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A Comprehensive Review on the Phytochemical and Pharmacological Activities of *Adiantum capillus-veneris* L.

Sanjay Kumar[1], Reshma Kumari[2*]

[1]*Department of Botany, Pt. Badridutt Pande Govt. PG College, Bageshwar, India*

[2]*Department of Botany and Microbiology, Gurukula Kangri Vishwavidhyalaya, Haridwar, India*

[*]***Corresponding author:*** *Reshma Kumari, Department of Botany and Microbiology, Gurukula Kangri Vishwavidhyalaya, Haridwar, India, E-mail: reshmagupta25@gmail.com*

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ABSTRACT

In the tropical and temperate regions *Adiantum* (*Pteridaceae*) genus forms a significant dominant component of many plant communities. These are commonly known as maidenhair ferns. In different parts of the world the species of this genus have been used for their medicinal values. They exhibit antiviral, antitumor, antiulcer, antimicrobial and ant dysenteric activities. The traditional uses of *Adiantum* species are known to be for respiratory problems such as pneumonia, fever, mucous formation and cough cold. The present review provides detailed information on the folk/traditional uses, phytochemical constituents and different pharmacological properties of *Adiantum capillus-veneris* to discover its therapeutic potential and evaluate future research opportunities.

Keywords: *Adiantum*, Ethno medicinal, Phytochemical constituents, Pharmacology.

INTRODUCTION

Pteridophytes, one of the oldest and primitive vascular plant groups on earth having leaves, roots and erect stems, represented by 48 plant families with 587 plant genera in the world. The genus name, *Adiantum*, is derived from the ancient Greek word “Adiantos”, meaning “unwetted”. *Adiantum* species, commonly known as maidenhair ferns, are traditionally used in respiratory problems such as cough cold, fever, pneumonia and mucous formation, astringent, demulcent, diuretic, emmenagogue, expectorant, tonic, febrifuge, emollient, anticatarrhal and in diabetes and erysipelas. *Adiantum capillus-veneris* L. has also been included in the ayurvedic pharmacopoeia of India and has been mentioned by dioscorides in his materia medica. Several studies have been conducted to substantiating their effectiveness in traditional medicine and to describe the chemical as well as pharmacological properties. The available information on this species was collected from scientific databases such as PubMed, SciFinder, Science direct, Scopus, Web of science and Google scholar. The search terms used for this review included *Adiantum capillus-veneris*, phytochemical composition, traditional uses, activity, pharmacology and toxicity [1].

LITERATURE REVIEW

Distribution

The plant is widely distributed in Southern Europe, Atlantic coast as far as Ireland, from the south to the southern Alpine valleys regions, from the central to the South America, Australia and Iran [2].

Botanical description

Stems short-creeping; scales golden brown to medium brown, concolored, iridescent, margins entire or occasionally with single broad tooth near base. Leaves lax-arching or pendent, closely spaced, 15 cm-75 cm. Petiole 0.5 mm diam-1.5 mm diam., glabrous, occasionally glaucous. Blade lanceolate, pinnate, 10 cm-45 cm × 4 cm-15 cm, glabrous, gradually reduced distally; proximal pinnae 3(-4)-pinnate; rachis straight to flexuous, glabrous, not glaucous. Segment stalks 0.5 mm-3.5 mm, dark color extending into segment base. Ultimate segments various, generally cuneate or fan-shaped to irregularly rhombic (plants in American southwest occasionally with segments nearly round), about as long as broad; base broadly to narrowly cuneate; margins shallowly to deeply lobed, incisions 0.5 mm-7 mm, occasionally ± laciniate, sharply denticulate in sterile segments; apex rounded to acute. Indusia transversely oblong or crescent-shaped, 1-3(-7) mm, glabrous [3].

Phytochemical constituents

Hop-22(29)-ene(=Diploptene); Hopan-22-ol(=Hopanol, Hydroxyhopane); 17α, 29-Epoxyhopane; Hopan-28,22-olide; Neohop-12-ene(=Neohopene); 22,29,30-Trisnorhopane; 17αH-Trisnorhopan-21-one(=Isoglaucanone); 21-Hydroxy-30-norhopan-22-one(=21-Hydroxyadiantone, Hydroxyadiantone); 30-Norhopan-22-one, (21α)(=Adiantone); Fern-9(11)-en-28-ol; Fern-9(11)-en-3α-ol; Fern-9(11)-en-12β-ol; Fern-9(11)-en-12-one; Fern-9(11)-ene(=Fernene, Davallene); Fern-7-en-3α-ol; Fern-7-ene(=7-fernene); Ferna-7,9(11)-diene; Fern-9(11)-en-28-ol; Adian-5-en-3α-ol; Adian-5-ene(=Adianene); Adian-5(10)-en-3α-ol; 4α-Hydroxyfilican-3-one; 3α,4α-Epoxyfilicane(=Adiantoxide); Olean-18-en-3-one; Olean-12-en-3-one; Pteron-14-en-7α-ol; Hopan-3β-ol(=capillirol B); 30-Normethyl fernen-22-one(=capillirone); 4α-Hydroxyfilican-3-one; 3-β,4α-Dihydroxyfilicane; 30-Norhopan-22-one, (21β)(=Isoadiantone); (22S)-30-Norisohopan-22-ol(=Isoadiantol B, Isoadiantol); 3-β,4α-Dihydroxyfilicane; 3-Methoxy-4-hydroxyfilicane; 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4Hchromen-4-one(Quercetin); Quercetin-3-O-β-D-rutinoside(Rutin); Quercetin 3-O-β-D-glucopyranoside(Isoquercetin/isoquercitrin); Quercetin-3-O-β-D-rutinoside(Rutin); Quercetin-3-O-β-D-glucuronide(Querciturone); Kaempferol-3-O-β-D-glucopyranoside(Astragalin); Kaempferol 3-glucuronide; Kaempferol-3-O-β-rutinoside(Nicotiflorin); Quercetin 3-O-(6"-malonyl)-D-galactoside; Kaempferol-3,7-diglucoside; Kaempferol-3-sulphate; Kaempferol-3-O-rutinoside sulfate; 1-p-Coumarylglucose-6-sulphate; l-p-Coumarylglucose-2-sulphate; l-Caffeylglucose-3-sulphate; 1-Caffeylgalactose-6-sulphate; 1-Caffeylglucose; Shikimic acid; Quinic acid; Daphnoretin(coumarin dimer); β-Sitosterol; Stigmasterol; Campesterol; triterpenoids(1-3), fern-7(8)-en-19α, 28-diol(1), pteron-14-ene-7α,19α,28-triol(2) and 3β,4α,25-trihydroxyfilican(3).

Pharmacological activities

Antibacterial and antifungal activity: *A. capillus-veneris* is a medicinally essential plant used for the treatment of diverse infectious diseases. Ishaq and coworkers examined the phytochemical and antimicrobial activities of the methanol, ethanol, ethyl acetate and hexane extracts of leaves, stems and roots (60 μL (1mg/1 mL of each extract)) against multidrug-resistant bacteria (*Citrobacter freundii, Escherichia coli, Providencia specie, Klebsiella pneumoniae, Proteus vulgaris, Salmonella typhi, Shigella, Vibrio cholerae, Pseudomonas aeruginosa* and *Staphylococcus aureus*) and medically important fungi (*Candida albicans, Pythium, Aspergillus flavis, Aspergillus niger* and *Trichoderma*). Phytochemical analysis showed the presence of flavonoids, alkaloids, tannins, saponins, cardiac glycosides, terpenoids, steroids and reducing sugars. They concluded that extracts of *A. capillus-veneris* have valuable phytochemicals and significant activities against most of the multidrug-resistant bacterial strains and medically important fungal strains. The all extract showed significant antibacterial activity against all bacterial strains leaves methanol extract has shown highest antifungal activity against *C. albicans* (30 mm), *A. flavis* (30 mm), *A. niger* (30 mm), *Pythium* (28 mm) and *Trichoderma* (28 mm) [4].

Hussain and coworkers studied the *in vitro* antibacterial activity of methanol and water extracts of leaves and stems of *A. capillus-veneris* and *Tagetes patula* against *Citrobacter freundii, Escherichia coli, Providencia, Pseudomonas aeruginosa, Staphylococcus aureus, Klebsiella pneumoniae, Proteus vulgaris, Salmonella typhi, Shigella* and *Vibrio cholerae*. Leaf methanol extract of *A. capillus-veneris* showed maximum activity against *Providencia* (29 mm), *K. pneumoniae* (28 mm), *Shigella* (29 mm), *V. cholerae* (28 mm), *S. aureus* (27 mm), *P. vulgaris* (24 mm) and *S. typhi* (24 mm), while its stem methanol extract showed maximum activity against *E. coli* (29 mm), *K. pneumoniae* (24 mm) and *S. typhi*

(24 mm) [5].

The crude and phenolic extracts of gametophyte and sporophyte of *A. capillus-veneris* showed antibacterial properties. The antibacterial activity of gametophytic part of *A. capillus-veneris* was more significant. Gram-positive species like *Bacillus subtilis* displayed more susceptibility to both gametophyte and sporophyte extracts. However, the ethanolic extract of *A. capillus-veneris* aerial parts showed no antimicrobial activity against *E. coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

Antioxidant activity

The antioxidant capacity of ultrasonic-assisted flavonoid extract of *A. capillus-veneris* through DPPH (1,1-diphenyl 1-2-picryl-hydrazyl), scavenging capacity of superoxide anion, chelating capability of ferrous ion and reducing power tests using acute mice liver injury experiment exhibited more potent antioxidant activity than some synthetic antioxidants such as Butylated Hydroxytoluene (BHT), Ethylenediaminetetraacetic Acid (EDTA) and ascorbic acid. *In vivo* evaluation displayed significant decrease in superoxide dis-mutase, catalase and glutathione levels and notable increase in malondial-dehyde levels. In another study the ethanolic leaf extract of *A. capillus-veneris* examined against hydrogen peroxide-induced oxidative damage in peripheral blood lymphocytes. The results demonstrated inhibition of lipid peroxidation and increase in the level of antioxidant enzymes including Superoxide Dismutase (SOD), Catalase (CAT), GPx and glutathione content. Antioxidant property of the essential oil through DPPH also give significant results because of phytoconstituents such as carvone, carvacrol and thymol. In addition, a compared study of *A. capillus-veneris* and *M. punctatum* were reported that the rises in the malondialdehyde levels and antioxidant enzymes including superoxide dismutase and glutathione peroxidase in *M. punctatum* were more potent [6].

Yadegari and coworkers studied the antioxidant activity of *A. capillus-veneris* (500 ml/kg) on wistar male rats (4 weeks, height=72 ± 8 gr). They observed that the extract in the supplemental hypoxia resulted in a significant decrease of the TNF-α expression of the lung parenchyma (34%) compared to the hypoxia group, decreased protein expression of the P53 parenchyma (41.08%) and increment in the respiratory surface of the lung parenchyma (36.57%). They concluded that *A. capillus-veneris* extract may possibly reduce the effects of proteins expression through elements such as flavonoids, terpenoids, phenylpropanoids and other antioxidant factors and it can possibly moderate, to some extent, the disruptions caused by hypoxia exposure to lung. *A. capillus-veneris* extract also significantly reduced P53 and TNF-a expression and increased respiratory surface in wistar rats [7].

Zeb and Ullah examined the leaves samples for carotenoids, chlorophylls and phenolic compounds using reversed phase High-Performance Liquid Chromatography (HPLC) with Diode-Array Detector (DAD). They obtained eight carotenoids, four pheophytins and two chlorophylls. Lutein (806.0 μg/g), chlorophyll b′ (410.0 μg/g), chlorophyll a (162.4 μg/g), 9′-Z-neoxanthin (142.8 μg/g) and all-E-violaxanthin (82.2 μg/g) were found in higher amounts. The relatively high amounts of lutein (806.0 μg/g) may be one of the key indicators of beneficial antioxidant properties. The phenolic profile revealed a total of 13 compounds, namely 4-hydroxybenzoic acid, chlorogenic acid, caftaric acid, kaempferol glycosides, p-coumaric acid, rosmarinic acid, 5-caffeoylquinic acid and quercetin glycosides. Kaempferol-3-sophorotrioside (58.7 mg/g), chlorogenic acid (28.5 mg/g), 5-O-caffeoylquinic acid (18.7 mg/g), coumaric acid (11.2 mg/g) and its derivative (33.1 mg/g) were present in high amounts [8].

Anti-diabetic activity

Ranjan and coworkers investigated the antidiabetic efficacy of aqueous (100 mg/kg, 200 mg/kg and 400 mg/kg, orally) and methanol (200 mg/kg and 400 mg/kg, orally) extracts of whole plant of *A. capillus-veneris* in streptozotocin induced diabetic rats. They observed higher amount of fats, flavonoids, triterpenoids, phenols, tannins, saponins and fats in leaves and stem. They found that the methanol (400 mg/kg; 273 mg/dl) and aqueous extract (100 mg/kg; 278 mg/dl) caused a significant decrease in the blood glucose levels of diabetic rats [9].

Kasabri, studied the dual anti-diabetic antiobesity pharmacotherapeutic effects of *A. capillus-veneris* using positive controls (acarbose, orlistat, guar gum, atorvastatin, glipizide and metformin) as appropriate, crude aqueous extracts of *A. capillus-veneris* aerial parts with a combination of *in vitro* enzymatic (0.24 mg/mL-100 mg/mL), acute *in vivo* carbohydrate tolerance tests (125 mg/kg, 250 mg/kg or 500 mg/kg body weight) and chronic *in vivo* studies (500 mg/kg) in high cholesterol diet fed wistar rats. Like acarbose, *A. capillus-veneris* as well as chlorogenic acid (IC50-0.8 and 0.2) were identified as *in vitro* potent dual inhibitors of a-amylase/a-glucosidase. Equivalent to orlistat, *A. capillus-veneris* and its phytoconstituents inhibited pancreatic triacylglycerol lipase. Incomparable to acarbose or metformin and glipizide, *A. capillus-veneris* (125 mg/kg, 250 mg/kg and 500 mg/kg) lacked antihyperglycaemic efficacies in acute starch or glucose-evoked postprandial hyperglycaemia increments in normoglycaemic overnight fasting rats. Superior to atorvastatin; *A. capillus-veneris* exerted significant antiobesity ($p<0.001$) with

marked triacylglycerol-reducing capacities [10].

Neuropharmacological activities

Jain, et al evaluate the neuropharmacological profile of ethanolic extract of *A. capillus-veneris* by using anticonvulsant activity, antidepressant activity, skeletal muscle relaxant activity and analgesic activity. In mice forced swim assay, the species displayed depressant property by prolonging the immobility time. The ethanolic extract of *A. capillus-veneris* (200 mg/kg and 400 mg/kg) did not showed a significant relaxation of skeletal muscle as like diazepam which was used as a standard reference drug. This extract delayed the latency of seizures induced by pentylenetetrazole suggesting that the extract is useful in suppressing absence seizures. Ethanolic extract was also effective in Maximal Electro Shock induced seizures (MES) Model like phenytoin and may prolong the Na^+ channel inactivation. They concluded that ethanolic extract has anticonvulsant activity against seizures induced by MES in a dose dependent manner [11].

Hypocholesterolemic effect

Al-Hallaq and coworkers obtained ellagic acid (5.48 mg/g), rutin (4.77 mg/g), quercetin-3-O-glucoside (3.96 mg/g), ferulic acid (3.88 mg/g), gallic acid (3.44 mg/g), caffeic acid (1.55 mg/g), epicatechine (1.34 mg/g) and quercetine (0.43 mg/g) from the dried aerial parts of *A. capillus-veneris*. They studied the hypocholesterolemic effect by using High Cholesterol Diet (HCD) fed model in rats. The results exhibited potent reduction of Total Cholesterol (TC), Low-Density Lipoproteins (LDL) and Very Low-Density Lipoproteins (VLDL) serum levels with no effect on High-Density Lipoprotein (HDL) level. Moreover, atherogenic index of TC/HDL was approximately normalized in rats that treated with *A. capillus-veneris*. The crude extracts of the aerial parts exhibited potent antioxidant activity by Oxygen Radical Absorbance Capacity (ORAC), 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) and DPPH assays (2184.95 ± 109.3, 762.50 ± 38.1 and 337.07 ± 16.9 Trolox equivalent µmol/mg, respectively) [12].

Antiobesity effect

A. capillus-veneris exerted significant antiobesity activity with marked triacylglycerol-reducing capacities. The aerial parts water extract of *A. capillus-veneris* exhibited phospholipase inhibitory effect through an *in vitro* model which was comparable to orlistat (114.0 ng/mL). Chlorogenic acid (38.4 µg/mL) is also reported as the most responsible phytoconstituent [13].

Goitrogenic and anti-thyroidal effects

Vijayalakshmi and Kiran Kumar showed that this plant extract significantly increase the levels of T3, T4; decreases the level of TSH and reversal of the thiouracil-induced increase in thyroid weight (goitre) suggesting its thyroid hormone enhancing effect and anti-goitrogenic effect.

Wound healing

Galehdari1 and coworkers studied the effect of the herbal mixture composed of aloe vera, henna, *A. capillus-veneris* and Myrrha on wound healing in streptozotocin-induced diabetic rats (200 g-220 g). They observed significant changes in the expression of the Tgfb1, Mmp3, Mmp9, Il6 and Tnf α genes by real-time-PCR (Polymerase Chain Reaction) at the day 7, the day 14 and the day 21 post-wounding in the diabetic and non-diabetic rats [14].

Anti-inflammatory activity

Ibraheim studied the anti-inflammatory activity of the dried powdered fronds of *A. capillus-veneris* (800 g) fractions of hexane (70 g), chloroform (12 g), ethyl acetate (22 g) and n-butanol (30 g) extracts using adult male mice (25 g-30 g) and rabbits (1.2 kg-1.5 kg). The alcoholic extract of *Adiantum capillus-veneris* showed significant hypoglycaemic effect in rabbit model, started after 30 min of administration of the extract and continued for 4 hours [15].

Yadegari and coworkers evaluated the effect of supplementation of *A. capillus-veneris* extract on Bax/B-cell lymphoma 2 (Bcl-2) ratio apoptotic index and remodeling of pulmonary alveolar epithelial cells in lung tissue of healthy wistar rats (4-week old, 72 gm) during stressful conditions (hypoxia). The observed that after three weeks of hypoxia following six weeks of high-intensity interval training in wistar rats, the Bax/Bcl-2 ratio and the number of type II pneumocytes were increased and the number of type I pneumocytes was reduced significantly which strongly suggest that an apoptosis state was induced in the lung parenchyma and consuming ACV extract modulated this state.

Haider, et al examined the anti-inflammatory activity of the crude ethanolic extract of this plant and its various fractions on albino wistar rats of either gender (150 g-200 g) at a dose of 200 mg/kg po and 300 mg/kg po. All the extracts have shown optimal anti-edema activity at 300 mg/kg

dosages. However, they exhibited moderate anti-edema activity at dosage of 200 mg/kg. They concluded that anti-inflammatory activity of the ethanolic extract and its fractions may be related to the inhibition in the functions of macrophages wherein the extract inhibits the release of inflammatory mediators *viz.* nitric oxcide and TNF-α. Triterpenes may play chief role in the anti-inflammatory property of the plant.

Yuan and team investigate the anti-inflammatory effect of ethanolic extracts of *A. capillus-veneris* and the involvement of NF-κB signaling in the regulation of inflammation through lipopolysaccharide-induced prostaglandin E2 generation in RAW 264.7 macrophage and interleukin 6 and tumor necrosis factor generation in the human mono-cyte model. They observed that extracts inhibited Lipopolysaccharide (LPS)-induced Prostaglandin E2 (PGE2), Interleukin 6 (IL-6) and Tumor Necrosis Factor (TNF-α) production in monocyte/macrophage, which are important inflammatory mediators involved in the pathogenesis of inflammatory diseases. The ethyl acetate fraction contained higher flavones and phenolics than other fractions. Indeed polyphenols can exert their anti-inflammatorical properties at multiple levels, through the modulation of MAPK, Akt and Nuclear Factor kappa B (NF-κB) signaling pathways, inhibiting the production of inflammatory cytokines and chemokines, suppressing the activities of COX and iNOS and decreasing the production of ROS/RNS.

In a study, two new triterpenoids characterised as 30-normethyl fernen-22-one (capillirone) and hopan-3β-ol (capillirol B), along with two known triterpenoids, 4-α-hydroxyfilican-3-one and 3-β,4-α-dihydroxyfilicane, have been isolated from the ethanolic extract of the fronds of *A. capillus-veneris*. Capillirone and 4-α-hydroxyfilican-3-one showed significant anti-inflammatory activity with 33.07% and 42.30% as compared to indomethacin that exhibited 60.00% inhibition in the carrageenan-induced hind paw edema test in rat.

Anti testosterone-induced hair loss effect

Noubarani, et al studied hair growth-promoting activity of *A. capillus-veneris* on albino mice using a testosterone induced alopecia model. They observed significant follicular density in the *A. capillus-veneris* treated group (1.92 ± 0.47) compared to testosterone-group (1.05 ± 0.21) and finasteride-treated animals (2.05 ± 0.49).

Urinary tract effect

Ahmed and coworkers evaluated the anti-calcium oxalate urolithiasic property of hydro alcoholic extract of *A. capillus-veneris* on healthy male Sprague Dawley rats (180 g-210 g). They observed that administration of ethylene glycol and ammonium chloride resulted in hyperoxyluria, caused almost no change and a nonsignificant elevation of calcium levels. The hydro alcoholic extract (127.6 mg/ kg) reduced the elevated level of CaOx crystals, serum urea and creatinine levels. The hydro alcoholic extract reduced super saturation and the size of the particles, therefore advantageous in preventing urinary stone formation by inducing excretion of small particles from the kidney and reducing the chance of retention in urinary tract. The antiinflammatory, antimicrobial and antioxidant activities may partially contribute in the process of lithotriptic effect by inhibiting lithogenesis.

DISCUSSION

The water extract of *A. capillus-veneris* inhibited all tested bacterial species in rat experiment. In mice systemic *Candida albicans* infection model was employed to observe the protective activity of the plant. The extract also reduced the Colony-Forming Units (CFU) of *C. albicans* in the spleen and improved the renal pathological characteristics. The urinary output is raised by the low dosage and high dose significantly reduced the urinary output. This effect is also conformed during an *in vitro* study. The plant controlled the crystal aggregation, crystallization and reduction in the number and the sizes of crystals.

Toxicity and adverse reactions: Haider, et al examined the toxicity of the crude ethanolic extract of this plant and its various fractions on albino wistar rats of either gender (150 g-200 g). Carboxymethylcellulose (1% w/v) was used as vehicle to suspend the extracts and experimental animals received the extract in one of the following doses 50 mg/kg, 100 mg/kg, 200 mg/kg, 300 mg/kg, 500 mg/kg and 1000 mg/kg. The ethanolic extract at a minimum dose of 300 mg/kg onwards shows the reaction in experimental animals. However, no mortality was reported even after 72 hours which indicates that the ethanolic extract is safe up to a single dose of 3 g/kg body weight.

Hydrocarbon Hydroxylase (AHH) and Epoxide Hydrolase (EH) enzyme are responsible for accelerating conversion of carcinogenic compounds like poly aromatic hydrocarbons to active components. Alwan and coworkers study the effects of the ethanolic and aqueous extracts of *A. capillus-veneris* on AHH and EH. They observed no inhibitory effect on AHH and EH enzymes.

Acute oral toxicity when performed on rats which received a single oral dose (2000 mg/kg body weight) of aqueous and methanolic extracts

revealed the non-toxic nature of aqueous and methanol extracts. There were no lethality or toxic reactions found at any doses. Crude extract of *A. capillus-veneris* at 1 g/kg, 3 g/kg and 7 g/kg was administrated orally in mice. After 6 h no sign of acute toxicity including seizure, piloerection and restlessness were observed however, no mortality was seen after 24 h.

Analgesic and antinociceptive activities

The ethyl acetate fraction of the ethanolic extract of *A. capillus-veneris* showed significant analgesic effect. Hot plate and tail immersion tests also confirmed same results in mice. 4-α-hydroxyfilican-3-on showed significant anti nociceptive activity in writhing test that isolated from ethanolic extract of the plant.

Antidiarrheal and antispasmodic activities

The crude extract of dried leaves of this plant was evaluated for antidiarrheal and antispasmodic capacities through castor oil-induced diarrhea mice model (20 g-25 g). The plant extract showed significant protection at tested doses of 300 mg/kg and 500 mg/kg, similar to the effects of loperamide, a standard antidiarrheal agent. The antidiarrheal and antispasmodic activities mediated predominantly through ATP-dependent K^+ channels activation like pathway. The KCO-like spasmolytic constituent(s) in *A. capillus-veneris* are likely to be responsible for antidiarrheal activity in mice.

CONCLUSION

This review provides comprehensive information on the traditional uses, ethnobotanical description, ethnopharmacological properties and phytochemical constituents that have been isolated from *A. capillus-veneris*. Further research should be conducted to explore new potential therapeutic agents and their ethnopharmacological properties of *A. capillus-veneris* for the treatment of life-threatening diseases.

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NA

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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