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Review Article

UTILITIES OF CRATAEVA NURVALA

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ABSTRACT

The discovery of a novel chemical component from a medicinal plant may form the basis of development of various therapeutic agents with better activity. More than 500 medicinal plants have been reported to possess medicinal properties. Crataeva nurvala Buch Ham, (family: Capparidaceae) is one of the most common species among them**.** The whole plant posses high medicinal value and traditionally used in treating various ailments for human beings. The plant is used internally as well as externally. Externally, the paste or its leaves or skin of bark is applied in cervical adenitis, abscess and edematous wounds. The same paste is salutary in rheumatic joint for relief of pain. The pulp of leaves is applied on abdomen in splenic enlargement, with great benefit. Internally, varuna is used in vast range of diseases. The decoction of leaves given along with ghee relieves flatulence and abdominal pain. It also works well as a laxative, cholegogue, appetizer and vermicide, hence useful in anorexia, tumors, liver disorders, flatulent dyspepsia and helminthiasis. Phytochemically the plant has been investigated for flavonoids, glucosinolates, plant sterols, including lupeol, saponins, tannins, cardenolides, alkaloids, triterpenes and saponins. The plant has been demonstrated to possess multiple pharmacological activities such as antiinflammatory, urolithiatic, antidiabetic, antibacterial, analgesic, antiinfertility, antidiarrhoeal, antinociceptive and cardioprotective activity. This review highlights on the existing information particularly on the phytochemistry and various pharmacological properties of crataeva nurvala which may provide incentive for proper evaluation of the plant as a medicinal agent.

Keywords: Crataeva nurvala, Lupeol, Anti-inflammatory, Urolithiatic, Antibacterial activity.

INTRODUCTION

In ancient times nature has been an important source of medicinal agents and a large number of natural products have been identified and developed from natural sources based on their use in traditional medicine. Numerous medicinal plants are of global interest today because of their therapeutic and economic significance. According to the World Health Organization, approximately 80% of the world's population currently uses herbal medicines directly as teas, decocts or extracts with easily accessible liquids such as water, milk, or alcohol.

Crataeva nurvala is commonly known as Varuna. Varuna is one of the best litholytic herbs and has been used throughout the ages for the treatment of urolithiasis and crystalluria. Varuna is mentioned in vedic literature, its therapeutic use being known to ancient Ayurvedic physicians, especially as a blood purifier, to maintain homeostasis. The plant has various synonyms in Ayurvedic scriptures delineating its peculiarities viz. triparna-trifoliate, bilvapatra- leaves resemble to those of bilva (Aegle marmelos). Vrttaphala – fruits, ovoid berries, asmari-ghna- litholytic, tikta- bitter etc. Maharsi Susruta has mentioned varuna as a litholytic agent in treating kapha and vata varieties of asmari (calculi) [1, 2].

It is an appetizer, febrifuge, diuretic and litholytic in properties. It is used in diseases like urinary disorders, urinary calculi, blood disorders, worms and tumors. The bark of the tree is an important drug for problem affecting the kidneys and bladder. In Ayurveda, the bark of the Crataeva has been traditionally used to heal kidney stones for more than 3,000 years. Findings of several studies undertaken by contemporary scientists have authenticated that the herb neutralizes the enzyme called glycolate oxidase and this particular effect of the herb lessens the production of oxalates by the body[3].

The purpose of the present study is to gather together the available published information on the different vernacular names, phytoconstituents and pharmacological activity of the plant.

Taxonomic description

The plant is classified as shown in Table.1.

Table 1: Taxonomic classification of crataeva nurvala

Kingdom	Plantae
Division	Magnoliophyta
Class	Magnoliopsida
Family	Capparidaceae
Genus	Crataeva
Species	Nurvala

Vernacular names [4]

Sanskrit: Varun, Tiktshaak

Hindi: Baruna, Barna

Bengali: Varne, Borun

English: Three-leaved caper

Kannada: Bitusi, Holenekki, Holethumbe, Maavilanga, Mata maavu, Naaram bele, Vitasi, Neervaala mara, Sethu bandhana, Vaayu varuna, Nervaala

Malyalam: Nirmatalam, Nirval

Marathi: Haravarna, Karvan, Kumla, Nirvala, Ramala, Varun, Vaayuvarna

Tamil: Mavilingam, Narvala, Varanam, Maavilangam, Maralingam

Telgu: Ulimidi, Bilvaram, Chinnavulimidi, Maagalingam, Maaredu, Peddamaagalingam, Peddavulimidi, Thellavulimidi.

Habitat

Varuna is a small tree, often cultivated throughout India, especially along the streams and riverbanks. It is distributed in sub-Himalayan tracts and is indigenous to Tamil Nadu, Kerala and Karnataka. It is found in abundance, in Kerala, Madhya Pradesh, Bengal and Assam. The plant flowers mostly grow in March and fruits in June.

Botanical description

Macroscopy

Crataeva nurvala is a moderate sized deciduous tree. The mature bark is typically 6-15 cm long and 3-10 cm wide with a thickness varying from 5-15 mm. The outer surface of the bark is gray to grayish-brown and rough, due to the presence of several small and rounded lenticels. The inner surface is smooth and whitish-brown to buff colored. Leaves are trifoliate. Flowers are white or cream colored. Fruits have multiple seeds and ovoid berries, 2.5 cm in diameter and seeds are embedded in the yellow, fleshy pulp of the fruits[5].

Microscopic

Transverse section of mature stem bark shows, an outer cork composed of thin walled, rectangular and tangentially elongated cells, phellogen single layered, thin walled, tangentially elongated cells followed by a wide secondary cortex, consisting of thin-walled,

polygonal to tangentially elongated cells with a number of starch grains, starch grains mostly simple, occasionally compound with 2-3 components also present, large number of stone cells in groups of two or more, found scattered in secondary cortex, single stone cells not very common, stone cells vary in size and shape, being circular to rectangular or elongated with pits and striations on their walls, stone cells distributed somewhat in concentric bands in phloem region except in inner region of phloem which is devoid of stone cells, secondary phloem comparatively a wide zone, consisting of sieve tubes, companion cells, parenchyma and groups of stone cells, alternating with medullary rays, sieve elements found compressed forming ceratenchyma in outer phloem region, whereas in inner region of phloem, intact, medullary rays mostly multiseriate composed of thin-walled, radially elongated cells, tangentially elongated towards outer periphery, a number of starch grains similar to secondary cortex also present in phloem and ray cells, few rhomboidal crystals of calcium oxalate also found in this region, inner most layer is cambium[2].

Phytoconstituents of Crataeva nurvala: Flavonoids, glucosinolates, plant sterols, including lupeol, saponins, and tannins. The largest group of plant secondary metabolites is the terpenes. Triterpenes are a major subgroup of the terpene superfamily[6]. These compounds are low-molecular-weight metabolites that are synthesized from mevalonate via a 30-carbon intermediate, 2, 3-oxidosqualene. The cyclization of 2, 3-oxidosqualene by oxidosqualene cyclases (OSCs) to either tetracyclic sterols, through the activity of cycloartenol synthase or pentacyclic triterpenes, through the activity of enzymes such as β-amyrin synthase, α-amyrin synthase and lupeol synthase represents a critical branch point between primary and secondary metabolism[7]. Sterols have been studied extensively and function as structural components of membranes and as precursors of steroidal hormones in both plants and animals, and also have important signaling functions[8].

Part used: Stem bark, Root bark, Leaves, Fruits, Flowers[9]

Plant extract: Extraction, as the term is used pharmaceutically, involves the separation of medicinally active portions of plant or animal tissues from the inactive or inert components by using selective solvents in standard extraction procedures. The purposes of standardized extraction procedures for crude drugs are to attain the therapeutically desired portion and to eliminate the inert material by treatment with a selective solvent known as menstrum.

The extract thus obtained may be ready for use as a medicinal agent in the form of tinctures and fluid extracts, it may be further processed to be incorporated in any dosage form such as tablets or capsules, or it may be fractionated to isolate individual chemical entities such as ajmalicine, hyoscine and vincristine, which are modem drugs. Thus, standardization of extraction procedures contributes significantly to the final quality of the herbal drug. General Methods of Extraction of Medicinal Plants- Maceration, Infusion, Digestion, Decoction, Percolation, Hot Continuous Extraction (Soxhlet), Aqueous Alcoholic Extraction by Fermentation, Counter-current Extraction, Ultrasound Extraction (Sonication), Supercritical Fluid Extraction and Phytonics Process[10].

Generally used plant extract are as- C. nurvala aqueous extract (CNAE), C. nurvala ethanolic extract (CNEE), C. nurvala chloroform extract (CNCE), C. nurvala petroleum ether extract (CNPEE).

PHYTOCHEMISTRY

Phytochemical studies showed that stem bark of the plant, fruits, leaves and root bark contain different constituents as-

Stem bark of the plant contains saponins, flavonoids, sterols and glucosilinates and ceryl alcohol, friedelin, cadabicine diacetate, lupeol, betulinic acid and diosgenin[11].

Fruits contain glucocapparin, beta-sitosterol, triacontane, triacontanol, cetyl and ceryl alcohol, pentadecane, octanamide, 12-tricosanone and friedelin[12, 13, 14, 15].

Leaves contain L-stachydrine, dodecanoic anhydride, methyl pentacosanoate, kaemferol-0-α-D-glucoside and quercitin-3-0-α-D-glucoside[16].

Root bark contains rutin, quercitin, lupeol, varunol and β-sitosterol. Presence of alkaloids has been reported in bark and stems[17].

ETHNOMEDICINAL USES

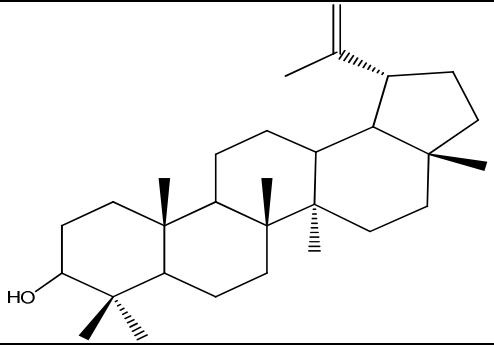
The stem, roots and leaves of varuna have great medicinal value. The plant is used internally as well as externally. Externally, the paste or its leaves or skin of bark is applied in cervical adenitis, abscess and edematous wounds. The same paste is salutary in rheumatic joint for relief of pain. The pulp of leaves is applied on abdomen in spleen enlargement, with great benefit.

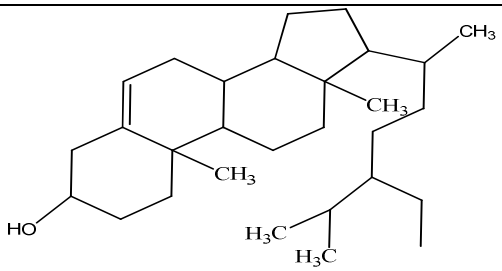
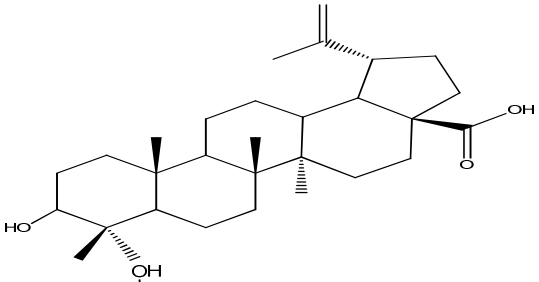
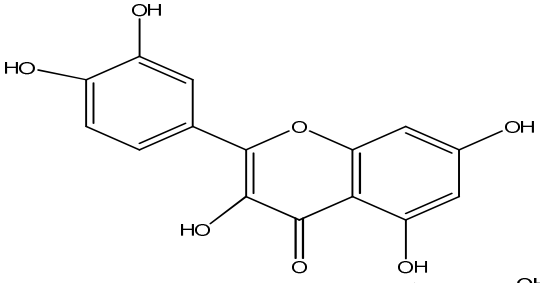
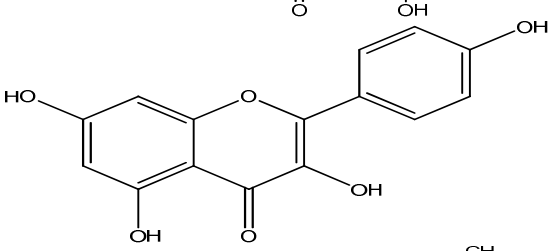
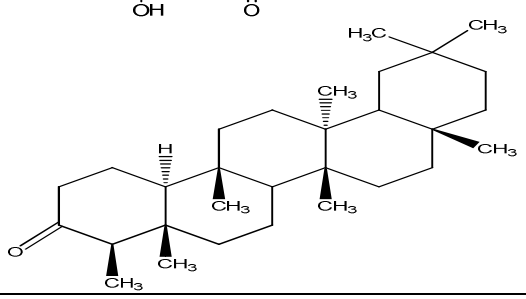
Internally, varuna is used in vast range of diseases. The decoction of leaves given along with ghee relieves flatulence and abdominal pain. It also works well as a laxative, cholegogue, appetizer and vermicide, hence useful in anorexia, tumors, liver disorders, flatulent dyspepsia and helminthiasis. The decoction of skin of varuna is given along with honey in abscesses for the potent anti inflammatory action. The decoction of skin of varuna alone is used as blood purifier in gout, internal abscess and adenitis and to reduce body fats in obesity. The leaves cooked as vegetables are also benevolent in obesity. Varuna has the cardinal properties as litholytic, diuretic and urinary antiseptic.

The decoction of bark skin or roots in beneficial in urinary calculi, dysuria and cystitis. The decoction of leaves effectively alleviates the fever and associated delirium. The fresh juice of its leaves is useful as a bitter tonic. Varuna is used as a cholegogue, anthelmintic and anti- amoebic in both intestinal and hepatic infestations[18].

Thus, the bark of C. nurvala is contraceptive and cytotoxic and is especially useful in urinary disorders, kidney bladder stones, fever, vomiting and gastric irritation. Root and bark are laxative and lithontripic and increase appetite and biliary secretion[19]. Leaves are externally rubefacient and used in rheumatism; internally they are given as febrifuge and tonic[20, 21]. Although, a large number of compounds have been isolated from various parts of C. nurvala, a few of them have been studied for biological activity and the structure of some of these bioactive compounds has been presented in Table 2.

Table 2: Structures and activities of some active compounds from crataeva nurvala.

Name	Structure	Uses
Lupeol		Responsible for antihepatotoxicity, antitumor, anti-inflammatory[22], chemoprotective agents[23], antimicrobial[24], antiarthritic[25], antihyperglycemic, antioxidant, cytotoxic,hypotensive, antiedemic, and antiperoxidant activities[26].

β –sitosterol		Responsible for antidiabetic, antioxidant[27], atherosclerosis, prostate enlargement, antihypercholesterolemia, androgenic,anticancer,antimutagenic, antifeedent, antigonadotrophic, and antiprostatic[28].
Betulinic Acid		Responsible for inhibition of HIV [29,30,31], antibacterial, antimalarial, anti-inflammatory, anthelmintic, antioxidant properties[32] and antitumor-activity selective against human melanoma cells[33].
Quercetin		Responsible for anti-inflammatory[34], antihistamine, antioxidant[35], anticancer[36, 37,38,39,40], cataracts, preprostatis[41], antiulcereffect[42], in heart diseases[43] and respiratory diseases as bronchitis and asthma[44].
Kaempferol		Responsible for Antiinflammatory, antioxidant, spasm, antiulcer, in diuretic, cough, inhibit fertility, anticancer[45] and antidepressants[46].
Friedelin		Responsible for antiulcerogenic activity [47], significance cytotoxic activity against T-lymphoblastic leukemia (CEM-SS) cell line with the LC50 of 5, 8 µg/ml. It has the ability to decrease the affinity of histamine on histamine H-1 receptor[48].

PHARMACOLOGICAL STUDIES

Pharmacological studies have confirmed that crataeva nurvala exhibit a broad range of biological effects. However, the crude extract of the plant have been used as a traditional medicine for the treatment of various diseases, some of which are very interesting for possible future development.

Anti-fertility activity

The ethanol and aqueous extracts of the dried stem bark of the plant Crataeva nurvala Buch-Hum have been found to possess significant anti-fertility effects in rats. Both ethanol and aqueous extracts exhibited partial and complete resorption of implants at 300 and 600 mg/kg dose levels, respectively. The ethanol extract is found to be more active than the aqueous extract .However in estrogenic activity study, both the extracts increased uterine weight and caused opening and cornification of vagina in immature rats. This work justifies its effectiveness in preventing pregnancy in all rats at dose levels[49].

Analgesic and antidiarrhoeal activity

The leaves of medicinal plant 'Crataeva nurvala Buch. Ham' was extracted in ethanol to evaluate the peripherally acting analgesic potential using acetic acid induced writhing and antidiarrhoeal activity using intestinal motility test both in mice. The crude extract showed significant (P<0.01) analgesic activity at oral doses of 200 and 400mg/kg body weight with an inhibition of writhing 68.4% and 76.3% compared to 67% for the positive control. In the motility test, the crude extract at same oral doses showed 31.16% and 35.31% inhibition of intestinal propulsion of charcoal marker where as positive control group exhibited 36.25% inhibition of propulsion of charcoal through the intestine[50].

The antidiarrhoeal activity of ethanol extracts of Crataeva nurvala stem bark was evaluated using castor oil-induced diarrhoea model in rats. The gastrointestinal transit rate was expressed as the percentage of the longest distance traversed by the charcoal divided by the total length of the small intestine. The weight and volume of intestinal content induced by castor oil were studied by

enteropooling method. Like atropine (3mg/kg, i.p.) there were significant reductions in fecal output and frequency of droppings when the plant extracts 500 mg/kg doses were administered intraperitoneally compared with castor oil treated rats. This dose of the plant extracts significantly retarded the castor-oil induced enteropooling and intestinal transit. It significantly inhibited ($P<0.001$) weight and volume of intestinal content[51].

Antiarthritic activity

Lupeol is a naturally occuring triterpene isolated from Crataeva nurvala stem bark, and its ester lupeol linoleate was synthesized. The effects of lupeol and lupeol linoleate on the development of complement in adjuvant arthritis in rats were studied and compared with those of indomethacin. The effect of lupeol linoleate in reducing the foot-pad thickness and complement activity in arthritic rats was even greater than that of unesterified lupeol and indomethacin. Because complement is highly involved in inflammation, the results suggest that the anti-inflammatory activity of triterpenes may be due to their anticomplementary activity[52].

Cardioprotective activity

Cyclophosphamide (CP), an alkylating agent widely used in cancer chemotherapy, causes fatal cardiotoxicity. In the present study, lupeol, a pentacyclic triterpene, isolated from Crataeva nurvala stem bark and its ester, lupeol linoleate were investigated for their possible cardioprotective effects against CP-induced toxicity. Male albino rats of Wistar strain were injected with a single dose of CP (200 mg/kg body weight, ip). In CP-administered rats, activities of lactate dehydrogenase and creatine phosphokinase were elevated in serum with a concomitant decline in their activities in the cardiac tissue. Significant increases ($P B < 0.001$) in the levels of lipid peroxides and a decrease ($P B < 0.001$) in the levels of enzymic (superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, glucose-6-phosphate dehydrogenase and glutathione-s-transferase) and nonenzymic (reduced glutathione, vitamin C and vitamin E) antioxidants in the heart were also observed. The cardioprotective effects of lupeol (50 mg/kg body weight for 10 days orally) and its ester, lupeol linoleate (50 mg/kg body weight for 10 days orally) were evident from the significant reversal of the above alterations induced by CP. These observations highlight the antioxidant property of triterpenes and their cytoprotective action against CP induced cardiotoxicity[53].

Urolithic property

Despite modern techniques, the recurrence rate of Urolithiasis is approximately 50% within 5 years. Thus, there must be some drug that corrects the metabolic errors and prevents the formation of stone. In Ayurveda, a detailed description of urolithiasis is mentioned under the heading of Ashmari. This work was designed to study the effect of Varuna (Crataeva nurvala) on the experimental model of urolithiasis (albino rats). The study was categorized into two groups: Group I, treated and Group II, control. In all albino rats, stone was surgically implanted into the urinary bladder. Estimation of the urinary and serum electrolyte done periodically and x-rays were exposed at a regular interval. This study suggests the decoction of Crataeva nurvala is effective in the management of urolithiasis[54].

Antinociceptive activity

The antinociceptive effect of crude ethanolic extracts was evaluated by 'acetic acid' analgesic test method in mice. Crude ethanolic extracts of Crataeva nurvala (250–500 mg/kg PO) produced dose-dependent, significant ($p < 0.05–0.001$) antinociceptive effect against chemically induced nociceptive pain stimuli in mice. The results obtained in this study suggest that the antinociceptive effect of the extracts of Crataeva nurvala are peripherally and centrally-mediated. The findings of this experimental animal study indicate that crude ethanolic extracts of Crataeva nurvala possesses antinociceptive properties and thus lend pharmacological support to folkloric, anecdotal uses of 'borun' in the treatment and/or management of painful, arthritic inflammatory conditions[55].

Antidiabetic activity

Crateva nurvala stem bark extracts have activity against in alloxan-induced diabetic albino rats. A comparison was made between the action of different extracts of C. nurvala and a known antidiabetic drug glibenclamide (600 µg/kg b. wt.). An oral glucose tolerance test (OGTT) was performed in diabetic rats: C. nurvala petroleum ether extract (CNPEE) and ethanolic extract (CNEE) showed significant ($P<0.001$) antidiabetic activities. In alloxan-induced model, blood glucose level of these extracts on seventh day of study were CNPEE (126.33±13.703 mg/dl) and CNEE (126.66±13.012 mg/dl) when compared with diabetic control (413.50±4.752 mg/dl) and chloroform extract (320.83±13.516 mg/dl). In OGGT model (glucose loaded rats), CNPEE showed a glucose level of 178.83±3.070 mg/dl after 30 min and 131.66±2.486 mg/dl after 90 min, whereas CNEE showed 173.66±4.224 mg/dl after 30 min and 115.50±3.394 mg/dl after 90 min. These extracts also prevented body weight loss in diabetic rats[56].

Antiinflammatory activity

Lupeol has been extensively studied for its inhibitory effects on inflammation under *in vitro* and in animal models of inflammation. A comprehensive study showed that topical application of Lupeol (0.5 and 1 mg/ear) alleviated 12-0-tetradecanoylphorbol acetate (TPA)-induced inflammation in an ear mouse model. This study showed that topical application of Lupeol decreases myeloperoxidase levels [neutrophil specific marker] thus causing reduction in cell infiltration into inflamed tissues in mice. The anti-inflammatory potential of Lupeol could be assessed from the observation that Lupeol pretreatment significantly reduced prostaglandin E2 (PGE2) production in A23187-stimulated macrophages[57]. Thus, lupeol treatment (5–9.37 mg/kg) was reported to exhibit anti-inflammatory activity with a maximum inhibition of 57.14%[58, 59]. Lupeol is also reported to treat or reduce inflammation in a mouse model of arthritis, which is an inflammation associated disease[52].

Anticancer activity

Recent studies have shown that diets rich in phytochemicals can significantly reduce cancer risk by as much as 20%. Epidemiological data suggest that the phytosterols content of the diet is associated with a reduction in common cancers including cancers of the colon, breast, and prostate[60, 61, 62]. A number of triterpenoids have shown promise as antineoplastic agents and exhibit anti-proliferative activity when tested against various cancer cell lines. These triterpenoids include members belong to the cycloartane, lupane, friedelane, dammarane, ursane, oleanane, limonoid and cucurbitacin family. Betulinic acid and its derivative also posses anticancer activity as have action against mouse leuckemia[63, 64, 65].

Topical application of Lupeol [40 mg/kg/3 times a week] for 28 weeks was shown to significantly decrease tumor burden, tumor multiplicity and increase tumor latency period in the mouse model[66]. Lupeol [2 mg/animal] was not only found to suppress the tumor growth, but also to impair head and neck cancer cell invasion by targeting NFκB signaling[67]. The chemotherapeutic potential of Lupeol was also tested against the human hepatocellular carcinoma cell SMMC7721 cells. Lupeol treatment was shown to inhibit the growth and induce the apoptotic death of SMMC7721 cells. This study showed that Lupeol-induced growth inhibition and apoptosis is due to down-regulation of DR3 expression in SMMC7721 cells[68].

USES

The skin, roots and leaves of varuna have great medicinal value. The plant is used internally as well as externally. It is applied externally on wounds, reduces inflammation, loss of appetite, abdominal pain in liver disorders, worm infestation, dysuria, pain in urinary tract, urinary tract infection, fever and in general weakness.

Classical ayurvedic preparations

Varunadi quath- Useful in treatment of urinary calculi and urinary tract disorders, Burning Micturition, Pylitis, Nephritis, U.T.I, Prostatitis, Dysurea,Prostate enlargement.

Varunadya ghrta- Used in Ayurveda for reducing phlegm, fat deposition, metabolic disorders, rheumatoid arthritis, migraine headaches and inflamatory conditions.

Varunadya taila- Used in treatment of renal calculus or stone.

Contraindications and Toxicology

No contraindications noted ever and no toxic effects seen.

CONCLUSION

In order to evaluate the overall implications of crataeva nurvala as having different activities as antidiabetic, anti-fertility activity, analgesic and antidiarrhoeal activity, antiarthritic activity, cardioprotective activity, urolithic property, antinociceptive activity, Antiinflammatory activity and anticancer activity due to having different phytoconstiuents. As this plant has no contraindication and no toxic effect, therefore it used as a valuable medicinal plant.

Thus, it is believed that detailed information presented in this review would help the researchers to get aware of this plant and extensive research should be undertaken on crataeva nurvala for establishing new therapeutic drugs for mankind.

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