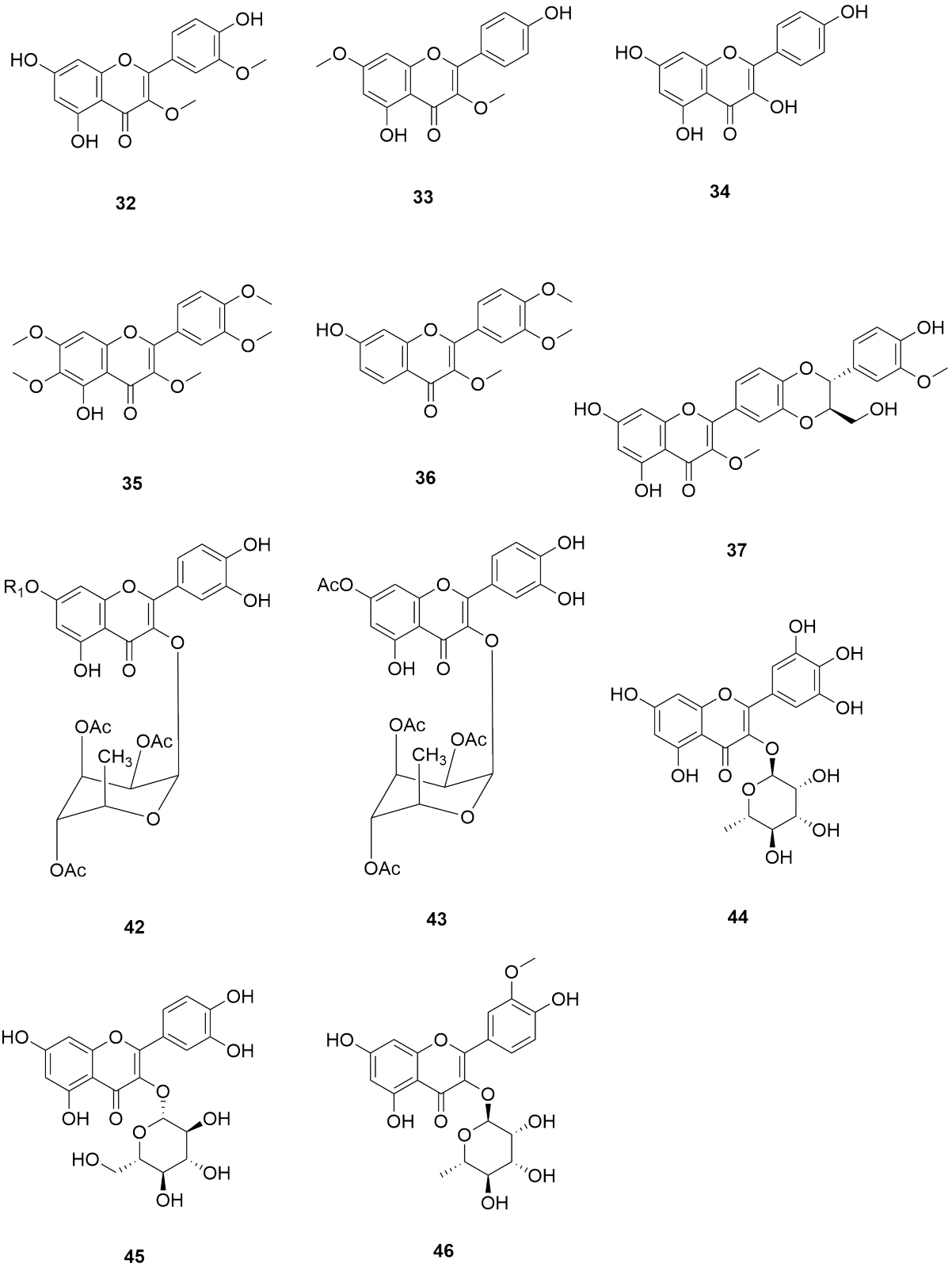


Figure S2: Chemical structure of flavonol derivatives (refer Table S1)



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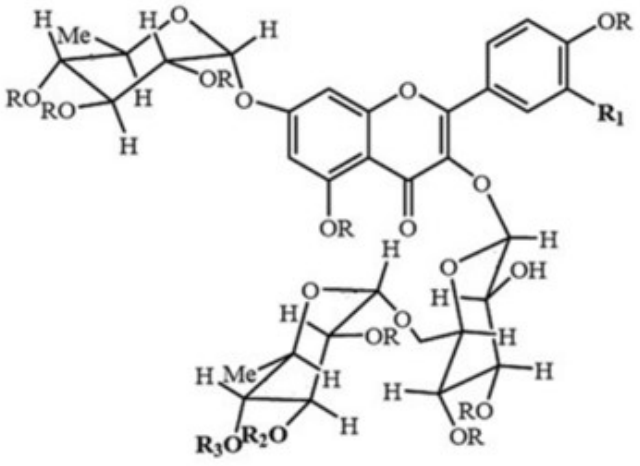
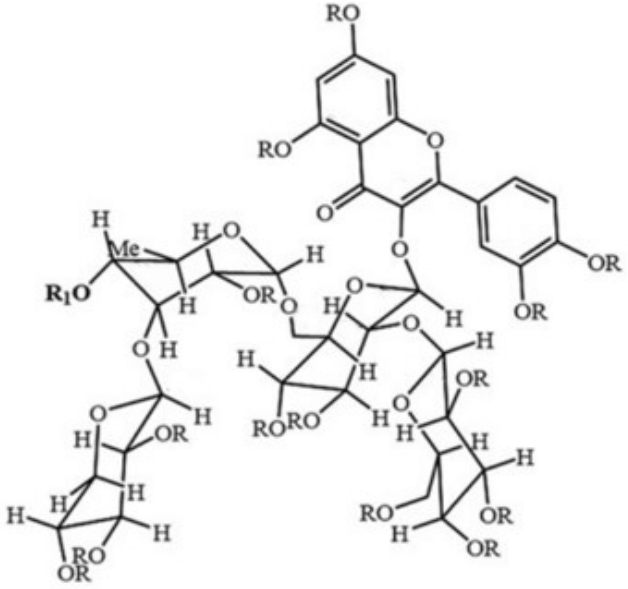


38: R_1 = OAc, R_2 = XylAc, R_3 = *trans-p*-coumaroylAc, R = Ac

39: R_1 = OAc, R_2 = GlcAc, R_3 = *trans-p*-coumaroylAc, R = Ac



40: R = H, R_1 = *trans-p*-caffeoyl

41: R = H, R_1 = *trans-p*-coumaroyl

Figure S4: Chemical structure of flavonol derivatives (refer Table S1). Adapted from "*In vitro* anti-*Acanthamoeba* activity of flavonoid glycosides isolated from *Delphinium gracile*, *D. staphisagria*, *Consolida oliveriana* and *Aconitum napellus*" by Martín-Escolano R, Molero Romero S, Díaz JG, Marín C, Sánchez-Moreno M, Rosales MJ, 2021, *Parasitology* 148, 1392–1400, Copyright 2021 by Cambridge University Press

Table S1: Antiparasitic activity of flavonol derivatives

Compounds	Source	Parasites	Study design	Results	Reference
Quercitrin **(11)**	*Pappea capensis*	*P. falciparum 3D7*	*In vitro*	Viability of *P. falciparum* at 50 µg/mL was 16.2 ± 2.2 percent	(Tajuddeen et al., 2021)
	Pelliciera rhizophorae	*L. donovani*	*In vitro*	IC_{50} 3.4 ± 0.1 µM	(López et al., 2015)
	Sigma–Aldrich	*L. amazonensis*	*In silico*	IC_{50} 10 µM	(Manjolin et al., 2013)
	Albizia zygia	*P. falciparum 3D7*	*In vitro*	IC_{50} 25.1 ± 0.25 µM	(Koagne et al., 2020)
Isoquercitrin **(12)**	*Pappea capensis*	*P. falciparum 3D7*		Viability of *P. falciparum* at 50 µg/mL was 18.4 ± 2.9 percent.	(Tajuddeen et al., 2021)
	Sigma–Aldrich	*L. amazonensis*	*In vitro* *In silico*	IC_{50} 3.8 µM	(Manjolin et al., 2013)
Quercetin 3-O-arabinopyranoside (guaijaverin) **(13)**	*Pappea capensis*	*P. falciparum* 3D7		Viability of *P. falciparum* at 50 µg/mL was 19.1 ± 0.5 percent	(Tajuddeen et al., 2021)
Quercetin pentaacetate **(14)**	Penta acetylation process	*L. amazonensis*	*In vitro*	IC_{50} 75.1 ± 4.7 µM	(da Silva et al., 2021)
Quercetin 3-(6-O-acetyl)-hexoside **(15)**	*Eryngium alpinum*	*Acanthamoeba trophozoites*	*In vitro* *In vivo*	IC_{50} 0.35 mg/ml	(Kikowska et al., 2020)
3,5-Dimethoxyquercetin **(16)**	*Dioscorea bulbifera*	*P. falciparum K1,* *P. falciparum 3D7*	*In vitro*	IC_{50} 44.03 µM (*P. falciparum K1*) IC_{50} 70.79 µM (*P. falciparum 3D7*)	(Chaniad et al., 2021)
Quercetin-3-O-β-D-galactopyranoside **(17)**				IC_{50}48.33 µM (*P. falciparum K1*) IC_{50} 68.93 µM (*P. falciparum 3D7*)	

Table S1: *Cont.*

Compounds	Source	Parasites	Study design	Results	Reference
Quercetin-3, 7-dimethyl ether **(18)**	*Croton gratissimus*	*P. falciparum,* *L. donovani*	*In vitro*	IC_{50} 7.3 µM against *P. falciparum* IC_{50} 4.5 µM against *L. donovani*	(Mahmoud et al., 2020)
3-O-methylquercetin **(19)**	*Vachellia xanthophloea*	*P. falciparum*		21.9 ± 1.5 percent of viability at 50 µg/mL	(Tajuddeen et al., 2022)

Kaempferol-3-O-α-L-rhamnopyranoside **(20)**	*Albizia zygia*	*P. falciparum 3D7*		IC_{50} 19.0 ± 0.25 µM	(Koagne et al., 2020)
Kaempferol-3-O-α-(3, 4-di-E-p-coumaroyl)-rhamnopyranoside **(21)**	*Nectandra oppositifolia*	*T. cruzi*		IC_{50} 6.7 µM	(Conserva et al., 2021)
Kaempferol 3-O-rutinoside **(22)**	*Moringa oleifera*	*L. major*		IC_{50} 206.40 ± 1.63 µg/mL	(Hammi et al., 2020)
Kaempferol 3-O-arabinopyranoside (juglalin) **(23)**	*Pappea capensis*	*P. falciparum 3D7*		Viability of *P. falciparum* at 50 µg/mL was 18.1 ± 1.0 percent.	(Tajuddeen et al., 2021)
Kaempferol triacetate **(24)**	Sigma–Aldrich	*L. major*	*In vitro* *In silico*	IC_{50} 14.93±2.21 µM	(Abdeyazdan et al., 2022)
4'-Methoxykaempferol **(25)**	Temperate Propolis	*T. brucei,* *L. mexicana*	*In vitro*	*T. brucei* IC_{50} 15.2 µM (TbS427WT) IC_{50} 22.4 µM (B48:) IC_{50} 21.1 µM (ISMR1) *L. mexicana* IC_{50} 41.4 µM (WT) IC_{50} 10.4 µM (C12Rx)	(Alotaibi et al., 2021)

Table S1: *Cont.*

Compounds	Source	Parasites	Study design	Results	Reference
Kaempferol 4', 7-dimethyl ether **(26)**				*T. brucei* IC_{50} 95.2 µM (TbS427WT) IC_{50} 103 µM (B48) IC_{50} 94.1 µM (ISMR1) *L. mexicana* IC_{50} 12.9 µM (WT) IC_{50} not tested (C12Rx)	
Rutin **(27)**	*Moringa oleifera*	*L. major*		IC_{50} 78.51 ± 1.09 µg/mL	(Hammi et al., 2020)
	TIPdb	*L. donovani*	*In silico* *In vivo*	IC_{50} 40.95 µM against promastigote and 90.09 µM against amastigote	(Kant et al., 2022)
	Sigma-Aldrich		*In vitro*	IC_{50} 98 µg/mL	(Mehwish et al., 2021)
		L. amaz/tc3	*In vitro*	IC_{50} 133 ± 8.25 µM	(García-Bustos et

			In vivo		al., 2021)
Dehydrolupinifolinol **(28)**	*Mundulea sericea*	*L. donovani* antimony-sensitive strain *(MHOM/IN/83/AG8)*	*In vitro*	IC_{50} 9.0 µM against the *L. donovani* antimony-sensitive strain	(Chepkirui et al., 2021)
Sericetin **(29)**		*L. donovani* antimony-resistant strain *(MHOM/IN/89/GE1)*		IC_{50} 5.0 µM against the antimony-sensitive and 38.0 µM against antimony-resistant	

Table S1: *Cont.*

Compounds	Source	Parasites	Study design	Results	Reference
Zinc derivatized 3,5-dihydroxy 4', 7-dimethoxyflavone (DHDM-Zn) **(30)**	Mixture of DHDM with zinc chloride	*L. donovani*		IC_{50} 63±0.73 µM	(Gupta et al., 2022)
Fisetindiol **(31)**	Saudi propolis	*T. brucei (S427 WT)*		MIC: 14.7 µg/ml	(Alanazi et al., 2021)
2-(5'-meth-oxyphenyl)-3,4',5,7,8-trihydroxychroman-4-one **(32)**	*Vitex simplicifolia*	*T. b. rhodesiense*		IC_{50} 10.2 µg/ml	(Nwodo et al., 2015)
2-(5'-methoxyphenyl) 4',5,7-trihydroxy-3-methoxychro-men-4-one **(33)**			*In vitro*	IC_{50} 12.3 µg/ml	
2-(4'-hydroxyphenyl)- 5-hydroxy 3,7- dimethoxy chromen-4-one **(34)**				IC_{50} 19.4 µg/ml	
2-(4- hydroxyphenyl)-3,5,7-trihydroxy chromen-4-one **(35)**				IC_{50} 23.7 µg/ml	
2-(3',4'-dimethoxyphenyl)-7-hydroxychromen-4-one (7) **(36)**				IC50 10.8 µg/ml	
Dehydroisosilybin A **(37)**	Silybin A	*L. infantum,* *L. donovani*		IC_{50} approximately 90.23 µM.	(Olías-Molero et al., 2018)
Flavonol glycoside acetate (1) **(38)**	*Delphinium gracile*	*A. castellanii*		IC_{50} 3.5 ± 3.0 µM	(Martín-escolano et al., 2021)
Flavonol glycoside acetate (2) **(39)**				IC_{50} 1.4 ± 1.2 µM	
Acylated flavonol tetraglycosides (3) **(40)**				IC_{50} 1.4 ± 0.4 µM	

Table S1: *Cont.*

Compounds	Source	Parasites	Study design	Results	Reference
Acylated flavonol tetraglycosides (4) **(41)**			*In vitro*	IC_{50} 2.3 ± 0.4 µM.	
Quercetin 2",3",4"-triacetate **(42)**	Acetylation of quercitrin	*P. falciparum* 3D7		IC_{50} 7.5 ± 0.25 µM	(Koagne et al., 2020)
Quercetin 7,2",3",4"-tetraacetate **(43)**	Acetylation of quercitrin	*P. falciparum* 3D7		IC_{50} 6.8 ± 0.25 µM	(Koagne et al., 2020)

Table S2: Antiparasitic activity of plant extracts containing flavonols

Extracts	Source	Parasites	*Study design*	Results	Reference
EtOH	*Eugenia uniflora*	*L. amazonensis*	*In vitro*	Myricitrin and quercitrin were predominant in the ethanol extract. The ethanol extract showed EC_{50} 47.0 µg/mL and 22.1 µg/ml against promastigote and amastigote form	(Santos et al., 2019)
HO_P	white grape marc	*P. falciparum,* *P. cinnamomi* (*Pc*)		Higher concentration of rutin and kaempferol was detected. Better anti toxoplasma and antiplasmodial against *P. falciparum* than HO_L	(Rama et al., 2021)
HO_L				Higher concentration of isoquercetin. 6 times better inhibition against *Pc* than HO_P.	
EtOAc	*Callistemon citrinus*	*P. falciparum,* *T. brucei*		Extract yields 438.38 ± 11.73 mg·RE/100 g of overall flavonol content. IC_{50} 9.7 µg/mL against *T. brucei* and 13 µg/mL against *P. falciparum*	(Larayetan et al., 2019)
MeOH				Extract contains 512.90 ± 11.00 mg·RE/100 g of overall flavonol content. IC_{50} 6.6 µg/mL against *T. brucei* and 8.4 µg/mL against *P. falciparum*	
EtOH	*Ziziphus joazeiro*	*L. braziliensis,* *L. infantum,* *T. cruzi*		The extract recorded IC_{50} 612.06 µg/ mL against *T. cruzi*, IC_{50} for *L. braziliensis* >5000 µg/mL and IC_{50} 693.67 µg/mL for *L. infantum.*	(Brito et al., 2015)
Leaf infusion	*O. hamiltonii*	*T. cruzi,* *L. braziliensis,* *L. infantum*		Quercetin presented in the infusion. The infusion recorded IC_{50} 10.6 µg/mL for IOH against *T. cruzi* IC_{50} 236.93 µg/mL against *L. braziliensis* and IC_{50} 342.90 µg/mL against *L. infantum*.	(Bitu et al., 2017)
Shoot culture	*E. planum*	*Acanthamoeba* sp. strain Ac55		IC_{50} 0.25 mg/ml	(Kikowska et al., 2022)
	E. maritimum			IC_{50} 3.70 mg/ml	

Table S2: *Cont.*

Extracts	Source	Parasites	*Study design*	Results	Reference
EtOH	*Myrcianthes pungens*	*L. amazonensis, L. braziliensis*	*In vitro*	The plant extract recorded IC_{50} 180 µg/ml against *L. amazonensis* and 210 µg/ml against *L. braziliensis*	(Ferreira et al., 2021)
EtOH	*Annona muricata*			IC_{50} 270 µg/ml against *La* and 210 µg/ml against *L. braziliensis*	
EtOH	*Brunfelsia uniflora*			IC_{50} 220 µg/ml against *L. amazonensis* IC_{50} 460 µg/ml against *L. braziliensis*	
EtOH	*Nectandra megapotamica*			IC_{50} 200 µg/ml against *L. amazonensis* IC_{50} 760 µg/ml against *L. braziliensis*	
EtOH	*Plinia cauliflora*	*T. cruzi*		EC_{50} of the plant leaf extract at 2 hour 9.94 ± 2.25 µg/mL and at 24 hour 6.84 ± 2.54 µg/mL	(Galvão et al., 2021)
EtOH	*Capsicum chinense*	*T. gondii*		The peel ethanol extract inhibited parasite proliferation at concentration of 256 µg/mL and 512 µg/mL	(Menezes et al., 2022)
EtOH	*Persea americana*	*P. berghei*	*In vivo*	The extract recorded chemosuppression of parasitemia (>50%)	(Uzor et al., 2021)
EtOH	*Guazuma ulmifolia*	*L. braziliensis, L. infantum, T. cruzi*	*In vitro*	Antipromastigote activity against *L. braziliensis* & *L. infantum* were 92.20% and 95.23% respectively and antitrypanosoma activity was 61.15%.	(Calixto Júnior et al., 2016)