1428/AJ 144

An updated review on medicinal importance, pharmacological activities and phytochemical compounds of an ayurvedic herb *Cynanchum annularium*(Roxb.) (*Jeevanti*) Liede & Khanum

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Received: 11-04-24 Revised: 26-07-24 Accepted: 29-07-24

Abstract: *Ayurveda*, the traditional Indian system of medicine explores the healing effects of plants and consider them as a boon from nature. *Cynanchum annularium* (*Jeevanti*), a well-known and less explored medicinal herb holds a special position among ayurvedic and traditional practitioners especially in South India. Its different parts were being used for a variety of medicinal uses for centuries. Each medicinal herb has its own unique medicinal properties by the virtue of its characteristic chemical constituents. The synergetic activity of these compounds imparts promising and desirable pharmacological activities to them. This review, delves into the domain of *Cynanchum annularium*, exploring its botanical characteristics, historical uses, phytochemical composition and the latest scientific research surrounding its medicinal properties. Present review also included its role in traditional ayurvedic practices to its modern-day applications and uncovers the diverse facets of this intriguing plant and evaluate its potential contributions to the world of herbal medicine. The updated review of *Cynanchum annularium* is enlightening its medicinal importance.

Key words: Cynanchum annularium, atapatiyan, Pharmacological activities, Phytochemical compounds

INTRODUCTION

Cynanchum annularium (syn. *Holostemma ada-kodien*, *Sarcostemma annulare* Roth, *Holostemma annulare* Roth) also known as *atapatiyan* or *arkapushpi*, is a fascinating and well-known botanical wonder that has been used for centuries in traditional medicine. In South India, *C. annularium* is considered as a substitute of *jeevanti*, though ayurvedic pharmacopoeia equates it to *Leptadenia reticulata* (Retz.) Wight & Arn. Ayurvedic texts mentioned it as a drug with well-intentioned rejuvenative properties that boosts the energy level of body. *C. annularium* is a native to several indigenous tropical and subtropical regions of South Asia, where it has been traditionally used in folk medicine. Distribution of the plant is mainly in India, Sri Lanka, Myanmar and Western China. It is described as a herb with sweet, cold, aphrodisiac, light to digest, rejuvenative properties, which enhances life, vigor and fertility. Its rich ethnobotanical history and the growing body of scientific literature on its bioactive compounds make it an important subject of investigation for researchers. It comes

under the family Apocynaceae. *C. annularium* is a laticiferous, perennial twining shrub ascending up to an altitude of 1,875 m. (See Figure 1.) It is used as a drug of choice for emaciation, weakness, fever, difficult breathing, burning sensation in body, fertility issues, eye diseases, cough, as a galactagogue, orchitis, in the treatment of diabetes, stomach-ache and spleen enlargement. The leaves, flowers and fruits are eaten as vegetables and also garnered attention for potential health benefits and therapeutic properties.[1,2]

Figure 1. *Cynanchum annularium*

Tuberous roots of *C. annularium* are utilized as a substitute for the drug *jeevanti* in ayurvedic medicine system, especially in South India. *C. annularium* rhizome is considered as a *rasaayana* medicine that is a tonic drug in *ayurveda*. The quick or premature aging is a disorder happening in youths, owing to unhealthy lifestyles including food. Reactive oxygen and related species reaching our system whether indigenously or not, can injure cells and will lead to diseases related to oxidative stress like rapid aging.[3] *C. annularium*, an important rejuvenating drug is considered as a choice for these irregularities in *ayurveda*. These beneficial medicinal properties might be related to the antioxidant and protective activities of *C. annularium* rhizome. There is a huge demand of root tubers of this plant by herbal pharmacies in South India. Confirming the authenticity of genuine drug for preparation of formulations is further a major problem faced by ayurvedic industries. In this review focus is given on the reported medicinal activities and valuable compounds from *C. annularium*. The present study on *C. annularium* with attention on pharmacological activities and phytochemical compounds might be helpful in highlighting its medicinal activities and to get recognition in modern research.

Medicinal importance

The roots of *C. annularium* are useful in treating ophthalmopathy, orchitis, cough, burning sensation, stomach pain, constipation, fever and for balancing *tridoshas*. The root can also be used as a rejuvenative drug, imparting resistance to diseases or improving immunity.[1] Many

pharmacological studies have been conducted on various parts of *C. annularium* and these medicinal properties can be considered as a cumulative output of synergistic effect of chemical compounds present.

PHARMACOLOGICAL ACTIVITIES

Anti-oxidant activity

Anti-oxidant activity can play a pivotal role in managing the accumulation of oxidative damage due to the reactive free radicals. Reactive oxygen and related species reaching our system whether indigenously or not, can injure cells leading to diseases related to oxidative stress like rapid aging. The compounds or extracts which have the potential to counteract these free radicals can act as a remedy. The natural antioxidants, especially polyphenols and flavonoids, exhibit a wide range of biological effects, especially anti-oxidant activity, the prime lead in anti-aging property. *C. annularium* root tuber extracts demonstrated good antioxidant benefits in different assays conducted. Extracts like ethyl acetate, methanol and hydroalcohol showed predominant results in various antioxidant tests including ABTS scavenging, Nitric oxide quenching and DPPH scavenging assays and in ferric reducing assays and identified hydroalcohol as the therapeutically more active.[3] Its extracts also exhibited dose dependent manner scavenging activity against superoxide radicals, hydroxyl radical, hydrogen peroxide and showed relatively higher reducing power compare to that of BHT. [2,4] Antioxidant compounds derived from medicinal plants were also been increasingly investigated for their various nutritional function and health benefits. Various compounds identified from *C. annularium* have well reported antioxidant activities. Compounds isolated from *C. annularium* such as 3,4 - dihydroxycinnamic acid, 7- hydroxyl -6 - methoxycoumarin, quercetin and acacetin showed prominent antioxidant activity and potential promising effects in various antioxidant tests conducted.[2,5,6]

Anti-inflammatory activity

The previously conducted studies provided a scientific rationale in using *C. annularium* roots in traditional drug preparations for diseases linked with inflammation. *C. annularium* extracts were widely studied for their anti-inflammatory activity. Methanol extract of the root tuber was evaluated for *in-vitro* anti-inflammatory activity by proteinase inhibition assay, cyclooxygenase and lipoxygenase inhibition assays. Promising results obtained revealed that root tuber possesses significant anti-inflammatory activities.[7,8] Anti-inflammatory activity of

water extract of *C. annularium* root tuber was determined *in-vivo* in carrageenan-induced rat paw edema model rats. Extracts at a concentration of 150 mg/kg showed a reduced swelling of 32.69%, when compared to the 100% swelling of the induced group. The result confirmed its good anti-inflammatory activity and the results were superior when compared with the *Leptadenia reticulata*.[9] The results emphasize the potential application of tuberin drug formulations for inflammatory diseases.

Anti-diabetic activity

The tuberous roots of *C. annularium* are well utilized in traditional medicine systems to treat diabetes.Anti-diabetic activity or hypoglycemic activity of *C. annularium* was researched in many studies and the results were worthy. Anti-diabetic activity of *C. annularium* was evaluated by streptozotocin induced diabetes and high-fat diet with streptozotocin-induced diabetes rats in a previous study. In diabetic control rats, glucose, cholesterol, triglycerides and LDL values were elevated to a high level during the study whereas HDL value was decreased. *C. annularium* treatment showed a noteworthy decrease in glucose level and decreased the elevated cholesterol level during study. Effect was superior to metformin,which was used as standard drug.[8]In another study anti-diabetic activity of ethanolic extract was evaluated in normal, glucose fed, alloxan-induced diabetic rats. Study was done by oral administration of extract (200 and 400 mg/kg body wt) for 7 days. The effect was comparable with glibenclamide, a synthetic drug. The alcoholic extract of *C. annularium* significantly lowered the blood sugar of hyperglycemic rats. From toxicity study performed, it was observed that *C. annularium* was nontoxic up to 5 g/kg body weight.[10] Anti-diabetic activity of *C. annularium* was also screened in high fructose diet induced insulin resistance and in C57BL/6J ob/ob diabetic mice. Chloroform and methanolic extracts of the roots were administered to normal and experimental diabetic rats for 21 days. Serum glucose, triglycerides, cholesterol levels and total protein in urine were analyzed. Vital results were observed in the estimated parameters of *C. annularium* treated group.[10] The antidiabetic potential of the alcohol root extract was also checked in the streptozotocin-nicotinamide–induced type 2 diabetic model. Alcohol extract was administered to normal and experimental diabetic rats for fifteen days. A significant ($p<0.05$) reduction was observed in the fasting blood glucose levels of normal as well as diabetic rats. Serum insulin levels were stimulated in the diabetic animals on treating with *C. annularium* extract. Body weight, serum lipid profiles, serum urea and creatinine levels were decreased on estimation in extract-treated normal and diabetic rats. The glycosylated hemoglobin and liver glycogen levels were also

assessed and significant results were observed in the estimated parameters. These data justify its use in formulations for the treatment of diabetes mellitus. Anti-diabetic activity of alcoholic and aqueous extracts of tuberous roots of *C. annularium* was compared in a study. The alcoholic extract at dose (300mg/kg) produced maximal serum glucose lowering effect in both normal and streptozotocin induced diabetic rats. The aqueous extract produced maximal percent reduction in serum glucose levels with dose (400mg/kg). The effect produced by alcoholic extract was found better than that of standard gliclazide, a hypoglycemic agent. The alcoholic extract has exhibited higher and better hypoglycemic and anti-diabetic activity for a prolonged period than that of the aqueous extract.[11,12,13]*C. annularium* has showed significant anti-hyperglycemic activity and anti-diabetic activity when compared to *Leptadenia reticulata*.

The root tubers were reported to contain compounds like β-sitosterol, lupeol and alpha-amyrin as major constituents which have both antioxidant and antidiabetic properties. Moreover, several studies have revealed that antioxidants ameliorate a number of altered physiological and metabolic parameters that occur as a result of type 2 diabetes. *C. annularium*, is reported to have potent antioxidant property and thereby justifying usage in treatment of diabetes mellitus in Indian system of medicine. The results justified the traditional use in the treatment of diabetes widely used in many ayurvedic preparations.

Anti-pyretic Activity

A study was carried out to measure the antipyretic activity of the leaf extracts of *C. annularium*. Methanol and ethyl acetate leaf extracts were challenged against the acetylsalicylic acid, a positive control for the assessment of antipyretic activity in wistar rats, on subcutaneously treated with aqueous suspension of brewer's yeast. The methanolic extract showed dose dependence reduction in hyperpyrexia when compared with the ethyl acetate extract and positive control. Hence further investigation will lead to a potent anti-pyretic agent from *C. annularium*.[14]

Hepatoprotective Activity

A previous reported study was focused on evaluating the potential hepatoprotective effect of methanolic extract of *C. annularium* on paracetamol-induced liver injury in mice. Pre-treatment of rats with alcoholic extract prior to paracetamol administration caused a significant reduction in the values of aspartate amino transferase, alanine amino transferase,

alkaline phosphatase and serum bilirubin ($p<0.01$) approximately comparable to the hepatoprotective drug silymarin.[15] Study showed that alcoholic extract possesses the hepatoprotective effect against paracetamol induced liver damage in rats. This study confirms the use of *C. annularium* as hepatoprotective as per the ethno pharmacological claims.

Anti-helminthic activity

A previous study was carried out to evaluate the anthelmintic activity of macerated ethanolic extracts of *C. annularium* roots. The data revealed that the ethanolic extract showed anthelmintic activity at concentration 50 mg/ml. Since modern drugs have serious side effects and development of resistance, herbal remedies can be a superior alternative for helminthiasis.[16].Another study was carried out to evaluate the in-vitro anthelmintic activity of ethyl acetate leaf extracts of *C. annularium* on Indian earthworm (Pheretimaposthuma) using the various concentrations ranging from 50, 100, 200 and 400μg/ml. Albendazole was used as the standard reference. The results exhibited the anthelmintic activity of leaf extract.[17]

Anti-proliferative activity

The anti-proliferative activity of the *C. annularium* rhizome extract was also reported. The results obtained from the anti-proliferative assay confirmed that the extract was effective in inhibiting HeLa cell line proliferation. Hydro alcohol extract at a concentration of 100 μg/ml inhibited the proliferation by 60% while comparing with the control. The activity is dose dependent and the inhibition increases with increasing the concentration. The obtained IC_{50}value at a concentration 53 μg/ml showed its high inhibition activity in anti-proliferative assay.[3]

Anti-bacterial activity

In vitro antibacterial and antifungal activity of different parts of *C. annularium* was a subject in many studies. Methanolic and aqueous leaf extracts of medicinal plant *C. annularium* had presented antibacterial activity in both gram positive and gram negative bacteria. And the plant extracts exhibited significant antimicrobial potency, comparable to standard antibiotic Gentamycin.[18] In a recent research, poly-dispersed and stable silver nanoparticles (AgNPs) using the leaf extract of *C. annularium* and its leaf extract were evaluated for efficacy in vector control against the mosquitoes Anopheles stephensi, Aedes aegypti and Culex

quinquefasciatus, which act as major vectors of important parasitic and arboviral diseases. AgNPs showed higher toxicity when compared to the *C. annularium* leaf aqueous extract, and LC_{50} towards larvae of A. stephensi, A. aegypti and C. quinquefasciatus were 12.18, 13.30 and 14.70 μg/mL, respectively. When the AgNPs were tested on non-target water bugs, Diplonychusindicus, the LC_{50} value was 623.48 μg/mL. Furthermore, 100 μl/mL of AgNPs achieved significant antimicrobial activity against Bacillus pumilus, Enterococcus faecalis, Pseudomonas aeruginosa, Proteus vulgaris and Candida albicans. *C. annularium*-synthesized AgNPshad major impact on the external topography and architecture of microbial biofilms, on both gram-positive and gram-negative bacteria. The study sheds light on insecticidal and antibiofilm potential of *C. annularium* synthesized AgNPs, a potential green resource.[19] Antibacterial and antifungal activity of oil extract of *C. annularium* and the selected antibiotics were evaluated against four bacterial strains (E. Coli, S. aureus and P. aeruginosa) and three Candida fungal strains (albicans, parapsilosis and tropicalis.). *C. annularium* extract zone of inhibition was compared with Fluconozole and Norfloxacin, Cefepime and Gatifloxacin. In results obtained *C. annularium* has shown significant anti-bacterial and anti-fungal activity.[20] *C. annularium* methanol leaf extract presented activity against microorganisms,E. coli, K. pneumonia, P. aeruginosa, P. vulgaris, S. aureus, B. subtilis and E.s faecalis in another study. These studies confirmed that the *C. annularium* extract can be employed as antimicrobial agents in herbal formulation.[21]

Analgesic Activity

A study was undertaken in order to evaluate the analgesic activity of alcoholic, aqueous and benzene extract of roots of *C. annularium* using acetic acid induced writhing test. Diclofenac sodium was the standard drug and test groups received different extracts of *C. annularium* orally. Study concluded that the aqueous extract of dose 300 mg/body wt. and 600mg/body wt. has shown a significant analgesic activity. Alcoholic and Benzene extract showed a significant analgesic activity at the dose of 600mg/body wt. These results indicated that *C. annularium* possesses significant analgesic activity.[22]

From the above reported studies we can reach a conclusion about the versatile pharmacological activities showed by *C. annularium* and these studies gave a justification to the use of this plant in different formulations. The roots of *C. annularium* did not show any noticeable toxicity in the conducted studies also.

Phytochemical compounds

Preliminary phytochemical investigation of *C. annularium* showed the presence of alkaloids, phenolic compounds, saponins, tannins, flavonoids, steroids,terpenoids, carbohydrates, amino acids and anthocyanins. Various studies including column chromatographic isolation and liquid chromatography mass spectroscopic analysis of the plant extract were also performed in *C. annularium* to identify the major chemical constituents, which were imparting the important pharmaceutical activities. Most of the compounds detected were from *C. annularium* root were medicinally noteworthy.

Terpenoids and steroids

Many important terpenoids and steroids were identified from the rhizome with reported medicinal activities. Terpenoids like alpha-amyrin, lupeol,betulin and ursolic acid were characterized from the roots of *C. annularium*. A steroid 22,23-dihydrostigmasterol was also detected from the root.[2,23]

Coumarins

Major coumarin found in the root was 7-Hydroxy-6-methoxycoumarin and another coumarin, 6,8-Dimethyl-4-hydroxy coumarin was also reported from *C. annularium* root.[2]

Phenolic compounds

Phenolic compounds are important compounds in plant due to their diverse medicinal actions including natural anti-oxidant activity. Many phenolic compounds including phenolic acids and their glycosides were reported from *C. annularium*. Phenolic compounds such as caffeic acid, caffeicacid-3-glucoside, gluconicacid, hydroxy gallic acid, lithospermic acid, ethyl vanillin,1-caffeoyl-5-feruloylquinic acid, 3-o-galloyl quinic acid,resveratrol,5-galloylshikimic acid,gallic acid hexoside and cis-caftaric acid were reported from plant root and their presence might be the reason for the improved anti-oxidant activities of plant.[3]

Flavonoids

Flavonoids have a broad range of medicinal activities reported.Many flavonoids were identified from *C. annularium* root such as phloretin, limocitrin, 5-hydroxy-3,4,7-trimethoxyflavone,myricetin, quercetin-o-galloyl hexose,rhamnetin, quercetin, 3',4',5-trihydroxy-6,7-dimethoxyflavone,gallocatechin,eriodictyol-7-glucoside,7,3′-dihydroxy flavone, 3,7-dihydroxy-3′, 4′-dimethoxyflavone, kaempferol, 3,4-dimethoxycinnamic acid,

pinocembrine, glabranine and 5,7-dimethoxyluteolin[3].The identification of these compounds help to recognize the unexplored medicinal activities of *C. annularium*.

In the present review, phytochemistry and pharmacological activities of *C. annularium* are tried to summarize.

CONCLUSION

C. annularium has garnered increasing attention in recent years due to its intriguing pharmacological properties and potential applications in various fields, particularly in the realm of medicine and pharmaceuticals. This detailed review paper was aimed to provide a comprehensive overview of the current state of research on *C. annularium,* synthesizing the key findings, advancements and emerging trends in the study of this remarkable plant. *C. annularium* is considered as an ayurvedic drug which helps in maintenance, promotion of health and major pharmacological activities like hypoglycemic and antidiabetic activity, antipyretic activity, antioxidant activity, antibacterial activity, anti-proliferative activity and analgesic activity were reported. The active and important chemical compounds identified from *C. annularium* by phytochemical studies like terpenoids, flavonoids, coumarins, steroids and phenolic compounds were also reported. The present review recognized the important therapeutic activities and major chemical compounds from *C. annularium* rhizome which will be benefit in proving its medicinal importance and to notice it for future research.

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