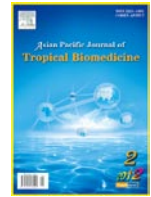




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# Phytochemical and ethno-pharmacological profile of *Crataeva nurvala* Buch-Hum (Varuna): A review

Atanu Bhattacharjee<sup>1\*</sup>, Shastry Chakrakodi Shashidhara<sup>2</sup>, Aswathanarayana<sup>2</sup><sup>1</sup>Department of Pharmacognosy, NGSIM Institute of Pharmaceutical Sciences, Deralakatte, Mangalore – 574 018, Karnataka, India<sup>2</sup>Department of Pharmacology, NGSIM Institute of Pharmaceutical Sciences, Deralakatte, Mangalore – 574 018, Karnataka, India

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## ABSTRACT

*Crataeva nurvala* Buch-Hum (Varuna) is well known traditional Indian medicinal plant used to treat various ailments in particular urolithiasis. During last two decades, numerous ethno-pharmacological and scientific reports have been cited in the literature to support its multi-directional therapeutic potential. The plant is rich in alkaloids, saponins, triterpenes, tannins, flavanoid glycosides, glucosinolates and phytosterols. The review emphasizes primarily on folkloric uses, biological activities of isolated compounds, pharmacological activities of the extracts, clinical studies and safety profile of *Crataeva nurvala* to provide a comprehensive data for researchers to hit upon new chemical entity responsible for its claimed traditional uses.

## 1. Introduction

*Crataeva nurvala* (*C. nurvala*) Buch-Ham (Family: Cappariaceae) commonly known as Varuna, is an evergreen tree indigenous to India [1]. It is a medium sized branched deciduous plant distributed throughout the river banks of southern India and other tropical, sub-tropical countries of the world, wild or cultivated [2]. It requires dry, hot climate and shady places to grow effectively [3]. Vedic literatures described its potentiality as blood purifier and to maintain homeostasis [4]. Its bark is hot, bitter at first and then sweet sharp taste, easy to digest, stomachic, laxative, anthelmintic, expectorant and anti-pyretic [5]. Moreover, pharmacological study reveals the potentiality of *C. nurvala* extract and its active principle, particularly lupeol as diuretic, anti-inflammatory, antioxidant, cardio-protective, hepatoprotective, lithonotriptic, anti-rheumatic, anti-periodic, contraceptive, anti-protozoal, rubifacient and vesicant [6]. An attempt has been taken to compile the upto date information regarding phytochemical and ethnopharmacological aspects of *C. nurvala*.

## 2. Taxonomy and Ethnobotany

The genus *Crataeva*, named in honor of the Greek botanist Crataevus comprises about 70 species distributed mainly in the warmer (tropical) parts of the world. Among them *C. nurvala* shows highest bio-diversity in India [7]. The taxonomical classification of *C. nurvala* is as follows

Kingdom: Plantae

Division: Magnoliophyta

Phylum: Tracheophyta

Class: Magnoliopsida

Order: Brassicales

Class: Magnoliopsida Brongniart

Family: Cappariaceae A.L. de Jussieu, nom. cons.

Genus: *Crataeva*Species: *nurvala* (Buch-Ham)

The trade name of this tree is three leaved capper as it contains “tri-parna” or trifoliate leaves. Flowers are whitish to milky white; 5–8 cm in diameter; polygamous and fragrant. Inflorescences appears as dense terminal corymbs; bracts minute. Fruit is berry, globes with woody rind with embedding seeds in the yellow pulp. The outer surface of bark is wrinkled and grey-white in colour, covered with large number of lenticels. The tree flowers and fruits in December–May and June–August [8].

\*Corresponding author: Mr. Atanu Bhattacharjee Lecturer, Department of Pharmacognosy NGSIM Institute of Pharmaceutical Sciences, Deralakatte, Mangalore – 574 018, Karnataka, India

Tel: +91–8088741374

Fax: +91–824–2203992

E-mail: atanu1983@gmail.com

### 3. Traditional uses and ethno-pharmacology

*C. nurvala* traditionally being used in treating blood flow, waste elimination and breathing problems, fever and metabolic disorders, joint lubrication, skin moisture, wound healing, memory loss, heart and lung weakness and weak immune system [1]. In Unani system of medicine, the bark is used to promote appetite and to decrease the secretion of bile and phlegm [1].

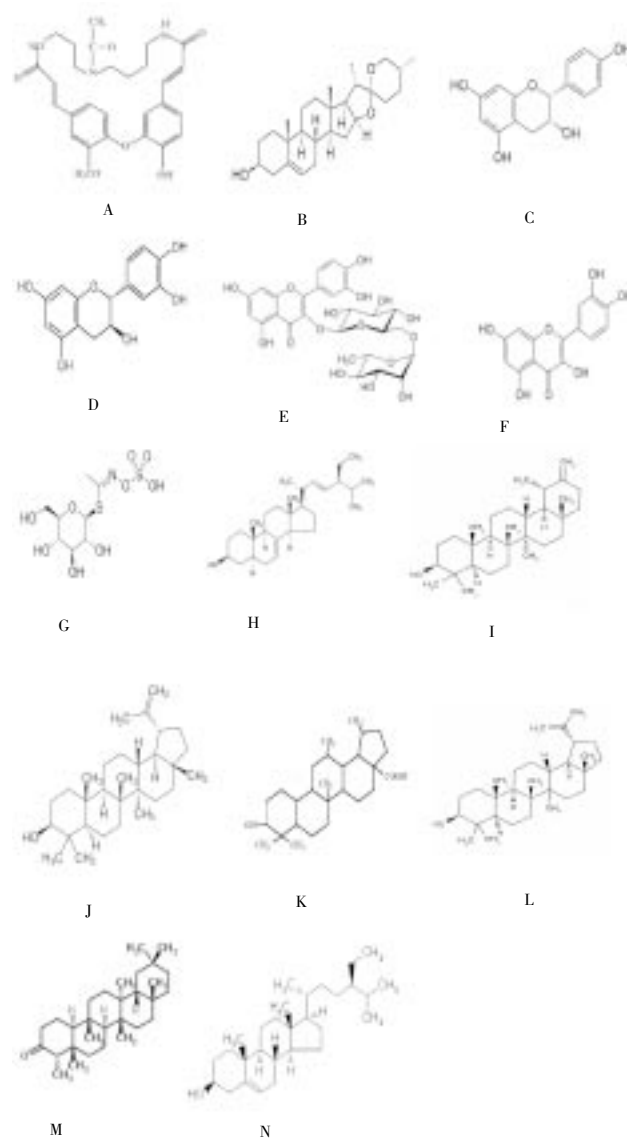
Folkloric uses suggest its potentiality as oxytotic, diuretic, laxative, anti-periodic, and bitter tonic [1]. In tribal areas of Muzaffarnagar (Uttar Pradesh, India), the bark is used against urinary disorders including kidney and bladder stones, anti-emetic and as antidote in snakebite [1]. Tribes of eastern India (Assamese, Khashi, Garo) apply the leaf paste against various joint disorders. Roots and barks are used as laxative and increase appetite and biliary secretion [1]. Varunal, a traditional Ayurvedic poly-herbal formulation containing *C. nurvala* is used against hepatitis, edema, ascites, and arthritis [10]. Pallaypatty villagers of Tamil Nadu, India, use leaves and bark to cure jaundice, eczema, rabies, fever and to control birth [1].

In Philippines, leaves are prescribed during irregular menstruation whereas the bark is used to cure convulsions and tympanites [1]. The tribes of Kango and Yurubas of Africa use leaf paste as counter irritant [1].

### 4. Phytochemistry

Preliminary phytochemical screening reveals the plant is rich in triperpenoids, saponins, flavonoids, phytosterols, alkaloids and glucosilicates [1]. Phytoconstituents like lupeol and its acetate, ceryl alcohol, friedelin, cadabicine diacetate, betulinic acid and diosgenin have been isolated from the stem bark [1]. Fruits contain glucocapparin, triacontanol, cetyl and ceryl alcohol. Leaves showed the presence of L-stachydrine, dodecanoic anhydride, methyl pentacosanoate, kaemferol- $\alpha$ -D-glucoside and quercetin-3-O- $\alpha$ -D-glucoside [1]. Root bark contains rutin, quercetin, varunol and  $\beta$ -sitosterol [1]. The isolated

compounds of different classes are summarized in Table 1 and the structures are displayed in Fig. 1.



**Figure 1:** Isolated phytoconstituents of *C. nurvala*

A: Cadabicine, B: Diosgenin, C: (-)Epiatzelechin, D: Catechin, E: Rutin, F: Quercetin, G: Glucocapparin, H: Spinasterol, I: Taraxasterol, J: Lupeol, K: Betulinic acid, L: Monogynol, M: Friedelin, N:  $\beta$ -Sitosterol.

**Table 1**

Phytoconstituents of *C. nurvala* Buch-Ham

Chemical nature of phytoconstituents	Example	Parts of plant
Alkaloids	Cadabicine, cadabicine diacetate,	Stem bark
Saponins	Diosgenin	Stem bark
Tannin	(-)-Epiatzelechin, (-) epiatzelechin-S-O- $\beta$ -D glucoside and catechin	Stem bark, root bark
Flavonoids	Rutin, quercetin, isoquercetin	stem bark
Glucosinolates	6-C-glycopyranosyl luteolin, glucocapparin	Leaves
Phytosterols	Spinasterol acetate, taraxasterol, cetyl alcohol, fagarasterol	Stem bark, root bark
Triperpene	Lupeol and their acetates,, $\beta$ -sitosterol, varunol, betulinic acid, 3-epilupeol and lupenone, phragmalin triacetate, monogynol; $\beta$ -viscol; 12-tricosanone, Lupa-21, 20 diene-3 $\beta$ , friedelin	Stem bark, root bark

## 5. Pharmacological activity

### 5.1 Treatment of urinary disorders

#### 5.1.1 Urolithiasis

Lupeol (50 mg/kg) showed potent anti-urolithiatic activity in-vivo in a dose dependant manner. Results indicated lupeol normalizes specific gravity, pH, ketone, bilirubin, blood, urobilinogen and protein in urine. Moreover, total leucocyte count reduced by 73% as compared to that of control.

Decoction of *C. nurvala* (800 mg/kg) increases the force of contraction, reducing the volume of residual urine in patients with prostatic hypertrophy.

#### 5.1.2 Hyperoxaluria

Administration of lupeol and betulin (35 mg/kg/day, p.o.) for 21 days to hyperoxaluric rats minimized the tubular damage and reduced crystal deposition in the kidneys.

Lupeol (25 mg/kg) reduces the risk of stone formation in experimental lithogenic animals by preventing oxalate and crystal-induced per-oxidative changes in renal tissues and increase urinary excretion of oxalate associated with reduction in citrate and glycosaminoglycans.

Administration of *C. nurvala* decoction in experimental models reduces urinary calcium excretion while increase in sodium and magnesium significantly and thus alter the relative proportions of urinary electrolytes, regulate calculus formation. It also lowered the levels of intestinal (Na<sup>+</sup>, K<sup>+</sup>)-ATPases.

UriflowTM (BioNeutrix), a formulation containing *C. nurvala* reduces size of kidney stones to 50% patients diagnosed with crystal urea.

#### 5.1.3 Urinary tract infection

Chloroform extract of stem bark of *C. nurvala* found to be effective against both gram positive (*B. cereus*) and gram negative (*E. coli*) mediated urinary tract infection and prostatitis at minimum inhibitory concentration (MIC) 62.5 μg/ml.

The diuretic potential of NR-AG-II, a poly-herbal formulation containing aqueous extracts of *C. nurvala* was studied in-vivo. The result was comparable with standard Furesemide.

PR-2000 (*C. nurvala* containing herbal formulation) at a dose of 2 tablets thrice daily for six months showed improvement in peak flow rate of urine and a subsequent decrease in sonographic size of prostate in human volunteers with benign prostatic hyperplasia (BPH).

Further, clinical trial with another herbal formulation of *C. nurvala* Himplasia® was found to possess 5-α-reductase inhibitory and α-adrenoceptor antagonist activity. 5-α-reductase inhibition blocks the conversion of testosterone to dihydro-testosterone, the major hormone in prostatic cells responsible for BPH.

### 5.2 Nephroprotective activity

Alcoholic extract of *C. nurvala* (250 and 500 mg/kg for 10 days) showed protective activity against cisplatin (5 mg/kg) induced nephrotoxicity. The results suggested, alcoholic extract significantly altered the dysfunction of renal proximal tubule cells by decreasing the concentration of blood urea nitrogen, creatinine, lipid peroxidation, glutathione and catalase.

Administration of aqueous extract of *C. nurvala* (200 and 400 mg/kg) for 28 days showed protective activity against ethylene glycol induced nephrotoxicity.

### 5.3 Hepatoprotective activity

The hepatoprotective effect of hydroalcoholic extract of the whole plant of *C. nurvala* (400, 600 and 800 mg/kg/day) was investigated in-vivo against carbon tetra chloride induced hepato-toxicity. Result indicated extracts booster antioxidant enzyme level and restore serum bilirubin, cholesterol level compared to diseased state.

### 5.4 Anti-arthritic and anti-inflammatory activity

Aqueous extract of *C. nurvala* stem bark and ω-3 fatty acid [Lupeol-EPA] (50mg/kg body weight) was tested in-vitro in adjuvant induced arthritis in rats. Result indicated decreased activity of lysosomal enzymes and glycoproteins nearly to that of control. The study was compared with standard indomethacin. Intra-peritoneal administration of lupeol and its ester (50mg/kg) isolated from *C. nurvala* showed protective activity against Complete Freund's Adjuvant (CFA) induced arthritis in rat paw edema. Lupeol modulates the expression or activity of several molecules such as cytokines IL-2, IL4, IL5, IL β, proteases, α-glucosidase, cFLIP, Bcl-2 and NF κ B.

### 5.5 Cardioprotective activity

Lupeol and its ester (50 mg/kg/day for 10 days) showed cardioprotective potential against cyclophosphamide (200 mg/kg) induced oxidative stress in-vitro. Results indicated decline proportion of lactate dehydrogenase and creatine phosphokinase in serum while improvement in cardiac tissue along with significant increase in antioxidant enzymes.

Moreover, hypo-cholesteromic activity of ethanolic extract of *C. nurvala* was established in-vivo. Results showed augmented activity of transmembrane marker enzymes like Na<sup>+</sup>-K<sup>+</sup>-ATPase, Ca<sup>2+</sup>-ATPase and Mg<sup>2+</sup>-ATPase along with decreased level of total cholesterol, triglycerides and phospholipids in blood. The activity may be associated with rapid excretion of bile acids that regulate cholesterol homeostasis causing low absorption of cholesterol.

### 5.6 Anti–protozoal activity

In–vitro assay revealed anti–protozoal potential of extracts of *C. nurvala* and isolated active compound lupeol against malaria, leishmaniasis and trypanosomiasis occurred by various Plasmodium, Leishmania and Trypanosoma species [1].

### 5.7 Anti–diabetic activity

*C. nurvala* stem bark extracts (500 mg/kg) showed potent anti–diabetic activity in alloxan–induced diabetes in–vivo. Results were comparable with standard glibenclamide (600  $\mu$ g/kg). The effect may be due to increase insulin secretion from  $\beta$ –cells of islets of Langerhans or its release from bound insulin due to enhanced glucose utilization by peripheral tissues [1].

### 5.8 Anti–nociceptive activity

Ethanol extract of *C. nurvala* stem bark (250–500 mg/kg p.o.) was evaluated for anti–nociceptive activity in–vivo by acetic acid induced analgesic model. Results suggested the anti–nociceptive effect was peripherally mediated. Hence, can be useful in the treatment of inflammatory arthritic conditions [1].

### 5.9 Wound healing activity

Ethanol extract of root bark of *C. nurvala* (150 and 300 mg/kg) showed wound healing and collagenation potential in–vivo. Moreover, supportive in–vitro studies suggest an increase level of antioxidant enzymes on granuloma tissue which further support the wound healing potential [1].

### 5.10 Anti–cancer activity

Topical application of Lupeol (200  $\mu$ g/mouse) prevents 7,12–dimethylbenz[a]anthracene [DMBA]– induced DNA damage in murine skin [39]. Recently, Lupeol was shown to inhibit Benzo[a]pyrene, a potent mutagen induced genotoxicity in mouse model. Study showed pre–treatment with Lupeol (1 mg/kg) for 7 days prior to Benzo[a]pyrene administration significantly decreased genotoxicity and caused increase in mitotic index [1].

Moreover, cell line study revealed that anti–tumor effects of lupeol was associated with modulation of signaling pathways such as nuclear factor kappa B (NF  $\kappa$  B) and the phosphatidylinositol 3–kinase [PI3K] /Akt (protein kinase B pathway), which play an important role during tumorigenesis. Further, lupeol significantly inhibit ornithine decarboxylase activity which is a well known biomarker of tumor promotion [1].

### 5.11 Antipyretic activity

Ethanol extract of *C. nurvala* (200 and 400 mg/kg) showed potent anti–pyretic activity against typhoid vaccine induced pyrexia in rabbits. The result was comparable with paracetamol (100 mg/kg p.o.), standard antipyretic drug [13].

### 5.12 Anti–fertility activity

Administration of aqueous and ethanol extract of *C. nurvala* (300 and 600 mg/kg/day) for 8 days showed anti–fertility activity in dose dependent manner. The activity may be due to modified estrogenic activity, causing the expulsion of ova from the urethral tube, disrupting the luteotropic activity of the blastocytes [1].

## 6. Safety and toxic profile

Topical application of the leaves of *C. nurvala* was reported to cause reddening and blistering in rodents. The decoctions of the root bark and stem bark appear to be well tolerated. The LD<sub>50</sub> of 50% ethanol extract of stem bark was found to be more than 1000 mg/kg i.p. to adult rats [46]. No toxic effects have been seen on the human body with *C. nurvala* consumption.

A summary of various pharmacological activities of *C. nurvala* is mentioned in table 2.

## 7. Conclusion

For ages, *C. nurvala* has been used for the treatment of various ailments in traditional and folklore medicine. Of the phytoconstituents reported from different parts of *C. nurvala*, lupeol and its acetate are the predominant bioactive constituents. Although the constituents responsible for the pharmacological properties of the plant seem to have been determined, the molecular mechanisms of most of these principles are still unknown. The bioassay guided isolation, identification of the bioactive components is essential and in depth research is also crucial to reveal the structure–activity relationship of these active compounds. Based on these facts, the authors made an upto date information highlighting the current ethno–pharmacological and phytochemical status of the plant.

## 8. Conflict of interest statement

We declare that we have no conflict of interest.

**Table 2**Pharmacological activity of *C. nurvala* in-vivo and in-vitro

Activity	Model	Extract/formulation	Mode of action	Reference
Anti-urolithiatic	Rats (in-vivo)	Stem bark powder, ethanolic extract	Lowering intensity of cellular infiltration in renal tubule Reduction in oxalate levels of urinary and renal tissues along with reduced liver glycolate oxidase activity	[22] [28]
		Ethanolic extract Stem bark powder	Hexuronic acid levels was significantly reduced in blood Reduction in phosphate, calcium and oxalate content of previously formed stones	[22] [22]
		Stem bark powder Lupeol	Decrease in urinary enzymes levels Lupeol reduces oxalate level; promote super saturation in renal tissues by diuretic activity	[25] [28]
	Human (in-vivo)	Stem bark powder, ethanolic extract	Reduction in crystal deposition leading to minimized tubular damage	[23]
		Stem bark powder, ethanolic extract of <i>C. nurvala</i>	Reduction in enzymurea	[47]
		Stem bark and root bark powder	Alteration of relative proportions of urinary electrolytes	[48]
Against Urinary tract infections	Rats (in-vivo)	Polyherbal formulation containing aqueous extract of <i>C. nurvala</i> stem bark	Increase in urinary output and level of urinary electrolytes	[30]
	Human (in-vivo)	Stem bark and root bark powder	Anti-inflammatory	[22]
	Human (in-vivo)	Polyherbal formulation containing 10mg extract of <i>C. nurvala</i> stem bark	Anti-inflammatory	[49]
Against Benign prostrate hyperplasia (BPH)	Human (in-vivo)	Polyherbal formulation (PR-2000)	Improvement in peak flow rate of urine and a subsequent decrease in sonographic size of prostate gland	[31]
		Himplasia	"Himplasia" possesses $\alpha$ -adrenergic receptor agonist and 5- $\alpha$ -reductase antagonist activity	[50]
Nephroprotective activity	Rats (in-vitro)	Alcoholic extract of stem bark	Decrease in lipid peroxidation and concentration of blood urea, nitrogen and creatinine	[32]
Hepatoprotective activity	Rats (in-vivo)	Lupeol and its acetate	By antioxidant property; increase level of antioxidant enzymes	[34]
Anti-arthritic activity	Rats (in-vivo)	Lupeol and its acetate	Lipid peroxide level increased in plasma but decreased in the liver; antioxidant enzymes were elevated in both liver and haemolysate	[36]
		Ethanolic extract	Prostaglandin synthase inhibitor activity	[35]
	Rats (in-vitro)	Stem bark powder Lupeol and its acetate	Decrease inflammation and complement activity Decrease in glucosaminoglycans enhances membrane stabilization	[39] [35]
Cardioprotective activity	Rats (in-vitro)	Lupeol and its acetate	Decrease in lipid peroxidation and increase in antioxidant enzyme level	[37]
		Lupeol and its acetate	Decrease in activity of Lactate dehydrogenase and creatine phosphokinase in serum and increase in their action in cardiac tissue	[38]
Wound healing activity	Rats (in-vivo)	Alcoholic extract of root bark	Free radical scavenging action and enhanced level of antioxidant enzymes in granuloma tissue.	[42]
Anti-diabetic	Rats (in-vivo)	Petroleum ether extract and ethanolic extract	Increasing insulin secretion from $\beta$ -cells of pancreas or its release from bound insulin due to enhanced glucose utilization by peripheral tissues.	[40]
Anti-nociceptive activity	Mice (in-vivo)	Ethanolic extract	Inhibiting the release, synthesis and production of cytokines, prostaglandins, histamine and polypeptide kinins,	[41]
Anti-fertility activity	Rats (in-vivo)	Aqueous and ethanolic extract	Modify estrogenic activity, causing the expulsion of ova from the tube, disrupting the luteotropic activity of the blastocytes	[45]



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