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SHORT REVIEW

Tabernaemontana divaricata: A Herbal Panacea

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Abstract

Tabernaemontana divaricata (pinwheel flower) is a flowering plant that can grow easily in gardens and along roadsides. This plant can be cultivated in every condition. No specific environmental condition is required for the growth of the plant. Growing evidence suggests that this plant has medicinal benefits for various diseases due to the presence of bioactive components in the plant. The plant is extensively found near Indian heritage to be used for worship. *T. divaricata* contains major alkaloids like apparicine, conophylline, coronardine, ibogamine, etc., exhibiting pharmacological activities. Their major pharmacological potential is against inflammation, pain, and other diseases. Plants' major activities, such as anti-diabetic, anti-inflammatory, antibacterial, antifungal, and so on, have been demonstrated by their responsible bioactive compounds. The review is to highlight the researchers' findings of different medicinal activities in *T. divaricata* along with the major responsible phytocomponents. There is a lot more scope for further research, which can be extended by the help of this review.

Keywords: Alkaloids, Bioactive Components, Latex, Pharmacological Activity, *T. divaricata*

1. Introduction

The plant which has medicinal value was always invaluable for humans and as the time passes, its utility will also increase. Compound that are found naturally are taken as safer in comparison to synthetic compound. Plants with medicinal value are more difficult to develop drug resistance than synthetic compounds[1]. The plant *Tabernaemontana divaricata* also known as crepe jasmine and pinwheel flower, is from the family *Apocynaceae*. A plant that grows in spring is as graceful as it is evergreen. This plant can be found throughout South Asia as well as the countries of Southeast Asia. It is considered an ornamental plant and is abundantly found in Indian heritage to worship the god and goddess. The phytochemical, nonalkaloids and alkaloids constituents such as flavonoids, phenylpropanoids, terpenoids, enzymes and steroids from the parts of the plant (stem, root, flower and leaves) have been reported. Along with its well-known analgesic and antidiarrheal properties, plant parts are also used as liver, spleen, and brain tonics; and it has been discovered that *T. divaricata* extract has antioxidant, anti-inflammatory, and reversible acetylcholinesterase inhibition properties[2-4]. A sticky milky liquid called latex comes out from the points of laticiferous tissue and contains secondary metabolites and proteins[5-8]. A milky fluid found in nature in 10% of all flowering plants is Latex[6]. The plants of the family *Apocynaceae* have latex as one of their pertinent features[9]. The easy and plentily availability of *T. divaricata* as an ornamental plant and its medicinal importance created

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this review. In the present review, an attempt has been made to enlist the important scientifically proven pharmacological applications along with the major phytoconstituents responsible for these activities of *T. divaricata*.

2. Bioactive Components of Plant

T. divaricata, also known as pinwheel flower, is commonly found in small trees throughout South Asia[10,11]. One of the investigators dug out the workings of the parts of the plant like stems and flowers to root extracts and extracts of leaves of *T. divaricata*. Moreover, the researcher screened 19,20-Dihydroervahanine and 19,20-Dihydrotabernamine along with isolated compounds like tabernaelegantine A. It gave out the result that the respective compounds' extracts show slightly higher anti-acetylcholinesterase activity. Moreover, it has been shown in studies that the compounds which were isolated from *T. divaricata* show action against cell lines and the plant also contains many non-alkaloid compounds like enzymes, terpenoids and phenolic acid (Figure 1)[12].

3. Major Alkaloids of *T. divaricata* with Pharmacological Importance

3.1 12-hydroxy akuammicine

12-hydroxy akuammicine is a major alkaloid of *T. divaricata*. One of the investigators administered intravenously. The IP administration in mice and rats of 12-hydroxy akuammicine stopped the growth of ascites and alveolar lymphoma, at a concentration of 15-20 mg/kg/day for 10-20 days[13].

3.2 19,20-Dihydrotabernamine and 19,20-Dihydroervahanine

The alkaloids mentioned above are generally seen in the roots of *T. divaricata*. Acetylcholinesterase activity can be witnessed in these alkaloids. The inhibitory effect of the alkaloids was proved to be specific and competitive, along with being capable of getting back to its previous position[14].

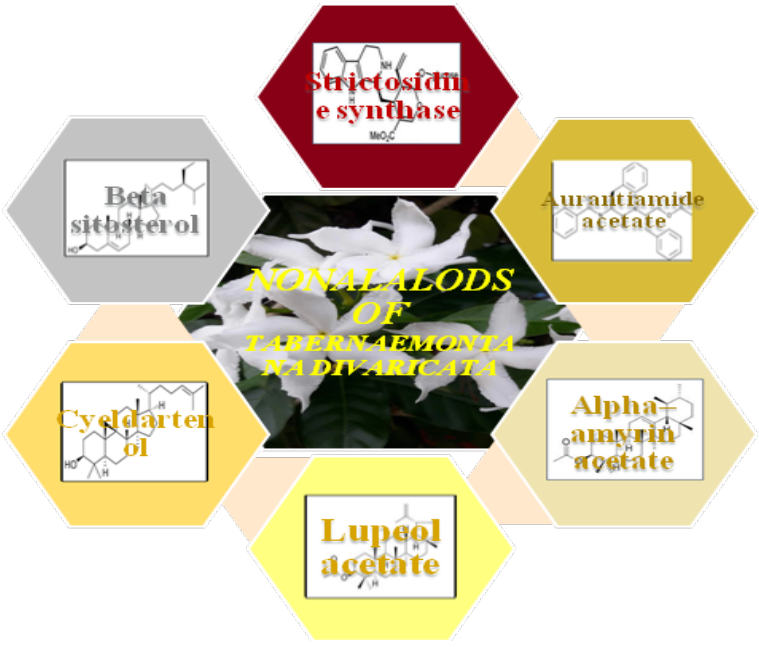


Figure 1. Nonalkaloid occurring of *T. divaricata* with medicinal importance.

3.3 Apparicine

In vitro studies have shown that polio virus activity can be resisted and brought to a halt by apparicine at a certain concentration[15,16]. In an *in vitro* study, this alkaloid also had antimicrobial activity against the microbes Salmonella, Pseudomonas, Escherichia, Shigella, Proteus, Staphylococcus and Corynebacterium at different concentrations[17].

3.4 Catharanthine

The study by Ehrlich of ascites tumour cells, where it is easily detected by a biological model for the investigation of tumour cells[18], catharanthine showed the aminoisobutyric acid kind of effects, an amino acid transporter in tumour cells. This revelation inferred that catharanthine might as well have anti-tumour properties[19].

3.5 Conophylline

Conophylline, which comes from *T. divaricata* happens to be a vinca alkaloid. It has been demonstrated in experiments that it induces the differentiation of pancreatic precursor cells[20]. Conophylline discourages and dissuades the development of cystic structures. Furthermore, they increased the number of insulin-positive cells in the rat pancreatic rudiment of organ culture[20]. Conophylline has also been demonstrated to help increase insulin production in rat pancreatic acinar carcinoma cells[21]. Conophylline has been used as a health food lately for ameliorating and helping patients avoid obesity and diabetes. Some studies suggest it may lower blood glucose levels[22]. Conophylline also happens to be a new anti-tumour alkaloid[23-26].

3.6 Coronaridine

Coronaridine is an alkaloid found in the parts of the plant of *T. divaricata* such as leaves and stems, along with bark and roots. It has been demonstrated that it influences central nervous and autonomic system activity as well[13]. In the writhing and pain response to submerging the tail in hot water, one of the researchers[27] also demonstrated that coronaridine has both anti-inflammatory and analgesic activities in rats. This can be witnessed in mice as well as in the carrageenan-induced paw oedema method. An intravenous injection (coronaridine) has been shown to cause dose-related hypotension along with bradycardial responses in a regular model of rats[28,29].

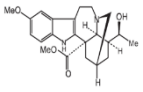
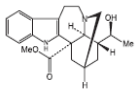
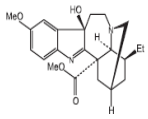
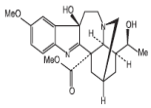
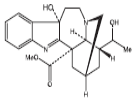
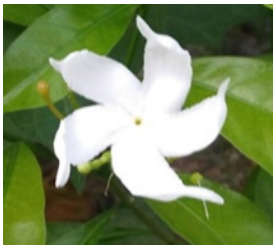
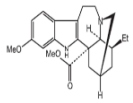
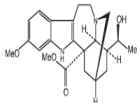
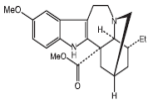
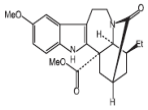
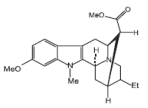
3.7 Dregamine

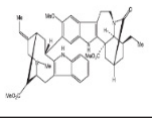
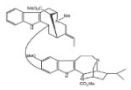
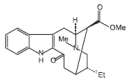
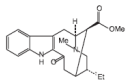
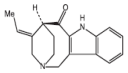
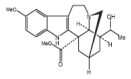
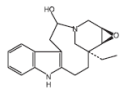
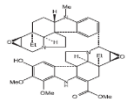
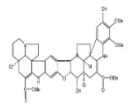
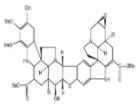
Dregamine can be found in the parts of the plant of *T. divaricata* such as leaves and stems, along with bark and roots. It has been demonstrated that dregamine has convulsive and respiration-related stimulating effects. It causes muscle pain in both *in vivo* and *in vitro* studies, apparently not very different from the activity of ibogaine. Dregamine has been used for the treatment of conditions such as muscular-related and nervous asthenia and respiratory depression[30].

3.8 Ibogamine

Ibogamine is an indole alkaloid found in the parts of the plant of *T. divaricata* such as leaves and stems, along with bark and roots (Table 1). In the study, it has been suggested that it can be used to minimise the monosynaptic reflexes of the knee-jerk in some of the animals. Surprisingly, the mechanism of action had no effect on neuromuscular transmission or postsynaptic reflex arcs[31]. However, it is also interesting to note that it possibly had an effect by way of nicotinic receptor stoppage at the meeting point of the neuromuscular system[32]. Not only that, ibogamine could not also function as a very strong anticonvulsant agent, as it was demonstrated in a mouse model[33]. The indole alkaloid ibogamine lately has been explored as a possibility that it can act as an agent that can fight and resist vigorously the drug withdrawal symptoms[34-36]. In rodent models of cocaine and opiate, studies done before the clinical investigations of ibogamine, administration done on its own infers a possibility that it is apparently an agent which is anti-addictive[37-43].

Table 1. Classification of alkaloids on the basis of plant parts and class of alkaloids[115]

Parts of plant	Alkaloid	Structure of alkaloid	Class of alkaloids
 Whole Plant	Vocristine		Ibogan
	Heyneanine		
	Voacangine hydroxyindolenine		
	Voacristine hydroxyindolenine		
	19-Heyneanine hydroxyindolenine		
 **Flowers**	Isovoacangine		Ibogan
	Isovoacristine		
	19-Epivoacangine		
	3-Oxovoacangine		
	11-Methoxy-N-methyldihydropericyclivine		Corynanthean

 **Stem**	Conodusarine		Bis-indole
	Voacamine		
	3S-Cyanocoronaridine		Ibogan
	Dregamine		Corynanthean
	Conolidine		Aspidospermatan
 **Leaves**	19-Epivoacristine		Ibogan
	5-Hydroxyvoaphylline		Plumeran
	Conofoline		Bis-indole
	Conophyllidine		
	Conophylline		

4. Pharmacological Activities of Plant

4.1 Antioxidant Activity

Antioxidants are molecules or compounds that interrupt the movement of free radicals such as hydrogen peroxide to regulate the process of autoxidation or do the same by directly squeezing their formation[43,44]. Constituents of therapeutic plants like phenolic diterpenes, carotenoids, volatile oils, flavonoids, phenolic acids and anthocyanidins prove to be and are used as antioxidants[45]. These compounds choose free radicals as their target by consuming molecules of oxygen, donating molecules of hydrogen, acting as reducing agents, or breaking up antioxidant chains[44,46]. The various parts of species *T. divaricata* are made of a compound or extract of methanol, ethanol, aqueous, petroleum ether, hexane, octyl benzoate or octyl benzoic acid, chloroform, and digalactosyl deconate. The models used for the activity are fluorescence recovery after photobleaching, 2,2-dipphenylpicrylhydrazyl assay - *in vitro*, H_2O_2 free radicals, minimising power – *in vitro*

along with superoxide anion radical scavenging, NO, Trolox equivalent antioxidant capacity assay), H_2O_2 scavenging, and Aβ25 - 35 peptides, NOR crystal violet assay and LPO assay[47-58].

4.2 Anti-inflammatory Activity

Inflammation is defined as the process by which an organism's body responds to an injury. Inflammation's development is often a result of infection, chemical or physical injury, injury to cells, and death[59,60]. One of the researchers investigated the anti-inflammatory activity of flower extract obtained from *T. divaricata*. Models were prone to chronic formalin and acute carrageenan[61]. The parts such as leaves, stems, flowers, and other parts of the plant are made into compounds with ethyl acetate, aqueous, ethanol, methanol and hexane fraction. The models this activity uses are: minimization of interleukin-6 secretion and TNF production; carrageenan and formalin prompt-mice models. The models of mice along with croton oil bring on oedema in the models of mice[53,55,61-63].

4.3 Anti-microbial Activity

Compounds that are complex and do not allow the development of microorganisms at petite assemblage are called antimicrobials[64]. Antimicrobials are often described as secondary metabolites. They are more or less regularly created and extracted either from therapeutic plants or even from microorganisms[65]. One of the researchers has proved *T. divaricata* extracts work as antibiotics. Monoterpenoid indole alkaloids, like voacamine type and 3-hydroxyiboga, are the compounds that are activated biologically and perform the function of antimicrobial agents, holding back the growth of bacteria, parasites and fungi[66].

4.4 Antifungal Activity

One of the researchers investigated and reported the antifungal activity of a compound that is pharmacologically active from *T. divaricata*. Coronaridine, a major compound from the plant *T. divaricata*, was found and cleared off from the method - ethanolic extraction of plant *T. divaricata*[67]. The parts flower and leaves of the plant make a compound or extract of ethanol and methanol along with aqueous. The cell lines used for activity are *Penicillium chrysogenum* and *Malassezia furfur,* and the method which is used for antifungal activity is the Poisoned food technique *in vitro*[68-70].

4.5 Anticancer Activity

Various leaf extracts in the study were made in a solvent containing methanol and ethyl acetate, along with chloroform and hexane, and were checked against these cell lines: HT-29-Human colorectal adenocarcinoma cell line, 502,713, HCT-15 is used for the colon, Michigan Cancer Foundation-7 (MCF-7) is for breast cancer , and Human prostatic carcinoma cell line (PC-3) is for prostate cancer[40]. Different parts of the plant *T. divaricata* are made into an extract

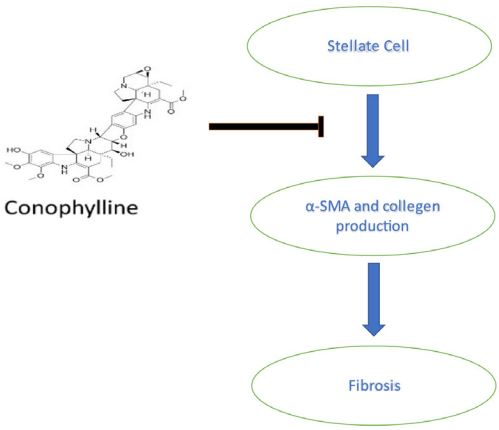


Figure 2. Mechanism of anticancer cancer activity of conophylline.

with different compounds like ethanol, hexane, etc. for anti-cancer activity (Figure 2). Different parts of the plant *T. divaricata* have several compounds that show anti-cancer activity. Root bark of plant contains 5 and 3- oxocoronidine, ibogamine, leaves of plant contains tabernaemontamine, mehranine, vocangine, voaphylline, and the root of plant contains major 2 alkaloid which is conodurine and tabernaelegantine. For anticancer activity, various cell lines were used, including HCT 15 (isolated from a cancer patient's large intestine), col-2 and HT-29 for colon cancer, S-10 for sarcoma, V79 and LUP for lung cancer, Human Leukaemia-60, P-388, MOLT-4 (T-cell derived cell line) for blood cancer, and ZR-75-1 and BC- for breast cancer. It has been scientifically proven that conophylline of *T. divaricata* inhibits the stellate cells from α-SMA (α-smooth muscle actin) and collagen production and protects them from fibrosis[67,71-84].

4.6 Acetylcholinesterase Activity

One of the investigators, Ingkaninan *et al.,* found the acetylcholinesterase activity of *T. divaricata's* methanolic extracts. Rats were used in the study as test models and were tested *in vivo*[85]**.** Almost all parts of the plant show acetylcholinesterase activity, but latex, flowers and roots show high acetylcholinesterase activity. These parts of the plant make an extract with different compounds like methyl alcohol, ethyl alcohol and PBS. There are several compounds present in plants which are responsible for AChE activity, like 19,20 dihydro tabernamine, conodurinbe, nitrogen-methyvofinine, conophylline etc. The method used for the activity is Ellman's method[71,86-91].

4.7 Anti-fertility Activity

An anti-fertility activity is shown in the ethanolic extract of *T. divaricata* in oestrogenic activity models in immature female rats. The rats that were used in this study were immature female Albino Wistar. Researchers performed the experiment and found the extract showed the existence of several compounds which have medicinal value. The compounds are carbohydrates, steroids, alkaloids, glycosides, flavonoids, tannins, and increased the uterus' weight tremendously. Some histopathological studies also showed normal architecture of the uterus in vehicle-treated rats. It tells us about the surface epithelium that has next to no secretory activity[92].

4.8 Anticonvulsant Activity

The plant is rich in alkaloids which have neurological activities like coronaridine, dregamine, ibogamine and many other alkaloids. Khan and Mukhram did the research for anti-convulsant activity of *T. divaricata* and found that the flowers of the plant have some compounds that are responsible for anti-convulsant activity. Researchers selected 2 models for the activity: the PTZ and MES induced convulsion method and the compounds epivocangine, vobasine, voaphylline and dihydro pericyclivine showed anti-seizure activity in rats and mice by using MES induced convulsions and the PTZ induced convulsions method. Researchers found that the methanolic extract of flowers can stop seizures in animals. It is due to the inhibition of sodium channels, but the exact mechanism is not known[93-101].

4.9 Antibacterial Activity

There has been major research going on for almost half a century to advance antibacterial medicines[102]**.** Roughly a quarter of the medicine in our time has plant-related compounds at its base, which is very significant[103]**.** *T. divaricata* indole alkaloids exhibit a wide range of pharmacological activities, including antibacterial activity against both gram-positive and gram-negative bacteria[104].The different parts of the plant like bark, flowers, roots are made into an extract with different compounds like chloroform, ethanol, dether , methanol and major natural compounds which are present in the plant like alkaloids, dichloromethane, taberdivamines A and B were used for their anti-bacterial activity . The cell line used for the activity are *Staphylococcus aureus, Staphylococcus saprophyticus, Streptococcus agalctiae, Streptococcus pyogenes, Enterococcus faecalis, Salmonella typhi, Escherichia coli, Shigella boydii, Shigella dysenteriae, Pseudomonas aeruginosa, Bacillus cereus, Klebsiella sp., Streptococcus uberis, Escherichia coli* (ATCC 25922), *Klebsiella pneumoniae* (ATCC 35657), *Salmonella typhimurium* (MTCC 441), *Shigella flexneri* (ATCC 29508), *Staphylococcus aureus* (ATCC25923), *Aeromonas hydrophila*, *Staphylococcus epidermidis*, *Gardnerella vaginalis*, *Streptococcus agalactiae*, *Propionibacterium acnes*, *Corynebacterium*

macbinleyi, *Bacillus subtilis*, *Enterococcus faecalis*, *Bacillus megaterium*, *Proteus mirabilis*, *Shigella flexneri* (BCH 995), *Shigella boydii* (8) which is a gram negative bacteria , *Shigella sonnei* (NK 840), *Shigella dysenteriae* (1), *Vibrio holerae* (1023), *Vibrio cholerae* (575), *Vibrio ncholerae* (1311), *Vibrio cholerae* (756), *Escherichia coli* (RH 07/12, 18/9 ,K88), *Streptococcus suis* (gram positive bacteria), *Salmonella species*, *Cornebacterium diphtheriae* (AP596), *Staphylococcus aureus* (ML 267), *Staphylococcus aureus* (MTCC 96, ATCC 6538), *Bacillus subtilis* (MTCC 441), *Bacillus pumilis* (8241) *Pseudomonas aeruginosa* (AP585 NLF), *Klebsiella pneumoniae* strains, *Salmonella Paratyphi, Lactobacillus, Proteus vulgaris, and Klebsiella aerogenes*[67,94,105-114].

4.10 Anthelminthic Activity

Helminths are commonly found infectious agents of humans in the developing world. The disease caused by them creates such chaos across the world that it is becoming difficult for countries to cope with it[115]. *T. divaricata* is one of the Indian medicinal plants that shows anti-helminthic activity[116]. The anti-helminthic activity was performed on a mature earth worm found in India called *Pheretima posthuman*. It was done so because it has a great resemblance not only anatomically but also physiologically with the human being's intestinal round worm parasites[117]. Chloroform and methanolic extracts of *T. divaricata* leaves were prepared, Radhika B and Vilasini S performed the experiment and observed anthelmintic activity of methanol extract is more potent compared to the chloroform extract[115].

4.11 Gastrointestinal Effect

Khan *et al.* found the gastro and intestinal effects of extract with methanol of *T. divaricata* flowers. To evaluate the possible effects in the study, the model of a rat pyloric ligation method (gastric ulceration induced) and as a standard drug one of the proton-pump inhibitors was used. The study resulted in the discovery that the extract reduced the gastric juice amount, free and total acidities, and ulcer index, along with the pH of gastric acid produced[118]. Khan *et al.* also did one more test using a range of concentrations of the methanol extract from the *T. divaricata* flower. After measuring, parameters such as catalase and superoxide dismutase, along with the mucin and total protein, when treated with extracts, displayed an index that declined[119].

4.12 Anti-diabetic Activity

The activity of *T. divaricata* (antidiabetic) from the extract (methanolic) was applied to alloxan-prompted diabetic rats. The results that came out showed a great amount of antidiabetic activity. Moreover, an additional decrease can also be seen in the oxidative damage effect that can be seen in rats[120]. Kanthlal *et al.* suggest in their study that the insulin receptors may be alerted by an extract (methanolic). Henceforth, it may result in the production of beta-stem cells in the subject of the test's pancreas. Antidiabetic activity can be seen by the compound conophylline, which is generally segregated from *T. divaricata*[120,121]. Increased plasma levels in diabetic rats were observed in the study. A severe decline in blood glucose levels can also be seen in the results, which indicates antidiabetic activity as well[122].

5. Conclusion

T. divaricata is easily and plentily available in India as it is easily grown in houses, gardens, or even by the roadside. This plant has been used as a medicinal plant for many years. The present review revealed its scientifically proven anticancer, antioxidant, anti-fungal, anti-bacterial activities, etc. The present review concludes an assessment of the compound within the plant *T. divaricata* which shows pharmacological activities. Numerous compounds, such as conophylline, cornaridine, vocamine, vincristine etc., are often utilised for their curative effects. There are several alkaloids present in the plant that show different pharmacological activities like 19, 20-dihydrotabernamine and 19,20-dihydroervahanine A., which are found in the roots of the plant, show acetylcholinesterase activity, apparicine shows antimicrobial activity, catharanthine and conophylline show anti-cancer activity, anti-inflammatory and analgesic activity due to coronaridine found in almost all parts of the plant. This plant can also be useful for the treatment of Alzheimer's disease. The alkaloids like vocangine, coronaridine and isovacristine are observed to be present in *T. divaricata and* have parasympathomimetic activity. The review also enlisted different chemical compounds within different parts

of *T. divaricata* that are biologically active. It has a lot more room for further biological evolution activities in the future based on the details presented in this review. The easy and plentily availability of the plant since ancient times needs further research to magnify insights about the biologically active compounds and relative pharmacological activities of this plant for socioeconomic benefits.

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