

REVIEW ARTICLE



Ethnopharmacology and phytochemistry-based review on the antimalarial potential of *Acacia pennata* (L.) Willd.

James H. Zothantluanga*

Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh 786004, Assam, India

A protozoan infection called malaria is caused by *Plasmodium* parasites. In 2018, it infected more than 228 million people and caused 405,000 fatalities. Worryingly, the present antimalarial drugs had developed drug resistance. Furthermore, they are associated with adverse effects and price issues. Amidst the gloomy scenario, drug discovery based on natural products had renewed the hope to overcome the burdens associated with the present antimalarial drugs. Auspiciously, medicinal plants had contributed significantly to the modern pharmacotherapy of malaria. Interestingly, *Acacia pennata* (L.) Willd. was also documented as a traditional antimalarial agent. However, there is still no scientific evidence regarding its antimalarial activity. Therefore, this article was aimed to study the phytochemical profile of *A. pennata* and explore their potential activity against malarial parasites. *A. pennata* contains different classes of bioactive compounds such as alkaloids, flavonoids, phenols, glycosides, terpenoids, phytosterols, and saponins whose antimalarial activities had been reported. Accordingly, the future scopes and challenges regarding the possible antimalarial activity for *A. pennata* are also discussed. To maximize the chances for finding a new antimalarial chemical entity from *A. pennata*, a schematic flow chart on the ethnopharmacology based drug discovery approach is also provided. Thus, this literary work may be used by researchers as a referential guide in the search for new antimalarial phytochemicals.

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*For correspondence:
jameshtta@gmail.com

Contact us:
sciencevision@outlook.com

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Introduction

Malaria is a protozoan infection caused by *Plasmodium* (Marchiafava & Celli, 1885) parasites. Although malaria is an infectious disease, it is treatable and can be prevented. With a single bite, a female *Anopheles* mosquito transmits malarial parasites (*P. knowlesi*, *P. ovale*, *P. falciparum*, *P. vivax*,

and *P. malariae*) into the blood of humans.^{1,2} A total of 228 million cases of malaria with 405,000 fatalities were recorded in the year 2018.³ *P. falciparum* is responsible for inducing cerebral malaria, i.e. the most fatal form of malaria and in general, *P. vivax* and *P. falciparum* seems to be more harmful.^{2,4} Few



Figure 1 | Leaves and stem of *A. pennata* (Image courtesy: Zothantluanga *et al.*, 2020¹⁷).

examples of antimalarial drugs are quinine, chloroquine, mefloquine, primaquine, amodiaquine, artemether, artesunate, atovaquone, lumefantrine, sulfadoxine and pyrimethamine.⁵

Problems such as adverse effects, drug resistance, and price issues are associated with the present antimalarial drugs.⁶⁻⁹ Therefore, scientists had renewed their interests in natural product-based drug discovery with the hope to overcome the burdens associated with the present antimalarial drugs.¹⁰ Providentially, it is a relief to state that a significant contribution was already made by plant derivatives (for instance, quinine and artemisinin) in the pharmacotherapy of malaria.^{11,12} Moreover, the phytotherapy of malaria included more than 1200 and 160 species of plants and families respectively.¹²

Therefore, the chances to find a newer and safer antimalarial drug might be increased by examining the correlation between the ethnopharmacological knowledge and the phytochemistry of a plant.

Laldinsanga *et al.*¹³ recorded *Acacia pennata* (L.) Willd. (Figure 1) as a traditional medicine against malaria. *A. pennata* (Family: Fabaceae) is a large thorny plant found in Bangladesh, Bhutan, India, Myanmar, Southwest China, Sri Lanka, Thailand and Vietnam.¹⁴⁻¹⁶ There are plenty of nutrients present in *A. pennata* (Figure 2) that accounts for its nutraceutical potential.¹⁵ However, specifications on the plant part, method of preparation, route of administration, and dosing regimen adopted for the traditional treatment against malaria were missing. Moreover, there is no scientific evidence on the

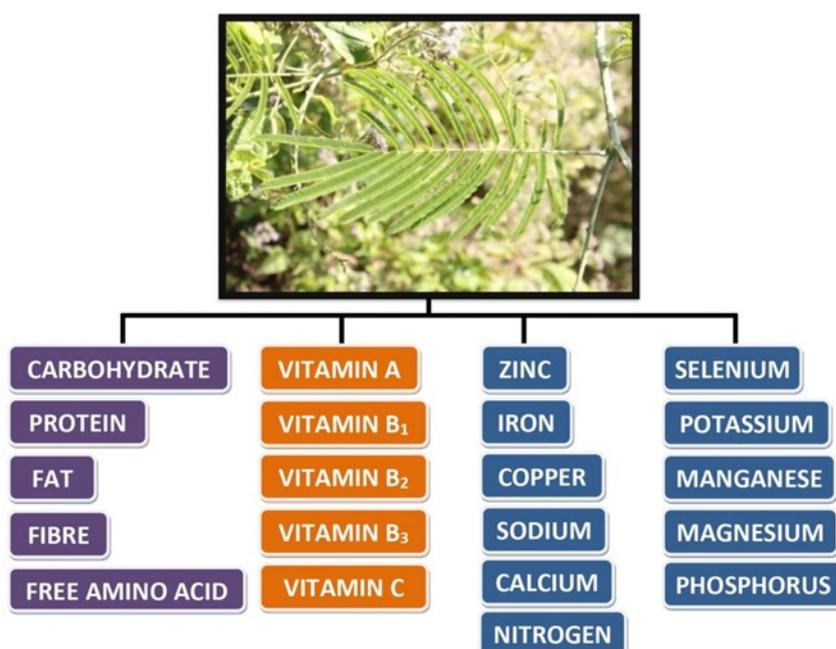


Figure 2 | Nutrients present in *A. pennata*.

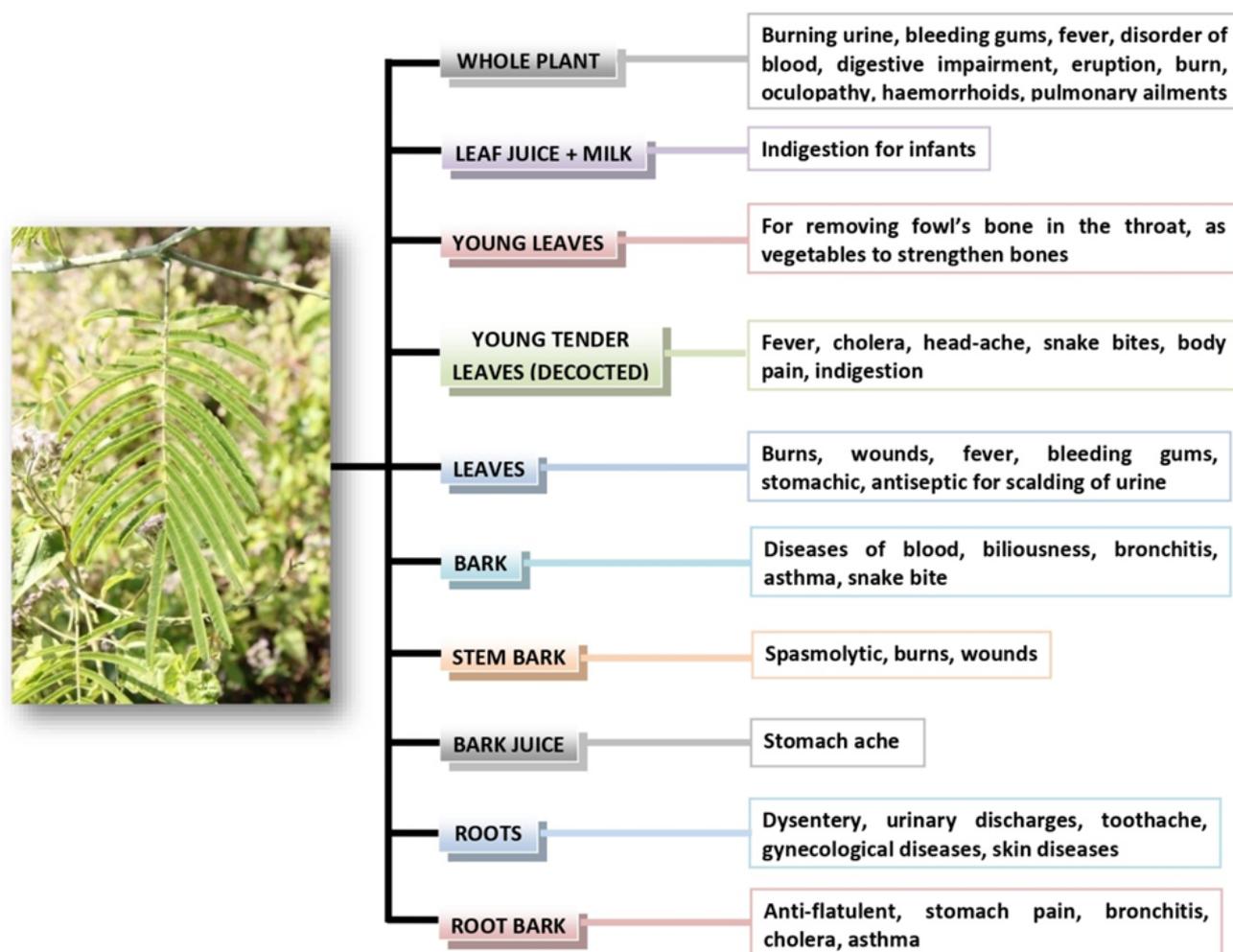


Figure 3 | Traditional indications for *A. pennata*.

antimalarial activity of *A. pennata*. Therefore, this article was aimed to systematically explore the antimalarial potential of *A. pennata* based on its phytochemical profile.

Phytopharmacology of *Acacia pennata* and evidences for their antimalarial activity

A. pennata is traditionally used for many health ailments (Figure 3) and had been investigated for a handful of pharmacological activities (Figure 4).^{15,17} Though the scientific evidence on the antimalarial activity of *A. pennata* is still not available, the phytochemical profile of *A. pennata* might provide some theoretical evidence that supports the traditional claim. The different classes of bioactive compounds present in *A. pennata* were identified to be alkaloids, flavonoids, glycosides, phenols, phytosterols, terpenoids and saponins.^{15,17,18}

Alkaloids are biologically active nitrogen-containing compounds that are found in plants, animals, bacteria, and fungi. Alkaloids exhibit various

pharmacological activities such as sympathomimetic, anticholinergic, antiulcer, antiviral, antidepressant, analgesic, anti-inflammatory, muscle relaxant, diuretic, antitumor, antimicrobial and antihypertensive.¹⁹ Ma *et al.*,²⁰ Kubo *et al.*²¹ and Promchai *et al.*²² had reported the antimalarial activity of alkaloids.

Flavonoids are naturally occurring polyphenolic compounds. They are an important secondary metabolites of plants and are widely distributed in vegetables and fruits. Owing to their anti-cancer, anti-mutagenic, anti-inflammatory, and antioxidant properties, flavonoids form a key element in many medicinal, nutraceutical, cosmetic, and pharmaceutical applications.²³ The antimalarial activity of flavonoids had been reported by Ichino *et al.*,²⁴ Khaomek *et al.*²⁵ and Penna-Coutinho *et al.*²⁶

Glycosides are bioactive compounds that attaches itself to an aglycone via a glycosidic bond. The glycoside moiety plays a crucial role in altering the pharmacology and pharmacokinetic profiles of the aglycone moiety. Glycosidic antibiotics,

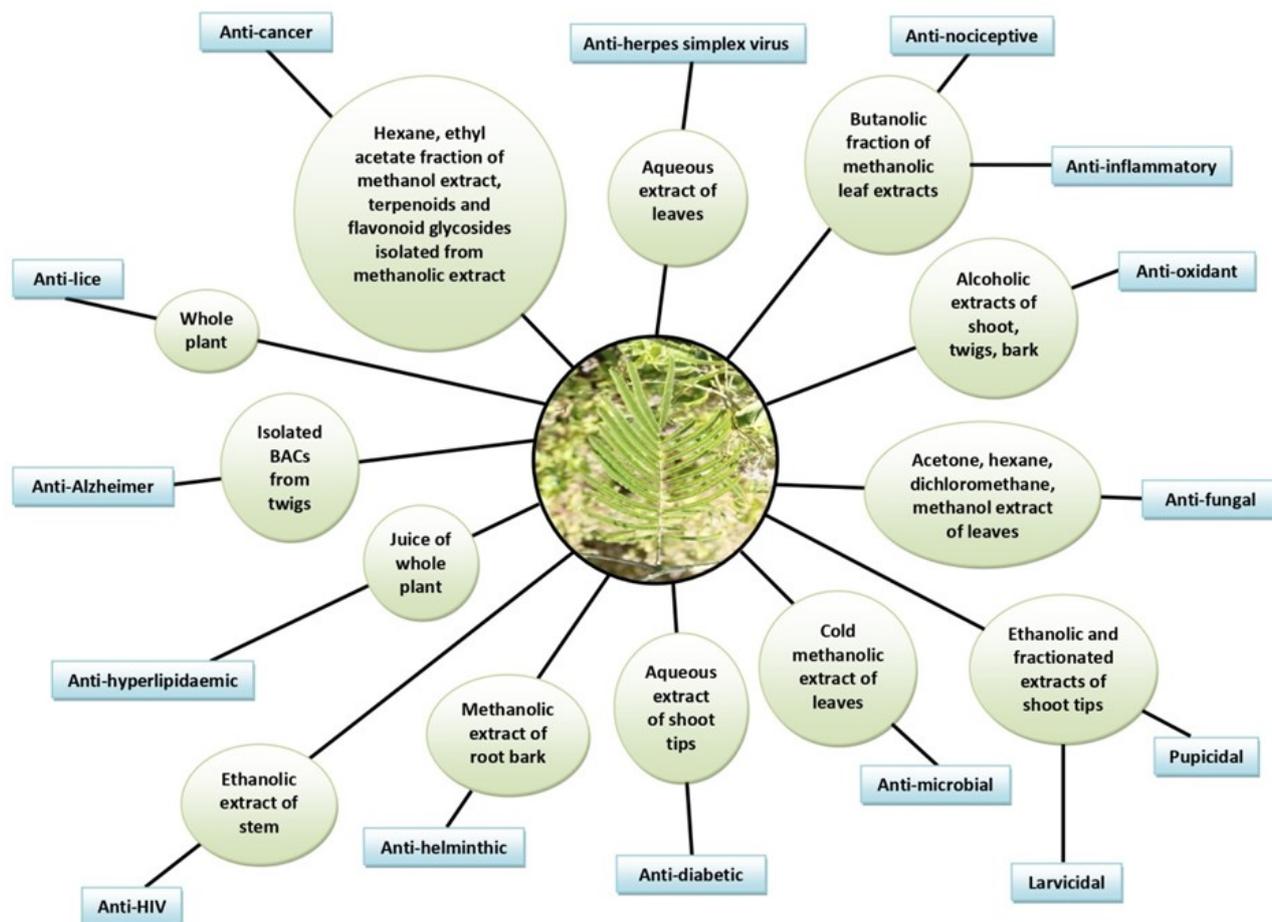


Figure 4 | Pharmacological activities of *A. pennata*.

glycosides of vitamins, alkaloid glycosides, steroid glycosides, terpenoid glycosides, and polyphenol glycosides are different classes of glycosides having a great value in health care.²⁷ Graziose *et al.*,²⁸ Ovenden *et al.*²⁹ and Park *et al.*³⁰ had reported the antimalarial activity of glycosides.^{28–30}

Phenols and polyphenols are secondary metabolites present in most of the plants. The C₆-C₃ phenylpropanoid pathway is responsible for biosynthesizing various plant phenols that have biological activities like antioxidant, anti-microbial, anti-inflammatory, anti-cancer, anti-allergenic, anti-hypertensive, anti-thrombogenic and anti-platelet.³¹ The antimalarial activity of phenols had been reported by Laphookhieo *et al.*,³² Morimoto *et al.*³³ and Alson *et al.*³⁴.

Phytosterols (also known as plant sterols) are present in all plant cells. Structurally, they differ from cholesterol and they belong to the family of triterpene. They act as precursors in the biosynthesis of bioactive compounds like steroidal glycoalkaloids, steroidal saponins, brassinosteroids, and

phytoecdysteroids. In general, they exhibited antiproliferative, antimicrobial, immunoprotective, hepatoprotective, nephroprotective, adaptogenic, anabolic, hypoglycaemic, hypocholesterolemic, and neuromodulatory activities.³⁵ Irungu *et al.*³⁶ and Perumal *et al.*³⁷ had reported the antimalarial activity of phytosterols.^{36,37}

Terpenoids serve as a wealthy reservoir for potential drug candidates. Among all the classes of natural products, they are the biggest class.³⁸ Terpenoids have pharmacological activities like anti-microbial, anti-cancer, anti-nociceptive, hepatoprotective, anti-foaming, carminative and anti-inflammatory activities.³⁹ The antimalarial activity of terpenoids had been reported by Saewan *et al.*,⁴⁰ Chukwujekwu *et al.*⁴¹ and Greve *et al.*⁴²

Saponins comprises of a large number of biologically active triterpene glycosides or steroids that are distributed throughout the marine animal and plant kingdoms. Saponins elicit a vast array of pharmacological activities such as immunomodulation, anti-cancer, anti-phlogistic, anti-allergic,

anti-hepatotoxic, anti-viral, anti-diabetic, and anti-fungal.⁴³ Ohigashi *et al.*,⁴⁴ Traore *et al.*⁴⁵ and Akanbi *et al.*⁴⁶ had reported the antimalarial activity of saponins.⁴⁴⁻⁴⁶

Future Challenges

A pre-clinical study (*in vitro* and *in vivo*) is a stage of the drug development process that precedes clinical trials wherein the safety and efficacy data of a drug candidate are collected.^{47,48} Worryingly, adverse effects that are induced by natural products had been reported.⁴⁹ Thus, it is important to consider the toxicity issues that might be associated with natural products. Therefore, pre-clinical techniques may be used to generate data on the pharmacological efficacy, safety as well as toxicity of a potential drug candidate.

Different classes of bioactive compounds like alkaloids, flavonoids, glycosides, phenols, saponins,

phytosterols, and terpenoids had been investigated for their antimalarial activity.^{20-22,24-26, 28-30,32-34,36,37,40-42,44-46} Auspiciously, all these classes of bioactive compounds are present in *A. pennata*.^{15,17,18} Moreover, it is worthy to re-state that *A. pennata* still lacks scientific evidence for antimalarial activity. Therefore, the extracts and fractions obtained from *A. pennata* may be investigated for their activity against malarial parasites using suitable pre-clinical techniques. Based on the results obtained from the pre-clinical study wherein various extracts and fractions of *A. pennata* will be used, bioactivity guided isolation of compounds may also be carried out.

On the other hand, there is no assurance that *A. pennata* will show antimalarial activity on account simply because it contained the classes of bioactive compounds whose anti-malarial activities had been reported. This is because the specific antimalarial phytochemical present under the same class of a

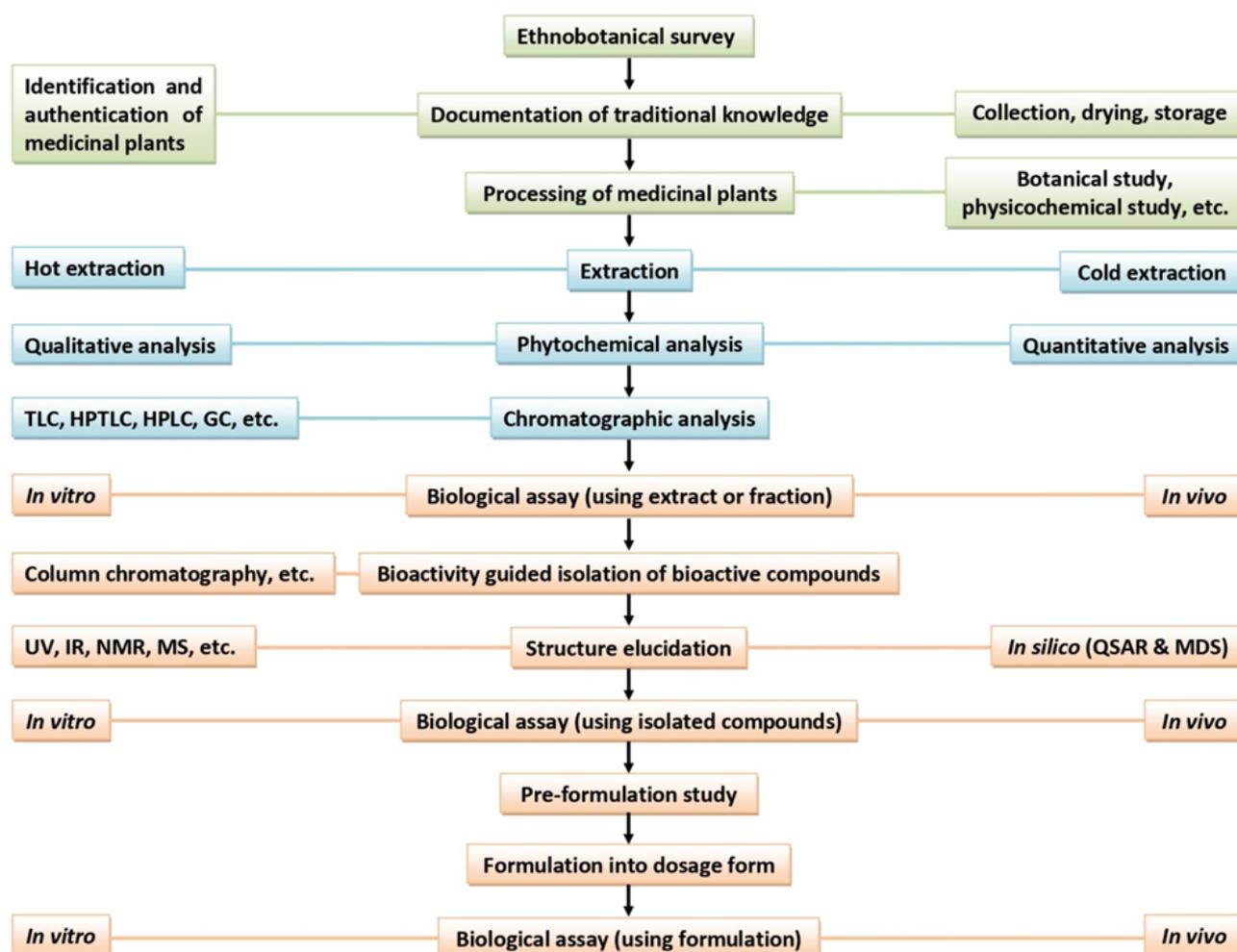


Figure 5 | Ethnopharmacological-based approach for discovering a new chemical entity (TLC = thin layer chromatography; HPTLC = high performance thin layer chromatography; HPLC = high performance liquid chromatography; GC = gas chromatography; UV = ultraviolet; IR = infra-red; NMR = nuclear magnetic resonance; MS = mass spectroscopy; QSAR = quantitative structure activity relationship; MDS = molecular docking study).

bioactive compound might differ in different plants. For example, two of the most widely used antimalarial drugs i.e. quinine (alkaloid) and artemisinin (terpenoid) are examples of bioactive compounds that had been isolated from *Cinchona officinalis* and *Artemesia annua* respectively.^{50–53} Thus, although *A. pennata* was reported to contain alkaloids and terpenoids,^{17,18} quinine and artemisinin were never reported to be isolated from *A. pennata*. Still, the possibility of *A. pennata* as having its antimalarial phytochemicals cannot be completely ruled out. Therefore, in addition to the attempt to isolate the bioactive compounds from *A. pennata* and screen their activity against malarial parasites, *in silico* techniques may also be utilized to screen the antimalarial activity of the known phytochemicals that are present in *A. pennata*.

Ligand-based drug-design involves the study of quantitative structure-activity relationship (QSAR) while structure-based drug-design involves molecular docking study (MDS). These approaches for *in silico* drug discovery falls under the category of computer-aided drug design that utilizes a library of known compounds.^{54,55} Interestingly, it was reported that many phytochemicals had been isolated from *A. pennata*.¹⁵ Therefore, the QSAR technique may be utilized to investigate the relationship between the pharmacological activity and chemical structure of the phytochemicals so that appropriate structure modifications may be made to yield a more potent and safer compound. Also, *in silico* screening of isolated phytochemicals of *A. pennata* for their antimalarial activity may be carried out with the MDS technique. Hence, further pharmacological investigations will depend on the results that are provided by the MDS technique. This can also prevent unnecessary loss of money and time.

In light of the above discussions, a modified ethnopharmacology-based drug discovery approach that was adapted from Brusotti *et al.*⁵⁶ and Novaes and Leite⁵⁷ is schematically represented in Figure 5. However, the ethnopharmacology based approach that is depicted in Figure 5 is a hypothetical proposal that might not be fully applicable for every research. Still, as it might aid in the search for new antimalarial drugs, it may be considered as a basic and referential blueprint that may be upgraded and modified as per personal requirements. Thus, the ethnopharmacological based approach might increase the chances of discovering a new chemical entity.

Conclusion

Review of the phytochemical profile of *Acacia pennata* reveals the antimalarial potential that is on par with the traditional claim.

Conflict of interest

Not applicable.

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