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A Review on Natural Sources of Antimalarials: Fungi and Plants

Tehzeeb[1,*], Dhanabalan[2]
[1]Rathnavel Subramaniam College of Arts and Science, Sulur, Tamil Nadu, INDIA.
[2]Department of Microbiology, Rathnavel Subramaniam College of Arts and Science, Sulur, Tamil Nadu, INDIA.

ABSTRACT
Recent progress in drug discovery in past decades reduced the high level of pain experienced due to infectious diseases by humans. A significant impact has been made on developing novel antimicrobial agents but is failing regularly due to development of resistance to drugs by the parasite or microbe. A continuing need of antimicrobials is there to protect humans from resistant microbes from different sources such as semisynthetic sources, synthetic and natural sources. Research in developing natural antimicrobials such as plant and fungal sources is still in its initial stages. In this review, we have concentrated on devastating disease malaria which is seen in several parts of world. Even though there are newly developed antimalarial artemisinin based combination therapy, recent reports are suggesting that resistance may also develop soon against the newer artemesinin products. Our search for literature and survey for natural antimicrobials motivated us to give concern to fungal source as promising antimalarial and most unexplored source for the same. This review throws light on recent reports on disease malaria, causative species and outline of its lifecycle, targets of drug action and mainly the fungal sources of antimalarial.

Key words: Natural antimicrobials, Plants, Fungi, Secondary metabolites, Microbial resistance, Malaria and antimalarial.

Correspondence

Mrs. Tehzeeb
Research Scholar, RVS College of Arts and Sciences, Sulur-641402, Tamil Nadu, INDIA.
Phone no: +919384769722
Email: tahirisha1011@gmail.com

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INTRODUCTION

Diseases in humans are majorly two types - Metabolic and Infectious diseases. The major type of disease is infectious, caused due to microbes such as bacteria, fungi, viruses and protozoan parasites. Among the parasites or microbes bacteria accounts for major part of infectious disease. Millions of people are affected due to these infectious diseases. Affected people include mainly the poor people in developing countries due to unhygienic conditions. Diseases among poor may contribute to prolonged illness caused due to drug resistant pathogen.[1] Pathogens faced by humans are resistant to even at least one of existing antimicrobial agent. The steady increase in evolution of drug resistant pathogen annually has been a cause of continuous demand for the development of novel effective antimicrobial drugs.[2]

Drugs developed against infectious disease have been developed as synthetic products and natural products in origin. Antimicrobial agents derived from microbes generally causes from fungi are secondary metabolites. Fungi represent one of the largest group of living world distributed across the length and breadth of the world.

Antimicrobial drugs are available in high quantity from natural products rather than from synthetic products. Natural antimicrobials forms two thirds of prevailing antibiotics and also forms half of drugs used in the treatment of cancer.[3] Diversity of molecules synthesized by fungi is more and are therapeutically useful chunk of natural antimicrobials. Most important use of fungi includes production of antimicrobial substances such as secondary metabolites which are inhibitory or deleterious to other microbes. They are used to treat diseases caused due to microbes by varied mechanisms of actions and with a high degree of specificity to target sites of pathogens. Mechanism of antimicrobial action of secondary metabolites from fungi includes cell wall synthesis inhibition – Vancomycin, Bacitracin and Penicillin, disruption of cell membrane- Polymyxin B and Colistin, Protein synthesis- Tetracycline's, aminoglycosides etc.

SECONDARY METABOLITES

These are small molecules which are organic in nature and are not essential for growth and development of the organism. They have ability to inhibit other living organisms by mechanism such as competition, self-defense and antagonism to occupy the later's niche and consume its food. Many secondary metabolites from fungi are produced by plant endophytic and pathogenic fungi which exhibit broad spectrum activity with some of them with high microbial activity against human pathogens. Even marine fungi are explored for isolation of antibiotics even though they are underrepresented resource of available natural products.[4]

History of bioactive secondary metabolites from fungi

Beneficial properties of ergot have not been recognized due to ill-fated incidents such as ergotism epidemic in 944 -1000AD in which half of the population of Aquitaine of France died.[5,6] First medical use of ergot for quickening child birth was in 1582. This has paved the way in the synthesis of LSD which has again got undermined because the compound has been used as an illicit recreational drug due to its hallucinogenic properties.[7] At present, ergot alkaloids obtained from *Claviceps purpurea* gave lead to many semisynthetic derivatives for their wide range of therapeutic benefits in treatment of cancer, parkinson's disease and for its synergistic antimicrobial activities.

The identification of penicillin, the first antibiotic isolated from *Penicillium notatum* discovered by Alexander Fleming. This was milestone and breakthrough in drug discovery.[8] The discovery and development of penicillin changed the quality of human life by paving a way for discovery of plethora of antibacterial compounds of which majority were isolated from *Saccharomyces* and *Actinomycetes*.[9]

Ongoing discovery of natural antimicrobials faced an obstacle due to rise of multidrug resistant pathogens. Antimicrobial resistance has

developed due to green revolution during (1950-1970) which is based on chemicals to control pathogens in plant and animal production.[10] This indirectly created a constant need for discovery of newer antibiotics in cost effective manner. Production of natural antimicrobials is only option before scientists to produce them in cost effective way within less time. This can be done only when micro-organisms like fungi are selected.

MALARIA PARASITE AND PLASMODIUM

Malaria is still serious threat to human society in various parts of tropics and subtropics. Aneskmate in 2016 tells that about 216 million malaria cases and deaths for about 445,000 occurred around the world.[11] WHO has stated that resistance has already developed against the available antimalarial drug and mosquito vectors have become resistant to insecticides across the regions specified in WHO.[11]

The most affected population belong to tropical and subtropical regions of world especially the southeast Asia and sub Saharan Africa where 80% of malaria positive causes are due to *Plasmodium falciparum*.[12] WHO report 2015 stated that more than 214 million of new cases were registered with about 4,38,000 deaths even after deployment of efforts to control it by providing access to preventive and curative measures.[13]

Researchers stated that eradication strategies which once were effective are also unsuccessful primarily due to complex life cycle of plasmodium and the emergence of drug resistant strains of it.[14] Antimalarial drugs will benefit the therapy of malaria if they are with diverse mechanisms of action and if used in combination can decrease the drug resistance. This can only be achieved by rigorous search for novel antimalarial.

Novel effective and affordable treatments against malaria can be obtained from natural products. Clardy and Walsh (2004) stated that natural products have better chances of becoming effective drugs than de novo designed and chemically synthesized molecules.[15] This can explained by the fact that – molecules produced by living organisms are the products formed as a result of long periods of biological evolution during which they have been exposed biological milieu such as proteins, nucleic acids and bio membranes.

Malarial parasite and its life cycle

Plasmodium species causes malaria. It is a digenetic parasite where it completes its life cycle in two hosts. Primary host is humans where asexual reproduction occurs and secondary host is female anopheles mosquito in which sexual reproduction. There are four species of malaria basically causing different types of malaria.

S.No	Species of Plasmodium	Type of Malaria	Fever relapse after every
1.	*P. vivax*	Benign tertian malaria	3rd day
2.	*P. ovale*	Mild tertian malaria	3rd day
3.	*P. malariae*	Quartan malaria	4th day
4.	*P. falciparum*	Malignant tertian malaria	3rd day

Identification of targets of drug action is an important step for treating any infectious disease. Similarly a close observation of life cycle of any parasite will throw light on discovery of drugs which can target specific step in its life cycle. Life cycle of malaria parasite can be easily understood from the bite of female anopheles mosquito to healthy human. Plasmodium shuffles between hosts (humans) through the mosquito (female anopheles).[16] Upon the bite of female anopheles mosquito, the mosquito sporozoites from the mosquito are released into human's blood. Sporozoite after setting in hepatocytes undergo schizogony and eventually forms merozoites.[17]

Merozoites of hepatic cycle infect the RBC and pass through different stages such as signet-ring stage, amoeboid stage and eventually transforms into erythrocytic schizont just before the bursting of RBC. Released merozoites from this stage again attack a new RBC and the cycle continues until there is no availability of fresh RBC.[18] Few of the merozoites in this repeating cycle will form gametocytes which continue to circulate within the blood stream until there is bite of female anopheles mosquito for a blood meal. Release of haemozoin into blood during erythrocytic cycle causes fever and relapse for every 24-72 hr of time based on the type of malarial parasite.

Even though the best antimicrobial drug is one which can target stages of hepatic, erythrocytic and gametocyte stages, most of the currently available antimalarial are targeting the stages of erythrocytic cycle.[19] As there is no complete eradication of malaria from the world, the parasite keeps on evolving by developing resistance to broadly used antimalarial. This has created requirement for novel antimalarial. Search for antimalarial lead compounds from natural resources may give unique options of molecules particularly the fungi

DISCUSSION

Molecular diversity in biosynthetic pathways in fungi makes it an excellent source of antimalarial lead compounds which has a power to alter biological process.[20] Fungi represents one fourth of all recognized bioactive products and exhibit a source for the search of diverse compounds with wide spectrum of activities such as antileishmanial, antibacterial, anticancer and antimalarial.[21]

Natural products are a consistent source for developing antimalarial drugs which is best explained by quinine and artemesisnin from medicinal plants. Microbes are another group of living organisms which are highly diverse. Unfortunately, studies on microbes revealed that only 1% of bacteria and 5% of fungi have been characterized and the remaining microbes are unexplored for their potential to generate new drugs against many diseases.[22]

In this review, we have included many reprints on antimalarial from different sources such as- marine fungi, endophytic fungi and works on the extracts of plants for antimalarial principles. Following are excerpts of molecules isolated/studied from fungi and plants for antimalarial drug screening.

S. No	Source	Compound or Nucleus or extract studied	Antimicrobial activity	Reference
1	*Neosartorya spinosa*	indole-quinazoline alkaloid tryptoquivaline	Activity against Plasmodium species	22
2	*Septoria pistaciarum*	alkaloid 111; 1,4-dihydroxy-5-phenyl-2-pyridinone skeleton	Activity against *Plasmodium falciparum*	23
3	*Pyrenochaetopsis* sp.	decalin-tetramic acid metabolite phomasetin (155)	Activity against *Plasmodium falciparum*	24
4	*Penicillium copticola* PSURSPG138	eremophilane sesquiterpenoids porogen	Activity against *Plasmodium falciparum*	25
5	*Phomopsis archeri*	aromatic sesquiterpenephomoarcherin B (172)	antiplasmodial activity	26

6	*Penicillium* sp. FKI-4410 (*Penicillium viticola* sp. nov) fungus	puberulic acid (352) and a new derivative viticolin B (353)	Activity against P. berghei-infected mice	27
7	*Favolaschia tonkinensis*	β-methoxyacrylate derivatives, 9-methoxystrobilurins A, B and G (357–359) and oudemansin B (360)	Activity against *Plasmodium falciparum* strain	28
8	*Torrubiella* sp. BCC 28517 (leafhopper pathogenic fungus)	dimericanthraquinone, torrubiellin B (392)	Antiplasmodial activity	29
9	*Mycosphaerella* sp. F2140	Compound 405 (cercosporin analogue)		30,31
10	*Chaetomium longirostre.*	azaphilones, longirostrerone A (411) and C (412)		32
11	*Annona muricata* L.	Ethyl acetate extract	chloroquine-sensitive Pf3D7, chloroquine-resistant PfINDO and PfDd2 strains of *P. falciparum*	33
12	*Symphonia globulifera*	ethyl acetate extract	against the chloroquine-resistant *P. falciparum* INDO (PfINDO) strain	34
13	*Ganoderma lucidum*	50% ethanol	survival rate of mice infected with P. berghei and the inhibition of the parasite growth	35
14	*Nemania* sp. (Xylariaceae)	EtOAc extract	against chloroquine-sensitive (D6) and chloroquine-resistant (W2) strains of P. falciparum	36
15	*Diaporthemiriciae* Endophytic fungi	epoxycytochalasin H (419)	antiplasmodial activity	37
16	*Paecilomyces* sp. SC0924	β-resorcylic acid lactones (RALs, Fig. 57) paecilomycins A (434), E (435), F (436), together with aigilomycin B (437) and aigialomycin F (438	Antimalarial activity	38
17	Fusarium sp an root endophytic fungi on *Mentha longifolia*	Cyclodepsipeptide 3-hydroxy-4-methylpentadecanoic acid moiety, fusaripeptide A (446)	Antimalarial activity	39
18	*Fusarium fujikuroi* Plant source	cyclic tetrapeptide, apicidin F (450),	Antimalarial activity	40
19	*Ancistrocladus ileboensis*	Dioncophyllines	*Plasmodium falciparum*	41
20	*Ancistrocladus tectorius*	Ancistrobenomines B&C	*Plasmodium falciparum* and *Trypanosoma brucei rhodesiense*	42
21	*Ancistrocladus tectorius*	shuangancistrotectorines	antiplasmodial activity	43
22	Cassia siamea	cassiarins G, H, J and K	antiplasmodial activity	44
23	*Dehaasia longipedicellata*	morphinandienones, (+)-sebiferine, (-)-milonine; aporphines, (-)-boldine, (-)-norboldine;benzyl isoquinoline, (-)-reticuline; and bisbenzylisoquinoline, (-)-O-O-dimethylgrisabine	*Plasmodium falciparum*	45
24	*Stephania venosa*	Stephanine, aporphine and one tetrahydroprotoberberine	antiplasmodial activity, Anticancer activity	46
25	*Stephania rotunda*	cepharanthine	antiplasmodial activity	47
26	*Cryptocary anigra*	(+)-N-methylisococlaurine, atherosperminine, 2-hydroxy atherspermine and noratherosperminine	antiplasmodial activity	48
27	*Ficus septica*	seco-phenanthroindolizine phenanthroindolizine	*Plasmodium falciparum*	49
28	*Zanthoxylum heitzii*	dihydronitidine, pellitorine and heitziquinone.	anti-malarials	50
29	*Geissospermum vellosii*	geissolosimine, geissospermine, geissoschizoline and vellosiminol	anti-malarials	51

30	*Aspidosperma excelsum* (stem bark)	Ethanolic extract	chloroquineresistant *P. falciparum* (W2 strain) and HepG2 cells,	52
31	*Aspidosperma pyrifolium* stem bark, roots and leaves	95% ethanol in a Soxhlet apparatus for 72 h and then partitioned with different solvents and acidified water to obtain an alkaloid- enriched extract	Activity against P. berghei	53
32	*Periploca linearifolia* stem bark	maceration in 80% methanol for 72 h	Antiplasmodial	54
33	*Aloe megalacantha* Baker leaves	chloroform/ methanol (4:1)	Antimalarial activity	55
34	*Vernonia amygdalina* Del.	80% methanol extract of the leaves	parasitemia suppression	56
35	*Artemisia nilagirica* (Clarke) Pamp.	n-hexane, chloroform, petroleum ether, ethanol, methanol and distilled water	Activity against *Plasmodium falciparum*	57,58
36	*Artemisia afra*	acetone	inhibits the viability of primarily late-stage gametocytes of *Plasmodium falciparum* (NF54 strain)	59
37	*Erigeron floribundus* (Kunth) Schultz-Bip Entire plant	ethanol/water (70:30)	Parasitemia supression	60
38	*Echinops kebericho Mesfin* Fresh rhizomes	70% methanol	parasitemia suppressive effects against the chloroquine- sensitive P. berghei strain ANKA	61
39	*Adansonia digitata* L. Stem bark	water or methanol	Plasmodium berghei	62
40	*Commiphora africana* Stem bark and whole stem	dichloromethane and methanol in a 1:1 ratio (v/v)	antiplasmodial activity against D6 strain of *P. falciparum*	63
41	*Dichrostachys cinerea* Stem bark and whole stem	dichloromethane and methanol in a 1:1 ratio (v/v)	activity against both D6 and Dd2 strains of *P. falciparum*	63
42	*Azadirachta indica A. juss* Neem oil characterized by the ECOCERT certificate (Biocert Italia IT013BC041– ICEA 264 BC001)	Neem oil	against W2, chloroquine (CQ)-resistant and D10, chloroquinesensitive, strains of *P. falciparum*	64
43	*Curarea toxicofera* (Wedd) Barneby and Krukoff	Decoction of plant fresh bark in boiling water for 30 min	*In vitro* antiplasmodial activity was evaluated on *P. falciparum* FCR3 chloroquine-resistant strain	65
44	*Keetia leucantha* and *Keetia venosa* Dried and ground twigs and leaves	dichloromethane	Antimalarial activity	66

CONCLUSION

The present review focused on antimalarial properties of natural products isolated from fungi. In present scenario, studies on isolation of fungal metabolite are more focused on marine fungi and endophytic fungi underestimating the potential of standard strains of pathogenic fungi. Considering large diversity of fungal species, only very few fungi have been studied and cultivated. This may account only to the surface of diverse world of fungi.

Vast majority of natural products with antimalarial potential remain yet to be identified. Fungi irrespective of its pathogenicity may produce highly potent and widely accepted natural metabolites if properly cultured at optimum environmental conditions. Using the existing information and most widely use target of plasmodium, we have selected a standard strain of fungi such as *Malassezia furfur* by cultivating it at different environmental conditions in a hope of finding potent antimalarial compounds.

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