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Review Article

Ethnopharmacological Use, Secondary Metabolites and Biological Activity of *Ayapana triplinervis* (VAHL) R. M. King and H. Rob.: A Systematic Review

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ABSTRACT
Ayapana triplinervis is a plant species widely used in healing processes and in mystical-religious rituals by traditional communities in South America, Africa and Asia. This study aims to make a systematic review of the ethnopharmacological employment, secondary metabolites and biological activity reported in the scientific literature for A. triplinervis. The systematic literature review included scientific articles and theses published between 1987 and 2021 in Google Scholar, Science Direct, Pubmed, Web of Knowledge and CAPES Periodicals databases in English, Portuguese and Spanish. The results indicated that A. triplinervis is chemodiverse in coumarins and validated the ethnopharmacological action cited by traditional communities as antiviral, antinociceptive, antiulcerative, anxiolytic, biocidal activities by *in vitro* and *in vivo* biological tests.
Keywords: Medicinal plants, Secondary metabolites, Biological activity, Coumarins.

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INTRODUCTION

The growing use of natural products as raw materials indispensable to the industry in the search for biologically active compounds: anticancer, antimalarial, biodegradable natural pesticides that contribute to the evolutionary success in plants, has led to the multidisciplinary study of numerous plant species, among the families of medicinal interest is the Asteraceae.[1]

The Asteraceae family developed in South America and Brazil emerges as the centre of the most primitive genera.[2] However, phylogenetic, taxonomic and chemosystematic information is incipient and indicates the presence of little known genus.[3] Ethnobotanical and ethnopharmacological studies indicate the therapeutic interest of species of the Asteraceae family through the medicinal use that traditional communities employ in their social practices, among which *Ayapana triplinervis* (Vahl) R. M. King e H. Rob. stands out.[4]

A. triplinervis can be found in two morphotypes (morphotype A and morphotype B) and is widely used in folk medicine and mystical-religious rituals in traditional communities of South America, Asia and Africa. Plants have different forms of defences from phytopathogens and herbivores, including a complex chemical mechanism of secondary metabolites. Species like A. triplinervis produce a broad spectrum of chemicals in various tissues above and below ground used for defence against biotic or abiotic stressors, and used by man as medicines, food and beverage flavourings, fragrances, textile dyes, hygiene products, insect control, among others.[5]

Thus, this study aims to make a systematic review of the ethnopharmacological employment, secondary metabolites and biological activity reported in the scientific literature for *A. triplinervis*.

MATERIALS AND METHODS

The databases used in the search for papers related to *Ayapana triplinervis* and its synominies were Scholar Google, Science Direct, Pubmed, Web of Knowledge and CAPES Periodicals. The keywords used were *Ayapana triplinervis, Eupatorium triplinerves,* "Japana-branca", "Japana-roxa", Ayapana, Asteraceae, medicinal plant, ethnopharmacology, ethnomedicine, metabolics, metabolite, botanic aspects, botanical aspects, phytochemistry, and/or essential oil.[6]

The search period comprised the years between 1987 and 2021 in English, Portuguese, and Spanish. Articles that did not present any aspect of the proposed theme or that were written in any other languages than those above mentioned, as well as thesis and dissertation results were adopted as exclusion criteria.

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RESULTS AND DISCUSSION

Asteraceae Family

The Asteraceae (Compositae) family comprises 1,535 genus, of which 180 are found in Brazil, with approximately 23,000 monophyletic species described and botanically accepted. Known as the family of sunflowers or daisies, the Asteraceae has a head made up of small flowers, called floscules, and anthers fused in a ring with pollen pushed by styles or cypselas, a species of dried fruit with varied aspects, 98% of the genera are small, such as herbs and shrubs and, rarely, trees. They are found in tropical, subtropical and temperate regions, being more abundant in arid regions than in humid tropical forests.[7-9]

The secondary metabolites produced by its chemical defense system contributed to the evolutionary success, making it the main responsible for the importance of this family in traditional medicine, with significant use in food, cosmetics and as an ornamental and insecticide plant.[3,8]

The family is known to produce polyacetylenes, sesquiterpenoids, terpenoids, tri-terpenoids, flavonoids, coumarins, benzefurans, and benzepyrans.[10] In Amapá, species of the Asteraceae family are used to treat malaria, flu, diarrhea, gastritis and high blood pressure. It is considered an important family of therapeutic interest due to the diversity of species used by traditional medicine, with special emphasis on *A. Triplinervis*.[11]

Ayapana triplinervis (Vahl) R.M. King and H. Rob.

Originally from South America, *A. triplinervis* (synonym: *Eupatorium triplinerves*) is found in Brazil, Ecuador, Peru, Puerto Rico and Guyana, in addition to being adapted in other countries such as India and Vietnam[12] and can be found in two morphotypes:[13] Japana-branca (morphotype A) and Japana-roxa (morphotype B), which can measure between 40 and 50 cm in height, erect or semi-prostrate..

The species is widely used by traditional communities in South America, Asia and Africa, with special emphasis on mystical-religious rituals in the Amazon. Its leaves are widely used in the form of teas, decoctions or baths for the treatment of viruses, respiratory, gynecological and spiritual diseases, as shown in Table 1.

Secondary Metabolites of *A. triplinervis*

The coumarins Ayapin (1), Ayapina (2), thymoquinol dimethyl ether (3), thymoquinone (4) and methylthymyl ether (5) were identified in the aqueous extract of *A. triplinervis* leaves.[22] Galvin-Bialecke and Marodon[12] cited the presence of 07 different categories of coumarins: ayapanin, ayapina, daphnetin (6), daphnetin dimethyl ether (7), 7-methyl-daphnetin ether (8), hydrangetin (9) and umbelliferone (10), in addition, the authors identified the presence in the essential oil of the leaves of the plant of dimethyl ether thymohydroquinone with 89.9 - 92.8% (11) in species from Reunion Island.

Gupta, Charles and Garg,[23] studying essential oil from the leaves of the species collected in Lucknow, described the presence of the major compounds selin-4(15),7(11)-dien-8-one with 36.6% (12), β-caryophyllene with 14.7% (13) and δ-elemene with 5.9% (14). Sugumar, Karthikeyan and Gowdhami[24] evaluated the chemical composition of the species from Kanchipuram district, India, and found 1,4-dimethoxy-2-tert-butylbenzene with 74.27% (15) and 1,4-dimethoxy-2-tert-butylbenzene as major compounds (15) β-selinene with 8.59% (16).

Unnikrishnan *et al*.[25] collected essential oils from Kerala, India, and found the dimethyl ether thymoquinone in greater amounts, ranging from 80.3% to 86.9% (11). In Brazil, Mala *et al*.[26] described the essential oils of *A. triplinervis* collected in the region of Lagoa Grande, Amapá, and showed as major compounds 2,5-dimethoxy p-cymene with 69.7% (11) and p-caryophyllene with 19.7% (17). Figure 1 demonstrates the molecular structure of the compounds identified in the literature from the species:

Biological Activity of *A. triplinervis*

Regarding phytochemical studies and validation of ethnopharmacological use, although most authors do not differentiate the chemical composition of each morphotype as a function of the species' biological activity, some studies have been dedicated to evaluating the medicinal use indicated by traditional communities, and its correlation with the secondary metabolites.

A. triplinervis is compared with Matricaria chamomilla in relation to its medicinais properties, thus, evaluations of the antinociceptive, anxiolytic, antidepressant, antiulcerative, antineoplastic and antimelanogenic potential *in vitru* and *in vivo* have received special attention by the scientific community, as demonstrated by the Table 2.

Pretreatment with hydromethanolic extract of *A. triplinervis* leaves prevented ulcerative lesions and stimulated the production of prostaglandins, as well as scavenging free radicals and inhibiting oxidative peroxidation in albino winstar rats as a mechanism of action of antiulcer activity.[33] Another study demonstrated that the major compound found in the essential oil of A. triplinervis, thymohydroquinone dimethyl ether, is able to block the initial stages of viral infection, preventing the entry of ZIKAV into the cell by default in the endocytosis stages of viral particles.[34] A. triplinervis extracts can also inhibit gene expression of IL-1β, IL-6, COX-2 and iNOS and protect against the deleterious action of hyperglycemic expression *in vitro* tests.[35]

Table 1: Ethnopharmacological and mystical-religious use of *A. triplinervis*.

Author	Study collection location	Plant organ	Use
Pattanayak and co-works.[14]	West Bengal (India)	Leaves	Dysentery and bloody enteritis
Roeder and Wiedenfeld[15]	Madagascar and Mascarene Islands (Africa)	Leaves	Stomach burning, indigestion, diarrhea, insomnia, nausea, ulcer, vomiting and flu. Astringent, emollient, fever, colds, pneumonia.
Ferreira and Tavares-Martins[16]	Pará (Brazil)	Leaves	Mystical-religious
Mahomoodally and Sreekeesoon[17]	Mauricio Islands (Africa)	Leaves	Vomiting, diarrhea, stomach pain and colitis
Coelho-Ferreira[18]	Pará (Brazil)	Leaves	Constipation, headache and cough
Pattanayak, Mandal, and Bandyopadhyay[14]	West Bengal (India)	Leaves	Control of menstrual bleeding
Maia and Andrade[19]	Amapá (Brazil)	Leaves	Diseases of the respiratory system and relief of their symptoms
Carmo and co-works.[20]	Pará (Brazil)	Leaves	Flu, constipation, headache and cold sore
Suroowan and Mahomoodally[21]	Mauritius Islands (África)	Leaves	Abdominal distension

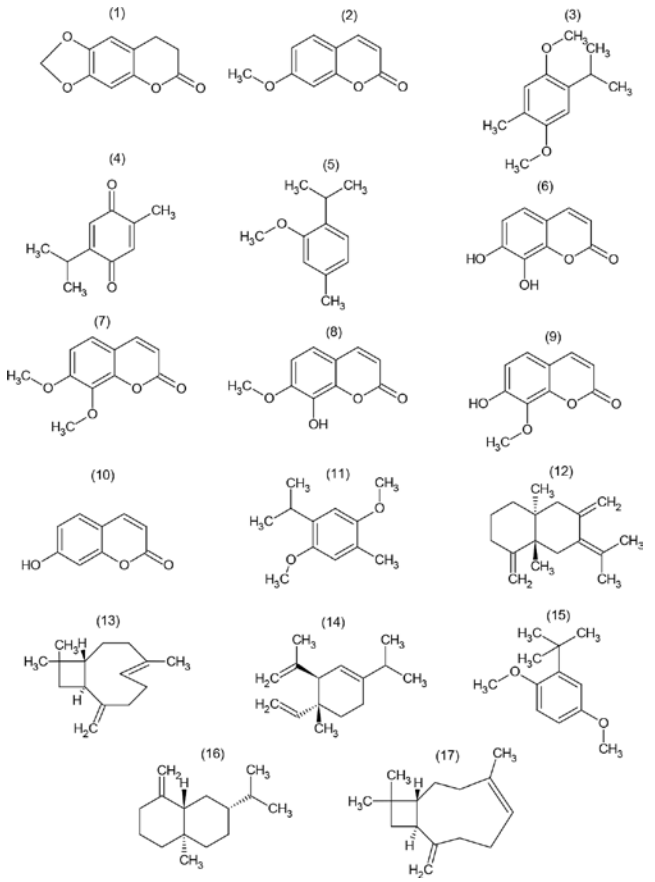

Figure 1: Secondary metabolites reported in the scientific literature for *A. triplinervis*.

Table 2: Phytochemical prospection and biological activity of *A. triplinervis*.

Authors	Substrate	Biological activity
Parimala, Binoy and Viswanathan[27]	Petroleum ether extract	Antinociceptive and anti-inflammatory activity
Arung and co-works[28]	7-methoxy coumarin	Antimelanogenic activity and inhibition of B16 melanoma cells.
Melo and co-works[29]	hydroalcoholic extract	Anxiolytic, antidepressant, antinociceptive and antioxidant in an animal model.
Krishnan and co-works[30]	methanolic extract	Anti-ulcerative effect in an animal model
Mayti, Bepari and Choudhury[31]	Aqueous and ethanolic extract	Antimitotic, apoptotic and antineoplastic potential in Ehrlich carcinoma *in vivo* and *in vitro*
Salvamangai and Bhaskar[32]	Methanolic extract	Hypocholestemic, antioxidant, antiproliferative and anticancer activity
Maity and co-works[33]	Hydrometanolic extract	Potential gastroprotective activity against indomethacin-induced gastric ulcer
Haddad and co-works[34]	Thymohydroquinone	Anti-ZiK infection
Taile and co-works[35]	Aqueous acetonic solution	Antioxidant and anti-inflammatory activity
Checkouri and co-works[36]	Aqueous extract	Oxidative Stress in Red Blood Cells

Evaluation of the Biocidal Activity of *A. triplinervis*

A. triplinervis has been evaluated for use as chemical control of harmful pathogens in agriculture or in the control of vectors of infectious diseases. Verpoort and Diwal[37] determined moderate biocidal activity of the ethanol extract on *Bacillus subtilis*. Jelager, Gurib-Fakime Adsersen,[38] evaluating the antimicrobial activity of methanolic plant extracts, observed moderate inhibition against gram positive and gram negative bacteria such as *Escherichia coli, Pseudomonas aeruginosa, Salmonella typhi, Staphylococcus aureus* and *Candida alicans* and antifungal activity in *Aspergillus Niger.*

Gupta and co-works[23] conducted a study evaluating the antimicrobial activity of extracts in petroleum ether and methanol with a positive test for steroids, coumarins, tannins and saponins; and determined high bactericidal activity in gram positive bacteria such as *B. subtilis, S. aureus, S. epidermidis, Micrococcus leuteus* and in gram negative bacteria such as *E. coli, P. aeruginosa, S. typhi, Vibrio cholerae, Vibrio parahaemolyticus*; and in the fungi *A. niger, A. flavus, Alternaria solani* and *Fusarium solani.*

In another study conducted by Lopes and co-works,[39] the authors described the antimicrobial activity of the non-polar fraction of the methanolic extract of the species against gram-negative bacteria *E. coli* with the presence of saponins, reducing sugars, coumarins, alkaloids, triterpenoids and steroids.

In other studies, Sugumar, Karthikeyan and Gowdhami[24] indicated that *A. triplinervis* essential oil has moderate antibacterial activity against *S. typhae* and *Shigella sonnei*, and high antifungal activity against *Macrophomina phaseoline* and *Botryodiplodia theobromae*. Unnikrishnan *et al.*[25] reported antimicrobial activity in *P. aeruginosa, Klebsiella pneumoniae, E. coli, S. aureus, Penicillium chrysogenum* and *C. albicans*. Its major compound, thymoquinone dimethyl ether, showed lower antimicrobial activity, suggesting that it depends on its minor constituents.

Facknath and Lalljee[40] evaluated different extractions of *A. triplinervis* in agricultural pests such as *Plutella xylostella, Crocidolomia binotalis* and *Myzus persicae* and concluded that alkaloids and tannins exhibited the greatest food deterrent in *P. xylostella* and *C. binotalis*, followed by phenols and flavonoids. In the case of *M. persicae*, extracts of *A. triplinervis* stopped the growth and development of nymphs and observed significant pest control properties, indicating them as good candidates for further study of their potential as botanical pesticides as an alternative to synthetic insecticides.

Rodrigues and co-works[41] evaluated the larvicidal activity in *Aedes aegypti* model of essential oils from *A. triplinervis* and their results indicated that morphotype A presents β-Caryophyllene (45.93%) and Thymohydroquinone Dimethyl Ether (32.93%) as major constituents (LC_{50} = 122.08 μg.mL^{-1}) and morphotype B has Thymohydroquinone Dimethyl Ether (84.53%) (LC_{50} = 86.19 μg.mL^{-1}) with low toxicity to mammals not targeted by the insecticidal action of the essential oil.

CONCLUSION

A. triplinervis is chemodiverse in coumarins, however, from the chemossystematic point of view, few studies have evaluated the biological activity as a function of the secondary metabolites of each morphotypes of the species. *In vitro* and *in vivo* biological activity studies demonstrate the validation of the ethnopharmacological action reported by traditional communities, such as antiviral, antinociceptive, antiulcerative, anxiolytic, biocidal and indicate the phytotherapic potential of the species.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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