Natural Resources for Human Health

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Review

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Received 21 October 2021
Revised 03 November 2021
Accepted 03 November 2021
Available online 10 November 2021

Edited by Si Mi

KEYWORDS:
Anopheles
Basidiomycete
Lanostane triterpenoid
Malaria
Mushrooms
Plasmodium falciparum

Natr Resour Human Health 2022; 2 (2): 129-141
https://doi.org/10.53365/nrfhh/143570
eISSN: 2583-1194

Mushrooms (Basidiomycetes) as a significant source of biologically active compounds for malaria control

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ABSTRACT: Mushrooms represent a large family of fleshy fungi that have been of high interest since ancient ages due to their medicinal and nutritional importance. Therefore, it can represent a significant source of bioactive compounds in malaria control. The few numbers of studies on *in vitro* antiplasmodial and insecticidal properties of their extracts and chemical constituents led to interesting results reported in numerous scientific publications. This review aims to provide a comprehensive compilation of literature up to 2021 on the antiplasmodial, insecticidal as well as cytotoxic chemical constituents of medicinal mushrooms that can help in the management of malaria both against the parasite *Plasmodium falciparum* and the mosquitoe *Anopheles stephensis* acting as a vector of malaria through its bites. For this purpose, some searches have been done in some online libraries using keywords like Basidiomycete, mushroom, malaria, Plasmodium, Anopheles and antiplasmodial without language restriction. Among the reported compounds, 51 selected ones displayed significant antiplasmodial potency with IC_{50} values lower than 10 μM against *P. falciparum* strains sensitive or resistant to chloroquine. For instance, ganoderic acid AW1 demonstrated a strong antiplasmodial activity with IC_{50} of 257.8 nM against *P. falciparum* D6, while strong activities were displayed by ganoweberianones A (IC_{50} = 0.050 μM) and B (IC_{50} = 0.46 μM) against *P. falciparum* K1. Moreover, some mushroom methanol extracts demonstrated good larvicidal and ovicidal activities against Anopheles stephensis. This paper provides further insights into the development of new antiplasmodial drugs or new potent eco-friendly pesticides to control mosquito vectors.

1. INTRODUCTION

Malaria is classified among the most harmful parasitic diseases that threaten the world population in tropical and subtropical regions (Nasomjai et al., 2014) . It is caused by one of the five *Plasmodium* species including *P. falciparum*, *P. ovale*, *P. malariae*, *P. knowlesi* and *P. vivax*, transmitted by the bites of the mosquitoes female *Anopheles* (Happi et al., 2015). In 2015, the World Health Organization (WHO) reports that a total of 214 million cases and 438 000 deaths were globally recorded due to malaria (WHO, 2015) . The parasite *P. falciparum* represents the most virulent species that causes the most severe forms of the disease and the greatest number of deaths (80% worldwide) with children and expectant mothers as the most vulnerable persons leading to high mortality if not taken in charge quickly (Júnior et al., 2012; Ogbole et al., 2018). During the last decades, after the discovery of artemisinin and quinine from the medicinal plants *Artemia annua* and *Cinchona succirubra*, respectively, the journey in fighting and controlling malaria has faced several challenges mostly attributed to the resistance of *P. falciparum* to the administrated potent antimalarial drugs such as chloroquine, mefloquine and artemisinin-based combination therapies (Ma et al., 2015; Nasomjai et al., 2014; Ogbole et al., 2018). This observation of resistance and the significant number of death annually keep continuous the urgent need for new chemotherapeutic compounds to address the current situation of drug resistance (Bathurst & Hentschel, 2006). Other non-neglected resistances were observed by the vector mosquitoes to insecticides (Happi et al., 2015), while several recent chemical investigations have been done to develop new insecticides from bioactive extracts or the natural products obtained from flora and fauna that could help to control larvae,

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adult mosquitoes and which can be effective, eco-friendly, and biodegradable (Benelli, 2015).

For several centuries, mushrooms have been appreciated for nutritional and medicinal purposes and constitute good sources of bioactive extracts and specialized metabolites (Annang et al., 2018). It is documented that medicinal mushrooms possess more than 100 medicinal functions and among them, *Ganoderma* is a genus of bracket fungi that is widely used in Chinese herbal medicine for the treatment of several illnesses (Annang et al., 2018). Furthermore, mushrooms are also renowned for their uses in the food industry as dietary foods or in agriculture as pesticides, herbicides and insecticides (Ogbole et al., 2018). Basidiomycetes, especially mushrooms, are a good source of diverse specialized metabolites with a large scale of biological activities including antimalarial properties (Isaka et al., 2011; Lakornwong et al., 2014). For instance, the extract of *Ganoderma lucidum* exhibited antimalarial activity (Ma et al., 2014; Oluba et al., 2012), and the antimalarial properties of *Cordyceps* species and *Bulgaria inquinans* have been also reported (Isaka et al., 2001). Despite the relevant and interesting data reported on the antimalarial potencies of extracts and compounds of some mushrooms, to the best of our knowledge, very few works have been done on their insecticidal activities while no review article has been published on the phytochemistry and pharmacology of mushrooms concerning their contribution in fighting against malaria as a source of antiplasmodial and insecticidal agents. This review covers the documented works up to 2021.

2. ANTIPLASMODIAL CONSTITUENTS OF MUSHROOMS

It is well reported that mushrooms represent an important source of bioactive secondary metabolites possessing antiplasmodial, antimicrobial, antitumoral, antioxidant or nematocidal potencies (Badalyan, 2004; Morrison et al., 2002; Zang et al., 2013; Zengin et al., 2016). More specifically, *Ganoderma* is one of the most investigated and used mushroom genus in Chinese herbal medicine (Paterson, 2006) . Previous pharmacological investigations on the identification of antiplasmodial extracts, fractions and compounds from mushrooms led to the report of interesting results that classified some mushroom extracts as promising references in new antimalarial drugs discovery. For instance, the ethyl acetate soluble extract of *Ganoderma lucidum* revealed antiplasmodial activity with 79% inhibition at 4.9 μg/ml (Adams et al., 2010), while the methanol and dichloromethane soluble extracts of *Phellinus linteus* showed activity with IC_{50} values of 3.15 and 3.08 μg/ml, respectively, against *P. falciparum* K1 (Samchai et al., 2009). In the same way, the literature survey indicated that the extracts of *H. fuscum* contain antiplasmodial compounds which support the potencies revealed by these extracts against the strains D6 and W2 of *P. falciparum* with IC_{50} values of 6.98 and 8.33 μg/ml, respectively (Ogbole et al., 2018). Moreover, the antiplasmodial screening of the *n*-hexane extract of the fruiting bodies of *Pleurotus ostreatus* revealed that the extract inhibited *in vitro Plasmodium* parasite lactate dehydrogenase with an IC_{50} of 25.18 μg/ml but remained less active than the standard drug chloroquine diphosphate (IC_{50} = 0.016 μg/ml) (Afieroho et al., 2019).

Numerous chemical investigations have been conducted on different mushroom species to identify and characterize their antiplasmodial constituents present in their extracts. To date, forty-four compounds have been reported from eighteen species belonging to eleven genera (Table 1).

The great majority of reported specified metabolites are triterpenoids with various changes in their skeleton. The genus *Ganoderma* includes more than 200 species distributed throughout the world, is one of the most investigated genera among the mushrooms from which numerous (over 200) lanostane-type triterpenoids with a large scale of structural diversity and large scale of biological activities are reported in the literature (Paterson, 2006) . The literature survey shows that twenty-nine compounds with relevant antiplasmodial activity documented have been reported from eight *Ganoderma* species (Figure 1 and 2).

Recently in 2020, Isaka and co-workers reported the isolation of two triterpenoids namely (24E)-3-oxo-7α,15α,26-trihydroxylanosta-8,24-diene (**1**) and (24E)-7α,26-dihydroxy-3-oxo-lanosta-8,24-diene (**2**) from *Ganoderma casuarinicola* with moderate antiplasmodial activity against *P. falciparum* K1 with IC_{50} values of 9.2 μg/ml and 9.7 μg/ml, respectively (Isaka, Chinthanom, Rachtawee, et al., 2020). Further triterpenoids with effect detected against the parasite *P. falciparum* K1 have been reported from the HPLC-based activity profiling and subsequent isolation of the antiplasmodial compounds of *G. lucidum* by Adams et al. (2010). From this previous work, ganoderic aldehyde TR (**3**) was the most potent with an IC_{50} value of 6 μM, while the chemical investigations of *Ganoderma colossus* led to the isolation of five antiplasmodial triterpenoids with moderate potency against the same strain K1 of *P. falciparum*. Briefly, the most active among them were ganocolossusin D (**4**) with an IC_{50} of 1.4 μg/ml, followed by ganodermalactone V (**5**), ganodermalactone T (**6**), ganocolossusin C (**7**) and ganocolossusin G (**8**) with IC_{50} values of 3.6 μg/ml, 5.0 μg/ml, 5.8 μg/ml and 8.2 μg/ml, respectively (Isaka, Chinthanom, Choeyklin, et al., 2020) .

The obtained results chemically demonstrated that the genus *Ganoderma* is close to the genus *Tomophagus* based on the similarity of isolated compounds and further supported the taxonomy of *Ganoderma colossus* as a synonym of *Tomophagus colossus* (Isaka, Chinthanom, Choeyklin, et al., 2020). Therefore, fifty compounds have been isolated from fruiting bodies *Tomophagus* sp. After their evaluation against *P. falciparum* K1, only eight compounds (**9**– **16**) have demonstrated significant or moderate activity. Especially, colossolactone VIII (**9**), ganodermalactones D, O–Q (**10**, **11**– **13**), tomophagusins B and D (**14** and **15**) showed activity with IC_{50} values <10 μM, ranging from 5.1 to 8.1 μM, while 11-oxo-colossolactone E (**16**) demonstrated potency with IC_{50} value of 10 μM (Isaka et al., 2019).

Table 1
Antiplasmodial compounds from mushrooms.

N°	Name of compound	Strain, IC_{50}	Source	
1	(24E)-3-oxo-7α,15α,26-trihydroxylanosta-8,24-diene	K1, 9.2 μg/ml	*Ganoderma casuarinicola*	Isaka, Chinthanom, Rachtawee, et al. (2020)
2	(24E)-7α,26-dihydroxy-3-oxo-lanosta-8,24-diene	K1, 9.7 μg/ml	*Ganoderma casuarinicola*	Isaka, Chinthanom, Rachtawee, et al. (2020)
3	Ganoderic aldehyde TR	K1, 6 μM	*Ganoderma lucidum*	Adams et al. (2010)
4	Ganocolossusin D	K1, 2.4 μM	*Ganoderma colossus*	Isaka, Chinthanom, Choeyklin, et al. (2020)
5	Ganodermalactone V	K1, 3.6 μg/ml	*Ganoderma colossus*	Isaka, Chinthanom, Choeyklin, et al. (2020)
6	Ganodermalactone T	K1, 5.0 μg/ml	*Ganoderma colossus*	Isaka, Chinthanom, Choeyklin, et al. (2020)
7	Ganocolossusin C	K1, 5.8 μg/ml	*Ganoderma colossus*	Isaka, Chinthanom, Choeyklin, et al. (2020)
8	Ganocolossusin G	K1, 8.2 μg/ml	*Ganoderma colossus*	Isaka, Chinthanom, Choeyklin, et al. (2020)
9	Colossolactone VIII	K1, 7.0 μM	*Tomophagus* sp.	Isaka et al. (2019)
10	Ganodermalactone D	K1, 6.3 μM	*Tomophagus* sp.	Isaka et al. (2019)
11	Ganodermalactone O	K1, 5.5 μM	*Tomophagus* sp.	Isaka et al. (2019)
12	Ganodermalactone P	K1, 8.1 μM	*Tomophagus* sp.	Isaka et al. (2019)
13	Ganodermalactone Q	K1, 6.6 μM	*Tomophagus* sp.	Isaka et al. (2019)
14	Tomophagusin B	K1, 7.7 μM	*Tomophagus* sp.	Isaka et al. (2019)
15	Tomophagusin D	K1, 5.1 μM	*Tomophagus* sp.	Isaka et al. (2019)
16	11-oxo-colossolactone E	K1, 10 μM	*Tomophagus* sp.	Isaka et al. (2019)
17	Ganoweberianone A	K1, 0.050 μM	*Ganoderma weberianum*	Isaka, Chinthanom, Vichai, et al. (2020)
18	Ganoweberianone B	K1, 0.46 μM	*Ganoderma weberianum*	Isaka, Chinthanom, Vichai, et al. (2020)
19	Ganoderic acid AW1	D6, 257.8 nM W2, 2000 nM	*Ganoderma* sp.	Wahba et al. (2019)
20	(24S)-24-hydroxy-3-oxo-lanosta-7,9(11),25-triene	K1, 6.3 μg/ml	*Ganoderma* sp. BCC 21329	Isaka, Sappan, et al. (2020)
21	(24S)-7α,24-dihydroxy-3-oxo-lanosta-8,25-diene	K1, 7.6 μg/ml	Ganoderma sp. BCC 21329	Isaka, Sappan, et al. (2020)
22	(24S,25R)-7α,26-Dihydroxy-24,25-epoxy-3-oxolanost-8-ene	K1, 3.8 μg/ml	*Ganoderma* sp. BCC 21329	Isaka, Sappan, et al. (2020)
23	24,25-epoxy-3-oxo-lanosta-7,9(11)-diene	K1, 7.4 μg/ml	*Ganoderma* sp. BCC 21329	Isaka, Sappan, et al. (2020)

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Table 1 continued

24	Ganodermalactone F	K1, 10.0 μM	*Ganoderma* sp. KM01	Lakornwong et al. (2014)
25	Schisanlactone B	K1, 6.0 μM	*Ganoderma* sp. KM01	Lakornwong et al. (2014)
26	Ganoboninketal A	3D7, 4.0 μM	*Ganoderma boninense* Pat.	Ma et al. (2015, 2014)
27	Ganoboninketal B	3D7, 7.9 μM	Ganoderma boninense Pat.	Ma et al. (2014)
28	Ganoboninketal C	3D7, 1.7 μM	*Ganoderma boninense* Pat.	Ma et al. (2015, 2014)
		K1, 3.8 μg/ml	Semi-synthetic	Isaka, Chinthanoma, et al. (2017)
29	Ganoboninone F	3D7, 2.03 uM	*Ganoderma boninense*	Ma et al. (2015)
30	Astraeusin M	K1, 3.0 μg/ml	*Astraeus asiaticus*	Isaka, Palasarn, et al. (2017)
31	/	3D7, 4.21 μM	*Pleurotus ostreatus*	Annang et al. (2018)
32	/	3D7, 7.63 μM	*Pleurotus ostreatus*	Annang et al. (2018)
33	/	3D7, 1.65 μM	*Scleroderma areolatum*	Annang et al. (2018)
34	/	3D7, 6.78 μM	*Scleroderma areolatum*	Annang et al. (2018)
35	/	K1, 4.85 μM	Synthetic	Nasomjai et al. (2014)
36	/	K1, 4.48 μM	Synthetic	Nasomjai et al. (2014)
37	/	K1, 4.16 μM	Synthetic	Nasomjai et al. (2014)
38	/	K1, 4.46 μM	Synthetic	Nasomjai et al. (2014)
39	/	K1, 3.45 μM	Synthetic	Nasomjai et al. (2014)
40	/	K1, 3.23 μM	Synthetic	Nasomjai et al. (2014)
41	/	K1, 3.41 μM	Synthetic	Nasomjai et al. (2014)
42	Hitoyopodin A	3D7, 6.7 μM	*Coprinopsis cinerea*	Otaka et al. (2018)
43	Aurisin A	K1, 1.43 μM	*Anthracophyllum sp.* BCC18695	Intaraudom et al. (2013)
		K1, 0.80 μM	*Neonothopanus nambi*	Kanokmedhakul et al. (2012)
44	Aurisin K	K1, 0.69 μM	*Anthracophyllum sp.* BCC18695	Intaraudom et al. (2013)
		K1, 0.61 μM	*Neonothopanus nambi*	Kanokmedhakul et al. (2012)
45	Aurisin G	K1, 0.27 μM	*Anthracophyllum sp.* BCC18695	Intaraudom et al. (2013)
46	Sterostrein A	K1, 2.3 μg/ml	*Stereum ostrea* BCC 22955	Isaka et al. (2011)
47	Chondrosterin B	K1, 3.10 μM	*Gloeostereum incarnatum* BCC41461	Bunbamrung et al. (2017)
48	Incarnatin A	K1, 9.80 μM	*Gloeostereum incarnatum* BCC41461	Bunbamrung et al. (2017)

Continued on next page

Table 1 continued

49	Incarnatin B	K1, 3.93 μM	*Gloeostereum incarnatum* BCC41461	Bunbamrung et al. (2017)
50	(−)-oudemansin X	K1, 1.19 μM	*Xerula sp.* BCC56836	Sadorn et al. (2016)
51	(−)-oudemansin A	K1, 9.23 μM	*Xerula sp.* BCC56836	Sadorn et al. (2016)

More interestingly, the artificially cultivated fruiting bodies of *Ganoderma weberianum* produced two lanostane dimers with strong antiplasmodial activity against *P. falciparum* K1. Indeed, ganoweberianone A (**17**) displayed a potency with IC_{50} value of 0.050 μM while ganoweberianone B (**18**) showed an IC_{50} value of 0.46 μM (Isaka, Chinthanom, Vichai, et al., 2020).

The chemical investigation of three incompletely identified *Ganoderma* species allowed the isolation and report of eight compounds that expressed an antiplasmodial activity:

Ganoderic acid AW1 (**19**) isolated from *Ganoderma* sp. revealed significant activity against *P. falciparum* D6 (IC_{50} of 257.8 nM) and *P. falciparum* W2 (IC_{50} of 2000 nM) (Wahba et al., 2019); the lanostane-type triterpenoids (24S)-24-hydroxy-3-oxo-lanosta-7,9(11),25-triene (**20**), (24S)-7α,24-dihydroxy-3-oxo-lanosta-8,25-diene (**21**), (24S,25R)-7α,26-dihydroxy-24,25-epoxy-3-oxolanosta-8-ene (**22**) and 24,25-epoxy-3-oxo-lanosta-7,9(11)-diene (**23**) isolated from *Ganoderma* sp. BCC 21329 displayed moderate activity with IC_{50} values ranging from 3.8 μg/ml to 7.6 μg/ml against *P. falciparum* K1 (Isaka, Sappan, et al., 2020); the two triterpenoids ganodermalactone F (**24**) and schisanlactone B (**25**) obtained from cultured biomass of the macrofungi Ganoderma sp. KM01 showed activity with IC_{50} values of 10.0 μM (for **24**) and 6.0 μM (for **25**) against *P. falciparum* K1 (Lakornwong et al., 2014) .

From the ethyl acetate extract of fruiting bodies of the medicinal mushroom *Ganoderma boninense*, three nortriterpenes named ganoboninketals A–C (**26**-**28**) containing rearranged 3,4-seco-27-norlanostane skeletons and highly complex polycyclic systems were isolated and showed moderate antiplasmodial activity against *P. falciparum* 3D7 with IC_{50} values of 4.0 μM, 7.9 μM and 1.7 μM, respectively (Ma et al., 2014). One year later, the same author reported the same potencies with the IC_{50} values of 4.04 μM, 7.88 μM and 1.72 μM against *P. falciparum* 3D7 for ganoboninketals A–C (**26**– **28**), respectively, isolated from *G. boninense* Pat (Ma et al., 2015). The compound ganoboninketal C (**28**) was prepared from methylation of ganoboninketal D isolated from the species *Ganoderma orbiforme* and was less active against *P. falciparum* K1 with an IC_{50} of 3.8 μg/ml equal to 6.8 μM (Isaka, Chinthanoma, et al., 2017). Furthermore, the chemical investigation of *G. boninense* gave another 3,4-seco-27-norlanostane triterpene ganoboninone F (**29**) displaying a significant activity with IC_{50} value of 2.03 μM against *P. falciparum* 3D7 (Ma et al., 2015).

Astraeusin M (**30**) from *Astraeus asiaticus* revealed an activity with IC_{50} of 3.0 μg/ml against *P. falciparum* K1 (Isaka, Palasarn, et al., 2017). Annang et al. (2018) carried out the bioassay-guided study of two mushrooms *Pleurotus ostreatus* and *Scleroderma areolatum* for searching their antiplasmodial constituents against *P. falciparum* 3D7. Two scalarane sesterterpenes **31** and **32** (Figure 3) isolated from the edible one *Pleurotus ostreatus* revealed effectiveness with IC_{50} values of 4.21 μM and 7.63 μM, respectively, while the triterpenes **33** and **34** obtained from *S. areolatum* showed potency with IC_{50} values of 1.65 μM and 6.78 μM, correspondingly. Additionnally, no cytotoxicity was observed for the four compounds **31**– **34** against HepG2 tumoral human liver cells.

The chemical modifications of astraodorol isolated as a major compound from the edible mushroom *Astraeus odoratus* led to the preparation of ten derivatives that were evaluated for their antiplasmodial activity. The seven triterpenes **35**– **41** exhibited strong antimalarial activity against *P. falciparum* K1 with IC_{50} values of 4.85, 4.48, 4.16, 4.46, 3.45, 3.23, and 3.41 μg/ml, respectively (Nasomjai et al., 2014) .

The aromatic sesquiterpenoids hitoyopodin A (**42**) (Figure 4) obtained from *Coprinopsis cinerea* showed potency with IC_{50} values of 6.7 μM against *P. falciparum* 3D7 (Otaka et al., 2018). The total synthesis of compound **42** was achieved and the synthetic compound was slightly more potent (IC_{50} of 6.2 μM) than the natural one (IC_{50} of 6.7 μM) against *P. falciparum* 3D7. Aurisins A (**43**) and K (**44**) (Figure 4) are dimeric sesquiterpenoids isolated from *Anthracophyllum* sp. BCC18695 (Intaraudom et al., 2013) and *Neonothopanus nambi* (Kanokmedhakul et al., 2012) were evaluated for their antiplasmodial potencies against *P. falciparum* K1. The results showed that aurisin A (**43**) from *Anthracophyllum* sp. BCC18695 exhibited moderate activity with IC_{50} of 1.43 μM (Intaraudom et al., 2013), while the activity was more significant for the one isolated from *N. nambi* with an IC_{50} of 0.80 μM (Kanokmedhakul et al., 2012). Aurisin K (**44**) displayed similar strong potency from both sources with IC_{50} of 0.69 μM (from *Anthracophyllum* sp. BCC18695) and 0.61 μM (from *N. nambi*), respectively (Intaraudom et al., 2013; Kanokmedhakul et al., 2012). A third dimeric sesquiterpenoid aurisin G (**45**) has been reported from *Anthracophyllum* sp. BCC18695 and exhibited a strong activity with IC_{50} value of 0.27 μM against *P. falciparum* K1 (Intaraudom et al., 2013).

From the cultures *Stereum ostrea* BCC 22955, the dimeric sesquiterpene sterostrein A (**46**) was isolated and exhibited antimalarial activity with IC_{50} of 2.3 μg/ml against *P. falciparum* K1 (Isaka et al., 2011). Among the compounds isolated from *Gloeostereum incarnatum* BCC41461 and tested for their antiplasmodial activity against *P. falciparum* K1, only chondrosterin B (**47**), incarnatins A and B (**48** and **49**) (Figure 5) demonstrated a moderate activity with IC_{50} values of 3.10 μM, 9.80 μM and 3.93 μM, respectively (Bunbamrung et al., 2017). The culture and chemical examination of *Xerula* sp. BCC56836 led to the isolation of (−)-oudemansin X (**50**) that showed significant activity with IC_{50} of 1.19 μM against *P. falciparum* K1, while (−)-oudemansin A (**51**) was found moderately active with IC_{50} value of 9.23 μM (Sadorn et al., 2016).

3. CYTOTOXICITY OF ANTIPLASMODIAL COMPOUNDS FROM MUSHROOMS

Along with the evaluation of their antiplasmodial potency, several reported metabolites from mushrooms have been tested for their cytotoxicity against cancerous and noncancerous cell lines (Table 2). Briefly, numerous specialized metabolites demonstrating a strong or moderate antiplasmodial activity

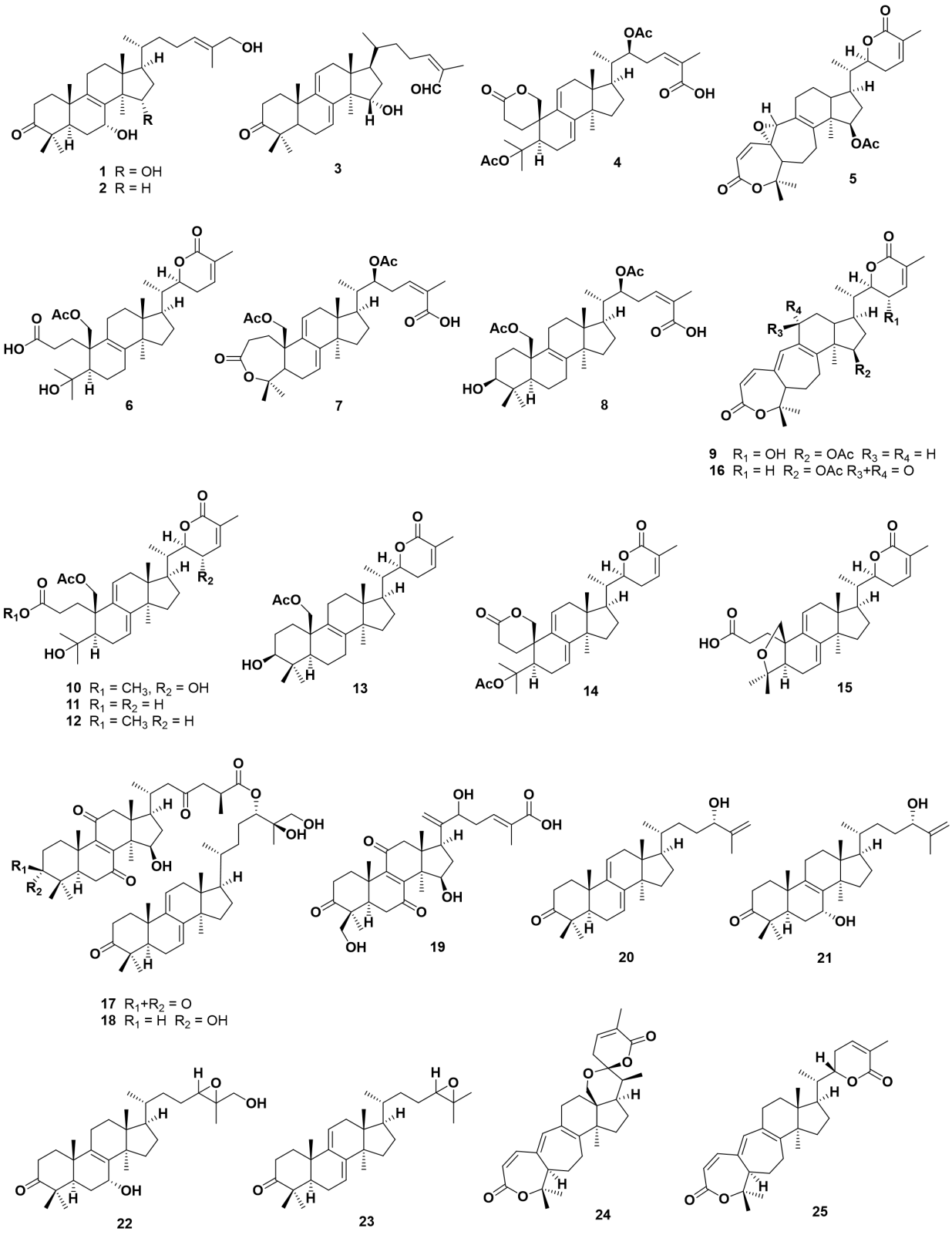

Figure 1. Antiplasmodial triterpenes from *Ganoderma* mushrooms

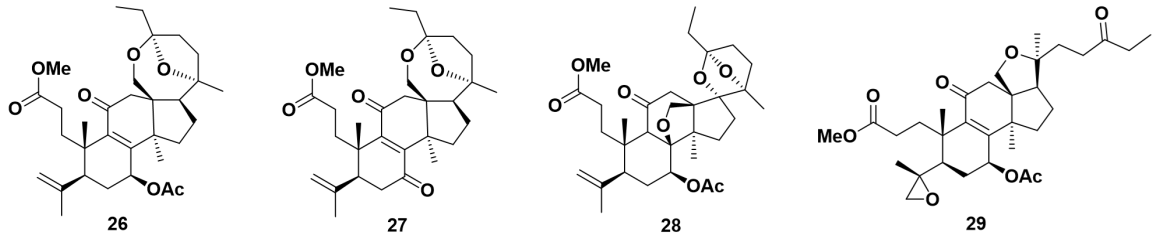

Figure 2. Antiplasmodial nortriterpenes from *Ganoderma* mushrooms

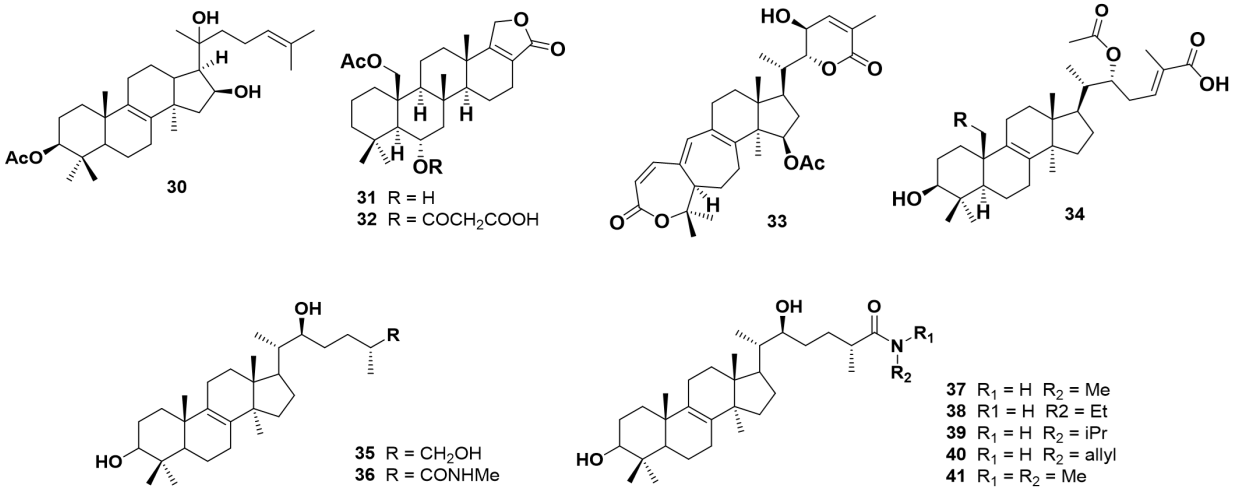

Figure 3. Additional antiplasmodial ses-(31,32) and triterpenes (30, 33-41) from mushrooms

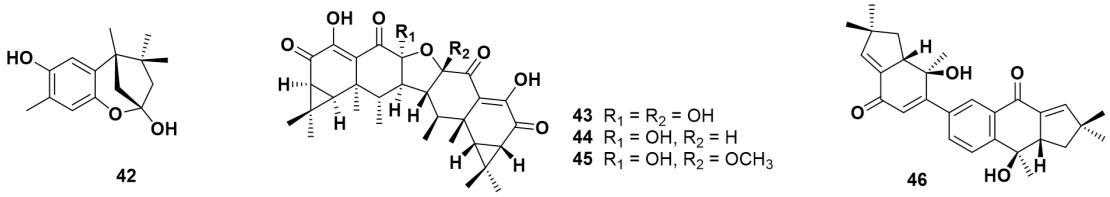

Figure 4. Antiplasmodial sesquiterpenoid and dimeric sesquiterpenoid from mushroom

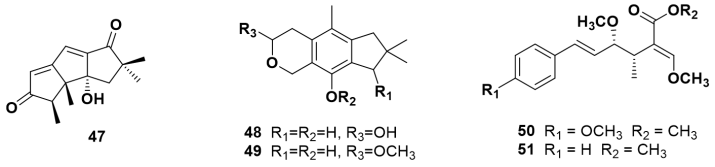

Figure 5. Other antiplasmodial compounds from mushrooms

were found inactive in cytotoxicity assay even at the highest concentration of 50 μM.

The isolated compounds from *Gloeostereum incarnatum* BCC41461 were assessed for cytotoxicity against MCF-7, KB, NCI-H187 and vero cells. Compound **47** demonstrated strong activity against cancerous cells (IC_{50} values of 0.63 μg/ml for NCI-H187, 2.05 μg/ml for KB and 4.98 μg/ml for MCF-7) and noncancerous cell vero (IC_{50} of 0.65 μg/ml) (Bunbamrung et al., 2017), but was reported in 2012 by Li and co-workers to be inactive against three cancer cell lines (human cancer cell A549, human nasopharyngeal carcinoma cell CNE2, and human colon cancer cell LoVo) with an IC_{50} value > 200 μM (Li et al., 2012). Moderate cytotoxicity was detected for compound **49** against the four same cell lines with IC_{50} values ranging from 18.86 μg/ml (for vero) to 29.76 μg/ml (for MCF-7), while compound **48** was inactive (IC_{50} > 50 μg/ml) against all the four cell lines (Bunbamrung et al., 2017).

Table 2
Cytotoxicity activity (IC_{50}) of some antiplasmodial agents from mushrooms.

N°	Name of compound	MCF-7	KB	NCI-H187	Vero	References
1	(24E)-3-oxo-7α,15α,26-trihydroxylanosta-8,24-diene	-	-	-	13.1 μg/ml	Isaka, Chinthanom, Rachtawee, et al. (2020)
2	(24E)-7α,26-dihydroxy-3-oxo-lanosta-8,24-diene	-	-	-	12.0 μg/ml	Isaka, Chinthanom, Rachtawee, et al. (2020)
5	Ganodermalactone V	-	-	-	8.5 μg/ml	Isaka, Chinthanom, Choeyklin, et al. (2020)
9	Colossolactone VIII	-	-	-	22 μM	Isaka et al. (2019)
10	Ganodermalactone D	-	-	-	32 μM	Isaka et al. (2019)
11	Ganodermalactone O	-	-	-	88 μM	Isaka et al. (2019)
12	Ganodermalactone P	-	-	-	32 μM	Isaka et al. (2019)
13	Ganodermalactone Q	-	-	-	34 μM	Isaka et al. (2019)
14	Tomophagusin B	-	-	-	38 μM	Isaka et al. (2019)
16	11-oxo-colossolactone E	-	-	-	92 μM	Isaka et al. (2019)
17	Ganoweberianone A	-	-	-	0.21 μM	Isaka, Chinthanom, Vichai, et al. (2020)
18	Ganoweberianone B	-	-	-	10 μM	Isaka, Chinthanom, Vichai, et al. (2020)
20	(24S)-24-hydroxy-3-oxo-lanosta-7,9(11),25-triene	-	-	-	18 μg/ml	Isaka, Sappan, et al. (2020)
21	(24S)-7α,24-dihydroxy-3-oxo-lanosta-8,25-diene	-	-	-	17 μg/ml	Isaka, Sappan, et al. (2020)
22	(24S,25R)-7α,26-Dihydroxy-24,25-epoxy-3-oxolanost-8-ene	-	-	-	28 μg/ml	Isaka, Sappan, et al. (2020)
23	24,25-epoxy-3-oxo-lanosta-7,9(11)-diene	-	-	-	34 μg/ml	Isaka, Sappan, et al. (2020)
37	/	-	-	23.36 μg/ml	-	Nasomjai et al. (2014)
38	/	-	-	34.28 μg/ml	-	Nasomjai et al. (2014)
39	/	49.60 μg/ml	16.94 μg/ml	9.84 μg/ml	26.48 μg/ml	Nasomjai et al. (2014)
43	Aurisin A	- -	2.50 μM 31.17 μM	0.86 μM 1.55 μM	30.52 μM	Intaraudom et al. (2013) Kanokmedhakul et al. (2012)
44	Aurisin K	-	2.06 μM 6.87 μM	18.93 μM 1.45 μM	55.23 μM	Intaraudom et al. (2013) Kanokmedhakul et al. (2012)
45	Aurisin G	-	1.64 μM	0.52 μM	-	Intaraudom et al. (2013)

Continued on next page

Table 2 continued

47	Chondrosterin B	4.98 μg/ml	2.05 μg/ml	0.63 μg/ml	0.65 μg/ml	Bunbamrung et al. (2017)
49	Incarnatin B	29.76 μg/ml	28.15 μg/ml	22.97 μg/ml	18.86 μg/ml	Bunbamrung et al. (2017)
50	(−)-oudemansin X	-	-	99.07 μM	85.90 μM	Sadorn et al. (2016)
51	(−)-oudemansin A	120.13 μM	160.18 μM	63.30 μM	26.73 μM	Sadorn et al. (2016)

In the same way, the cytotoxicity of aurisins A (**43**), G (**45**) and K (**44**) against the four previous cell lines were conducted and led to the observation that the three compounds were inactive against the MCF-7 cell lines, while the three compounds were less active against the noncancerous cell line vero with IC_{50} values above 30.52 μM, but displayed relevant activity against the KB cell line with potency recorded in term of IC_{50} values ranging from 1.64 μM to 2.50 μM. However, aurisins A (**43**) and G (**45**) isolated from *Anthracophyllum* sp. BCC18695 displayed strong activity against NCI-H187 with IC_{50} values of 0.86 μM and 0.52 μM, respectively (Intaraudom et al., 2013). However, compounds **43** and **44** obtained from *N. nambi* displayed good cytotoxicity against NCI-H187 cell lines with IC_{50} values of 1.55 μM and 1.45 μM, respectively (Kanokmedhakul et al., 2012).

Furthermore, aurisin A (**43**) showed cytotoxicity against BC1 cell lines (IC_{50} of 3.72 μM) and aurisins K (**44**) against KB cell lines (IC_{50} of 6.87 μM). Both compounds were not active against MCF-7 cell lines while compound **43** exerted strong cytotoxicity against cholangiocarcinoma cell lines KKU-100, KKU-139, KKU-156 and KKU-213 with IC_{50} values of 2.77 μM, 1.83 μM, 1.57 μM and 1.75 μM, respectively. At the same time, compound **44** gave a moderate activity against the cell lines KKU-139, KKU-156 and KKU-213 with IC_{50} values of 28.61, 7.63, and 20.90 μM, respectively (Kanokmedhakul et al., 2012).

Among the derivatives obtained from chemical modifications of lanostane-type triterpene astraodorol, compounds **37**– **39** possessed moderate cytotoxicity with IC_{50} values of 23.36, 34.28, and 9.84 μg/ml, respectively, against NCI-H187. Additionally, compound **39** was also active against KB cell line with IC_{50} of 16.94 μg/ml and displayed activity against MCF-7 cell line with IC_{50} value of 49.60 μg/ml (Nasomjai et al., 2014).

The compounds (−)-oudemansins A (**51**) and X (**50**) demonstrated low cytotoxicity against both cancerous (KB, MCF-7, NCI-H187) and non-cancerous (vero) cells (Sadorn et al., 2016) . Compounds **20**– **23** showed weak cytotoxicity to vero cells (African green monkey kidney fibroblasts) with IC_{50} values ranging from 17 μg/ml to 34 μg/ml (Isaka, Sappan, et al., 2020). The cytotoxicity of compounds **1** and **2** was evaluated against vero cells and led to the observation of significant cytotoxicity with IC_{50} values of 13.1 and 12.0 μg/ml, respectively (Isaka, Chinthanom, Rachtawee, et al., 2020). The triterpenoids ganoweberianones A (**17**) and B (**18**), presented important cytotoxicity against vero cell lines with IC_{50} values of 0.21 and 10 μM, respectively (Isaka, Chinthanom, Vichai, et al., 2020), while ganodermalactone V (**5**) showed a potency of IC_{50} equal to 8.5 μg/ml (Isaka, Chinthanom, Choeyklin, et al., 2020).

In cytotoxicity assay, ganoboninketals A (**26**) and C (**28**) demonstrated IC_{50} values of 47.6 μM and 35.8 μM, respectively, against the A549 cell line while ganoboninketal B (**27**) also showed weak potency (IC_{50} = 65.5 μM) against HeLa cell line (Ma et al., 2014).

4. INSECTICIDAL PROPERTIES OF MUSHROOM EXTRACTS

The challenge in the management of malaria is both at the curative level in fighting against *P. falciparum* as well as at the prevention level in mosquito control programs. In addition to the previous presented chemical and pharmacological works on the search for antiplasmodial extracts and compounds from mushrooms, few investigations have been done on the evaluation of their insecticidal activity. The works done by Sivanandhan et al. (2018) aimed to evaluate the mosquitocidal activity of 6 mushroom species including *Clitocybe rivulosa*, *Calocybe indica*, *Lentinus squarrosulus*, *Laetiporus sulphureus*, *Marasmius sullivantii* and *Marasmiellus candidus* on eggs and larvae of *Culex quinquefasciatus* and *Anopheles stephensi*.

Their results reported that the *Laetiporus sulphureus* methanol extract was the most active against mosquitoes with 96% larvicidal activity against *A. stephensi* (LC_{50} of 155.862 ppm and LC_{90} of 424.128 ppm) and 76% larvicidal activity against *C. quinquefasciatus* (LC_{50} of 227.225 ppm and LC_{90} of 1011.663 ppm). Furthermore, after 120 hours of treatment, at 500 ppm, that *L. sulphureus* methanol extract displayed significant ovicidal activity against *A. stephensi* eggs (100% activity) and *C. quinquefasciatus* eggs (91% activity).

Additionally, more recent investigations of the methanol extract of *Psathyrella candolleana* against *C. quinquefasciatus* and *Anopheles stephensi* showed good larvicidal activity with LC_{50} and LC_{90} values of 166.713 and 259.17 ppm, respectively, against the third instar larvae of *C. quinquefasciatus* after 24 hours of treatment, as well as 88% ovicidal activity against *C. quinquefasciatus* eggs at 500 ppm concentration 120 h after treatment (Sivanandhan et al., 2019).

These two works on the insecticidal activity of some mushroom extracts showed that the methanol extract of *L. sulphureus* is a good natural source for controlling mosquitoes like *A. stephensi* and *C. quinquefasciatus* while the methanol extract of *P. candolleana* could be used in the development of new eco-friendly insecticides to control *C. quinquefasciatus*. Therefore, mushrooms require more attention because they represent a non-negligible and unexplored source of bioactive extracts and compounds for the development of new insecticides to control the mosquitoes like *A. stephensi* which is the major vector of the malaria parasite *P. falciparum*.

5. CONCLUSION AND FUTURE PROSPECTS

The present review summarizes the previously-reported investigations on the chemistry and biological evaluations of compounds isolated from mushrooms for their antiplasmodial, cytotoxicity and insecticidal activities up to 2021. A total of forty-four distinct compounds including twenty-four lanostane-type triterpenoids as a major class of isolated compounds mostly from the genus *Ganoderma*, have been reported with significant antiplasmodial efficiency against two major strains K1 and 3D7 of *P. falciparum*. Among the tested compounds, some of them displayed very significant effectiveness against chloroquine-resistant strain *P. falciparum* K1, this includes ganoweberianones A (**17**) and B (**18**), ganoderic acid AW1 (**19**), as well as aurisins

A (**43**), K (**44**) and G (**45**). These compounds more specifically, represent promising data that deserve further investigations for new antiplasmodial drug discovery. Furthermore, the reported works on the insecticidal activities of some mushrooms extracts showed that some methanol extracts of mushroom species could contain significant insecticidal agents. However, several investigations as ADMET, chemical modifications of active compounds to increase their activity and decrease their toxicity, some pharmacokinetics or clinical trials could be done in the continuity. Since very few studies have been done on the search for antiplasmodial and insecticidal constituents from mushrooms, we expect that this review will be a significant summary to motivate and empower further investigations in this field to obtain new additional potent leads from mushrooms against *P. falciparum* and the mosquitoes *Anopheles*.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

This paper is part of the preliminary works of the DIPES II research project carried out by the graduating students of Second Cycle under the supervision of Gervais Mouthé Happi at the Department of Chemistry of the Higher Teacher Training College Bambili, The University of Bamenda. Livine Zemo Meikeu thanks the Department of Chemistry, Faculty of Sciences, University of Douala for the workplace in their laboratory during her research work. Jean Duplex Wansi also thanks the Alexander von Humboldt Foundation for the laboratory facilities.

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