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Antimalarial potential of quinones isolated from plants: an integrative review

Potencial antimalárico de quinonas isoladas de plantas: uma revisão integrativa

Potencial antipalúdico de quinonas aislados de plantas: una revision integradora

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Abstract
Antimalarial treatment is often associated with the resistance developed by *Plasmodium* which generate ineffective drug treatment. Based on this, the search for therapeutic alternatives is necessary and urgent. This review intends to assess the antimalarial potential of quinones isolated from plants. The search for scientific articles was carried out on the CAPES Journal Portal (PPC), Virtual Health Library (VHL), PUBMED, NCBI and SCIELO, using the following descriptors: quinones and antimalarials. Inclusion criteria were adopted based on studies about quinones isolated from plants and tested against *Plasmodium falciparum* and *Plasmodium berghei*. The exclusion criteria were based mainly on articles that tested extracts, fractions and synthesis of quinones obtained from plants and other natural products. A total of 1344 publications were collected for screening (PPC = 5, VHL = 248, PUBMED = 525, NCBI = 462 and SCIELO = 94). From this total, 1280 articles were excluded, with only 64 articles selected for full reading. All benzoquinones were active against *P. falciparum.* Naphthoquinones were active, inactive and moderately active against the *P. falciparum* e *P berghei*. Anthraquinones and anthrones were active and moderately active against *P. falciparum.* The naphthoquinone 2-acetylnaphtho- [2,3b] -furan-4,9-dione was the most active of all the molecules tested against *Plasmodium.* Whereas lapachol was the most studied naphthoquinone and structural changes do not seem to contribute to the activity. In summary, quinones are promising as antimalarials, however, need *in vivo* studies.
Keywords: Quinones; *Plasmodium*; Antimalarials; Plants.

Resumo
O tratamento antimalárico frequentemente está associado aos fatores de resistência desenvolvidos pelo *Plasmodium* e que geram ineficácia do tratamento medicamentoso. Baseado nisso, a busca por novas alternativas terapêuticas é necessária e urgente. O objetivo desta revisão é avaliar o potencial antimalárico de quinonas isoladas de plantas. A busca de artigos científicos foi realizada no Portal de Periódicos CAPES (PPC), Biblioteca Virtual em Saúde (BVS), PUBMED, NCBI e SCIELO, sendo os descritores utilizados: quinonas e antimaláricos. Foram adotados os critérios de inclusão baseados em estudos sobre quinonas isoladas de plantas e testadas contra o *Plasmodium falciparum* e *Plasmodium berghei*. Em relação aos critérios de exclusão, foram baseados principalmente em artigos que testaram extratos, frações e síntese de quinonas obtidas de plantas e outros produtos naturais. Um total de 1344 publicações foi coletado para triagem (PPC = 5, BVS= 248, PUBMED = 525, NCBI= 462 e SCIELO = 94). Deste total, foram excluídos 1.280 artigos, sendo selecionados somente 64 artigos para leitura na íntegra. Todas as benzoquinonas foram ativas contra o *P. falciparum.* As naftoquinonas foram ativas, inativas e moderadamente ativas contra o *P. falciparum*

e *P. berghei*. Já as antraquinonas e as antronas foram ativas e moderadamente ativas contra o *P. falciparum.* A naftoquinona2-acetylnaphtho-[2,3b]-furan-4,9-dione foi a mais ativa dentre todas as moléculas testadas contra o *Plasmodium*. Enquanto, o lapachol foi a naftoquinona mais estudada e mudanças estruturais parecem não contribuir para a atividade. Em síntese, as quinonas são promissoras como antimaláricos, entretanto, são necessários estudos *in vivo*.
Palavras-chave: Quinonas; *Plasmodium*; Antimaláricos; Plantas.

Resumen
El tratamiento antimalárico suele asociarse a los factores de resistencia desarrollados por *Plasmodium*y que generan un tratamiento farmacológico ineficaz. En base a esto, la búsqueda de nuevas alternativas terapéuticas es necesaria y urgente. El propósito de esta revisión es evaluar el potencial antipalúdico de las quinonas aisladas de plantas. La búsqueda de artículos científicos se realizó en el Portal de Revistas CAPES (PPC), Biblioteca Virtual en Salud (BVS), PUBMED, NCBI y SCIELO, con los descriptores utilizados: quinonas y antimaláricos. Los criterios de inclusión se adoptaron basándose en estudios sobre quinonas aisladas de plantas y probadas contra *Plasmodium falciparum* e *Plasmodium berghei*. En cuanto a los criterios de exclusión, se basaron principalmente en artículos que probaron extractos, fracciones y síntesis de quinonas obtenidas de plantas y otros productos naturales. Se recopilaron 1344 publicaciones para cribado (PPC = 5, VHL = 248, PUBMED = 525, NCBI = 462 y SCIELO = 94). De este total, se excluyeron 1.280 artículos, con solo 64 artículos seleccionados para lectura completa. Todas las benzoquinonas fueron activas contra *P. falciparum*. Las naftoquinonas fueron activas, inactivas y moderadamente activas contra el *P. falciparum* e *P. berghei*. Las antraquinonas y antronas fueron activas y moderadamente activas contra *P. falciparum*. La naftoquinona 2-acetilnafto- [2,3b] -furan-4,9-diona fue la más activa entre todas las moléculas probadas contra *Plasmodium*, considerándose la más prometedora en el desarrollo de fármacos futuros. Mientras que el lapachol fue la naftoquinona más estudiada y los cambios estructurales no parecen contribuir a la actividad. En resumen, las quinonas son prometedoras como antipalúdicos, sin embargo, necesitan estudios *in vivo*.
Palabras clave: Quinonas; *Plasmodium;* Antimaláricos; Plantas.

1. Introduction

About 3.3 billion people are exposed to malaria in endemic areas at risk of contracting the disease in more than 100 countries. In 2018 there were 228 million cases of malaria, with the African continent having the highest morbidity rate with 213 million cases, and almost 1 million deaths (WHO, 2019). In the Americas, 138 million people live in risk areas. The Venezuela, Brazil, Peru, Nicaragua and Colombia are the countries with the highest number of cases and deaths (OPAS, 2020).

The widespread increase in resistance to antimalarial drugs is one of the main problems in reducing the mortality caused by *Plasmodium*, which results in delay or failure of remission of blood forms, allowing the selection of resistant gametocytes. Resistance to antimalarials is associated with the irrational use of medicines, counterfeit drugs, long drug half-lives, host immunity, parasite and environmental factors (Winstanley, 2001). In addition to quinine and chloroquine, resistance to primaquine, proguanil, atovacone, mefloquine and combined artemisinin therapy (Wongsrichanalai et al., 2002; Noeldl et al., 2008; Van Bong et al., 2014) has been reported.

Based on this, there is a search for new drugs that are more selective, less toxic and do not induce resistance in *Plasmodium* (Gamo et al., 2010; Penna-Coutinho et al., 2011; Aguiar et al., 2012; Coutinho et al., 2013; Souza et al., 2014). One of the new strategies for creating antimalarial drugs is the characterization and isolation of compounds from medicinal plants, especially quinones such as naphthoquinones, with atovaquone as its main representative, a very active and less toxic naphthoquinone that acts by inhibiting purine biosynthesis in the parasite (Hage et al., 2009; Hughes et al., 2011).

The development of new therapeutic alternatives to treat malaria is necessary, mainly due to the drug resistance of the *Plasmodium*, therefore, metabolites such as quinones, isolated from medicinal plants have shown promising results as a potential drug in the treatment of infectious diseases such as malaria. The purpose of this literature review is to evaluate the antimalarial potential of quinones isolated from different plant species.

2. Methodology

In this integrative review, a research was carried out to select scientific articles available on the following platforms: CAPES Journal Portal (PPC), Virtual Health Library (VHL), PUBMED, NCBI and SCIELO, without limiting the publication year of articles.

The search period was between August and September 2020, and only articles in Portuguese, English and Spanish were adopted as inclusion criteria, and adaptation of the title to the theme and compatible summary as well.

The exclusion criteria adopted were articles that did not address the topic of study, papers in other languages, articles that tested extracts and fractions, quinones obtained through synthesis and other natural products, articles not available in full, duplicates and studies that have not been analyzed by experts.

The representative descriptors for searching the articles on platforms were quinones and antimalarials. Initially, 1344 were collected for screening (PPC = 5, VHL = 248, PUBMED = 525, NCBI = 462 and SCIELO = 94). However, after analyzing the title and abstract, 1,280 articles were excluded, with only 64 articles selected for full reading and likely inclusion in the integrative review.

The selection was based on the title and abstract, being carried out by three reviewers who took into account the inclusion and exclusion criteria. In cases of divergences during the selection analysis, a fourth reviewer was consulted to ensure compliance with the study requirements. After reading the articles, 38 were used in the results and 38 were used in the discussion of this review, with 24 articles excluded from the 64 initially included. In addition, to facilitate the organization and tabulation of the data, it was divided into two stages of analysis: first, a table with the title and summary was made. In the second stage, full reading and synthesis of the articles were carried out to produce the results and discussion.

The antimalarial activity of quinones *in vitro* was considered active when the IC_{50} was less than or equal to 10 µg.mL^{-1}against the plasmodium; moderately active with an IC_{50} greater than 10 µg.mL^{-1} and less than 100 µg.mL^{-1}and inactive with an IC_{50} greater than 100 µg/ml^{-1}.

3. Results and Discussion

As a causative agent of malaria, *Plasmodium* is responsible for approximately two million deaths worldwide. In almost all endemic populations, the parasite has developed resistance against drugs used in first-line treatment, such as chloroquine and its derivatives. An important area in antimalarial research is based on finding a potent and reliable antiparasitic medication capable of inhibiting *Plasmodium* infection and growth (Najera, 2001; Hyde, 2002). In this context, quinones have been increasingly studied, since the antimalarial activity of Atovaquone was described (Basco et al., 1995).

Quinones represent a wide and varied family of compounds found in nature, especially in plants, fungi, lichens and bacteria, and can be synthesized (Thomson, 1971). Based on their molecular structure, quinones can be classified according to the type of aromatic ring that supports the basic quinoid nucleus: benzoquinones (benzene ring), naphthoquinones (naphthalenic ring) and anthraquinones (linear or angular anthracene ring). These three types of quinones are the most frequently found in nature (Silva et al., 2003). When we analyzed the *in vitro* antimalarial activity of benzoquinones, we found few studies reporting the activity of these compounds against *P. falciparum* (Ichino et al., 2006; Tasdemir et al., 2006; Boonphong et al., 2007; Radwan et al., 2008).

The benzoquinones Primin (1) Marcanine A (2) and Bauhinoxepin I (3) showed activity with IC_{50} of 2.27 µg.mL^{-1}, 2.51 µg.mL^{-1} and 3.0 µg.mL^{-1}, respectively (Table 1, Figure 1), while Bauhinoxepin J (4; Figure 1) was active against a chloroquine-resistant strain of *P. falciparum* (k1; 1.48 µg.mL^{-1}) and 5-acetoxy-6-geranyl-3-npentyl-1, 4-benzoquinone (5)

showed activity against both sensitive (D6) and resistant (W2) strain to chloroquine with an IC_{50} of 2.8 and 2.6 μg.mL^{-1}, respectively (Table 1, Figure 1).

Kumar, Musiyenko & Barik (2003) demonstrated that a naturally occurring benzoquinone, geldanamycin, interferes with regulation of the cell cycle and signal transduction through specific inhibition of the Hsp90 protein, in CQ-sensitive and CQ-resistant strains (3D7 and W2, respectively) in all erythrocytic phases of the parasite. Hsp90 is the chaperone responsible for folding and, therefore, for the functioning of many essential proteins for parasite survival (Richter & Buchner, 2001).

In the present study, from the quinones evaluated against antimalarial activity, naphthoquinones are the most studied subclass. Twenty-eight compounds were tested in different chloroquine-resistant and sensitive strains and from these, nine showed moderate activity and eighteen naphthoquinones were active. It is worth mentioning that, six naphthoquinones (Lapachol; 2-acetylnaphtho-[2,3b]-furan-4,9-dione; Sterekunthal A; 2-(1-hydroxyethyl)-naphtho-[2,3-b]-furan-4,9-quinone; Isopinnatal and Plumbagin) showed high activity with IC_{50}below 1 μg.mL^{-1} (Table 1; Figure 1). From these, 2-acetylnaphtho-[2,3b]-furan-4,9-dione showed high activity when evaluated against *P. berghei* (IC_{50} = 0.002 μg.mL^{-1}), and against *P. falciparum*, Plumbagin showed greater activity (IC_{50} = 0.05 μg.mL^{-1}). Such results show that naphthoquinones are the most promising against malaria.

One of the most studied naphthoquinones with great antimalarial potential is Atovaquone. It is even used as an alternative therapy in cases of resistance against first-line drugs, and for malaria prophylaxis. Due to the quinonic nature of the compounds evaluated in the present study, and the structural similarity of naphthoquinones with Atovaquone, the antimalarial activity of these compounds may be related to the inhibition of parasite's mitochondrial cytochrome bc1 complex, interrupting electron transport and consequently the synthesis of pyrimidines and, therefore, preventing the replication of the parasite's DNA (Birth et al., 2014). Just to clarify, a study showed that Atovaquone binds to the mitochondrial bc1 complex inhibiting the electron transport system in the apicoplast (Waller & McFadden, 2005).

In an antimicrobial and cytotoxicity study of *Eleutherine bulbosa*, a plant rich in quinones, identified activity of the extracts and fractions for *Staphylococcus aureus*, however the fractionation contributed to the increase in cytotoxicity (Borges et al., 2020). In a similar study, do Nascimento Brandão et al. (2020) evaluated the antimalarial and toxicity activity of *Aspidosperma nitidum* and demonstrated that the extracts and fractions showed high activity for *P. falciparum* (strain W2) *in vitro* and action against *P. berghei* in infected mice. In addition, the extracts and fractions showed low toxicity, both *in vitro* and *in vivo*. Da Veiga et al. (2020) also identified that metabolites isolated from plants are effective in destroying parasites *in vitro*.

When we analyze the antimalarial activity of anthraquinones, we observe that it is the second most studied subclass of quinones. A total of 17 anthraquinones were evaluated to assess their antimalarial potential, from these 15 substances presented IC_{50} below 10 μg.mL^{-1}, therefore, they were considered active, and we can highlight the 3 most promising substances: Joziknipholone A, Joziknipholone B, Isoknipholone and Knipholoneanthrone that showed high activity against sensitive (3D7) and resistant (K1, D6 and W2) strains of *P. falciparum* with IC_{50} less than 1 μg.mL^{-1} (Table 1, Figure 1).

During the data analysis about anthrones, we found that only 8 molecules have been evaluated. However, 7 compounds have antimalarial potential, mainly because they showed activity against a chloroquine-resistant strain of *P. falciparum* (W2). The 10- (chrysophanol-7'-yl)-10-(ξ)-hydroxychrysophanol-9-anthrone presented the lowest IC_{50} value (0.26 μg.mL^{-1}), being the compound with the greatest potential. Another 3 compounds (Bazouanthrone; 3-geranyloxyemodin anthrone and 3-prenyloxyemodin anthrone) also showed high activity, with IC_{50} below 1 μg.mL^{-1}(Table 1, Figure 1).

Table 1: Antimalarial activity of quinones.

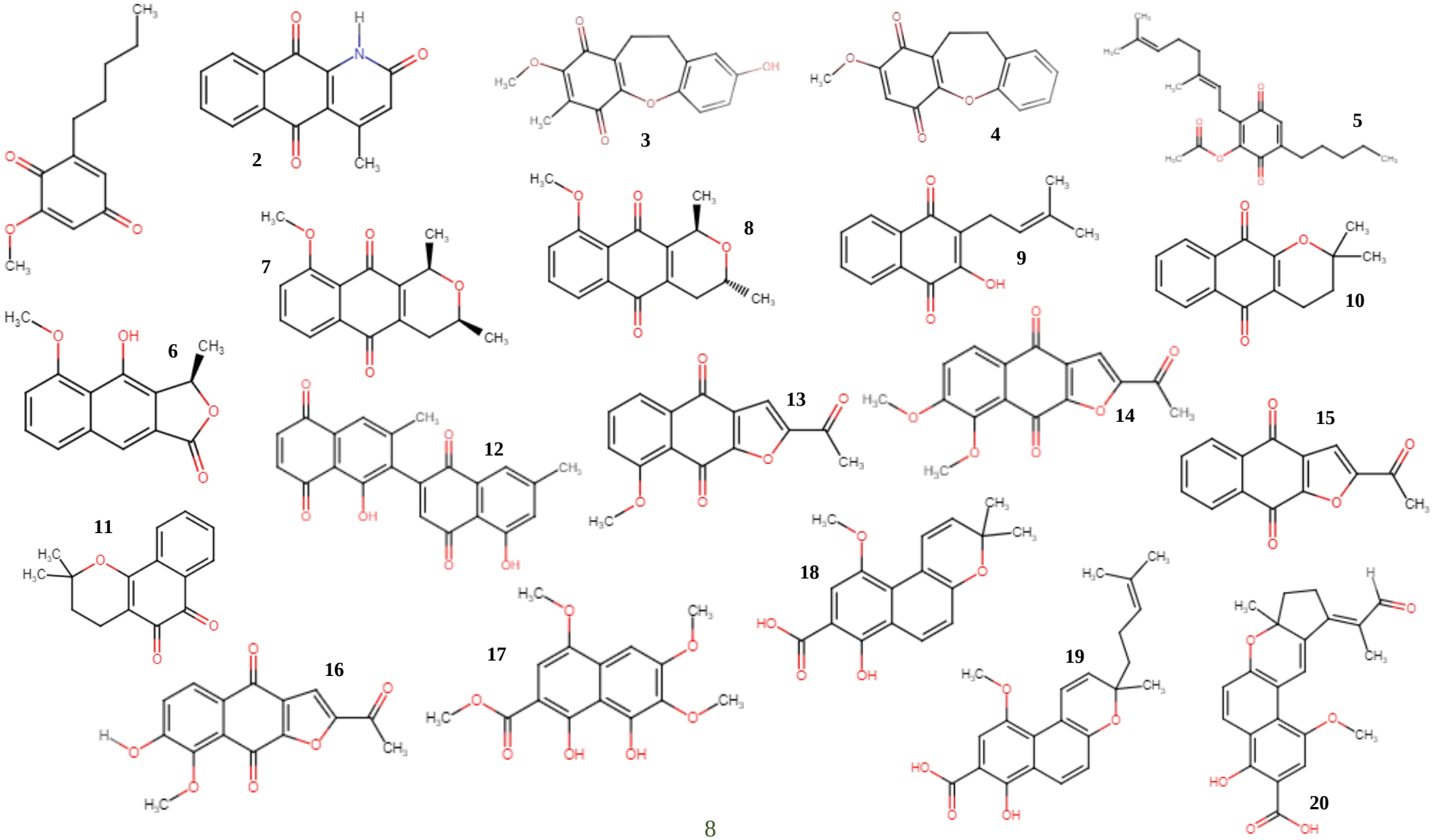
Name (class)	Antimalarial activity (IC_{50} µg.mL^{-1})	*Plasmodium* species (strain)	Data analysis	Reference
Benzoquinones				
Primin[1]	2.27	*P. falciparum* (K1)	Active	Tasdemir et al., 2006
Marcanine A [2]	2.51	*P. falciparum* (K1)	Active	Ichino et al., 2006
Bauhinoxepin I [3]	3.0	*P. falciparum* (K1)	Active	Boonphong et al., 2007
Bauhinoxepin J [4]	1.48	*P. falciparum* (K1)	Active	Boonphong et al., 2007
5-acetoxy-6-geranyl-3-n-pentyl-1,4-benzoquinone [5]	2.8 and 2.6	*P. falciparum* (D6 and W2)	Active	Radwan et al., 2008
Naphthoquinones				
Eleutherol[6]	>200	*P. falciparum* (3D7)	Inactive	Vale et al., 2020
Eleutherin[7]	10.45 ± 3.13	*P. falciparum* (3D7)	Active	
Isoeleutherin[8]	8.70 ± 2.45	*P. falciparum* (3D7)	Active	
Lapachol[9]	2.7 ± 1	*P. falciparum*	Active	Barbosa et al., 2014
	0.76 ± 0,01	*P. falciparum* (BHz26/86)	Active	
	2.28 ± 0.04	*P. falciparum* (HB3)	Active	de Andrade-Neto et al., 2004
	0.9 ± 0.006	*P. falciparum* (D6)	Active	
	0.85 ± 0.007	*P. falciparum* (W2)	Active	
	46.31± 2.9	*P. falciparum* (W2)	Moderatelyactive	do Nascimento et al., 2020
	19.47 ± 4.84	*P. falciparum* (W2)	Moderatelyactive	Moreira et al., 2015
	1.18	*P. berghei**	Active	Gómez-Estrada et al., 2012
α-lapachone[10]	5.48 ± 0,55	*P. falciparum* (W2)	Active	do Nascimento et al., 2020
	3.82 ± 0.84	*P. falciparum* (W2)	Active	Moreira et al., 2015
β-lapachone[11]	>4.84	*P. falciparum*	Active	de Andrade-Neto et al., 2004
	9.16 ± 0.93	*P. falciparum* (W2)	Active	do Nascimento et al., 2020
	4.96 ± 0.24	*P. falciparum* (W2)	Active	Moreira et al.,2015
Diospyrin[12]	3.29	*P. falciparum* (K1)	Active	Theerachayanan et al., 2007
2-acetyl-8-methoxy-naphtho-[2,3b]-furan-4,9-dione [13]	51.80	*P. berghei**	Moderatelyactive	Gómez-Estrada et al., 2012
2-acetyl-7,8-dimethoxy-naphtho-[2,3b]-furan-4,9 –dione[14]	2.96	*P. berghei**	Active	Gómez-Estrada et al., 2012
2-acetylnaphtho-[2,3b]-furan-4,9-dione [15]	0.002	*P. berghei**	Active	Gómez-Estrada et al., 2012

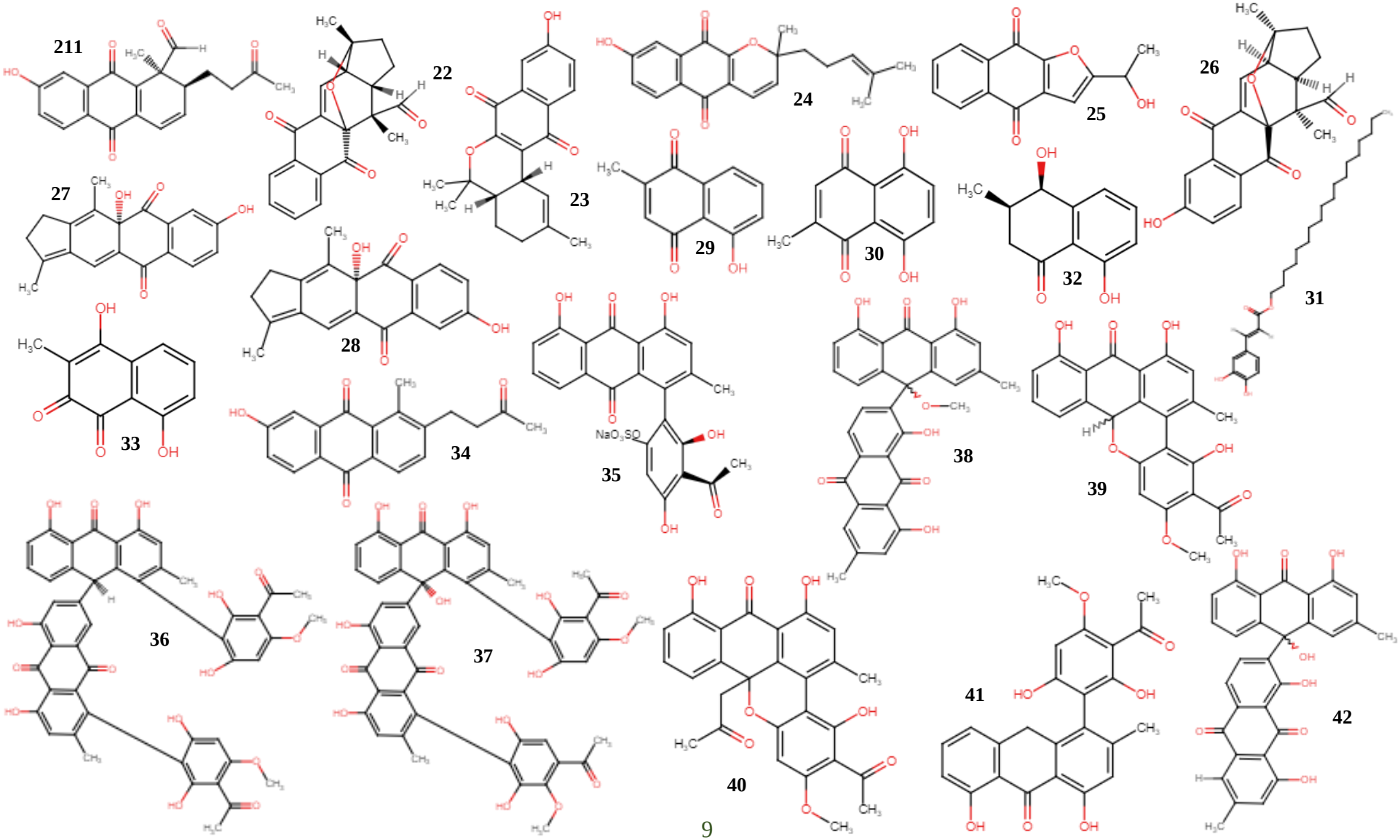
2-acetyl-7-hydroxi-8-methoxynaphtho-[2,3b]-furan-4,9-dione [16]	11.80	*P. berghei**	Moderatelyactive	Gómez-Estrada et al., 2012
Busseihydroquinone A [17]	36.03, 144.43	*P. falciparum* (D6 and W2)	ModeratelyactiveandInactive	Endale et al., 2012
Busseihydroquinone B [18]	27.82, 126.36	*P. falciparum* (D6 and W2)	ModeratelyactiveandInactive	Endale et al., 2012
Busseihydroquinone C [19]	32.65, 60.08	*P. falciparum* (D6 and W2)	Moderatelyactive	Endale et al., 2012
Busseihydroquinone D [20]	19.59, 80.10	*P. falciparum* (D6 and W2)	Moderatelyactive	Endale et al., 2012
Sterekunthal A [21]	1.3 ± 0.1, 0.4 ± 0.1	*P. falciparum* (poW and Dd2)	Active	Onegi et al., 2002
Sterekunthal B [22]	23.3 ± 4.2 and 15.2 ± 1.7	*P. falciparum* (poW and Dd2)	Moderatelyactive	Onegi et al., 2002
Pyranokunthone A [23]	11.7± 4.0,>25.0	*P. falciparum* (poW and Dd2)	Moderatelyactive	Onegi et al., 2002
Pyranokunthone B [24]	8.9 ± 1.2, 7.8 ± 1.3	*P. falciparum* (poW and Dd2)	Active	Onegi et al., 2002
2-(1-hydroxyethyl)naphtho[2,3-b]furan-4,9-quinone [25]	0.152 ± 0.129, 0.174 ± 0.061	*P. falciparum* (K1 and T9-96)	Active	Weiss et al., 2000
Isopinnatal[26]	0.258 ± 0.107, 0.525 ±0.49	*P. falciparum* (K1 and T9-96)	Active	Weiss et al., 2000
Kigelinol[27]	5.139 ± 0.921, 4.68 ± 0.896	*P. falciparum* (K1 and T9-96)	Active	Weiss et al., 2000
Isokigelinol[28]	4.048 ± 0.79, 3.679 ± 1.335	*P. falciparum* (K1 and T9-96)	Active	Weiss et al., 2000
Plumbagin[29]	0.05	*P. falciparum* (T9/94)	Active	Likhitwitayawuid et al., 1998
2-methylnaphthazarin[30]	1.18	*P. falciparum* (T9/94)	Active	Likhitwitayawuid et al., 1998
Octadecylcaffeate[31]	5.08	*P. falciparum* (T9/94)	Active	Likhitwitayawuid et al., 1998
Isoshinanolone[32]	4.0	*P. falciparum*(T9/94)	Active	Likhitwitayawuid et al., 1998
Droserone[33]	4.5	*P. falciparum* (T9/94)	Active	Likhitwitayawuid et al., 1998
Anthraquinones				
Anthrakunthone[34]	14.7 ± 0.25, 14.7 ± 5.3	*P. falciparum* (poW and Dd2)	Moderatelyactive	Onegi et al., 2002
Sodium 4' -O-demethylknipholone 6' -O-sulfate [35]	4.13	*P. falciparum* (K1)	Active	Mutanyatta et al., 2005
Joziknipholone A [36]	0.142	*P. falciparum* (K1)	Active	Bringmann et al., 2008
	0.4± 0.1, 0.3± 0.1	*P. falciparum* (D6 and W2)	Active	Induli et al., 2013
Joziknipholone B [37]	0.23	*P. falciparum* (K1)	Active	Bringmann et al., 2008
	2.5 ± 0.6, 1.5 ± 0.2	*P. falciparum* (D6 and W2)	Active	Induli et al., 2013
10-methoxy-10,7'-(chrysophanolanthrone)-chrysophanol[38]	4.07 ± 1.54,1.17 ± 0.12	*P. falciparum* (D6 and W2)	Active	Abdissa et al., 2013
Knipholonecyclooxanthrone[39]	3.96 ± 0.70, 6.13 ± 1.59	*P. falciparum* (D6 and W2)	Active	Abdissa et al., 2013
	4.0 ± 0.7, 6.1±1.6	*P. falciparum* (D6 and W2)	Active	Induli et al., 2013

10-acetonylknipholonecyclooxanthrone[40]	4.4± 1.5, 3.1± 1.2	*P. falciparum* (D6 and W2)	Active	Induli et al., 2013
Knipholoneanthrone[41]	4.1 ± 0.8, 3.6 ± 0.9	*P. falciparum* (D6 and W2)	Active	Induli et al., 2013
	0.3	*P. falciparum* (3D7)	Active	Feilcke et al., 2019
10-hydroxy-10-(chrysophanol-7′-yl)-chrysophanolanthrone[42]	1.7 ± 0.2, 0.7 ± 0.2	*P. falciparum* (D6 and W2)	Active	Induli et al., 2013
10-methoxy-10-(chrysophanol-7′-yl) chrysophanolanthrone[43]	4.1 ± 1.5, 1.2 ± 0.1	*P. falciparum* (D6 and W2)	Active	Induli et al., 2013
Asphodelin[44]	8.2 ± 1.7, 6.4 ± 1.4	*P. falciparum* (D6 and W2)	Active	Induli et al., 2013
	0.96	*P. falciparum* (3D7)	Active	Feilcke et al., 2019
Knipholone[45]	10.1 ± 0.2, 8.0 ± 0.5	*P. falciparum* (D6and W2)	Active	Induli et al., 2013
Isoknipholone[46]	8.6 ± 1.6, 7.9 ± 1.2	*P. falciparum* (D6 and W2)	Active	Induli et al., 2013
	0.12	*P. falciparum* (K1)	Active	Mutanyatta et al., 2005
Dianellin[47]	5.5 ± 1.2, 3.3 ± 0.2	*P. falciparum* (D6 and W2)	Active	Induli et al., 2013
	3.28 ± 0.19, 5.47 ± 1.20	*P. falciparum* (D6 and W2)	Active	Abdissa et al., 2013
Chrysophanol[48]	21.05 ± 0.64, 36.09 ± 3.32	*P. falciparum* (D6 and W2)	Moderatelyactive	Abdissa et al., 2017
Aloesaponarin I [49]	7.80 ± 1.11, 20.13 ± 5.12	*P. falciparum* (D6 and W2)	Active andModeratelyactive	Abdissa et al., 2017
Aloesaponarin II [50]	5.00 ± 0.36, 18.60 ± 7.10	*P. falciparum* (D6 and W2)	Active andModeratelyactive	Abdissa et al., 2017
Anthrones				
10-(chrysophanol-7’ -yl)- 10-(ξ)-hydroxychrysophanol-9-anthrone [51]	0.26	*P. falciparum* (D7)	Active	Wube et al., 2005
Bazouanthrone[52]	0.85	*P. falciparum* (W2)	Active	Lenta et al., 2007
Glaberianthrone[53]	2.10	*P. falciparum* (W2)	Active	Lenta et al., 2008
Bianthrone 1[a] [54]	1.98	*P. falciparum* (W2)	Active	Lenta et al., 2008
3-geranyloxyemodinanthrone[55]	0.66	*P. falciparum* (W2)	Active	Lenta et al., 2008
3-prenyloxyemodinanthrone[56]	0.64	*P. falciparum* (W2)	Active	Lenta et al., 2008
2-geranylemodin[57]	2.17	*P. falciparum* (W2)	Active	Lenta et al., 2008
Peperovulcanone A [58]	22.28	*P. falciparum* (W2mef)	Moderatelyactive	Ngemenya et al., 2015

Legend:µg- micrograms; mL-milliliter; the variations of *P. falciparum* strains were: 3D7-sensitive to chloroquine; W2- resistant to chloroquine; K1-resistant to chloroquine; D6-sensitive to chloroquine; poW-sensitive to chloroquine; Dd2-resistant to chloroquine; T9/94 and T9-96-sensitive to chloroquine. Active when the IC_{50} was less than or equal to 10 µg.mL^{-1} against the *Plasmodium*; moderately active with an IC_{50} greater than 10 µg.mL^{-1} and less than 100 µg.mL^{-1} and inactive with an IC_{50} greater than 100 µg.mL^{-1}.*Assay was performed *in vitro.*
Source: Gomes ARQ et al., (2021).

Figure 1. Chemical structures of quinones isolated from plants.

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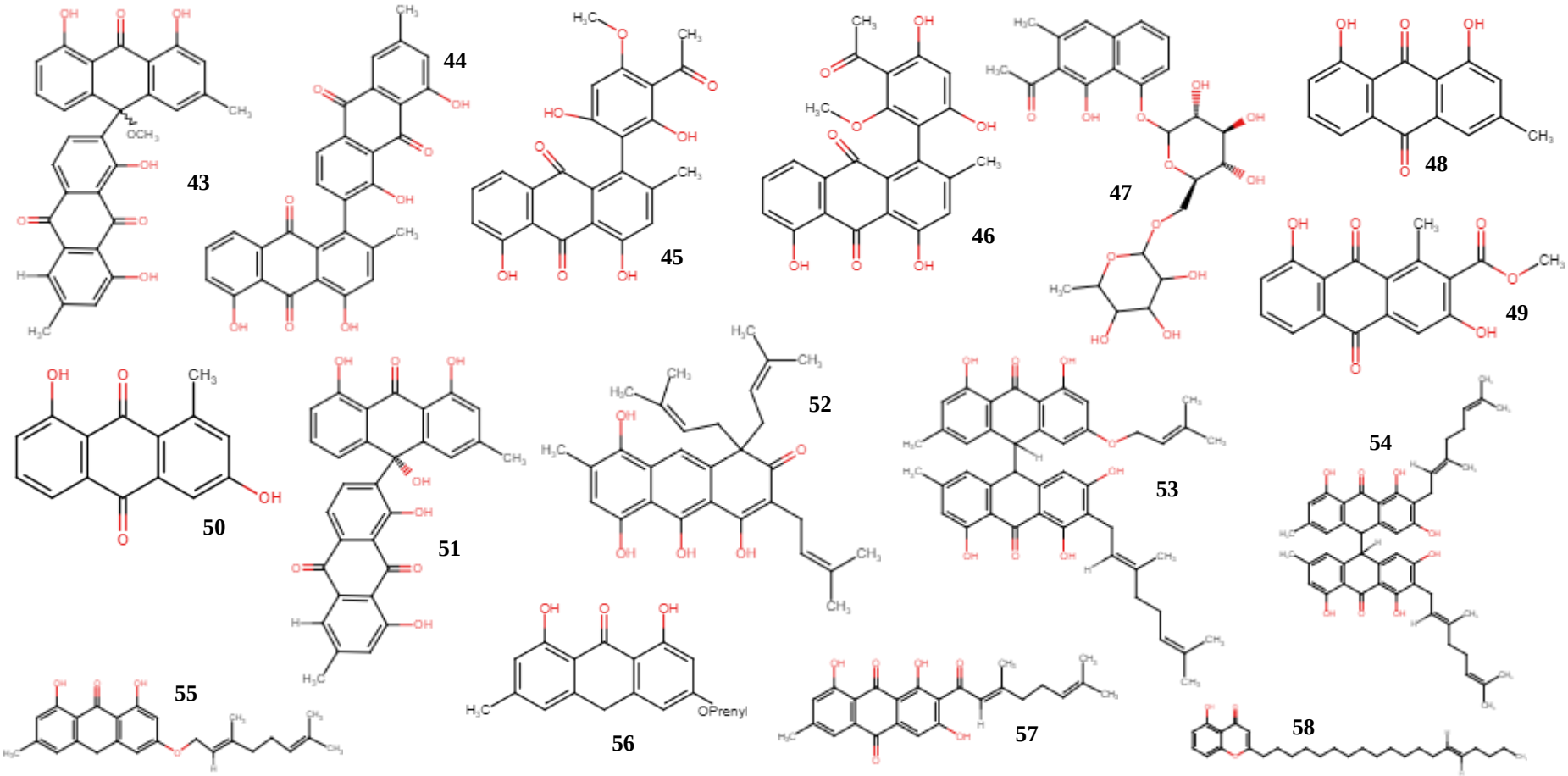

Legenda:1: Primin; **2:**Marcanine A;**3:**Bauhinoxepin I; **4:**Bauhinoxepin J; **5:**5-acetoxy-6-geranyl-3-npentyl-1,4-benzoquinone; **6:**Eleutherol; **7:**Eleutherin; **8:**Isoeleutherin; **9:**Lapachol; **10:**α-lapachone;**11:**β-lapachone; **12:**Diospyrin; **13:**2-acetyl-8-methoxy-naphtho-[2,3b]-furan-4,9-dione; **14:**2-acetyl-7,8-dimethoxy-naphtho-[2,3b]-furan-4,9-dione; **15:**2-acetylnaphtho-[2,3b]-furan-4,9-dione; **16:**2-acetyl-7-hydroxi-8-methoxynaphtho-[2,3b]-furan-4,9-dione; **17:**Busseihydroquinone A; **18:**Busseihydroquinone B; **19:**Busseihydroquinone C;**20:**Busseihydroquinone D; **21:**Sterekunthal A; **22:**Sterekunthal B; **23:**Pyranokunthone A; **24:**Pyranokunthone B; **25:**2-(1-hydroxyethyl)naphtho[2,3-b]furan-4,9-quinone; **26:**Isopinnatal;**27:**Kigelinol; **28:**Isokigelinol; **29:**Plumbagin; **30:**2-methylnaphthazarin; **31:**Octadecylcaffeate; **32:**Isoshinanolone; **33:**Droserone; **34:**Anthrakunthone; **35:**Sodium 4'-O-demethylknipholone 6'-O-sulfate; **36:**Joziknipholone A; **37:**Joziknipholone B; **38:**10-methoxy-10,7'-(chrysophanolanthrone)-chrysophanol; **39:**Knipholonecyclooxanthrone; **40:**10-acetonylknipholonecyclooxanthrone; **41:**Knipholoneanthrone; **42:**10-hydroxy-10-(chrysophanol-7'-yl)chrysophanolanthrone; 4**3:**10-methoxy-10-(chrysophanol-7'-yl)chrysophanolanthrone; **44:**Asphodelin; **45:**Knipholone; **46:**Isoknipholone; **47:**Dianellin; **48:**Chrysophanol; **49:**Aloesaponarin I; **50:**Aloesaponarin II; **51:**10-(chrysophanol-7'-yl)-10-(ξ)-hydroxychrysophanol-9-anthrone; **52:**Bazouanthrone; **53:**Glaberianthrone; **54:**Bianthrone 1ª; **55:**3-geranyloxyemodin anthrone; **56:**3-prenyloxyemodin anthrone; **57:**2-geranylemodin; **58:**Peperovulcanone A.
Source: Gomes ARQ et al., (2021).

4. Conclusion

Quinones are promising as an antimalarial, however, there is a lack of in vivo studies for compounds belonging to the benzoquinone, anthraquinone and anthrax classes. *In vitro* studies, carried out with resistant *P. falciparum* clones, suggest that compounds belonging to these classes are promising antimalarials.

Regarding naphthoquinones, the compound 2-acetylnaphtho- [2,3b] -furan-4,9-dione presented the highest activity against *Plasmodium berghei*, and studies that aim to evaluate its safety should be prioritized. Without a doubt, the most studied naphthoquinone, promising as an antimalarial, is lapachol. For some biological activities, the lapachol ortho isomer (β-lapachone) is the most active and most cytotoxic form. In the present study, lapachol appears to be more promising than β-lapachone and α-lapachone.

The pharmacological therapies used to treat malaria are a source of free radicals to fight the parasite, since it is known that the *Plasmodium sp.* is highly sensitive to such molecules. Thus, studies on the generation of free radicals in the treatment and development of new drugs in malaria are necessary, especially those for the characterization and isolation of compounds from medicinal plants and their metabolites, both *in vitro* and *in vivo*.

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