PLANT DERIVED ANTIMALARIAL AGENTS: NEW LEADS AND EFFICIENT PHYTOMEDICINES

Mukta Gupta[a,b]*, Naresh Singh Gill[c]

[a]School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India

[b]Department of Pharmaceutical Sciences, I. K. Gujral Punjab Technical University, Kapurthala, Punjab, India

[c]Rayat Institute of Pharmacy, Railmajra, SBS Nagar, Punjab, India

ABSTRACT

Malaria is a disease caused by parasite i.e. female anopheles Plasmodium falciparum and is the major cause of death worldwide. Current therapy for treatment of malaria includes 4-aminoquinolines (chloroquine, amodiaquine); 8-aminoquinones (primaquine, tafenoquine); 4-methanolquinolines (mefloquine); antifolates (pyrimethamine); naphthoquinone (atovaquone); non-antifolate antibiotics (clindamycin, doxycycline, azithromycin, fosmidomycin).[11] All pharmacological agents used for malaria treatment possess many demerits and also lack specificity. Approximately 80 percent of the world's population depends on herbal remedies because of more safety and less disadvantages reported by the World Health Organization (WHO). Some of the important natural products reported to possess ant malarial activity includes *Cinchona zeylenicum, Artemesia annua, Clerodendrum viscosumm, Cymbopogen citrates, Glycyrrhiza glabra, Capsicum frutescence and Azadiracchita indica.* In present date, many researches are performed on medicinal, herbal and natural products globally for the treatment and prevention of malaria. Although a number of herbal medicines are recommended for malaria, further research is required investigate their safety, efficacy, and potential drug interactions.

Keywords: Malaria; Herbal products; Plasmodium falciparum.

INTRODUCTION

Malaria parasite is a disease caused by parasite of genus plasmodium and is the major cause of death worldwide.[1] The plasmodium species which causes malaria includes P. falciparum, P.vivax, P.ovale, P.malarie, among which P.falciparum is the most common cause of malaria (about 66%) which is followed by P.vivax (34%).[2]

Female Anopheles mosquito is vector which inject sporozoites in the blood stream which invade and replicate in liver with life span of 5-6 days.[1]Plasmodium parasites undergo asexual replication forming mature schizonts whose rupture and releases merozoites that invade new erythrocytes. Some of the parasite

differentiates in to male and female gametocytes which produce gametes[3],[4]. Gamete fuses to produce zygote which develops in to motile ookinete which transform into oocyst and produces thousands of sporozoites. The life cycle is closed when sporozoites, migrated from the ruptured oocyst to the mosquito salivary glands, are injected in a new human host by the insect bite.[5]

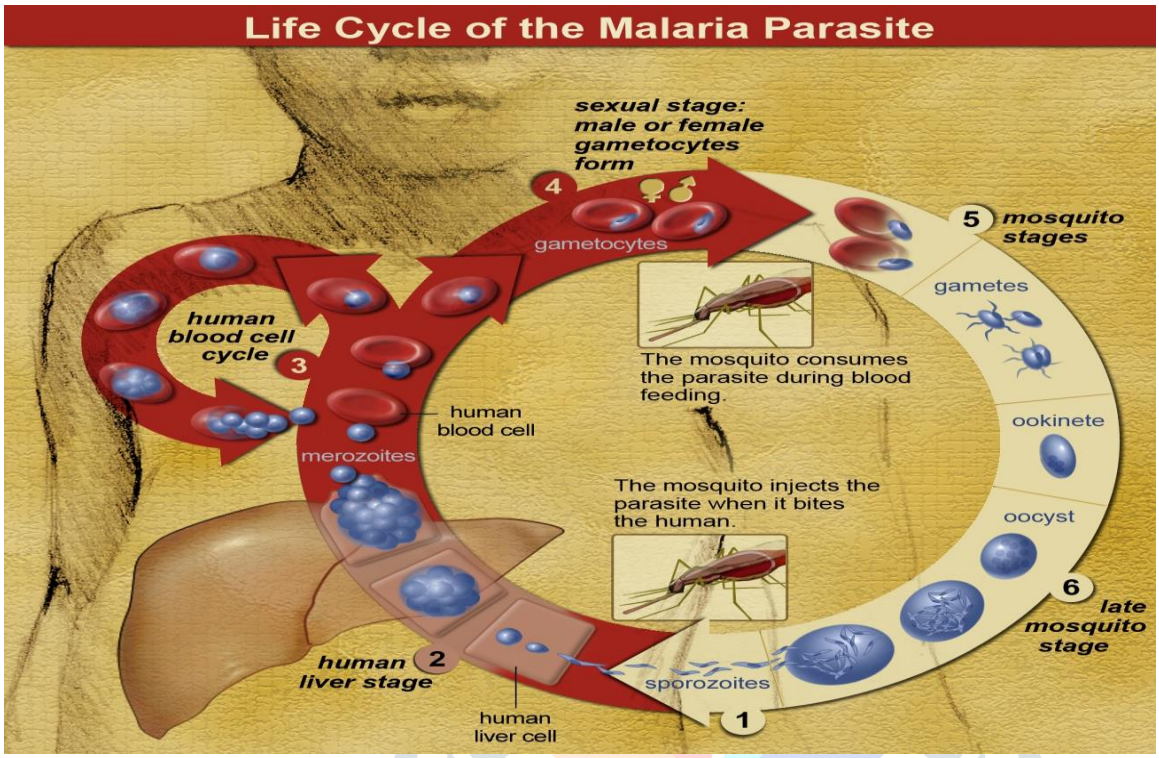

Figure 1:- Life cycle of malarial parasite

It is characterized by shaking chill, fever, sweating, headache, nausea, vomiting, anemia, muscle pain and may also lead to coma. Malaria affects both sexes and can affect person of any age but usually affects children of age between 1 to 5 years and pregnant women Epidemiological data indicates that the entire southeast region reports more than 100 million cases among which India counts for 2 million cases of malaria annually.[6-9] The exact etiology of malaria is not understood but research and advancement in study of pathogenesis of malaria reveal that there is multifaced interaction with immune system of host and parasite which results in overproduction of inflammatory mediators like tumors necrosis factor α (TNF-α), interferon-γ (IFN-γ), interleukin-1 (IL-1) and there is up regulation of intercellular adhesion molecule-I (ICAM-I).[1, 10]

Treatments of Malaria

The current treatment goal of malaria includes treatment and prophylaxis of malaria and also to achieve inhibition of resistance by new drugs. Current therapy for treatment of malaria includes 4-aminoquinolines (chloroquine, amodiaquine); 8-aminoquinolines (primaquine, tafenoquine); 4-methanolquinolines (mefloquine); antifolates (pyrimethamine); naphthoquinone (atovaquone); non-antifolate antibiotics (clindamycin, doxycycline, azithromycin, fosmidomycin).[11] All pharmacological agents used for malaria

treatment possess many demerits and also lack specificity, so dissatisfaction with current therapy has made a urgent need to find safe and effective drugs from plant sources.

1. **Quinine**

   Quinine is obtained from bark of *Cinchona zeylenicum* and is known as Kunain and is belonging to the Rubiceae family. It has been used as first line treatment for malaria. Cinchona bark contains two pairs of stereo isomer such as quinine, quinidine, cinchonine, cinchonidine. All of these stereoisomers are used for malaria treatment along with the same quinidine is also used as antiarrythmic drug.[11, 12] Side effects associated with Quinine are nausea, blurred vision, headache, hypotension.[13] The exact mechanism of quinine is unknown but it is believed that quinolines act by process of inhibition of heme crystal formation in digestive vacuole by binding reversibly with Π- Π interaction.[11]

2. **Artemesin**

   Artemesin is obtained from plant *Artemesia annua.*[14] But it has been also be isolated from plant qinghau which was identified by youyou in 1971 for which he has also been given nobel prize. It has been used from long time for treatment of malaria.[15]The semisynthetic derivative of artemesin are artesunate, arteeter, artimisone and artemether all are used for treatment of malaria in combination with artesunate and artemether for anticancer properties.[16] The combination therapy of artemesin is also recommended for effective in treatment of malaria which has combination of Artesunate and meflloquine tablets which contains 100mg of artesunate and 220mg of mefloquinine shows a good effect on malaria patients.[17] Artemesin acts by interacts with intraparasitic haeme to activates the artemesin for the generation of toxic free radicals.[18]

3. **Clerodendrum viscosum vent**

   Clerodendrum viscosum vent is a shrub belonging to the family Lamiacea.[19]Various chemical constituents involved are terpenes, alkaloids, phenols, phenolic acids, tannin, flavonoids.[20] All parts of the plant are used for the malaria.[21]It has been also used for the treatment of various diseases like asthma, tumours and certain skin diseases.[20] It is recommended that one teaspoonful of this plant juice in a week shows a good effect on the malarial patients.[22]

4. **Glycyrrhiza glabra**

   Glycrrhiza glabra also known as liquorice or sweetwood is a plant belongs to the family leguminosae. It contains important constituents such as glycyrrhizin, glycchizinic acid, glycerrhytenic, glabrin A and glabrin B, and isoflavones.[23] Along with antimalarial it has been recommended for treatment of some other disorders such asfungal, viral infection, inflamation, hyperglycemic, ulcer, allergy, spasmolytic, convulsant, pyretic, memory enhancement ,skin whitening.[24]The licocancole A and the 18β glycyrrhetenic acid which are the major constituent of glycerrhiza shows a good antimalarial activity on the malarial patients.[25] The Licochalcone A present in liquorice possess very good

antimalarial activity. In mice the *invivo* studies are done against p. yoelii with oral doses of 1000 mg kg-1 and have shown to eradicate the malarial parasite.[23]

5. **Cymbopogen citrates**

Cymbopogen citrates known as Lemon grass is a perennial aromatic grass of the family Graminacae.[26] The chemical constituents involved are citral α, citral β, nerol, citronellal, terpinolene, geranyl acetate.[27] The active chemical constituent citral along with the antimalarial property possess many other activities also like bactericidal, fungicidal, astringent, antiseptic, antidepressant, analgesic, spasmolytic, dyspeptic.[28]Antimalarial activity of the oil on mice against plasmodium berghei was studied against the malarial parasite plasmodium falciparum.[26]

6. **Azadirachta indica**

Azadirachta indica(Neem) an important Indian medicinal plant used for long time for the treatment of fever and belonging to the Meliaceae family.[29]The chemical constituents includes nimbidin, azadirachtin, gedunin, nimbolide, margolone, sodium nimbidate, polysachharideG1A, G2A.[30] It is also beneficial for curing the eczema, acne, heal chronic wounds, diabetes, removes toxins, purify the blood. The seed oil of active constituent of nimbolide, gedunin possess a good antimalarial property and shows a positive effect on malarial patients. The exact mechanism is not known but it is found the limonoid present in seed is responsible for toxic effects and inhibited the growth of cell wall of malarial parasite.[30]

7. **Capsicum frutescence**

The fruit *Capsicum frutescence* (Green chilli) of family solanaceae is known from ancient time in Indian history for being used as spices. The capsaicinoid present in this fruits responsible for the hot taste. The capsaicinoid consists of capsaicin, dihydrocapsaicin, homocapsaicin, homodihydrocapsaicin.[31]Almost whole plant constituents have shown antimalarial activity.The exact mechanism is unknown but it is found that it reduces the B2 formation and suggests a membrane stabilizing property that interferes with the activation of phospholipase A2 It is also used foranti inflamtory, analgesic,convulsant, gastrointestinal.The unripe fruit possess a good antimalarial property on the malarial patients[32]

8. **Carica papaya**

The fruit of plant *carica papya*(caricaceae) is being used for malaria.The phytoconstituents involved are enzymes, terpenoids, alkaloids, flavonoids, carbohydrates, glycosides, saponins and steroids.[33]. All of these constituents are used for malarial patients and along with that these are also used as antiinflamatory, wound healing properties, antitumour, antioxidant, dengue fever.[34]The leaves of papaya in tea possess a good antimalarial property on malarial patients. The exact mechanism of this is not known and had not significantly proven.[33]

9. **Tamarind indica L**.

The tropical fruit of *Tamarind belongs* of family leguminosae is being used for malaria (fabaceae).[35]The chemical constituents involved in this are tartaric acid, carbohydrates, reducing sugar, phenolic compounds, saturated fatty acids. The pulp contains furan derivatives and carboxlic acids. All these constituents have ability of antimalarial property along with that they also possess diabetic, hepatoprotective, cardioprotective, antiasthmatic, laxative.[36]

10. **Citrullus colocynthis**

Citrullus colocynthis commonly known as cucumber is belongs to the curcurbitaceae family.[37] The chemical constituents involved in this are curcurbitacin, flavonoids, caffeic acid derivatives, terpenoids, lenolic acid and phenolic compounds. All of these are used as an antimalarial activity Along with that they are also used for stomach pain, cathartic, constipation, bacterial infection, diabeties.[38],[39] The seed also contains high content of lenolic acid which is beneficial in treatment of malaria.[39]

11. **Alluvium sativum**

Alluvium sativum (garlic) belongs to the family alliaceae is a very popular plant because of its pharmacological actions.[40]The chemical constituents present are allicin, alliin, ajoene , enzymes (allicinase, peroxidase, carbohydrates, amino acids, Vitamin A, B, C). Along with antimalarial property it is also known to possess other pharmacological activities such as antidiabetic, antitumour, insecticidal, antihypertensive, antimicrobial, hypolipidemic, carminative, stimulant, antiprotozoal, antifungal.[41]

12. **Nigella sativum**

Nigella sativum (Ramunculaceae) contains[42] various constituents like thymoquinone, p-cymene, carvacrol, thymohyroquinone, αinene, β pinene, *α*thujene[22]. Along antimalarial activity it is also used for the various disorders such as cancer, diabetic, inflammation, pain, gastroprotection. It has been reported that chloroform and ethanol extract of seed of nigella sativum when given to mice against *P. berghei* by orally has shown significant reduction in parasite malaria which increases life of mice.[43]

13. **Cassia accidentals L**.

The plant *cassia accidentalis linn* of (leguminosae) has been used tradionally for the treatment of malaria. The phtyochemicals constituents involoved in this are anthraquinones and their glycosides, flavonoids, polysaccharides, fatty acids, phenanthracene derivatives, phytosterol, sugar alchohal, essential oils, trace metals.[44]The root bark are preferred for the malarial patients and the other phytochemicals are used for anxienty, depressant, skindiseases, diabetic, wound healing, sun protective, inflammatory, analgesic, pyretic, hepatoprotective, nephroprotective, bone fracture, typhoid.[45] Antimalarial activity of cassia accidentalis plant was tested against plasmodium berghei in mice and was significantly proven for malaria.

14. Lantana camara linn

Lantana camara linn of family verbenaceae family contains many chemical constituents like essential oils, phenolic compounds, flavonoids, carbohydrates, proteins, alkaloids, glycosides, phenyl ethanoid, oligosaccharides, quinine, saponins, sesquiterpenoides and tannin as the major phytochemical.[46] All these constituents have been known to possess various pharmacological activities like carminative, antispasmolytic, analgesic, antipyretic, fungicidal, microbial, insecticidal.[47]All parts of plant have been tested for malaria and the use of lantana flower extract and coconut oil gives a protection for the mosquito bite. The leaf, root and flower of this plant are possessing the antimalarial property.[14]

15. **Kalanchoe pinnata**

Kalanchoe also called master herb is a medicinal plant which is used to treat the malaria and other diseases like cancer, anticonvulsant activity, diabetic, ulcer, diuretic, hepatoprotective, immunomodulatory, and stimulant and is belonging to the Madagascar family. It is generally called master herb. The various chemical constituents present in this are flavonoids, phenolic compounds, tannin macro elements like magnesium, calcium, phosphorus, caffeic acid, syringic acid, alkaloids.[48]The plant part leaf preparations are used to treat the malaria in malarial patients.[49]

16. **Cryptolepis sanguinoplenta**

The plant *cryptolepis sanguinoplenta* is majorly used for the malaria and is of the Apocynaceae family. The major constituents in the root part are cryptolepine, indoloquinolene are responsible for antimalarial activity. Other constituents are spirnonacyclic alkaloid, cryptolepinone, biscryptolepine[50]. They also possess other biological activities like muscarinic, vasodilation, hypoglycemic, inflammatory, noradregenic, microbial.[50]The active constituent in root indoloquinolene or cryptolepine are found to be show *invitro* and *invivo* activity against plasmodium falciparum contains chloroquine resistant strains. The roots extract are shown to possess antimalarial property on malarial patients.[51]

17. **Morinda lucida**

Morinda lucida(Brimstone tree) and is belongs torubiaceae. The phychemicals like tannins, flavonoids, alkaloids, steroids, terpenoids, saponins, glycosides, and anthraquinones.[52] The anthraquinones present possess antimalarial activity It is used for treatment of fever, dysentery, abdominal colic and intestinal worm infestation.[53] Cold decoction of the plant leaves are used to treat the malarial patients. Morinda lucida have reported to shown an antimalarial activity against plasmodium berghei in mice.[54]

18. **Coula edulis**

The plant coula edulis which also named as african walnut or gabon nut belongs to the family olacaceae.[55] Chemical constituents such as tannius, terpenes, saponins, flavonoids, cardiac glycosides, alkaloids, anthraquinones along with malaria It can also be used in the treatment of diseases like

cancer, diabetes, neurodegenerative, digestive and gastrointestinal can also be treated.[56] The stem bark is used to treat the malarial activity in malarial patients.

19. **Acacia nilotica**

This medicinal plant is belonging to the family Fabaceae. The chemical constituents are secondary metabolites, such as tannins, terpenes, alkaloids, flavonoids, and phenolic with many pharmacological properties which possess to treat many diseases.[57] The plant is used as anti-cancer, anti tumours, antiscorbutic, astringent, anti- oxidant, natriuretic, antispasmodial, diuretic, intestinal pains and diarrhea, nerve stimulant, cold, congestion, coughs, dysenter, fever, hemorrhages, leucorrhea, ophthalmia and sclerosis The antimalarial activity of acacia nilotica was active against Plasmodium berghei and Plasmodium falciparum in mice. The seeds of this plant possess antimalarial activity[58]

Antimalarial drugs from marine sources

1. **Manzamines**

The *manzamine* is an alkaloid which is isolated from marine sources and was identified by Higa in 1986 by *onkinawan sponge* which is belongs to the Haliclona genus. It has been used as antimalarial and also possess.[59]antimicrobial, insecticidal, antiinflamatory ,cytotoxicity, immunosuppressant properties. The malarial parasite plasmodium falciparum which is caused by cerebral malaria and mycobacterium tubercolusis, toxoplasma gondii are inhibited by the Manzamines.[60]

2. **Isonitrites**

The *isonitrites* which contains the marine secondary metabolite namely axisonitrile-1 is responsible for are malaria are produces by the marine sponge *Axinella cannabina* by cafiera marine . The isonitriles can be divided into four categories such as sesquiterpenoids, the diterpenoids carbonimidic dichlorides and miscellaneous structures All of these show antimalarial property and also with this The isonitriles show antitubercular, antifouling and antiplasmodial properties[61, 62] In 1992, axisonitrile was produces from the sponge *Acanthella klethra* and *Pulitzer-Finali* and it was concluded that it possess an antimalarial property both on chloroquine-sensitive and chloroquine resistant P. falciparum strains.[59]

3. **Plarkotin**

The *plarkotin* is obtained from the marine sponge *Plakortis halichondroides* which is belongs to the Plakinidae family.[63]Along with antimalarial property it possess other properties includes antitumor, antiparasitic, antimicrobial, anticancer, antifungal. The bioactive metabolites are 3-epiplakortin and plakortides F, G, and H shows an antimalarial potential activity. The exact mechanism of this is unknown but it is found that it stimulates the cardiac uptake in sarcoplasmic reticulum vesicles from canine ventricle tissue.[64]

4. **Curcuphenol**

The *curcuphenol* is obtained from the Didiscus oxeata, D.flavus, Myrmekioderma and Epipolasis species.It is found that curcuphenol and its closely related compound15-hydroxycurcuphenol shows *invitro* antimalarial activity against plasmodium falciparium.[10, 65]Along Antimalarial It has many other applications such as natural food coloring agents, food additives, drugs, color enhancer, improvement of the health and fertility of cattle, and use in the cosmetic industries also curing for inflammation and ulcers.[66]

5. **Peptides**

The *peptides* from marines are also used to treat malaria.The Peptides cyanobacterial bacterial consists a number of compounds contains alkylated phenols, alkaloid peptides and linear peptides out of which gallinamide A which is obtained from the *Schizothrix species* are active against the malarial parasite plasmodium falciparum.The linear compound dolastatin has having structure resembles with gallinamide A and also shows an antimalarial activity. These peptides are also used to treat the leishmaniasis, Chagas disease, and dengue fever, as well as against cancer cells.

S. No.	Plant source	Mechanism of action	Reference
1.	Quinine	Π- Π interaction	11,12,13
2.	Artemesin	Intraparasitic haeme	14,15,16,17,18
3.	Clerodendrum viscosum vent	____	19,20,21,22
4.	Glycyrrhiza glabra	Growth inhibition	23,24,25
5.	Cymbopogen citrates	____	26,27,28
6.	Azadirachta indica	Cell wall synthesis	29,30
7.	Capsicum frutescence	Phospholipase A2	29,30
8.	Carica papya	____	31,32
9.	Tamarind indica L	Phospholipase A	33,34
10.	Citrullus colocynthis	Regulatory harmones	35,36

11.	Alluvium sativum	Cysteine protease	41,42
12.	Nigella sativum	TNF	42,43,22
13.	Cassia accidentals L	Exhibited by toxic effects of larvae	44,45
14.	Lantana camara linn	HEp-2, NCIH-292	46,47,14
15.	Kalanchoe pinnata	PLA2 activity	48,49
16.	Cryptolepis sanguinoplenta	ppARY	50,51
17.	Morinda lucida	PPGG	52,53,54
18.	Coula edulis	____	55,56
19.	Acacia nilotica	____	57,58
20.	Manzamines	Growth inhibition at 132 ppm dose	59,60
21.	Isonitrites	Complexation with haeme	59,61,62
22.	Plarkotin	____	63,64
23.	Curcuphenol	Induced dna binding	10,65,66
24.	Peptides	____	59,67

Table1: Herbal products used for treatment of malaria and their biological targets

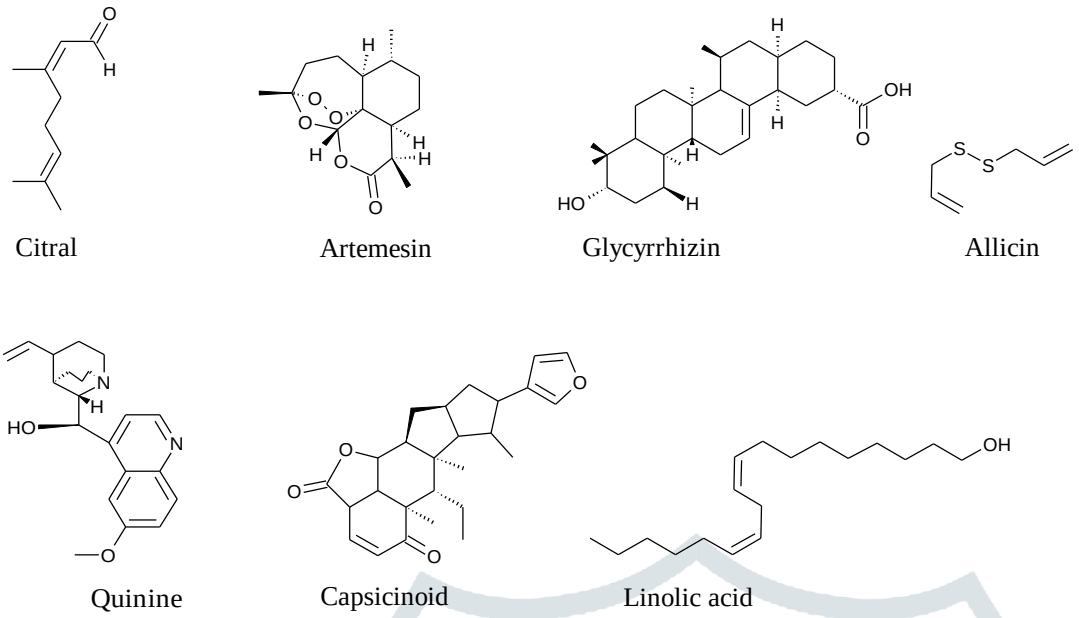

Figure2: Chemical Structures of active plant constituent for antimalarial activity

Conclusion

Malaria is major health problem worldwide. Although, many current treatment for malaria has been reported but all these are associated with few limitations such as safety and efficacy. Herbal medications are alternative drug used to relief symptoms of malaria and can overcome side effects associated with conventional drugs Plant derived products are much more promising in malaria treatment but still further investigation should be carried are prove their usefulness and confirm its safety and efficacy.

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