Review Article

Potential pharmacognostic interventions of *Crataeva nurvala*: A pharmacological views

Ganesh S. Tolsarwad[1], Mahesh M. Biradar[2], Shrikrushna A. Shinde[2]

[1]Department of Pharmacology and Toxicology, Swami Vivekanand College of Pharmacy, Udgir, Maharashtra, India, [2]Department of Pharmaceutics, S. R Institute of Diploma in Pharmacy, Udgir, Maharashtra, India

Correspondence:
Ganesh S. Tolsarwad, Department of Pharmacology and Toxicology, Swami Vivekanand College of Pharmacy, Udgir, Maharashtra, India.
E-mail: tolsarwadganesh988@gmail.com

How to cite this article:
Tolsarwad GS, Mahesh MB, Shrikrushna AS. Potential pharmacognostic interventions of *Crataeva nurvala*: A pharmacological views. Innov Pharm Pharmacother 2020;8(3):66-73.

Source of Support: Nil.
Conflicts of Interest: None declared.

ABSTRACT

Plants are precious for mankind in many ways. From ancient time, *Crataeva nurvala* was used as an essential herb in Ayurvedic system of medicine. It is also known as *varuna* and belongs to family Capparidacae. *C. nurvala* is often cultivated throughout India, especially along the streams and riverbanks. It is dispersed in sub-Himalayan tracts and is indigenous to Tamil Nadu, Kerala, and Karnataka. *C. nurvala* is a moderate-sized deciduous tree with trifoliate leaves, it has many flowers with terminal corymbs, greenish-white in color, and fruits are smooth or scurfy berry with a globose or ovoid shape. Stem bark available in pieces and roots are long, cylindrical in shape. It is leaves, stem bark, and root contains various *phytoconstituents* such as alkaloids, saponins, triterpenes, tannins, flavonoid glycosides, glucosinolates, and phytosterols. Due to the presence of these phytochemicals, it has various pharmacological activities. Mainly used in urinary disorders such as kidney stones, fever, vomiting and gastric irritation, cytotoxic activity, and contraceptive. It is also useful in diseases such as anti-periodic, waste elimination and breathing and lung problems, fever and metabolic disorders, weak immunity, joint lubrication, skin problems, wound healing, memory loss, and heart disease. Bark is used as an appetite stimulant and to decrease the secretion of bile and phlegm according to Unani system of medicine. Laxative, lithontriptic, increase appetite, and biliary secretion type of action are shown by root and bark extraction. When leaves are applied externally, it acts as antirheumatic due to its rubefacient activity and as febrifuge and tonic.

Keywords: *Crataeva nurvala*, Capparidacae, kidney stones, saponins, triterpenes, flavonoid

Introduction

From ancient time *Crataeva nurvala* also known as *varuna*. It belongs to family Capparidacae and essential herb in Ayurvedic system of medicine. Since from distant past different medicinal preparation of *C. nurvala* were used for numerous disorders of human. According to the Ayurvedic system, proper use of *varuna* can restore to health and save from various life-threatening disorder such as asmari, mutrakrichha, vatarakta, gulma, and krimi.[1] It has different Ayurvedic properties such as taste (Rasa): Tikta, madhura, kashay, physical property (Guna): Laghu, ruksha, potency (Virya): Ushna, and Vipaka: Katu and Probhav: Bhedan.[2]

Due to the bitter taste of leaves, *C. nurvala* Buch-Ham plant is known as Tikta saka and further it has expulsion property of renal calculus and known as Setu briksh.[3] This plant is also known as kumarak because its leaves remain younger for many days and due to the white color of flower, it is known as Sweta Puspa. In according to our ancient Indian medicine books like Charak Samhita which did not mention this plant among the Mahakashay.[4] Whereas in Susrut Samhita, Susrut Quoted Varunadi Gana which is used for the treatment of Asmari and Mitrakichra (S.S.Su. 38/8)[5] and in Astanga Hriday Vagbhata has to be found it in Varunadi Gana (A.H.Su. 15/21-22).[6]

This plant has various traditional uses, especially in urinary disorders such as kidney, bladder stones, fever, vomiting, and gastric irritation. It acts through its cytotoxic activity further. It also acts as contraceptive and oxytocic and given to women post-pregnancy.[7,8] The plant is also useful in several diseases such as anti-periodic, waste elimination and breathing and lung problems, fever and metabolic disorders, weak immunity, joint lubrication, skin problems, wound healing, memory loss, and heart disease.[9] The bark is used as an appetite stimulant and to decrease the secretion of bile and phlegm according to Unani system of medicine.[10] Laxative, lithontriptic, increase appetite, and biliary secretion type of action are shown by

Access this article online	
Website: www.innpharmacotherapy.com	**e-ISSN:** 2321-323X
Doi: 10.31690/ipp.2020.v08i03.004	**p-ISSN:** 2395-0781

root and bark extraction.[11] When leaves are applied externally, it acts as antirheumatic due to its rubefacient activity and internally acts as febrifuge and tonic.[12,13]

Basic Information about Plant

Plants provide various valuable things to mankind. They supply not only food but also useful various useful medicaments to treat disorders of a human being. As they are a very cheap and effective source of drugs and so they are more prone to adulteration in any crude drug market. Proper identification of these medicinal plants should be done for the correct use of these plants.[14]

So for identification, various scientific methods are incorporated to assess the pure drug from the adulterated product in the crude form. Preliminary pharmacognostical studies are performed to standardize the crude drug. This study gives valuable information about the morphology, microscopical, and physical quality of the crude drug further; these studies have been done on many important drugs. The consequential observations have been included or published in various medicinal official books such as national formularies and pharmacopoeias,[15] and consequently, pharmacognostical study gives the technical information concerning the purity and superiority of the plant drugs which is based on scientific methods[16] [Figure 1].

Common names of *Crataeva nurvala*: Three leaved caper, barun, baruna, *Crataeva*, borun, holy garlic pear, scared lingam tree, triune, triune leaf tree, and Lengam tree.[17]

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

Figure 1: Plant *Crataeva nurvala*

Natural Habitat

Varuna is a small tree in size and often cultivated throughout India, especially along the streams and riverbanks. It is dispersed 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's flowers mostly grow in March and fruits in June.[18]

Botanical Description

Macroscopy

C. nurvala is a moderate-sized deciduous tree with a much-branched head. Height of the tree is around 25–30 m

Leaves

They are deciduous and they are trifoliate, petioles 3.8–7.6 cm long, leaflets 5–15 by 3.8–6.3 cm ovate, entire, lanceolate or obovate, acute or acuminate, attenuate at the base, entire, glabrous on both surfaces, pale beneath and reticulately veined, the lateral leaflets oblique at the base; petiolules 6–9 mm long.

Flowers

Flowers are many in number and terminal corymbs and greenish-white. Size of pedicels is 2.4–4.4 cm – long stout and glabrous. Sepals of the flower are petaloid, small, distant, ovate, and acute. Petal size is nearly 2.5 by 0.9 cm and claw is up to 6 mm long. Stamens size is bigger than petals size and they are spreading in nature. Gynophores are nearly 5 cm long, terete and smooth. Ovary is ellipsoid in shape and stigma is flat.

Fruits

Structurally, it is a smooth or scurfy berry with a globose or ovoid shape. Seeds are embedded in fruit pulp with smooth and brown in color. The filaments of the stamens are purple or white in color when they are young and turn lilac when become old. Likewise, the sepals turn their color into yellow or pale pink from green.

Stem bark

The stem bark available in pieces with size of 6–15 cm long and 3–10 cm wide and 5–12 mm thick. It has ash color from the outer side and the surface of the bark is rough due to the presence of lenticels but from the inner surface, it is smooth, whitish-brown, or buff in color.

Root

The roots are long, cylindrical in shape with woods root bark. Wood bark is around 1.0 mm–4.0 mm thick in size with outer surface yellowish-brown in color. Root has a longitudinally wrinkled surface with fractures which are tough and fibrous in nature. The root is slightly bitter in taste.[19]

Naming category[17]					
Indian vernacular names		International names		Indian Nighantus names	
Language	Name	Country Language	Name	Name of Nighantus	Name
Hindi	Baruna, Barna	Burmese	Kadat	Bhavprakas nighantu	Varana, kumāraka
English	Three-leaved caper	Coong	Nerajane	Dhanwantari nighantu	Kumāraka, swetapuspa
Sanskrit	Varun, Tiktshaak	Malay	Cadat	Kaidev nighantu	Kumāraka, *varuna*
Bengali	Varne, Borun	Meehi	Bunboronda	Madanpal Nighantu	Varana, sweta, hakavriksha
Gujarati	Vayvarno, varano	Sinhalese	Lunuwarana	Saligram nighantu	Shakavriksha, kumāraka
Malyalam	Nirmatalam, Nirval			Raj Nighantu	Kumāraka, swetapuspa
Kannada	Bitusi, Holenekki, Holethumbe			Priya Nighantu	*Varuna*
Konkani	Nervol			Sankar Nighantu	Tiktashak, marutapana
Marathi	Haravarna, Karvan, Kumla			Nighantu Adarsha	Varana, sweta, shakavriksha
Tamil	Mavilingam, Narvala, Varanam				
Telgu	Ulimidi, Bilvaram, Chinnavulimidi				
Uriya	Boryno				
Lepana	Purbong				
Punjabi	Barna				

Microscopic

Stem bark: Microscopically stem bark consists of epidermis which is made up of a single layer of cubical cells in its transverse section. Followed by epidermis, 6–10 layers of collenchyma are present in cortex and further 5–10 layers of parenchyma containing chloroplasts and starch grains. Stele is characterized by a large number of vascular bundles. Starch grains are simple and compound, whereas calcium oxalate crystal are found in prismatic shape in parenchyma.

Roots

Microscopically, the root shows tetrarch stele in its TS section. Periderm consisting of 8–10 layers of cork, 2–3 layered phellogen, 6–8 layers of phelloderm, and a wide zone of phloem and central wood. The phloem consists of sieve tubes, companion cells, and phloem parenchyma, a few stone cells traversed by phloem rays. The xylem is composed of vessels, tracheids, wood fibers, and wood parenchyma, traversed contain a resinous substance. The fibers are thick walled.[17]

Phytochemistry

Sitosterol, betulinic, diosgenin, acid, and betulinaldehyde are many medicinally important compounds which are extracted *C. nurvala*.[11,20-22].

Extraction of essential oils, terpenoids, alkaloids, sugars, steroids in various phytochemicals studies of Capparidaceae species.[20] Bioactive triterpenoid is lupeol and lupeol acetate, epicatechin-5-glucoside, epifzelechin, spinasterol acetate, taraxasterol, 3-epilupeol, cadabacine, cadabacine acetate, catechin, and glucocapparin are also isolated[23] and further phytochemistry of aqueous extract of the stem with butanol partitioned found succinic acid, mannitol, and lactic acid in the extract.

Similarly, chloroform fraction of the *C. nurvala* isolated betulinic acid, stigmasterol, and β-sitosterol. Tri-terpenoids and steroids very rich in quantity are isolated from stem bark of *C. nurvala*.[24] Several other phytochemicals are isolated from fruit extract of *C. nurvala* such as octanamide, friedelin, pentadecane, and 12-tricosanone.[20] Methyl pentacosanoate, kaempferol-3-O-α-D-glucoside, quercetin-3-O-α-D-glucoside, and dodecanoic anhydride are isolated from the leaf extracts of *C. nurvala*.[10] Isolation of varunol, βsitosterol, and lupeol from the ether fraction of bark from *C. nurvala* was completed[25] further from ethanolic extract of bark isolated lupeol and its derivatives;[26] Momata *et al.* isolated stearic acid from petroleum fraction of root bark.[27] Benzene fraction of root bark resulted in the isolation of taraxasterol, αspinasterol acetate, 3-Epilupeol, βsitosterol, and lupenone.[28] The most uncommon compound is a glucoside of a flavan-3-ol, (-) epiafzelechin-5-0- β-D glucoside. As mostly such compounds occur as gallates. Another interesting constituent identified in the bark is diosgenin, which was found to vary with age and season.[29] Alcoholic extract of root bark resulted in the isolation of glucose, galactose and maltose, cysteic acid, lysine hydrochloride, arginine hydrochloride, hydroxyproline, glutamic acid, α-amino caprylic acid rutin, and quercetin.[30] Hexane fraction of *C. nurvala* fruit resulted in the isolation of tricontanol, cetyl alcohol, glucocapparin, and tricontane leaves of *C. nurvala* showed the presence of L'Stachydrine further hexane fraction of the bark resulted in the isolation of diosgenin, ceryl alcohol, betulenic acid, and friedelin.[31] Cadabicine and its derivatives were isolated from the alcoholic extract of bark from stem.[32]

Leaf extract showed the presence of quercitin-3-O-α-D-glucoside, dodecanoic anhydride, methyl pentacosanoate, and kaemferol-3-Oα-D-glucoside 17. Several other phytochemical studies of *C. nurvala* revealed the presence of various types of compounds in its different parts. The bark of this plant majorly contains various phytoconstituents such as cadabicine, cadabicine diacetate, phragmalin triacetate,

mannitol, lactic acid, betulinic acid, lupeol, lupenone, succinic acid βsitosterol, and stigmasterol.[24,33-35] Its fruit possesses pentadecane, octanamide, 12- tricosanone, and friedelin.[36] Heneicosane, 1- octadecanol, methyl pentanoate, 1-eicosanol, and 9- heptadecanone were also isolated from the flowers of this plant.[37] *C. nurvala* root contains lupeol, β-sitosterol, and varunol.[25]

Pharmacology

Several pharmacological studies on the lead molecule, lupeol, have been carried out, established its mode of action in the treatment of various diseases and other benefits.

The studies on lupeol provide insight into its mechanism of action and suggest that it is a multitarget agent involving a number of molecular pathways such cFLIP,Wnt/β-catenin, Fas, ras, phosphatidylinositol-3-kinase/Akt, and nuclear factor kappa B, in a variety of cells. Lupeol has a modulatory effect on 7,12-dimethylbenz anthracene (DMBA) -induced alterations on cell proliferation in the skin of Swiss albino mice. Lupeol induces p53 and cyclin-B-mediated G2/M arrest and targets apoptosis through activation of caspase. Cell-cycle analysis exhibits lupeol-induced G2/M-phase arrest and the inhibitory activities were mediated through inhibition of the cyclin-B-regulated signaling pathway involving p53, p21/WAF1, cdc25C, cdc2, and cyclin-B gene expression. Further lupeol-induced apoptosis was observed, with upregulation of Bax and caspase-3 genes and downregulation of anti-apoptotic bcl-2 and survivin genes. Thus, our results indicate that lupeol has novel anti-proliferative and apoptotic potential that may be helpful in designing strategies to fight skin cancer.[38]

Antimalarial Activity

Biological testing of natural products revealed that lupeol moderates *in vitro* growth inhibition of *Plasmodium falciparum* but lack *in vivo* activity. Lupeol possess antimalarial activity (inhibiting *P. falciparum* growth by 45% at 25 mg/mL and Oriciarenieri IC50 and IC90 at 46.8 and 96.9 mg/ mL, respectively)[39,40] and its fatty acid ester isolated from Holarrhena floribunda showed *in vitro* inhibition against the chloroquine-resistant strain FCR-3 and the chloroquine-sensitive standard strain 3D7, this lead, paved the path for developing more semi-synthetic molecules but the discrepancy persists between *in vitro* and *in vivo* activity.

Antifertility Activity

Ethanolic and aqueous fractions of the dried stem bark of the plant *C. nurvala* Buch-Hum (Capparidaceae) possess anti-fertility capability when tested on rats, ethanolic fraction at 300, and aqueous fraction at 600 mg/kg body weight (b.wt) exhibited partial and complete resorption of implants respectively. In estrogenic activity study, both the extracts increased uterine weight and caused opening and cornification of vagina in immature rats. The present work provides insight into the effectiveness of fractions in preventing pregnancy in all rats at dose levels. The effect is most probably due to the activity of lupeol.[41]

Antiurolithic Effect

Urinary stones affect 10–12% of the population in industrialized countries; the incidences are increasing over the past few years, with the age of onset decreasing. Although oxalate, an important stone-forming constituent, is excreted mainly through the kidneys, it is harmless to the renal epithelial cells at low concentration. Oxalate exposure imposes oxidative stress on renal cells by generating reactive species and accumulation of lipid peroxides. Reactive oxygen species (ROS) damage the membrane and help it anchor the crystals, serving as a substratum for stone growth; this initiates a self-perpetuating cycle, ultimately leading to stone formation. ROS generated during the metabolism of oxalate and by oxalate itself are considered as the major contributors for the renal damage in lithogenesis. It has long been recognized that antioxidants may contribute to protection against stone formation. This hypothesis has been supported by findings, such as the administration of Vitamin E and lipoic acid are able to counteract oxalate-induced oxidative changes. *C. nurvala* Buch.-Ham (Capparidaceae) is a medicinal plant, from which the bark decoction was used against calcium oxalate urolithiasis in experimental rats. Lupeol, isolated from the stem bark of the plant, has been identified as the active compound for antiurolithic effects.[42,43]

Gastroprotective Activity

Lupeol demonstrated a gastroprotective effect on gastric mucosal damage induced in rats by intragastric ethanol (1 mL/rat). Rats, when treated with lupeol suspended in Tween 80 at concentrations 3, 10, 30, and 100 mg/kg, displayed 21, 60, 79, and 77% gastroprotection, respectively. Taking into account this medicinal property of the principal constituent of *C. nurvala*, lupeol (pentacyclic triterpenes), the molecule could be derivatized to enhance its potency.[44]

Hepatoprotective Activity

Lupeol has displayed hepatoprotective activity in alleviating the action of aflatoxin B1, a fungal metabolite known for its hepatotoxic and hepatocarcinogenic effect, treatment with lupeol substantially normalized degenerative alterations in hepatocytes. Lupeol is reported to reestablish antioxidant enzyme activities in mouse liver affected by DMBA-induced oxidative stress.[45]

Cardioprotective Activity

Cyclophosphamide (CP), an alkylating agent widely used in cancer chemotherapy, it is cardiotoxic, the possible cardioprotective activity of lupeol was investigated against CP-induced toxicity. Male albino rats of Wistar strain were injected with a single dose of CP (200 mg/kg b.wt, ip) on administering CP to rats, levels of lactate dehydrogenase (LDH), and creatine phosphokinase were elevated in serum and at the same time marked decrease in the activities of cardiac tissue was observed. Significant increases in the levels of lipid peroxides and a decrease in the levels of enzymatic and non-enzymatic antioxidants in the heart were also observed, administration of lupeol at 50 mg/kg b.wt for 10 days orally, significantly reversed

the above alterations induced by CP. These observations highlighted the antioxidant property of triterpenes and their cytoprotective action against CP-induced cardiotoxicity. Another evidence which establishes the pharmacological efficacy of lupeol against CP-induced mitochondrial-cardiomyopathy, a decrease in the activities of tricarboxylic acid cycle enzymes such as succinate dehydrogenase, malate dehydrogenase, and isocitrate dehydrogenase were observed in CP-treated rats; simultaneously there was a decrease in the activities of mitochondrial complexes of electron transport chain. Electron microscopical observations were also in agreement with the above changes. Mitochondria were swollen with numerous electron-dense granules and showed damaged cristae, revealing the cytotoxic effect of CP. Lupeol (50 mg/kg b.wt for 10 days orally) showed reversal of the above alterations induced by CP. These data suggest that the protective effects of lupeol against CP-induced cardiac damage were achieved by the restoration of mitochondrial structure and function.[46]

Antimicrobial Activity

Lupeol has shown inhibitory effect against strains of Gram-negative bacteria *Pseudomonas aeruginosa* and *Klebsiella pneumonia* at a concentration of 30 ug/100 ul, zones of inhibition were also observed in *Salmonella typhi* and *Escherichia coli* cultures using lupeol impregnated disk at concentration 10 mg/ml.[47]

Antidiabetic Activity

C. nurvala stem bark extracts (500 mg/kg) showed potent antidiabetic activity in alloxan-induced diabetes *in vivo*. Results were comparable with standard glibenclamide (600 μg/kg). The effect may be due to increasing insulin secretion from β-cells of islets of Langerhans or its release from bound insulin due to enhanced glucose utilization by peripheral tissues.[48]

Antipyretic Activity

Ethanolic extract of *C. nurvala* (200 and 400 mg/kg) showed potent antipyretic activity against typhoid vaccine-induced pyrexia in rabbits. The result was comparable with paracetamol (100 mg/kg p.o.), standard antipyretic drug.[49]

Role of *C. nurvala* in Inflammation

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-induced inflammation in an ear mouse model. This study showed that topical application of lupeol decreases myeloperoxidase levels (neutrophil specific marker), thus causing a 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 production in A23187-stimulated macrophages.[50] Thus, lupeol treatment (5–9.37 mg/kg) was reported to exhibit anti-inflammatory activity with a maximum inhibition of 57.14%. Lupeol is also reported to treat or reduce inflammation in a mouse model of arthritis, which is an inflammation-associated disease.[51,52] The anti-inflammatory activity of extracts of *C. nurvala* bark was studied by human RBC membrane stabilization method. The results showed that the extracts of *C. nurvala* bark containing lupeol as the active constituent may be utilized for their anti-inflammatory properties.[53]

C. nurvala Buch. Ham. is an important medicinal plant in India, and its extracts and components were used to treat various inflammatory diseases, such as urinary tract infection, rheumatoid arthritis, and colitis. A non-cytotoxic concentration of ethanol extracts of *C. nurvala* Buch. Ham (≤200 μg/ml) significantly reduced the production of nitric oxide (NO) and Interleukin (IL)-6, but not tumor necrosis factor (TNF)-α, in lipopolysaccharides (LPS)-stimulated RAW 264.7 macrophages. Decreased production of NO by ethanol extracts was correlated with reduced expression of inducible NO synthase at the mRNA and protein levels. The mRNA expression of IL-6 and IL-1β, but not TNF-α (inflammatory mediators) was also inhibited by ethanol extracts of *C. nurvala* Buch. Ham treatment in LPS-stimulated RAW 264.7 macrophages.[54] Methanolic extract of the leaves of *C. nurvala* produced significant dose-dependent antinociception when assessed using hot plate test, tail immersion test. Likewise, this extract produced significant dose-dependent inhibition in both neurogenic and inflammatory pain induced by intraplantar injection of formalin.[55] The methanol extract of *C. nurvala* has a strong antioxidant capacity which was influenced mostly by terpenoid and alkaloid content. However, the petroleum ether extract containing most terpenoid fraction appeared to be showing potent anti-inflammatory activities. Proteases, especially serine proteases, are key players in recruiting the initiation and progression of the inflammatory process inhibition of trypsin by the petroleum ether extract of *C. nurvala* was graded as the most effective antiproteolytic agent.[56]

Role of *C. nurvala* in Oxidative Stress

Oxidative metabolism is essential to the survival of cells. A side effect of this dependence is the production of free radicals and other ROS that causes oxidative changes.[57] The oxidative stress can be contributed either by the cells generating ROS as part of normal aerobic metabolism or by the ROS generated secondary to plant and animal responses to injury and invading organisms or by the ROS generated in polluted atmospheres. Oxidative stress could mediate damage to cell structures, including lipids, proteins, RNA, and DNA, which lead to a number of diseases.[58] The lack of antioxidants facilitates the development of degenerative diseases, including cardiovascular diseases, cancers, neurodegenerative diseases, Alzheimer's disease, and inflammatory diseases. The therapeutic uses of traditional medicinal products in various inflammatory diseases and cancers have been generally observed. The ethnopharmacological usages of traditional plants for the treatment of skin disorders, inflammatory, and other infectious diseases can be taken into account because they reflect disease states bearing relevance to cancer or a cancer symptom. The efforts have been made to discover new therapeutic agents from traditional medicinal plants that lack the toxic effects associated with current therapeutic agents.[59]

The *C. nurvala* Buch. Ham. (Family Capparidaceae) is one of such plants that are ethnopharmacologically important and is used for the treatment of various disorders. The plant parts of *C. nurvala* are commonly applied to regulate equilibrium among vata (blood flow, waste elimination, and breathing), pitta (fever and metabolic disorder), and kapha (joint lubrication, skin moisture, wound healing, strength and vigor, memory loss, heart and lung weakness, and weak immune system) in Ayurvedic system.[60]

Aqueous alcoholic extracts of Bark of *C. nurvala* has the highest antioxidant capacity. Total phenolic and tannin contents were found to be the highest in *C. nurvala* (195 gallic acid equivalent mg/g and 218.3 mg/g catechin equivalent). Superoxide dismutase (SOD) mimetic activity was found to be the highest in *C. nurvala*, although all barks showed activity more than 100 units/mg extract. Lipid peroxidation inhibitory potential was found to be the highest in *C. nurvala* (83.4% inhibition of malondialdehyde formation/10 mg extract), and also showed a comparatively high NO quenching capacity (45.5% per 10 mg extract) when comparing *C. nurvala* Buch.-Ham to *Buchanania lanzan* Spreng., *Aegle marmelos* Corr., *Dalbergia sissoo* Roxb. ex DC, and *Cedrela toona* Roxb.[61]The plant extract (250 and 500 mg/kg) is effective in significantly altering the indices of cisplatin-induced dysfunction of renal proximal tubule cells under oxidative stress by decreasing the concentration of blood urea nitrogen, creatinine, and lipid peroxidation. The increase in glutathione and catalase activity is indicative of the antioxidant properties of stem bark extract.[22]

Antioxidative activity of *C. nurvala* leaf polyphenols was estimation by evaluating its radical scavenging and lipid peroxidation inhibition properties. As leaf of *C. nurvala* is a rich source of polyphenols, which can be better recovered in mixtures of the organic and aqueous mixture which attributed potent antioxidative effect against free radical generation and lipid peroxidation *in vitro*.[62]

Antioxidant properties of *C. nurvala* bark contain a variety of bioactive phytochemical constituents such as flavonoids, phenolic compounds, and essential oils which play an important role in scavenging free radicals generated by mutagens and carcinogens. Significant protective effects were shown by the ethanolic extract of *C. nurvala* bark in oxidative stress-induced damage of the prostate in rats.[63]

Lupeol, isolated from *C. nurvala* stem bark in doses 40 and 80 mg/kg b.wt, po, for 10 days, decreased the concentration of lipid peroxidation and increased glutathione and catalase activities in cisplatin (5 mg/kg b.wt, ip) -induced nephrotoxicity in rats. The increased glutathione and catalase activities are indicative of the antioxidant properties of lupeol.[64]

Role of *C. nurvala* in Renal Complications

The *C. nurvala* bark decoction on calcium oxalate lithiasis has been studied in rats. The increased deposition of stone-forming constituents in the kidneys of calculogenic rats was lowered with *C. nurvala* bark decoction. The increased urinary excretion of the crystalline constituents along with lowered magnesium excretion found in stone-forming rats was partially reversed by decoction treatment,[65] lupeol isolated from stem bark extract of *C. nurvala* Buch-Ham (*Capparaceae*) offered significant activity against free radical-induced nephrotoxicity in rats.[66]

Oxalate synthesizing enzymes mainly present in liver is glycolate oxidase (GAO) and LDH which were significantly increased in the calculogenic group of animals. Bark decoction treatment lowered the liver GAO activity considerably. The decrease in liver GAO activity was seen during bark decoction treatment, with a concomitant decrease in kidney oxalate level, which proved beneficial as a prophylactic measure in preventing stone recurrence.[67]

Gentamicin-treated animals have nephrotoxicity and evidenced by significant decrease in urea clearance which was prevented by polyherbal formulations containing *C. nurvala* extract. The study of renal microscopy also showed necrosis, epithelial loss with granular degeneration, and fatty changes in gentamicin-treated rats and was reversed by polyherbal formulations.[68] Lupeol, isolated from *C. nurvala* stem bark in doses 40 and 80 mg/kg b.wt, po, for 10 days, decreased cisplatin (5 mg/kg b.wt, ip) -induced nephrotoxicity in rats.[64]

Decoction of Varuna (*C. nurvala*) is effective in the treatment of urolithiasis and proven by a study done on albino rats. Albino rats are surgically implanted stone into the urinary bladder. Controlled and treated animals were assessed urinary and serum electrolyte level at a regular interval. Beneficial action was shown against urolithiasis in treated animals.[69] Aqueous extract of *C. nurvala* Bark treated animals shown protection to kidney against gentamicin-induced nephrotoxicity by getting improvement in parameters such as blood urea and serum creatinine. This was further confirmed protection action of *C. nurvala* by histopathological examination of kidney tissue.[70] Further, this water decoction of *C. nurvala* significantly protected against cisplatin-induced acute kidney injury by showing improvement in urea, creatinine, and creatinine clearance. This decoction of *C. nurvala* has also improved values of SOD and catalase in treated groups and shown antioxidant properties due to the presence of tannins, flavonoids, and phenolic content of the fraction.[71]

References

1. Sharma V. Dravyaguna Vijnan. New Delhi: Choukhamba Bharati Academy; 1999. p. 652.
2. Nadkarni, KM. Indian Materia Medica. Vol. 2. Bombay: Popular Prakashan Pvt. Ltd.; 1976. p. 1308.
3. Bopana N, Saxena S. *Crataeva nurvala*: A valuable medicinal plant. J Herbs Spices Med Plants 2008;14:107-27.
4. Gautam P, Singh AK, Bairwa OP. Review of Varuna with special reference to Kosha and Nighantus. Int J Ayurveda Pharm Chem 2018;9:67-74.
5. Sastry A. Hindi Commentary by Kaviraja Ambikadutta Shashtri. 6th ed. New Delhi: Chaukhamba Sanskrit Samsthan; 1987.
6. Khade R, Sangoram A, Jadhav A, Gadekar S, Bhujbal S. Varun (*Crataeva nurvala* Buch.-Ham.): A review from Bruhatrayi, Kashyap Samhita and Nighantu. World J Pharm Sci 2018;6:163-6.
7. Ghani A. Medicinal Plants of Bangladesh with Chemical Constituents and Uses. 2nd ed. Dhaka: Asiatic Society of Bangladesh; 2003. p. 184.
8. Lakshmi V, Agarwal SK, Mahdi AA. An overview of *Crataeva nurvala* Buch-Ham. Nat Prod Indian J 2015;11:119-21.

9. Patil AG, Koli SP, Patil DA, Naresh C. Pharmacognostical standardisation and HPTLC fingerprint of *Crataeva tapia* Linn. SSP. Orora (Jacob) Almedia leaves. Int J Pharm Biol Sci 2010;1:1-14.
10. Mhaskar KS, Blatter F, Caius JF. Kirtikar and Basu's Illustrated Indian Medicinal Plants: Their Usage in Ayurveda and Unani Medicines. New Delhi: Sri Satguru Publications; 2000. p. 254-9.
11. Malini MM, Baskar R, Varalakshmi P. Effect of lupeol, a pentacyclic triterpene, on urinary enzymes in hyperoxaluric rats. Jpn J Med Sci Biol 1995;48:211-20.
12. Walia N, Kaur A, Babbar SB. An efficient, *in vitro* cyclic production of shoots from adult trees of *Crataeva nurvala* Buch. Ham. Plant Cell Rep 2007; 26:277-84.
13. Sanayaima RK, Kaur A, Aggrawal A, Babbar SB. Cryopreservation of *in vitro*-grown shoot tips of *Crataeva nurvala*, Buch. Ham, an important medicinal tree. Cryo Lett 2006;27:375-86.
14. Padnekar PA, Raman B. Pharmacognostic and phytochemical studies of *Semecarpus anacardium* (Linn.) F. leaves. Int J Pharm Pharm Sci 2012;4:682-5.
15. Sharma SK. Recent approach to herbal formulation development and standardization. Int J Integr Biol 2004;2:195-203.
16. Dhanabal SP, Suresh B, Sheeja E, Edwin E. Pharmacognostical studies on *Passiflora quadrangularis*. Indian J Nat Prod 2005;2:9-11.
17. Saha S, Bhakat A. A critical review of varuna (*Crataeva nurvala*). Int Ayurvedic Med J 2018;6:1284-7.
18. Kuvar NA, Lambole VB, Shah BN, Shah PK, Shah DP. A valuable medicinal plant *Crataeva nurvala*. J Herbs Spices Med Plants 2013;4:210-27.
19. Nigamanand B, Chaubey S, Tiwari RC, Kour G, Dhyani S. Varun (*Crataeva nurvala* Buch-Ham): A critical review W.S.R. to urinary tract disorder. Int J Ayurveda Pharm Res 2016;4:49-52.
20. Gagandeep M, Kalidhar SB. Chemical constituents of *Crataeva nurvala* (Buch-ham) leaves. Indian J Pharm Sci 2006;68:804-6.
21. Lakshmi V, Chauhan JS. Triterpenoids and related compounds from *Crataeva nurvala*. Plant Med 1975;27:254-6.
22. Hossain US, Biazid AS. Triterpenoids from the stem bark of *Crataeva nurvala*. Dhaka Univ J Pharm Sci 2008;7:71-4.
23. Mohammad S. Lupeol a novel anti-inflammatory and anticancer dietary triterpene. Cancer Lett 2009;285:109-15.
24. Parvin S, Kader MA, Muhit MA, Haque ME, Mosaddik MA, Wahed MI. Triterpenoids and phytosteroids from stem bark of Buch Ham. J Appl Pharm Sci 2011;1:47-50.
25. Bhandari PR, Dhar ML, Sharma VN. Chemical constituents of the root bark of *Crataeva nurvala* Ham. J Sci Ind Res 1951;10B:195-6.
26. Chakravarthi RN, Dabi C, Roma B. Triterpene from *Crataeva religiosa*. Bull Cal ST M 1959;7:105.
27. Momota B, Ray AB, Dasgupta B. Chemical investigation of *Crataeva nurvala* a search for the anti-inflammatory principle. Curr Sci 1975;44:227-8.
28. Vijayalakshmi V, Chauhan JS. Triterpenoids and related compounds from *Crataeva nurval*. Plant Med 1975;27:254-6.
29. Sharma PC, Yelne MB, Dennis TJ. Data Base on Medicinal Plants Used in Ayurveda. Vol. 2. New Delhi: Central Council for Research in Ayurveda and Sidda; 2001. p. 538-49.
30. Lakshmi V, Chauhan JS. Chemical examination of *Crataeva nurvala*. *J Indian Chem* Soc 1974;1:1058.
31. Sethi VK, Jain MP, Thakur RS. Chemical constituents of *Crataeva religiosa*. Plant Med 1978;34:223-4.
32. Viqar UA, Kaniz F, Aziz UR, Shoib A. Cadabicine and cadabicine diacetate from *Crataeva nurvala* and *Cadaba farinosa*. J Nat Prod 1987;50:1186.
33. Haque ME, Islam MN, Gupta DD, Hossain M, Shekhar HU, Shibib BA. Triterpenoids from the stem bark of *Crataeva nurvala*. Dhaka Univ J Pharm Sci 2008;1:71-4.
34. Slipi C, Padmaa MP, Deepak M, Agarwal A. Phytochemical studies on stem bark of *Crataeva nurvula* Ham. J Pharm Res 2011;4:401-2.
35. Rao GV, Annamalai T, Mukhopadhyay T. Chemical examination and biological studies on the bark of *Crataeva nurvala* Buch. Ham. Pharm J 2011;3:1-4.
36. Gagandeep, Meera, Kalidhar SB. Chemical investigation of *Crataeva nurvala* Buch. Ham. Fruits. Indian J Pharm Sci 2009;71:129-30.
37. Gagandeep, Meera, Kalidhar SB. Chemical constituents of flowers of *Crataeva nurvala* (Buch-Ham). Natl J Plant Improv 2005;7:95-6.
38. Saleem M, Kaur S, Kweon MH, Adhami VM, Afaq F, Mukhtar H. Lupeol, a fruit and vegetable based triterpene, induces apoptotic death of human pancreatic adenocarcinoma cells via inhibition of RAS signaling pathway. Carcinogenesis 2005;26:1956-64.
39. Caniato R, Puricelli L. Natural antimalarial agents (1995-2001). Crit Rev Plant Sci 2003;22:79-105.
40. Schwikkard S, van Heerden FR. Antimalarial activity of plant metabolites. Nat Prod Rep 2002;19:675-92.
41. Bhaskar VH, Profulla KM, Balakrishnan BR, Balakrishnan N, Sangameswaran B. Evaluation of the anti-fertility activity of stem bark of *Crataeva nurvala* buch-hum. Afr J Biotechnol 2009;8:6453-6.
42. Patankar S, Dobhada S, Bhansali M, Khaladkar S, Modi J. A prospective, randomized, controlled study to evaluate the efficacy and tolerability of Ayurvedic formulation "varuna and banana stem" in the management of urinary stones. J Altern Complement Med 2008;14:1287-90.
43. Malini MM, Lenin M, Varalakshmi P. Protective effect of triterpenes on calcium oxalate crystal-induced peroxidative changes in experimental urolithiasis. Pharmacol Res 2000;41:413-8.
44. Chávez-Piña AR, Sandoval A, Arrieta J, Reyes B, Flores AM, Navarrete A. Gastroprotective effect of β-Lupeol: Role of prostaglandins, sulfhydryls and nitric oxide. Rev Lat Am Quím 2009;37:133-43.
45. Karwani G, Singhvi IJ, Kapadiya NJ, Agarwal N. Heparoprotective activity of *Crataeva nurvala* in carbon tetra chloride induced hepatotoxicity in rats. Inveti Rapid 2011;2011:84-92.
46. Sudharsan PT, Mythili Y, Selvakumar E, Varalakshmi P. Cardioprotective effect of pentacyclictriterpene, lupeol and its ester on cyclophosphamide-induced oxidative stress. Hum Exp Toxicol 2005;24:313-8.
47. Lagnika L, Anago E, Atindehou M, Adjahoutonon B, Dramane K, Sanni A. Antimicrobial activity of *Crataeva religiosa* forst against bacteria isolated from *Thryonomys swinderianus* Temminck. Afr J Biotechnol 2011;10:1034-9.
48. Sikarwar MS, Patil MB. Antidiabetic activity of *Crateva nurvala* stem bark extracts in alloxan-induced diabetic rats. J Pharm Bioallied Sci 2010;2:18.
49. Chidambaram K, Albert J, Karpagam K. Antipyretic activity of *Crateva magna* bark on tab-vaccine induced pyrexia. Int J Pharm Sci Res 2011;2:856.
50. Fernández MA, de las Heras B, Garcia MD, Sáenz MT, Villar A. New insights into the mechanism of action of the anti-inflammatory triterpene lupeol. J Pharm Pharmacol 2001;53:1533-9.
51. Nguemfo EL, Dimo T, Dongmo AB, Azebaze AG, Alaoui K, Asongalem AE, *et al*. Anti-oxidative and anti-inflammatory activities of some isolated constituents from the stem bark of *Allanblackia monticola* Staner LC (Guttiferae). Inflammopharmacology 2009;17:31-41.
52. Saleem M. Lupeol, a novel anti-inflammatory and anti-cancer dietary triterpene. Cancer Lett 2009;285:109-15.
53. Jayaprakasam R, Velayutham S, Jyothi BA, Philips N, Ravi TK. Quantitative estimation of lupeol in polyherbal formulation and successive extracts of *Crataeva nurvala* and their *in vitro* anti-inflammatory activity study. Int J Res Dev Pharm Life Sci 2013;2:699-704.
54. Cho YC, Ju A, Kim BR, Cho S. Anti-inflammatory effects of *Crataeva nurvala* Buch. Ham. are mediated via inactivation of ERK but not NF-κB. J Ethnopharmacol 2015;162:140-7.
55. Moniruzzaman M, Imam MZ. Evaluation of antinociceptive effect of methanolic extract of leaves of *Crataeva nurvala* Buch.-Ham. BMC Complement Altern Med 2014;14:354.
56. Swati N, Prachi AH. Joshi HH, Wadegaonkar VP, Wadegaonkar PA. Evaluation of *Crataeva nurvala* extracts as antioxidant, antiproteolytic and cytotoxic

against hepato-carcinoma and mouse melanoma cell lines. J Appl Pharm Sci 2016;6:189-96.

57. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol 2007;39:44-84.
58. Antolovich M, Prenzler PD, Patsalides E, McDonald S, Robards K. Methods for testing antioxidant activity. Analyst 2002;127:183-98.
59. Hade SN, Joshi PA, Pilley HH, Wadegaonkar VP, Wadegaonkar PA. Evaluation of *Crataeva nurvala* extracts as antioxidant, antiproteolytic and cytotoxic against hepato-carcinoma and mouse melanoma cell lines. J Appl Pharm Sci 2016;6:189-96.
60. Warrier P, Nambiar V, Ramankutty C. Indian Medicinal Plants: A Compendium of 500 Species. Vol. 1. Kottakal, Kerala: Orient Longman; 1993.
61. Kumari A, Kakkar P. Screening of antioxidant potential of selected barks of Indian medicinal plants by multiple *in vitro* assays. Biomed Environ Sci 2008;21:24-9.
62. Behera PC, Senapati MR. Spectrophotometric assay of anti-oxidative and free radical scavenging activities of *Crataeva nurvala* leaf extract. Int J PharmTech Res 2014;6:582-8.
63. Kumar DG, Deepa P, Rathi MA, Periasamy M, Gopalakrishnan VK. Modulatory effects of *Crataeva nurvala* bark against testosterone and N-methyl-N-nitrosourea-induced oxidative damage in prostate of male albino rats. Pharmacogn Mag 2012;8:285-95.
64. Shirwaikar A, Setty M, Bommu P. Effect of lupeol isolated from *Crataeva nurvala* Buch.-Ham. Stem bark extract against free radical induced nephrotoxicity in rats. Indian J Exp Biol 2004;42:686-90.
65. Varalakshmi P, Shamila Y, Latha E. Effect of *Crataeva nurvala* in experimental urolithiasis. J Ethnopharmacol 1990;28:313-21.
66. Anand R, Patnaik GK, Kulshreshtha DK, Dhawan BN. Anti-urolithiatic activity of Lupeol, the active constituent from *Crateva nurvala*. Phytother Res 1994;8:417-21.
67. Baskar R, Saravanan N, Varalakshmi P. Effect of *Crataeva nurvala* bark decoction on enzymatic changes in liver of normal and stone forming rats. Indian J Clin Biochem 1995;10:98.
68. Samiulla DS, Harish MS. Comparative effect of NR-AG-I and NR-AG-II (polyherbal formulations) against gentamicin induced nephrotoxicity in rats. J Nat Remedies 2001;1:42-4.
69. Agarwal S, Gupta SJ, Saxena AK, Gupta N, Agarwal S. Urolithic property of Varuna (*Crataeva nurvala*): An experimental study. Int Q J Res Ayurveda 2010;31:361-6.
70. Meher SK, Mukherjee PK, Banarjee SK, Marjit M, Shaw BP. Experimental studies on the renal protective effect of Gokshura (*Tribulus terrestris* Linn) and Varuna (*Crataeva nurvala* Buch-Ham). Res J Pharmacol Pharm 2016;8:75-82.
71. Yadav D, Sharma AK, Srivastava S, Tripathi YB. Nephroprotective potential of standardized herbals described in Ayurveda: A comparative study. J Chem Pharm Res 2016;8:419-27.