Review Article

A Comprehensive Review: *Medicago sativa*

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Received: 22-08-2020; **Revised:** 28-10-2020; **Accepted:** 05-11-2020; **Published on:** 15-11-2020.

ABSTRACT

India has a great wealth of different plant drugs that occur naturally and have great pharmacological activities. *Medicago sativa* L. (*M. sativa*) is one of the widely well-known folklore medicinal herbs. The *M. Sativa* is a medicinal plant and has been shown to have considerable pharmacological potential with great usefulness and use in folklore medicine. Saponins, Sterols, high molecular weight alcohols, Flavones and isoflavones have been proven to be found in *M. sativa*. The plant has contributed to different pharmacological activities in the scientific field of Indian medicinal systems, such as anti-diabetic, anticancer and anti-atherosclerotic activities. This paper provides an exclusive review on the plant's ethnopharmacological, Pharmacological and phytoconstituents.

Keywords: *Medicago sativa*; ethnopharmacological; anticancer activity; phytoconstituents; folklore herb

QUICK RESPONSE CODE →

DOI:
10.47583/ijpsrr.2020.v65i01.029

DOI link: http://dx.doi.org/10.47583/ijpsrr.2020.v65i01.029

INTRODUCTION

Alfalfa (*Medicago sativa* L.) is a perennial forage legume that belongs to the sub-family of Papilionoideae. Though a diploid form exists, cultivated alfalfa is a predominantly cross Pollinated, tetraploid species.[1] However, the genetic improvement of salt tolerance in alfalfa is challenging, mainly as the response of alfalfa plants to salt stress is physiologically and genetically complex, because salt tolerance is controlled by multiple genes and involves various biochemical and physiological mechanisms.[2] Soil salinity is one of the most influential stressors that limit agricultural production. Saline soil is characterized by an excess concentration of soluble salts (chloride; sulfate; and carbonate of sodium, calcium, magnesium, potassium) in the root zone, making it difficult for plants to extract water and nutrients from the soil and causing plant injury.[3]

Phenolic compounds in plants include flavonoids. Flavonoids are usually found in plants as glycosides, i.e. provided with sugar substituents such as galactose, rhamnose or glucose, or glycoside malonates.[4] Apigenin glycosides play a very important role in plant development and physiology, especially during their interactions with other living organisms. Flavonoid glycosides and free aglycones are involved in pathogenic and symbiotic interactions with microorganisms.[5-6] In addition to the nutritional components (proteins and carbohydrates) that are important in the use of alfalfa and other plants as animal feed or food supplements, the plants produce a variety of secondary metabolites. Many of these secondary metabolites help to protect the plant against herbivores.[7] It is one of the commonest endocrine disorders and its prevalence is expected to intensify almost five times in another 10 years. Chronic hyperglycaemia leads to the production of free radicals as a result of glucose oxidation, non-enzymatic glycation of proteins and subsequent degradation of glycated proteins which in turn can lead to damage of cellular organelles and enzymes, all contributing to the promotion and development of complications of diabetes mellitus.[8]

HISTORY AND DISTRIBUTION

In his description of Media, Strabo, a famous historian states that the plant constituting the chief food of the horses is called by the Greeks Mēdikē from its growing in Media in great abundance. He also mentions as a product of Media silphion, from which is obtained the medic juice. Pliny, famous classical physician intimates that Medica is by nature foreign to Greece and that it was first introduced there from Media in consequence of the Persian wars under King Darius.[9] Dioscorides, a Greek medical herbalist, describes the plant without referring to a locality, and E4De added that it is used as forage by the cattle-breeders. In Italy, the plant was disseminated from the middle of the second century B.C. to the middle of the first century Anno Domini (A.D.).[10]

A historian called A. de Candolle states that *Medicago sativa* has been found wild, with every appearance of an indigenous plant, in several provinces of Anatolia, to the south of the Caucasus, in several parts of Persia, in Afghanistan, Baluchistan, and Kashmir. Hence the Greeks, he concludes, may have introduced the plant from Asia Minor as well as from India, which extended from the north of Persia. This theory seems to be inadmissible and

superfluous, for the Greeks allude solely to Media in this connection, not to India. Moreover, the cultivation of the plant is not ancient in India but is of recent date, and hardly plays any ro1e in Indian agriculture and economy. In ancient Iran, alfalfa was a highly important crop closely associated with the breeding of superior races of horses. Pahlavi aspast or aspist, New Persianaspust, uspust, aspist, ispist, or isfist, is traceable to an Avestan or Old- Iranian aspo-asti (from the root ad, "to eat"), and means "horse-fodder". This word has penetrated Syriac in the form aspesta or pespesta (the latter in the Geoponica). The king of ancient Persia, Khosrau I (A.D. 531-578) of the Sasanian dynasty included alfalfa in his new organization of the land-tax:3, the tax laid on alfalfa was seven times as high as that on wheat and barley, which gives an idea of the high valuation of that forage-plant. It was also employed in the pharmacopeia, being dealt with by Abu Mansur in his book on pharmacology.[10]

The seeds are still used medicinally. The Arabs derived from the Persians the word is fist, Arabicized into fisfisa; Arabic designations being ratba and qatt, the former for the plant in its natural state, the latter for the dried plant. The mere fact that the Greeks received Medicago from the Persians, and christened it "Medic grass", by no means signifies or proves at the outset that Medicago represents genuinely Iranian cultivation. However, the case of alfalfa presents a different problem. The Chinese, who cultivate alfalfa to a great extent, do not claim it as an element of their agriculture but have a circumstantial tradition as to when and how it was received by them from Iranian quarters in the second century B.C. As any antiquity for this plant is lacking in India or any other Asiatic country, the verdict as to the centre of its primeval cultivation is decidedly in favour of Iran.[10]

In the inscription of Persepolis, King Darius says, "This land Persia which Aura Mazda has bestowed on me, being beautiful, populous, and abundant in horses, according to the will of Aura Mazda and my own, King Darius, it does not tremble before any enemy." Thus, he obtained the seeds of alfalfa in Fergana, and presented them in 126 B.C. to his imperial master, who had wide tracts of land near his palaces covered with this novel plant, and enjoyed the possession of large numbers of celestial horses. From the palaces, this fodder-plant soon spread to the people and was rapidly diffused throughout northern China.[9]

MORPHOLOGICAL CHARACTERS

M. sativa is a cool-season perennial legume living from three to twelve years, depending on variety and climate. The general morphology of *M. sativa* plant was considered by Teuber and Brick (1988), and Barnes and Sheaffer (1995).[11-12] The mature *M. sativa* plant is characterized by a strong taproot. This taproot may eventually surpass 6 m or more in length with several to many lateral roots connected at the crown when *M. sativa* is grown in deep, well-drained, moist soils. The crown, a complex structure near the soil surface, has perennial meristem activity, producing buds that develop into stems. Tri- or multi-foliolate leaves form alternately on the stem, and secondary and tertiary stems can develop from leaf axils. A plant in a typical forage production field has between 5 and 15 stems and can reach nearly 1 m in height. Flowers vary in color yet purple, variegated, yellow, cream and white are the most common. After pollination, these flowers most commonly produce spiral-shaped seed pods.[11-12]

Seed

The alfalfa seed consists of the embryo, endosperm, and testa (seed coat). The seeds are formed in the fruit (pod) and usually are somewhat kidney-shaped. However, many seeds are angular as a result of internal and external forces in the pod that shape the seed during maturation. Mature seeds are approximately 1 to 2 mm long, 1 to 2 mm wide, and 1 mm thick; usually, they are about twice as long as wide. The average count among 418 seed lots representing 39 cultivars was 464.5 seeds/g.[13]

Roots

Primary root growth

The structures of the primary root are derived from the apical meristem of the radicle. They consist of a well-defined epidermis, a cortex, and the stele, which is a solid cylinder of vascular tissue in the central axis of the root. Differentiation of vascular elements (protoxylem) usually begins from three points in the stele near the pericycle. Vascular elements are recognizable < 1 mm behind the growing tip.[14]

Secondary Root Growth

Procambial cells that remain undifferentiated, between the primary xylem and phloem, begin to divide upon completion of primary root growth. Hence, at the onset of secondary growth, the vascular cambium is formed in strips that lie between rows of primary xylem. Subsequently, the pericyclic cells located directly outside the primary xylem rows become active as a cambium, and the cambium encircles the xylem core. This activity results in the formation of a continuous vascular cambium that forms the same outline as the primary xylem (i.e., triangular in triarch roots). As secondary growth continues, the vascular cambium produces the first secondary xylem between rows of primary xylem. This causes the cambium to be displaced outwardly until its circumference becomes circular in cross-section. The early secondary phloem is formed by the activity of cambial cells contiguous with the primary phloem.[14]

Lateral Root Growth

Lateral roots originate in the region of the pericycle on the same radii as the rows of protoxylem. Hence, the lateral roots formed during early life.

Stem

The cortex usually contains one layer of collenchyma cells to the inside of the epidermis; however, at the angles of

the stem, collenchymas cells are more numerous and may form a pronounced longitudinal ridge. In mature stem tissue, collenchyma may occupy the area from the epidermis to the starch sheath. Chlorenchyma forms in the area between the collenchyma and the starch sheath. Starch sheath cells often contain starch and calcium oxalate crystals that appear late in the ontogeny of the stem, and usually do not have casparian strips.[15]

Leaf

The primary features of the leaflet include an upper and lower epidermis, palisade and spongy mesophyll, and vascular tissue. The epidermal cells on the axial (upper) surface are approximately 35 in diameter with sinnuous radial walls.[16]

Traditional uses

Alfalfa is a plant from family Fabaceae. The medicinal parts of this plant are the whole flowering plant or the germinating seeds. The clover-like flowers can be yellow to violet-blue. This is 9 to 10 mm long and appears in oblong, many-blossomed racemes. The fruit is a spiraled pod with 2 or 3 twists; the centre is hollow and not thorny. The annual, succulent plant grows from 45 to 100 cm high. The stems are erect, smooth and sharply angled. The leaves are trifoliate, petiolate, and alternate. The leaflets are thorny-tipped, dentate toward the front, obovate and villous beneath. The stipules are ovate, lanceolate, slightly dentate and acuminate. The taste is unpleasantly salty, bitter and dry. The plant is indigenous to the Mediterranean region and has been widely cultivated elsewhere for centuries.[17] In folk medicine, the drug is used in the treatment of diabetes and malfunctioning of the thyroid gland. Alfalfa has isolated using as a diuretic and aromatic. It is also used in Indian and Ayurvedic medicine. The Ayurvedic names of this plant are Vilaayatigawuth, Lasunghaas and Lusan. Its well-known properties include anticholesterolemic, rich in essential enzymes, minerals and vitamins; a preventive of high blood pressure, diabetes, peptic ulcer.[18] Alfalfa tea is used to strengthen the digestive system. Sprouts (of seeds) are used by diabetics. Alfalfa seed extracts prevented hypercholesterolemia, triglyceridaemia and atherogenesis in cholesterol-fed rabbits & cynomolgus monkeys. The saponins in the extract reduce the intestinal absorption of cholesterol in rabbits. [19]

Alfalfa is available as a supplement in various forms. Pills, capsules and dry leaves are all available at health food stores. There has only been a small number of official animal and human studies on the effects and benefits of alfalfa. The preliminary studies in humans found that cholesterol and glucose levels were decreased by using alfalfa as a feed additive. [20]

Alfalfa is high in mineral content, and, because of this, it is ideal for bones, joints and skin. It promotes both bone and teeth health. The high chlorophyll content of alfalfa also supports the growth of connective tissue and is beneficial for people suffering from arthritis. It also aids in tissue repair. It is useful to heal wounds, ulcers and abscesses. Other Uses: Alfalfa is also believed to work in lowering cholesterol. It has been used as an antibacterial and to relieve sinus infections. Because alfalfa is rich in anti-oxidants, it is useful for breaking down toxins in the blood system. [21] *M. sativa* has a long tradition of use as Ayurvedic and homeopathic medicine in CNS disorders. [22] *M. sativa* has been used by the Chinese since the sixth century to treat kidney stones, fever, gravel, dysuria and to relieve fluid retention and swelling. Ancient Indian Ayurvedic physicians used *M. sativa* to treat ulcers, arthritis pain and fluid retention. In Mexico *M. sativa* is believed to improve the memory, to cure sore muscles and inflammation. Early Americans used *M. sativa* to treat arthritis, boils, cancer, scurvy, and urinary bowel problems. In Iraq, *M. sativa* is used in arthritis. In Turkey, it is used as a cardiotonic and to treat scurvy and arthritis. [22-25]

Moreover, it is considered beneficial in bladder disorders, blood clotting disorders, boils, cough, diuresis, gastrointestinal tract disorders, breast cancer, cervical cancer, kidney disorders, prostate disorders, appetite stimulation, inflammation, increasing breast milk, asthma, indigestion, insect bites, jaundice, menopausal symptoms, allergies, increasing excretion of neutral steroids and bile acids in fecal matter, nutritional support, stomach ulcers, skin damage from radiation, galactagogue, increasing peristaltic action of the stomach and bowels, thrombocytopenic purpura, uterine stimulant, rheumatoid arthritis, scurvy, vitamin supplementation (vitamins A, C, E, K) and wound healing. [25-28]

Pharmacological Uses

Anti-atherosclerotic activity

The evaluation was carried out as anti-atherosclerotic effects of alfalfa meal ingestion in chicks. The seed extract of *M. sativa* has been reported to exhibit a significant reduction of total cholesterol, phospholipid, triglyceride, LDL-cholesterol and VLDL-cholesterol in chicks, where clofibrate was used as a standard drug.[29]

A study was performed and showed that the highest saponin content extract just before the fruiting stage (free from both coumestrol and canavanine) of *M. sativa* exhibited significant hypocholesterolemic and antiatherosclerotic activity. This study proved that *M. sativa* was found to safely reduce natural cholesterol and to possess a strong anti-atherosclerotic activity. The extracts produced the most significant decrease in total cholesterol and LDL-cholesterol by 85.1 and 88%, respectively, of the corresponding levels in hypercholesterolemic rabbits. This decrease was more significant than that produced by gemfibrozil (73 and 74%) upon concomitant administration with a cholesterol-enriched diet using the same animal model at the tested dose level. Moreover, it was also observed that all *M. sativa* preparations produced significant antioxidant properties. [30]

Anticancer Activity

Evaluation of the estrogenic effects of legume extracts containing phytoestrogens was carried out by a group of scientists. The methanol extract of *M. sativa* has been shown significant estrogenic activity using an estrogen-dependentMCF-7 breast cancer cell proliferation assay. The extract showed significant competitive binding to estrogen receptor β (ER). The pure estrogen antagonist, ICI 182,780, suppressed cell proliferation induced by the extract, suggesting an ER-related signaling pathway was involved. The ER subtype-selective activities of extract were examined using transiently transfected human embryonic kidney (HEK 293) cells. Methanol extract exhibited preferential agonist activity toward ER. Phytoestrogens of the extract were determined to be responsible for estrogenic activity. [31]

Anti-diabetic Effect

The level of hyperglycemia was reduced when *M. sativa* was supplied in the diet (6.25% by weight) and infusion (1 g/400 mL) in streptozotocin-induced diabetes**.**[28] Aqueous extract of the plant (1 mg/mL) stimulated 2-deoxy-glucose transport (1.8-fold), glucose oxidation (1.7-fold) and incorporation of glucose into glycogen (1.6-fold) in mouse abdominal muscle. In acute, 20 min tests, 0.25-1 mg/mL aqueous extract of *M. sativa* evoked a stepwise 2.5-6.3-fold stimulation of insulin secretion from the BRIN-BD11 pancreatic beta cell line. This effect was abolished by 0.5 mM diazoxide, and prior exposure to the extract did not affect subsequent stimulation of insulin secretion by10 mM l-alanine, thereby negating a detrimental effect on cell viability. The effect of the extract was potentiated by 16.7 mM glucose and by 1 mM 3-isobutyl-1-methylxanthine.l-Alanine (10 mM) and a depolarizing concentration of KCl (25 mM) did not increase the insulin-releasing activity of *M. sativa*. Sequential extraction with solvents revealed insulin-releasing activity in both the methanol and water fractions, indicating a cumulative effect of more than one constituent. [32] The manganese content of *M. sativa* (45.5 mg/kg) is reported to be the active principle responsible for a hypoglycemic effect documented for *M. sativa*. A diabetic patient, treated with soluble insulin but poorly controlled, found that an *M. sativa* extract adequately controlled his diabetes. When administered separately, only small doses of manganese chloride (5-10 mg) were required to have a hypoglycemic effect. However, no effect was seen on the blood sugar concentrations of non-diabetic controls or of other diabetic patients, who were also administered manganese. It was concluded that manganese lowered the blood sugar concentration in this particular diabetic patient because he was unable to utilize manganese stored in his body.[33]

Anti-HIV activity

A group of scientists evaluated the inhibition of refined components of *Medicago sativa* polysaccharides to the activities of the reverse transcriptase of HIV and protease of HIV. Refined components of *M. sativa* polysaccharides have been shown to inhibit the activities of the reverse transcriptase of HIV and protease of HIV. [34]

Antimicrobial Effect

The evaluation was carried out as the antimicrobial activity of saponins from Medicago. The antimicrobial activity of saponins isolated from *M. sativa* against selected medically important yeasts, Gram-positive and -negative bacteria has been investigated. The increasing antibiotic activity was observed going from the saponin extracts to the sapogenin samples, suggesting that the sugar moiety is not important for the antimicrobial efficacy. The activity was found especially high against Gram-positive bacteria (*Bacillus cereus*, *B. subtilis*, *Staphylococcus aureus*, and *Enterococcus faecalis*). Discrete antifungal activity was also observed, mainly against *Saccharomyces cerevisiae*. The observed antimicrobial properties of *M. sativa* were related to the content of medicagenic acid.[35]

Cerebroprotective Effect

Evaluation of antioxidant and cerebroprotective effect of *Medicago sativa* Linn, against ischemia and reperfusion insult, were carried out and have shown that *M. sativa* exhibited significant antioxidant and cerebroprotective effects against ischemia and reperfusion insult in mice. Pretreatment with *M. sativa* extract (100 or 200 mg kg−1, p.o.) markedly reduced cerebral infarct size, xanthine oxidase, superoxide anion and thiobarbituric acid-reactive substance levels, significantly restored reduced glutathione, superoxide dismutase and total tissue sulfhydryl levels and attenuated impairment in short-term memory and motor coordination. Also, *M. sativa* directly scavenged free radicals generated against a stable radical 1,1-diphenyl-2-picrylhydrazyl and superoxide anion radicals generated in phenazine methosulfate-nicotinamide adenine dinucleotide systems, and also inhibited xanthine dehydrogenase/xanthine oxidase conversion and resultant superoxide anion production.[36]

Effect on cholesterol

In a study, the ability of *M. sativa* plant to reduce liver cholesterol accumulation in cholesterol-fed rats was enhanced by the removal of saponins. Therefore, *M. sativa* saponins appear to play an important role in neutral steroid excretion but are not essential for increasing bile acid excretion. In an experiment with prairie dogs, the lowest incidence of cholesterol gallstones was served with the diet of the higher fiber content (85% alfalfa).[37-38]

An evaluation was carried out on alfalfa seeds lower low-density lipoprotein cholesterol and apolipoprotein B concentration in patients with type II hyperlipoproteinemia. In a short-term study involving three normolipidemic individuals given *M. sativa* seeds (80-60 g daily), serum cholesterol concentrations were reported to be reduced. In another small study in which heat-treated *M. sativa* seeds (40 g three times daily for eight weeks) were taken by eight type-IIA hyperlipoproteinemic patients and three type IIB patients,

a significant decrease was noted in total serum cholesterol concentrations, low-density lipoprotein (LDL) cholesterol and apolipoprotein B. The LDL cholesterol concentration fell by less than 5% in two of the 11 patients Cholestaid™, a product available in the USA containing 900 mg of *M. sativa* extract with 100 mg citric acid, is said to neutralize the cholesterol in the stomach before it reaches the liver, thus facilitating the excretion of cholesterol from the body with no side effects or toxicity.[39-41]

M. sativa top saponins have been shown to decrease cholesterolemia without changing the levels of high-density lipoprotein-cholesterol; hence, they reduced the total cholesterol/high-density lipoprotein-cholesterol ratio in *Macaca fascicularis*. Furthermore, they decreased intestinal absorption of cholesterol, increased fecal excretion of endogenous and exogenous neutral steroids and bile acids, and decreased the percentage distribution of fecal deoxycholic and lithocholic acids[42]

Health beverage manufactured from *M. sativa* buds was found beneficial in maintaining normal digestive function and nutrition balance in the human body, reducing cholesterol, and preventing osteoporosis, arteriosclerosis and aging**.** Xiong (2003) evaluated medical–use extracts of *Medicago sativa* root and demonstrated that extracts prepared from *M. sativa* roots may be used to prepare medical preparations like powder, pill, or decoction for lowering the levels of cholesterol and lipid in blood, improving the liver function and the control and transmission of nerve tissue, and treating calculus[43]

Effect on hepatic drug-metabolizing enzymes

An investigation into the effect of various herbs on hepatic drug-metabolizing enzymes in the rat, showed that *M. sativa* potentiated the activity of aminopyrine N-demethylase but had no effect on glutathioneS-transferase or epoxide hydrolase activities.[44]

Effect on the reproductive system

Evaluate the treatment of neurovegetative menopausal symptoms with a phytotherapeutic agent. Extract of the leaves from *M. sativa* is used in the treatment of neurovegetative menopausal symptoms in women. Hot flushes and night sweating completely disappeared with the treatment of *M. sativa* extract. The plant product induced a significant increase in prolactin and thyroid-stimulating hormone response to thyroid releasing hormone. Basal levels of estradiol, luteinizing hormone, follicle-stimulating hormone prolactin, and thyroid-stimulating hormone were unchanged. Thus, *M. sativa* suggested having a central slight antidopaminergic action without side effects**.**[45]

Estrogenic Effect

Among *M. sativa* secondary metabolites, saponins and phytoestrogens offer interesting medicinal and nutraceutical prospects. Phytoestrogens, mainly coumestrol, apigenin and quercetin exhibit strong estrogenic activity and have potential for use in the treatment of hormone-related cancers. [46]

Immunomodulatory Effect

Evaluated immune potentiating effect of polysaccharides isolated from *M. sativa* L. In an *in vitro* experiment, polysaccharides isolated from *M. sativa* exhibited immune potentiating activity by increasing mouse lymphocyte uptake of [^{3}H] thymidine. [47]

Nematicidal activity

Scientist Evaluated nematicidal properties of saponins from medicago spp. Medicagenic acid isolated from *M. sativa* exhibited significant nematicidal activity against the plant-parasitic nematode Xiphinema index. [48]

AN ALTERNATIVE FOR CAROTENOID

Evaluated by the scientist about the use of alfalfa as a natural carotenoid source in diets of goldfish *Carrassius auratus. M. sativa* can be used as an alternative natural carotenoid instead of the synthetic apo-ester in goldfish diets. [49]

PHYTOCHEMICAL PROPERTIES

Chemical constituents of *Medicago sativa* include Calcium, carotene, chlorophyll, cowmarine derivative, choline, 8 essential amino acid, flavonols, lime, magnesium, phosphorous, protein, silicon, potassium, sterol, vitamine A, D, E, K. and iron. It also contains Saponins (2 3%) that on hydrolysis yield the aglycones medicagenic acid, soya sapogenols A, B, C, D, and E, and hederagenin and the glycones glucose, arabinose, xylose, rhamnose, galactose, and glucuronic acid; sterols (β-sitosterol, spinasterol, stigmasterol, cycloartenol, and campesterol, with sitosterol as the major component); high molecular weight alcohols (octacosanol, triacontanol); and paraffins (nonacosane, triacontane, hentriacontane). - Sitosterol also occurs as esters with fatty acids (mainly palmitic, lauric, and myristic). Triacontanol is a plant growth regulator that increases the growth of rice, corn, and barley as well as the yield of tomato, cucumber, and lettuce. Flavones and isoflavones (tricin, genistein, daidzein, biochanin A and formononetin are also reported along with Alkaloids (trigonelline, which is in seeds only; stachydrine; and homostachydrine); plant acids (malic, oxalic, malonic, maleic, and quinic, etc.); vitamins and growth factors (vitamins A, B1, B6, B12, C, E, and K1; niacin; pantothenic acid; biotin; folic acid; etc.); amino acids (valine, lysine arginine, leucine, isoleucine, tryptophan, phenylalanine, methionine, and threonine; asparagine in high concentrations in seeds); sugars (sucrose, fructose, arabinose, xylose, galactose, ribose, mannoheptulose.

CONCLUSION

The review of *Medicago sativa* provides its ethnobotanical uses and scientific information for many diseases and disorders. The various parts of plant in different extract exhibit antidiabetic, antimicrobial, anticancer, anti-HIV and Immunomodulatory and Nematicidal responses.

There are number of constituents present in the different part of the plants. Hence, more scientific data is required for exploring its chemical constituents in the treatment of diseases and disorders for making new therapeutic drugs.

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Source of Support: None declared.

Conflict of Interest: None declared.