Review Article

Review on the Pharmacognostical, Phytochemical and Pharmacological aspects of *Tabernaemontana coronaria*

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Sekar *et al.*: Review of *Tabernaemontana coronaria* plant

***Tabernaemontana coronaria* is an ornamental, evergreen, dichotomously branched shrub or small tree with large, shiny dark green leaves and white coloured flowers, pinwheel arrangement of petals, which are especially fragment at night. Stems exude milky latex when broken. The root is acrid, digestible with a bitter and bad taste. No specific environmental conditions are required for the growth of the plant. It can easily grow in garden and along roadsides. The plant is highly used in Chinese, Ayurvedic and Thai traditional medicine for the treatment of several diseases. Phytochemical studies revealed the bioactive chemical constituents of the plants such as monoterpene indole alkaloids, flavonoids, proteins, glycosides, carbohydrates, steroids, enzymes and phenolic acids from leaves, stems and roots of the plant. Pharmacological studies found that the plant extract has an anti-inflammatory, anticancer, antioxidant, antifertility, antifungal, antimicrobial, antidiabetic, antimalarial, cardiovascular effects, hypolipidemic, anticataract, antitussive, insecticidal, antidepressant, anxiolytic activity, local anaesthetic activity, anti-acetylcholinesterase activity, wound healing, hepatoprotective and gastroprotective properties. This article briefly describes the ethanomedicinal uses, pharmacognostical studies, phytochemical constituents and pharmacological activities of *Tabernaemontana coronaria* plant and it's bring the research up-to-date on the bioactive compounds produced by *Tabernaemontana coronaria*, directly or indirectly releated to the human health.**

Key words: *Tabernaemontana coronaria*, diabetes, imipramine, atherosclerosis, indomethacin

Tabernaemontana coronaria species have been used in folk medicine since ancient times. Approximately 100 species of this genus are widely distributed in tropical parts of the world, including Sri Lanka, India, Thailand, Brazil, Egypt, Australia and Polynesia. About 4 species are distributed in India. The species of *Tabernaemontana* are rich in indole and bisindole alkaloids. *Tabernaemontana* genus was named after the birthplace of its discoverer, J. Th. Mueller, Bergzabern. One of the most useful species, *Tabernaemontana coronaria* (*Tabernaemontana divaricata*) belongs to the family Apocyanaceae. *Tabernaemontana divaricata* first described by Linnaeus in 1753. This plant is a small evergreen glabrous shrub or small tree, 4-8 feet high, very attractive plant in roadsides and gardens. It has large and deep green shiny leaves, silvery grey bark, horizontal branches, fragrant flowers with white colour, five-petal pinwheels, gathered in small clusters on the stem tips. Plants commonly referred as milkweed due to the latex content. The plant is considered to be indigenous to India, found throughout sub-Himalayan tracts, from Uttarakhand to Assam and Bengal, extending North Circars and hills of Visakhapatnam. Due to its ornamental and fragrance flowers, the plant is cultivated in gardens. The plant is propagated by the method of cuttings or layering. It is hardy and thrives in rich, well drained garden soil in sunny situations[1,2-6].

Synonyms of *Tabernaemontana coronaria* include *Tabernaemontana divaricata*, *Ervatamia coronaria* and *Ervatamia divaricata*.

ETHNOMEDICINAL USES

The plant is used in paralysis, epilepsy, biliousness, ophthalmia, toothache, blood disease, against intestinal worms, limb weakness, scorpion sting,

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tonic for liver, spleen and brain. Fruits used for ulcers. Flowers and fruits are used in enhanced heartbeat. Leaves used in conjunctivitis, sores, boils, rheumatic pain and diabetes. Wood is refrigerant. Root and bark used against snake bite[4]. The root used as a local anodyne, chewed for relief of toothache. It is applied with lime juice to clear opacity of the cornea. Root is rubbed with water and administered as a vermicide. The milky juices of the leaves are used in ophthalmia and to prevent wound inflammation. The juice of flowers used for burning sensation in eye inflammation[1].

PHARMACOGNOSTICAL STUDIES

Leaves:

Leaves are simple, entire, opposite, elliptic or elliptic-lanceolate, dark green in colour, acuminate, pinnate venation, smooth and glossy leathery texture, 3-6 inches long, margin irregularly wavy and submarginal venation absent[3,4]. Lower epidermal cells are smaller than upper epidermal cells. Double layered palisade cells. Sclerotic epidermis is absent with saucer shape arrangement of vascular bundles and there are a few cells lined with secretary canals and paracytic stomata, spongy tissue 7-8 cells deep, thin-walled[4].

Stem:

Stem of plant is woody, solid, tuber-like and thick, horizontally branched, milky latex exudate when wounded and silvery grey bark[1,3]. Solitary-square and hexagonal prisms of calcium oxalate crystals present in throughout bark. The bark powder appears dull yellow in normal light and pale yellow in Ultraviolet (UV) light[4].

Flowers:

Flowers are small, milky white in colour, borne almost throughout the year, inodorous during day with sweet fragrant at night and has pin-wheel arrangement of 5 petals[1,3].

Root:

The roots are long, solid, cylindrical, more or less tortuous. The root is acrid and bitter taste, no distinct odour. The fracture is short and the outer surface is finely wrinkled longitudinally and occasional bearing thin branches[3,4].

Microscopically, the cork is composed of 8-14 layers and lignified cells which are rectangular shape and tangentially elongated. It has indistinct phellogen and phelloderm composed of rounded or oval shaped parenchyma cells with numerous strach grains. In the phelloderm and adjoining region latex duct are found in transverse section. Individual latex ducts are very long and contain thick, granular viscid latex. The cambium zone is continuous ring layers of meristematic cells and the medullary rays have slightly thickened pitted walls[4].

Fruits:

Follicles 1-3 inches long, curved and ribbed, 3-6 seeds embedded in red fleshy aril. Seeds are dull brown colour and minutely pitted[1,3].

PHYTOCHEMICAL STUDIES

Leaves:

Coronaridine, voacristine, tabernaemontanine, dregamine, lupeol, Alpha (α)-amyrin, lupeol acetate, Beta (β)-amyrin acetate, α-sitosterol, β-sitosterol, kaempferol, quercetin, phenolic acids *viz*., vanillic acid, syringic acid, benzoic acid, protocatecheic acid, salicylic and sinapic acid[4].

11-methoxy-N-methyldihydropericuclivine, 19-epivoacangine, 19-epivoacristine, conofoline, conophyllinine, hyderabadine, ervaticine, ervatinine, isovoacangine, isovoacristine, 5-hydroxyvoaphylline, 5-oxo-11-hydroxtvoaphylline, dregamine, lahoricine, lochnericine, mehranine, N1-methylvoaphylline, N-methylvoafinine, pachysiphine, taberhanine, voacangine, voacamine, vobasine, voaphylline, voaharine, voafinidine, voafinine voaharine[7], conophylline, conophyllidine, voacristine, voacristine-7-hydroxyindolenine, apparicine[8], monoterpeneindole alkaloids 3α-hydroxymethyl-ibogamine, 3α-acetylmethoxyl-ibogamine, 16α-hydoxyl-ibogamine, taberdivarine G, heyneanine and coronaridine hydroxyindolenine[9,10].

Roots:

11-methoxy-N-methyldihydropericuclivine, 19,20-dihydrorabernamine, 19-epivoacangine, conodurine, dregamine, isovoacangine, isovoacristine, pseudovobparicine, voacamine, tabernaelegantine A, vobasine[7] and D-mannitol[4].

Root bark:

Coronaridine hydroxyindolenine, Coronaridine,

5-hydroxy-6-oxocoronaridine, 5-oxocoronaridine, 6-oxocoronaridine, 3- oxo-coronaridine, Voacamine, (+)-heyneanine, (-)-ibogmine, (-)-heyneanine, benzoic acid, cycloartenol, Campesterol, (+)-19-hydroxycoronaridine, aurantiamide acetate, (±)-19-hydroxycoronaridine, β-sitosterol, α-amyrin, β-amyrin acetate, lupeol, lupeol acetate[4].

Stem:

19,20-dihydroervahanineA,3S-cyanocoronaridine, 3S-cyanoisivoacangine, conodusarine, conolidine, conolobine A, conolobine B, dregamine, vobasine[7], tabernaemontanine, coronarine, lupeol, β-Sitosterol, lupeol acetate, α-amyrin, β-amyrin acetate[4].

Flowers:

11-methoxy-N-methyldihydropericuclivine, 19-epivoacangine, isovoacristine, isovoacangine[7], 3,4,14,19-tetrahydro-olivacine, 11-methoxy-N-methyl dihydro-pericyclivine, 19-epivoacangine, apparicine, isovoacangine, isovoacristine, tabermaemontanine, tabersonine, voaphylline, vobasine, N-1-methyl-voaphylline[9].

Latex:

Bacteriolytic enzymes, ervatamins, cysteine protease heynein[4].

Whole plant:

19-heyneanine hydroxyindolenine, 3-oxovoacangine, ibogamine, voacangine hydroxyindolenine, voacristine, voacristine hydroxyindolenine[7].

Aerial parts:

Tabernacricatines (A-G), ervachinine A, ervachinine B, ervachinine C, conofoline, conophylline, hydroxyindolenine, voacangine hydroxyindolenine, voacristine, ibogain, voacristine hydroxyindolenine,3-(2-oxopropyl) voacangine, tabernanthine, isovoacangine, picrinine, 19-epi-isovoacristine, 19S-heyneanine, 1-methylvoaphylline, 19,20-E-vallesamine, voaphyllinediol[11].

Cell suspension culture:

12-Hydroxyakuammicine, apparicine, catharanthine, pericyclivine, perivine, o-acetylvallesamine, stemmadenine, tubotaiwine, vallesamine, voaphylline hydroxyindolenine[7].

PHARMACOLOGICAL STUDIES

Antidepressant activity:

Tadkase *et al.*[12] screened the antidepressant effects of methanolic and ethyl extract of leaves of *Tabernaemontana divaricata* in Wistar rats at the dose 100 mg/kg and 200 mg/kg by using animal model despair swim test. The results revealed that methanol (200 mg/kg) extract activity was equivalent as compared to standard drug imipramine. The methanol extract shows more significant activity as compared to ethyl acetate extract.

Anxiolytic activity:

Tabernaemontana divaricata alcoholic flowers extract and evaluated the anxiolytic activity by using mice at the doses of 100, 200 and 400 mg/kg. Anxiolytic effect was studied by using following animal models, Elevated Plus Mace (EPM) test, Open-Field Test (OFT) and Light-Dark Transition (LDT) test. The results showed that alcoholic extract of plant possessed anxiolytic activity[13]. Chanchal *et al.*[14] evaluate the effect of ethanolic extract of *Tabernaemontana divaricata* leaves on burying behavior in mice at the doses of 100, 200 and 300 mg/kg. The results showed that leaf extract dose dependently inhibited the obsessive and compulsive symptoms and produced anti-anxiety effects.

Antidiarrheal activity:

Kumari *et al.*[15] evaluated the antidiarrheal potential of methanolic extract of leaves of *Tabernaemontana divaricata* by using castor oil induced diarrhea in Wistar rats at doses of 50, 100 and 200 mg/kg body weight. Plant extract showed marked antidiarrheal effect by producing significant defecation at the dose of 100 and 200 mg/kg. The same research work also assessed the diuretic activity of the methanolic extract by using Lipschitz value and diuretic index. At the dose of 200 mg/kg the diuretic index was calculated as 1.55 which is significantly compared to the standard drug furosemide having diuretic index of 1.70. In another study, antidiarrheal activity of hydroalcoholic and aqueous extract of *Tabernaemontana divaricata* leaves were evaluated against castor oil induced diarrhea in rats at the doses of 100, 200 and 300 mg/kg loperamide used as a standard. The results

showed that significant activity against diarrhea and decreased gastrointestinal motility[16]. Khan *et al.*[17] studied the antidiarrheal and antioxidant activity of leaves of *Tabernaemontana divaricata* by using castor oil induced method and 2,2-Diphenyl-1-Picrylhydrazyl (DPPH) free radical scavenging assay in mice respectively. The results showed that diarrheal inhibition was found to 52.6 % at the dose of 200 mg/kg and 54.7 % at the dose of 400 mg/kg. Free radical scavenging activity having half-maximal Inhibitory Concentration (IC_{50}) value 74.5 µg/ml.

Gastroprotective effect:

500 mg/kg of methanolic extract from the flower of *Tabernaemontana divaricata* showed gastro protective effect in Wistar rats by pyloric ligation induced gastric ulceration model. The results observed that the test extract significantly reduced the volume of gastric juice and total acidities and ulcer index. It also raised the pH of the gastric acid, like the standard drug omeprazole. The extract provided 79.5 % protection, that means plant extract exhibits remarkable gastroprotective effect[18]. In another study, *Tabernaemontana divaricata* flower methanolic extract was evaluated for antiulcer activity against aspirin and ethanol induced gastric ulcers in adult male Wistar rats at 3 doses 125, 250 and 500 mg/kg. Mistoprostol was used as a standard drug. The results demonstrated that significant increase in the levels of catalase, superoxide dismutase, nonprotein sulphhydryls and mucin, while revealed a reduction in levels of total protein, malondialdehyde and ulcer index. Extract exhibits gastro-protective effects by enhancing the production of gastric mucosa or preventing its depletion by aggressive factors[19].

Analgesic activity:

In this study, Swiss male mice (20-25) g treated with alcoholic extract of *Ervatamia coronaria* stems are intraperitoneally at 150 mg/kg, 30 min before being placed on a hot plate. The results showed significantly greater response times to the heat stimulus in mice treated with alcoholic plant extract than the control[20]. In another study, analgesic and anti-inflammatory activity of ethanolic flower extract of *Tabernaemontana divaricata* was evaluated by using acetic acid induced writhing, hot plate reaction time and carrageenan induced hind paw edema method in Wister rats. The results showed that, decreased number of writhings, increased reaction time and inhibition of paw edema as compared to the standard drug indomethacin[21].

Methanolic extract of *Tabernaemontana divaricata* flowers was evaluated for antinociceptive activity by using acetic acid induced abdominal writhing test and formalin induced paw licking test at the doses of 125, 250 and 500 mg/kg. The result showed significant dose dependent antinociceptive activity. The extract of flower inhibit the paw licking time in both early and late phases[22]. In another study, antinociceptive activity of ethanolic extract of *Tabernaemontana divaricata* leaves was screened using the model of acetic acid induced writhing in young Swiss-albino mice, at the doses of 250 and 500 mg/kg body weight; diclofenac sodium used as a standard drug. The extract produced significant writhing inhibition in mice. The results revealed the leaves ethanolic extract possessed antinociceptive activity[23].

Hepatoprotective activity:

Hepatoprotective activity of ethanolic extract of whole plant of *Tabernaemontana divaricata* was investigated against Diethylnitrosamine (DEN) and ferric reducing antioxidant power using N,N,N',N'-Tetra(2-pyridyl)ethylenediamine (TPEN) induced liver necrosis in adult male albino rats. Extract was given at doses of 200 and 400 mg/kg body weight, daily for 24 w and 5-fluorouracil used as a standard drug. The results demonstrated increased levels of liver marker enzymes in serum and decreased level liver indicators of cellular damage and functional integrity of the cell membrane due to the carcinogen administration[24].

Stalin *et al.*[25] screened the hepatoprotective effects of leaves and flowers extracts of *Ervatamia coronaria* at the dose of 200 mg/kg against Carbon tetrachloride (CCl_4) induced hepatic damage in male albino mice. The result showed that the decreased levels of total protein in tissue and serum and restoration of increased levels of hepatic marker enzymes. These observations confirm the hepatoprotective efficiency of the leaves and flowers extract.

Anthelmintic activity:

Anthelmintic activity of petroleum ether, ethanol and chloroform crude extracts of leaves of

Tabernaemontana coronaria assessed against Indian adult earthworms *Pheritima posthuma*. This study measured the paralysis time and death time of the worms in the four concentrations (10, 15, 20 and 25 mg/kg) of each extract. The results demonstrated that the ethanolic extract of plant caused paralysis and death of worms when it is comparable time to standard drug albendazole, especially at high concentration 25 mg/kg[26]. In another study, hydro alcoholic flower extract of *Tabernaemontana divaricata* anthelmintic activity was evaluated in Indian earthworms *Eudrilus eugeniae* and *Eisenia foetida*. The results showed that, time of death was around 20 min for 500 mg concentration and time taken for paralysis of *Eudrilus eugeniae* by extract was within 20 min for a concentration 300 and 500 mg. This study was concluded with good activity against the worms at higher concentrations[27].

Anticonvulsant activity:

Anticonvulsant potential of alcoholic extract of flowers the *Tabernaemontana divaricata* was investigated by using animal models like Maximal Electroshock Induced Convulsion (MESIC), Pentalenetetrazol Induced Convulsion (PTZIC), Picrotoxin Induced Convulsion (PIC), Isoniazide Induced Convulsion (IIC), Strychnine Induced Convulsion (SIC), and 4-Amino Pyridine Induced Convulsion (4-APIC) in albino mice (18-22) g. In MESIC the plant extract showed reduced duration of tonic extensor phase of the animals. In PTZIC, IIC, 4-Aminomethylbenzoic acid (4-AMIC), SIC and Plant Tissue Culture (PTC) models plant extract possessed increased latency and onset of tonic convulsion. The result showed the anticonvulsant property may be due to the modulation of GABAergic system and decreased neuronal excitability mainly through the voltage dependent Na^+ channels[28]. In another study, anti-seizure activity of methanoilc flower extract of *Tabernaemontana divaricata* was evaluated against maximal electoshock and pentylene tetrazole induced convulsions in rats and mice respectively at 250 and 500 mg/kg doses. Phenytoin and diazepam were used as a standard drug. The results indicated that metanolic extract inhibits electrically and chemically induced seizures in animal models[9].

Raj *et al.*[29] studied antiepileptic activity of aqueous and ethanolic extracts of *Tabernaemontana divaricata* leaves using electrically and chemically induced seizures in adult male Swiss-albino mice at the doses of 50, 100 and 150 mg/kg. The study reveals the ethanolic extract at high doses showed significant anticonvulsant property whereas aqueous extract did not show any significant effect.

Antimicrobial activity:

Bijeshmon *et al.*[30] carried out the study for detecting the antimicrobial activity of flower extracts of *Tabernaemontana divaricata* against the standard bacterial strains are *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Serratia mascescens* and *Klebsiella pneumoniae*. Antibacterial activity tested by disc diffusion method. The results observed that only the methanolic extract showed an inhibition zone 10-15 mm against the *Staphylococcus aureus* and *Escherichia coli*. Aqueous and petroleum ether extract were non active against *Pseudomonas aeruginosa*, *Serratia mascescens* and *Klebsiella pneumoniae*.

In another study, *in vitro* antimicrobial activity of flower extract of *Tabernaemontana divaricata* was tested against oral pathogens such as *Streptococcus mutans*, *Streptococcus salivarius*, *Streptococcus mitis* and *Lactobacillus acidophilus*. The antimicrobial potency was screened by agar well diffusion method and the zone of inhibition was recorded. The results showed that *Tabernaemontana divaricata* was effective against all the bacteria with highest activity against *Lactobacillus*. The highest activity was seen in the methanolic extract where acetone extract showed weak activity[31]. Purushothaman *et al.*[32] studied the antibacterial activity of *Tabernaemontana divaricata* secondary metabolites capped Gold Nanoparticles (AuNPs) and Silver Nanoparticles (AgNPs). AuNPs and AgNPs were prepared by using the aqueous flower extract of *Tabernaemontana divaricata*. The antibacterial potency of Single-Nucleotide Polymorphisms (SNPs) and AuNPs determined against various bacterial culture using the agar well diffusion method. In this study, SNPs showed the highest antibacterial activity against gram positive and gram negative bacteria than AuNPs. On the other hand in flower extract-loaded agar, it was well observed that there was no zone of inhibition.

Antifungal activity:

The antifungal activity was evaluated by Minimum Inhibitory Concentration (MIC) determined by

microdilution method. Coronaridine is an active constituent isolated from the ethanolic extracts of aerial parts of *Tabernaemontana divaricata*. It shows maximum antifungal activity against *Penicillium chrysogenum* at the concentration of 60 µg/ml while compared with nystatin and 5-oxocoronaridine showed strong antibacterial activity against *Klebsiella pneumoniae* at 50 µg/ml dose. Coronaridine showed selective cytotoxic effect against Chinese hemster V79 cells[33]. Wankhede *et al.*[34] looked at the *in vitro* antifungal activity of extracts of *Tabernaemontana divaricata* leaves by 96 well microtiter plate assay using human fungal pathogen *Candida albicans* ATCC90028 strain. MIC and minimum fungicidal concentration of the extracts was determined by spectrophotometric method and plate assay respectively. Ethyl acetate extract of leaves indicated MIC of 1 mg/ml against growth of strain. 8 mg/ml was potent enough to kill all the cells in the strain. Petroleum ether, methanolic and sequential distilled water extract killed all the cells at the concentration of 16 mg/ml showed to be the most efficient candidacidal.

Wound healing activity:

Zaineb *et al.*[35] investigated the wound healing activity of ethanolic extracts of leaves of *Tabernaemontana divaricata* by using incision and excision wounds in healthy Wistar rats of either sex. The results showed that, animals treated with 5 % ethanolic extract produced faster rate of epithelialization in excision wound model and gaining of tensile strength in incision wound model. Dhole *et al.*[36] studied *in vivo* wound healing effect of methanolic and ethanolic extracts by using excision wound model on Wistar albino rats at different concentrations of extract ointment such as Tabernaemontana divaricate 2 % Methanolic (TDM 2 %) ointment, *Tabernaemontana divaricata* 5 % Methanolic (TDM 5 %) ointment, *Tabernaemontana divaricata* 2 % Ethanolic (TDE 2 %) ointment and *Tabernaemontana divaricata* 5 % Ethanolic (TDE 5 %) ointment. The observation found that TDM 2 % and TDM 5 % showed a highly significant decrease in wound area when compared with positive control. TDE 5 % extract showed a significant decrease in wound contraction.

Antifertility effect:

Antifertility effect was demonstrated from the chronically administered *Tabernaemontana divaricata* ethanolic leaves extract on male albino rats at the doses of 50, 100 and 200 mg/kg body weight. The results indicated that, significant decreases in the weight of testes, seminal vesicle, epididymis, ventral prostate were observed. A dose related suppression of testicular and epididymal sperm count. Spermatogenesis arrested at the secondary spermatocyte stage and significant reduction of Luteinizing Hormone (LH) and testosterone in serum concentration were observed. No morphological changes in sertoli cells. *Tabernaemontana divaricata* leaves extract produced dose related effect on male reproduction without altering general body metabolism[37].

Jain *et al.*[38] studied antifertility activity of chronically administered *Tabernaemontana divaricata* leaf extract on virgin female albino mice at the 250 and 450 mg/kg orally for 21 d. The results revealed that ethanolic leaf extract caused the disturbance on the estradiol secretion with significant decrease during estrous stage of the cycle, it may be due to impairment in the release of LH and Follicle Stimulating Hormone (FSH).

In another study, anti-fertility activity of ethanolic leaf extract of *Tabernaemontana divaricata* was assessed in immature female rats at the daily doses of 200 and 400 mg/kg. The results showed that extract caused significant increase in uterine weight of the rats as compared to the control. The ethanolic extract of the plant exhibited oestrogenic activity[39]. Jain *et al.*[40] investigated the anti-implantation activity of the ethanolic extract of *Tabernaemontana divaricata* leaf at the doses of 250 and 500 mg/kg were administered from 1st-7th d of pregnancy. In results, the dose of 500 mg/kg showed 66.66 % inhibition of implants in uterine horns compared to the vehicle groups.

Mukhram *et al.*[41] evaluated the antifertility effect of methanolic and aqueous flower extracts of *Tabernaemontana divaricata* in female Wistar rats by using two experimental animal models, estrogenic activity in immature rats using ethinylestradiol as standard and anti-implantation and early abortifacient activity in female rats. The results found that oral administration of methanolic extract at 500 mg/kg possessed significant estrogenic, anti-implantation and early abortifacient activity. The aqueous extract at 500 mg/kg showed significant estrogenic activity.

Antidiabetic activity:

Tabernaemontana divaricata ethanol extract was tested for antidiabetic activity in alloxan induced diabetic male Wistar albino rats at doses of 100 and 200 mg/kg body weight. Antidiabetic activity evaluated by using oral glucose tolerance test in rats. The findings showed significant antidiabetic potential in terms of reduced blood glucose levels and correction of altered biochemical parameters[42]. In another study, *Tabernaemontana divaricata* methanolic extracts of leaves and flowers evaluated for antidiabetic activity by using alloxan induced diabetic male Swiss albino mice. Leaf extract was given intraperitoneally at different doses 300 and 400 mg/kg body weight. Flower extract was given intraperitoneally at the doses of 200 and 300 mg/kg body weight. The antihyperglycemic effect of the leaf and flower extract was compared with metformin, a standard drug. The leaves and flower extracts at the dose of 400 and 300 mg/kg showed a reduced maximum blood glucose level at 12th and 10th h of the treatment period, respectively. These extracts also performed a brine shrimp bioassay. The results showed low cytotoxicity compared with standard drug vincristine sulphate[43,44]. Conophylline, a bisindole alkaloid isolated from several *Tabernaemontana* species. Conophylline induce differentiation of pancreatic beta cells both *in vitro* and *in vivo*. It is effective in reversing hyperglycemia in streptozotocin treated rats, and increased the insulin content and the beta cell mass[45].

Cytotoxicity effect:

Anticancer property was demonstrated from the ethanolic extract of whole plant of *Tabernaemontana coronaria* in adult male albino rats, at doses of 200 and 400 mg/kg body weight against DEN and Ferric Nitrilotriacetate (Fe-NTA) induced clear cell carcinoma. The result showed that the plant extract acts against DEN and Fe-NTA induced renal cell carcinoma in rats in terms of normalization of altered renal oxidative stress parameters such as lipid peroxidation, enzymatic and non-enzymatic antioxidants in kidney of rats[46].

In vitro anticancer activity of hydroalcoholic flowers extract of *Tabernaemontana divaricata* was evaluated against human cervical adenocarcinoma cell line and 3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide (MTT) assay was used to analyse the inhibition of cell growth. The results founded that the plant extract possessed a moderate amount of anticancer activity[47]. The study demonstrated that anti-colorectal cancer activity of an alkaloid rich fraction of *Ervatamia coronaria* leaves extract through modulating Adenosine Monophosphate-activated Protein Kinase (AMPK) and mammalian Target of Rapamycin (mTOR) signaling pathways without affecting the normal cells[48].

In another study, antiproliferative efficacy of chloroform extract of aerial parts of *Tabernaemontana divaricata* on the human epidermal larynx carcinoma cell line (Hep2) and Vero cell line estimated by the MTT assay and enzymatic parameters catalase, superoxide anion scavenging activity, reduced glutathione activity. The result showed that extract produce significant effect on Hep2 cell line but lesser effect on Vero cell line. If the drug produce more effect on Vero cell line, it cause side effect on normal healthy body cell. So, it has an anticancer activity with no adverse effect[49]. In this study, evaluated *in vitro* antioxidant activity using Phosphomolybdenum (PM) method, Ferric ion Reducing Antioxidant Power (FRAP) assay and DPPH assay. Morphological variations showed human bladder cancerous cells undergoing cell shrinkage and membrane blebbing leading to cell death inducing apoptosis in cell line[50].

Tabernaemontana divaricata leaves extract were found to have *in vitro* cytotoxic activity against HCT-15 (colon), HT-29 (colon), 502713 (colon), MCF-7 (Breast), PC-3 (prostate) by using sulforhodamine B dye assay. The results showed that ethyl acetate extract was effective against only one colon cancer cell line (502 713) at the lowest dose 10 µg/ml, whereas the chloroform extract significantly inhibited the growth of all 3 colon cancer cell lines, at 30 µg/ml. They also assessed the extract ability to scavenge hydroxyl radicals in plasmid nicking assay with pBR322. The results showed all the extracts significantly inhibited the unwinding of super cooled DNA except hexane extract, showed the least effect. Furthermore, the ethyl acetate extract (200 µg/ml) selectively showed weak inhibition of topoisomerase II (topo II) relaxation assay[51]. In another study, five new bisindole alkaloids, tabernaricatines A-E (1-5),

two new monomers, tabernaricatines F and G (6 and 7) and 24 known alkaloids were isolated from the *Tabernaemontana divaricata* aerial parts. All the compounds expect 3 were investigated for their cytotoxicity against five human cancer cell lines, conophylline showed significant bioactivity[11].

Anti-acetylcholinesterase activity:

The methanolic extract from roots of *Tabernaemontana divaricata* was evaluated for Acetylcholinesterase (AChE) inhibitory activity using Ellman's colorimetic method in 96-well microplates. Results observed that highest inhibitory activity at the concentration of 0.1 mg/ml, inhibition >90 % of AChE activity[52]. In another investigation, bioassay guided fractionation using the isolation of 2 bisindole alkaloids, 19,20-dihydrotabernamine and 19,20-dihydroervahanine A. The compounds showed higher AChE inhibitory activity. The activity of 19,20-dihydroervahanine A was specific, reversible and competitive. During the separation process, 2 inactive bisindole alkaloids, were also isolated such as Conodurine and Tabernaelegantine A. Higher activity was found in stem and root extracts while leaf and flower extracts showed lower activity[53]. Chattipakorn *et al.*[54] investigated *in vivo* effects of ethanolic extracts of *Tabernaemontana divaricata* roots on AChE inhibitory effects and Fos expression on neuronal activity in the cerebral cortex. The extracts increased Fos expression in cortical neurons, that increased endogenous acetylcholine and significantly inhibiting AChE in the cerebral cortex, which result in increased neuronal activity. AChE inhibitory activity of extract is time-dependent and reversible.

Nakdook *et al.*[55] evaluated the effects of ethanolic root extracts of *Tabernaemontana divaricata* on amyloid β 25-35 peptides induced cognitive deficits in mice and AChE activity. Cognitive performance was evaluated using the step-down avoidance test and Morris Water Maze (MWM). The Result was found to significantly improved the memory improvement and increased levels of cortical and hippocampal AChE activity. An alkaloidal extract from *Tabernaemontana divaricata* stem loaded in liquid crystalline and microemulsion systems act as alternative formulation for increasing acetylcholine levels in Alzheimer's patients. Formulations with the ratio of oil surfactant is 1:5 containing 0.1 µg/ml extract showed a significantly higher AChE inhibiton[56]. Bisindole alkaloid 3'-R/S-hydroxyvoacamine isolated from stem extract which shows a non-competitive inhibitor of AChE[57].

Anti-inflammatory activity:

Anti-inflammatory studies were demonstrated using the ethanol and aqueous extracts of the flowers of *Tabernaemontana coronaria* in male Swiss mice at doses of 100 mg/kg and 250 mg/kg body weight. This study showed that acute and chronic anti-inflammatory activity of ethanolic extract of *Tabernaemontana coronaria* in carrageenan-induced inflammation and formalin induced inflammation. Diclofenac used as a standard drug. This study also found that ethanol extract of *Tabernaemontana coronaria* showed significant *in vitro* antioxidant activity by superoxide radical, hydroxy radical, nitric oxide and lipid peroxidation scavenging activities as compared with the aqueous extract[58]. In another study, the flavonoid fraction of *Tabernaemontana divaricata* leaves was evaluated for anti-inflammatory potential. The *in vitro* and *in vivo* anti-inflammatory activity was determined by using membrane stability method and carrageenan induced odema (acute), formalin and dextran (chronic) method respectively. The results showed that maximum flavonoid content present in the ethyl acetate extract and exhibited a significant *in vitro* and *in vivo* anti-inflammatory activity[59].

Jain *et al.*[60] demonstrated that *Tabernaemontana divaricata* leaves extract had *in vivo* anti-inflammatory activity on male albino Swiss mice. The methanol leaves extract showed dose dependent inhibition in the croton oil induced ear edema in mice. The hexane fraction showed a very high activity (42.1 % inhibition) as compared to the control indomethacin.

Antioxidant activity:

The study was investigated the anti-oxidant and free radical scavenging efficacy of methanolic extract of *Ervatamia coronaria* leaves by using various studies such as DPPH radical, superoxide anion radical, nitric oxide radical, hydroxyl radical scavenging assays were performed and found that extracts showed significant anti-oxidant activity in a dose dependent manner[61]. *In vitro* antioxidant activity of *Tabernaemontana coronaria* whole

plant ethanolic extract at the concentration of 500 µl/ml showed high DPPH radical scavenging capacity. The results exhibited dose-dependent inhibition of superoxide radical scavenging, hydroxyl radical scavenging, and nitric oxide radical scavenging activity[62]. Antioxidant effect of *Ervatamia coronaria* leaves was evaluated by using CCl_4 induced hepatotoxicity model. Results showed a significant hepatoprotective effect, lipid peroxidation decreased and significantly antioxidant agents were increased in a dose dependent manner[63]. In another study, anti-oxidant was screened by hydroxyl, superoxide and DPPH free radical scavenging activity, reducing power and metal-chelating activity. The extract exhibited the most potent radical scavenging activity at a maximum concentration of 10 mg/ml. Gas Chromatography-Mass Spectrometry (GC-MS) analysis of the extract reveals the presence 96 phytoconstituents, 17 are reported bioactive and 11 possess antioxidant potential[64].

Enzymatic activity:

Proteases isolated from the latex of *Tabernaemontana divaricatea* flowers. The protein yield was 30 mg/ml. The proteases are serine protease responsible for clot and clot dissolving properties. Enzymes showed dose-dependent caseinolytic, fibrinogenolytic, plasma and blood clot activities[65]. In another study, a highly stable cystein protease, named as ervatamin, was isolated from the latex of *Ervatamia coronaria* by a simple purification procedure ion exchange chromatography and ammonium sulfate precipitation. This is the first protease isolated from the latex of the plant. The enzyme hydrolyzed and denature natural substrate like casein, hemoglobin with high specific activity but showed low activity towards synthetic substrates[66]. Hemostatic potential of latex proteases from *Tabernaemontana divaricata* was estimated for proteolytic activity using casein as the substrate. Caseinolytic activity for 100 µg of latex protein was found to be 56.16±0.57. The results observed a significant reduction in clotting time exhibited by *Tabernaemontana divaricata* compared to *Artocarpus altilis*[67].

Local anaesthetic activity:

Milky latex obtained from *Tabernaemontana coronaria* possessed the local anaesthetic activity. The latex at dilutions 1:10, 1:50 and 1:100 showed the anaesthetic activity in a dose dependent manner compared to the standard drug xylocaine (2 %). Evaluation of this activity by nerve block anaesthesia, muscle twitches method in frog and infiltration anaesthesia in guinea pig. The results showed the onset of action at 3 min for 1:10 concentration, 5 min for 1:50 concentration and 6 min for 1:100 concentration in nerve block method. In muscle twitch and infiltration method, the duration of local anaesthetic activity was approximately 30 min[68].

Anticorrosive activity:

The corrosion inhibition of mild steel in 1 m Hydrochloric acid (HCl) and Sulfuric acid (H_2SO_4) acid solutions by ethanolic leaves extract of *Ervatamia coronaria* investigated by using weight loss, Tafel polarization, scanning electron microscopy, electrochemical impedance and X-ray diffraction techniques. Ervatinine is an indole alkaloid isolated from leaves of the plant. It acts as a good corrosion inhibitor. The results showed that ervatinine forms the protective film on mild steel surface, which supports the inhibition of corrosion in a dose dependent manner[69].

Nephroprotective effect:

Nephroprotective effect of ethanolic extract of *Tabernaemontana coronaria* was evaluated in mercuric chloride induced renal oxidative damage in adult male Wistar albino rats. Results indicated that decreased levels of protein content, membrane bound ATPases, enzymic and non-enzymic antioxidants and increased levels of serum cholesterol, uric acid, creatinine and urea were observed. In conclusion, extract may be a clinically valuable agent in the prevention of acute renal failure caused by intoxication of inorganic mercury[70].

Cardiovascular effects:

This study evaluated ethanolic extract of root of *Tabernaemontana divaricata* on cardiovascular activity in anaesthetized male Wistar rats at doses of 5, 10, 20 and 25 mg/kg body weight. Inject the extract immediately after treatment with phenylephrine, norepinephrine and atropine respectively. The results showed that significant hypotensive action of root extract through activation of muscarinic cholinergic receptors and

induction of nitric oxide[71].

Antimalarial activity:

Divaricamine, is a trimeric monoterpenoid indole alkaloid, it consist of a vobasine-iboga type skeleton structure, which was isolated from root extract of *Tabernaemontana divaricata*. The isolated compound divaricamine possessed potent antimalarial activity[72].

Insecticidal activity:

Tabernaemontana divaricata chloroform, petroleum ether and methanol leaf and stem extracts were subjected to repellency and dose mortality assay using the pest *Callosobruchis chinensis* in stored product. The result demonstrated that petroleum ether and methanol extract of the *Tabernaemontana divaricata* showed repellent and potential insecticidal activity. While chloroform extract did not showed insecticidal activity against test pest[73].

Anticataract activity:

AgNPs biosynthesized using an Ethanolic extract of *Tabernaemontana divaricata* leaves and evaluated for efficacy in preventing *in vitro* selenite-induced opacification of the ocular lens (cataractogenesis) in Wistar rat lens cultured in Dulbecco's Modified Eagle Medium (DMEM). Extract treated lenses showed minimal opacification occurred in one lens and there is no opacification occurred in other seven out of eight lenses. AgNPs treated lenses remain transparent and did not show any opacification. The result suggest that ethanol leaves extract of *Tabernaemontana divaricata* and biosynthesized AgNPs of the extract, possessed potential to prevent *in vitro* selenite-induced opacification[74].

In another study, comparison of cataract formation preventing effect of a *Tabernaemontana divaricata* extract and biosynthesized AgNPs in an *in vivo* selenite-induced cataractogenesis in Wistar rats. *Tabernaemontana divaricata* extract given at dose of 350 mg/kg body weight and biosynthesized AgNPs given at dose of 200 mg/kg body weight. In this study, expression pattern of genes at messenger Ribonucleic Acid (mRNA) transcript, lenticular reduced glutathione, malondialdehyde, protein levels for calcium transporters, calpain isoforms and lenticular proteins were observed. These observations indicated that biosynthesized AgNPs with extract have the potential to prevent cataract *in vivo* animal model by maintaining normal calpain cascade activity and lenticular calcium homeostasis and by preventing alteration in key lenticular proteins[75].

Anti-asthmatic and antitussive activity:

Anti-asthmatic activity of ethanolic leave extract of *Tabernaemontana divaricata* was evaluated by *in vitro* guinea pig tracheal chain method and *in vivo* guinea pig bronchoprotective test method. Aminophylline used as a reference drug. The results of *in vivo* showed, extract produce maximum bronchi relaxation of 91.66 % and 92.83 % in acetylcholine-induced and histamine-induced bronchocontraction, respectively. And *in vitro* study extract was given at the dose of 100 and 200 mg/kg body weight, results showed significant bronchoprotection about 42.28 % at the dose of 200 mg/kg body weight. Antitussive activity was evaluated by *in vivo* citric acid-induced tussive response. Aerosolic dose of 6 % (w/v) decreased average cough frequency[76].

Antiobesity and hypolipidemic activity:

The present study was aimed to evaluate the potential effect of methanol extract of aerial parts of *Tabernaemontana coronaria* on obesity and hyperlipidemia on atherogrnic diet induced obese rats at the doses of 100 mg/kg and 200 mg/kg. Sibutramine used as a standard drug. The results showed that altered parameters such as body weight, body temperature, serum lipid profiles, Serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum Glutamic Pyruvic Transaminase (SGPT) were significantly corrected as compared to the standard drug[77]. Anbukkarasi *et al.*[78] studied the anti-atherogenic, antioxidative and anti-inflammatory activity of Tabernaemontana dicariacata ethanolic extract in a Wistar rat model of hypercholesterolemia. The lipid profile parameters and C-Reactive Protein (CRP) were investigated in serum samples and enzymatic, non-enzymatic antioxidants, malondialdehyde, nitric acid, gene and protein expression levels, inducible Nitric Oxide Synthase (iNOS), Tumor Necrosis Factor-α (TNF-α) and gene expression levels of Interleukin-1β (IL-1β) were determined in liver samples. The findings suggested that a *Tabernaemontana divaricata* leaf extract protects against experimental atherosclerosis in rats. Anti-inflammatory effect due to blocking the activation

of inflammatory markers such as CRP, iNOS and cytokines, so that preventing the initiation of atherosclerosis and atherogenic diet-mediated inflammation[78].

CONCLUSION

This review article outlines the ethnomedicinal uses, pharmacognostical studies, phytochemical constituents and pharmacological properties of *Tabernaemontana coronaria*. The review of phytochemical analysis reveals the presence of various alkaloids, terpenoids, saponins, tannins, flavonoids, phenolic acids, carbohydrates in the extracts of various plant parts which can be applicable for future research process. Bioactive indole alkaloids derived from the plant plays a major role in human health, nutrition, disease prevention and treatment. Many alkaloids are present in this plant and whose activities have not yet been investigated. Therefore, more research can be focused on this plant based on the traditional claims[79].

Conflict of interest:

The authors declare no competing interests.

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