A standardized natural extract offers comprehensive urinary health support and more…

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INTRODUCTION

Crataeva nurvala Buch-Ham. (Syn. *Crataeva religiosa* Frost.) (Fam. Capparidaceae) is an evergreen tree that is indigenous to South India. Although it is known by different names throughout India, it is commonly identified by its Sanskrit name, Varuna. In Ayurvedic medicine, Varuna is valued for its benefits in the management of urinary and inflammatory disorders (1,2). Pharmacological studies using the root bark and stem bark of *C. nurvala,* in recent years, have confirmed its beneficial effects in supporting the management of urinary disorders, including urolithiasis, and revealed its potential benefits in supporting the management of inflammatory conditions, such as arthritis. Cratavin®* is a standardized extract containing a minimum of 1.5% w/w of lupeol, prepared from the bark of *Crataeva nurvula*.

BOTANICAL ASPECTS

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

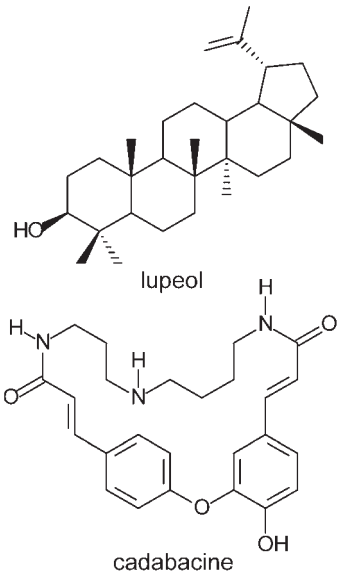

Figure 1 – Some chemical constituents of Crataeva nurvala *("Varuna") extract*

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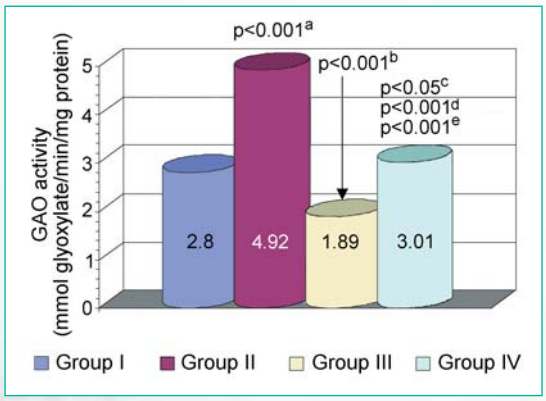

Figure 2 – Effect of C. nurvala *on stone forming constituents in the kidney tissue of stone forming and normal rats (15).*
Values are expressed as the mean SD (n=6). Comparisons were made between groups: a I & II; b I & III; c I & IV; d II & IV; and e III & IV.
Group I: (normal controls) fed a standard diet for 40 days; Group II: standard diet mixed with 3% gycolic acid for 40 days; Group III: standard diet for 40 days + C. nurvala *decoction for the last 10 days; and Group IV: standard diet mixed with 3% glycolic acid for 40 days +* C. nurvala *decoction for the last 10 days*

colored. Leaves are trifoliate. Flowers are white or cream colored. Fruits have multiple seeds and ovoid berries, and seeds are embedded in the yellow, fleshy pulp of the fruits (1,2).

PHYTOCHEMISTRY

Fatty acids, sugars, amino acids, flavones, sterols, and triterpenes have been isolated and identified in the root bark of *C. nurvala* (5,8,9). Triterpenoids, lupeol and varunol, have been isolated from the root and stem bark (6). According to the Indian Herbal Pharmacopoeia, the major chemical constituent of the root bark is lupeol (1) (Figure 1). Other major constituents of the root bark include lupeol acetate, α-spinasterol acetate, ψ-taraxasterol, 3-epilupeol, and β-sitosterol (3,4). Lupenone (3,4), β-sitosterol acetate (3,4), and a pentacyclic triterpene alcohol, [Lupa-21,20 (29) diene-3β-ol] (10), are also present in the root bark. Alkaloids, cadabacine and cadabacine diacetate (11), flavonoids, (–)-catechin, (–)-epicatechin-5-glucoside, and (–)-epiafzelechin (12), and an isothiocyanate glucoside, glucocapparin (13), have been identified in the stem bark. Flavonoids, rutin, quercetin, and isoquercetin, have been isolated from the leaves (7).

Diseases of the urinary system affect the kidneys, ureters, bladder and urethra, and they are classified as obstructive – e.g. urolithiasis ("stones" in the urinary system) and prostatic hypertrophy – or non-obstructive – e.g. infection of the urinary tract and neurogenic bladder (14).

Urinary stones form from the deposition of various stone forming, urinary constituents in the renal tissues. People with a family history of urinary tract stone disease are more susceptible to developing urolithiasis. The most common stone forming constituents are calcium with either oxalate or phosphate. Urinary tract infections, kidney disorders, and metabolic disorders have been linked to stone formation. For example, calcium oxalate stones are attributed to disorders such as absorptive hypercalciuria, the absorption of too much calcium from food, and hyperoxaluria, the defective regulation of oxalate synthesis that causes excessive excretion of the salt oxalate. In each case, the excess constituent cannot be dissolved in the urine. Thus, it settles out as crystals and forms stones (28-30).

Surgery is the conventional method for removing urinary stones. However, surgery does not cure urolithiasis. Stone formation persists in the patient and stones recur. Similarly, antibiotics may be used to treat urinary tract infections; however, the infection may recur due to the resistance of the organisms to antibiotics.

Preclinical and clinical studies have shown that the stem and root bark of *C. nurvala* promote a healthy urinary system. *C. nurvala* is beneficial in the management of urinary tract stone disease and other urinary disorders such as urinary tract infection. Thus, it may be an alternative to conventional antiurolithic drugs and antibiotics (14).

For example, in a controlled animal model study wherein rats with induced urolithiasis were tested, the urinary stone weights in rats treated with *C. nurvala* were significantly less than those of untreated controls. In addition, histopathological examination of the rats' bladder mucosa on the 20th day showed that the *C. nurvala*-treated group had reduced edema, ulceration and cellular infiltration than rats of the control group (14).

The results of another animal model study indicated that *C. nurvala* is an important regulator of oxalate synthesis. As shown in Figure 2, *C. nurvala* reduced the levels of stone forming constituents, calcium, oxalate, and phosphorous, in the kidneys of stone forming/treated rats (Group IV) compared to the untreated/stone formers (Group II) (15).

In addition, *C. nurvala* significantly increased the magnesium levels of the stone forming/treated rats (Group IV) compared to the stone forming controls (Group II) that had low magnesium levels (Figure 3). Magnesium is an important inhibitor of crystal growth, and it has considerable solubilizing power. Increased magnesium levels are associated with a lower Ca/Mg ratio (15).

In a follow-up study, the researchers (16) examined the effects of the *C. nurvala* decoction on certain biochemical constituents in the small intestinal tract tissues of rats.

The results revealed that *C. nurvala* has a laxative effect similar to conventional drugs, bisacodyl and phenolphthalein, that seems to be mediated by the inhibition of Na^+ reabsorption in the intestinal epithelial cells via the inhibition of the enzyme,

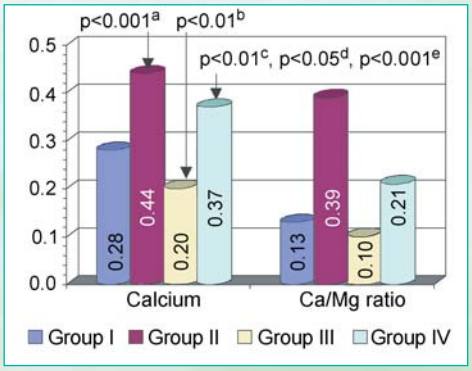

Figure 3 – Effect of C. nurvala *on the urinary excretion of Calcium and the Ca/Mg ratio in stone forming and normal rats (15).*
Values are expressed as the mean SD (n=6). Note: Calcium (Ca) levels are expressed as mg Ca/24 h/rat. Comparisons were made between groups: a I & II; b I & III; c I & IV; d II & IV; and e III & IV. Group I: (normal controls) fed a standard diet for 40 days; Group II: standard diet mixed with 3% gycolic acid for 40 days; Group III: standard diet for 40 days + C. nurvala *decoction for the last 10 days; and Group IV: standard diet mixed with 3% glycolic acid for 40 days +* C. nurvala *decoction for the last 10 days*

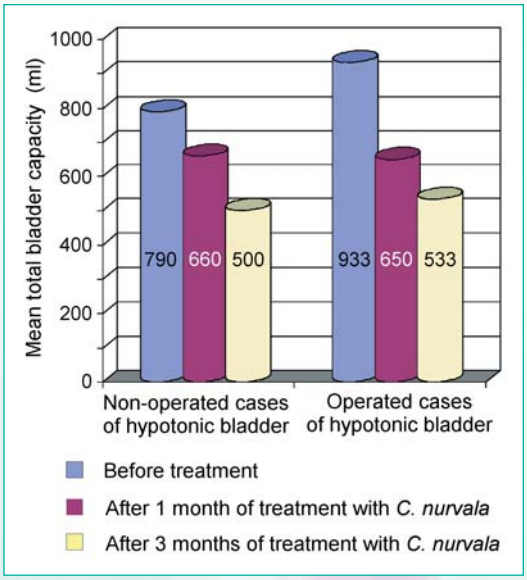

Figure 4 – Changes in the mean total bladder capacity in non-operated and operated patients with hypotonic bladders before and after treatment with C. nurvala *(14).*
n=5 for non-operated and operated groups. In the operated cases of hypotonic bladder, the mean total bladder capacity was 766 before the operation

(Na^+,K^+)-ATPase. In addition, *C. nurvala* considerably reduced DNA and RNA levels in treated/stone forming rats (Group IV) in comparison to stone forming controls (Group II). DNA content gives an index of the number of cells, and it is suggestive of atrophy (shrinkage) of tissues. Thus, an increase in DNA content observed in the stone forming control rats in this study indicates tissue shrinkage. In contrast, the herbal decoction did not influence the nucleic acid levels in normal animals (Group III) (16).

Other researchers found that supplementation with lupeol, the marker active in *C. nurvula* extract, reduced the levels of urinary oxalate and considerably lowered the release of Lactate dehydrogenase (LDH), another major oxalate-synthesizing enzyme, in hyperoxaluric/treated rats compared to hyperoxaluric controls. The authors noted lupeol was effective in reducing the levels of various enzymes. This protective effect may be attributed to its diuretic activity that facilitates regular excretion of oxalate. This in turn reduces saturation of oxalate in the renal tissues, thereby minimizing cellular injury (17).

ARTHRITIS AND CARDIOVASCULAR HEALTH SUPPORT

Early studies (23) reported that the water extract of *C. nurvala* increased the tone of smooth muscle of the intestine and ureters in guinea pigs, dogs, and humans *in vitro*. Also, it increased the tone of skeletal muscle in frog rectii *in vitro*. Das et al. (24) reported that the petroleum ether extract of *C. nurvala* bark inhibited the acute, subacute, and chronic inflammations induced in albino rats by carrageenin, histamine, croton oil, and formaldehyde. *C. nurvala* extract's anti-inflammatory activity was similar to the conventional drug, betamethasone, but minus the side effects.

Adjuvant arthritis induced in animal models is similar to the rheumatoid arthritis that humans experience (25). Arthritis involves the damage and inflammation of joints and associated tissues, and free radicals are implicated in the pathogenesis of rheumatoid arthritis. One group of researchers (26) studied the effects of lupeol and its ester lupeol linoleate against free radicals generated during complete Freud's adjuvant-induced arthritis in rats. Both lupeol and lupeol linoleate restored the levels of antioxidant enzymes closer to normal control levels. Similarly, values for reduced glutathione in the blood were restored closer to normal control values when arthritic rats were treated with lupeol and lupeol linoleate (26).

In a later study, researchers (27) studied the effects of lupeol, lupeol linoleate, and indomethacin, a known anti-inflammatory drug, in adjuvant-induced arthritic rats. Lupeol linoleate was more effective than either unesterified lupeol or indomethacin in reducing footpad thickness and complement activity. It was concluded that the anti-inflammatory activity of the triterpenes, lupeol and lupeol linoleate, was attributed to their anticomplementary activity. Recent studies revealed that lupeol suppresses T-lymphocyte activity as well. Oral administration of lupeol at doses of 12.5-200 mg/kg p.o. inhibited CD4+ T and CD8+ T cell counts and cytokines IL-2, IFN-gamma (Th1) and IL-4 (Th2) (31).

Cyclophosphamide (CP), an alkylating agent widely used in cancer chemotherapy, is implicated in fatal cardiotoxicity through inducing oxidative stress. Lupeol and its ester were shown to have an antioxidant protective effect against CP induced cardiotoxicity in animal models (32). Similar antioxidant protective effects against nephrotoxicity due to cisplatin were also reported (33).

CLINICAL STUDIES

Clinically, *C. nurvala* was beneficial in the management of chronic urinary tract and neurogenic bladder infections, calculi, and prostatic hypertrophy.

Prostatic Hypertrophy and Bladder Tone (14)

A decoction of *C. nurvala* was administered to patients in the form of a decoction prepared from the stem bark of *C. nurvala*. Patients suffering from prostatic hypertrophy with hypotonic bladder received 50 ml of the *C. nurvala* decoction twice daily. (Hypotonic bladder due to prostatic hypertrophy is characterized by a marked increase in the total bladder capacity.)
The following results were observed after treatment with the *C. nurvala* decoction:

- The symptoms, frequency of urination, incontinence, pain, and retention of urine, significantly improved.
- The expulsive force of urination was increased.
- Bladder tone improved significantly. In addition, the volume of residual urine was reduced.

Improvement in bladder tone and other functions was also observed in cases of persistent hypertonia of the bladder in patients who received surgery and

Table I – Sample Actives Blend for functional beverage formulation for Urinary Health Support

Actives (per effervescent tablet)	
Cratavin® * (*Crataeva nurvala* extract)	400mg
Lactospore® *^ (15 billion count/g)	20 mg
Olive leaf Extract (20% oleuropein)	50 mg
Cranberry juice solids	530 mg
Actives Total	1000 mg

* Trademark of Sabinsa Corporation
^ Probiotic

those who did not after 3 months of *C. nurvala* therapy as shown in Figure 4 – Hypotonia, the state of reduced tension in muscles, may occur as a complication of pelvic swellings (e.g. ovarian cyst or fibroid tumor), and it may persist even after the tumor is surgically removed. Similarly, *C. nurvala* therapy furnished beneficial effects in cases of neurogenic bladder and post-prostatectomic atony of the bladder.

Urinary Stones

A decoction of *C. nurvala* (50 ml twice daily) was administered to patients with urinary stones. After one month of receiving the decoction, urinary electrolytes were estimated and compared with initial values. Treatment with *C. nurvala* shifted the relative proportion of urinary electrolytes, particularly those that participate in calculus formation, towards the non-lithogenic (avoid stone formation) zone. Because of its effect on urinary electrolytes, *C. nurvala* seemed to effect a 75% cure in patients with crystalurea (a disease that increases the tendency for developing urinary stones) after 4 weeks of treatment (14).

Seventy-three patients who had kidney, bladder, or ureter stones participated in a clinical study. Of the 73 patients, 27 received surgery and 46 received a 50 ml decoction of *C. nurvala* twice daily for 1 week to 47 weeks. Of the 46 patients given the *C. nurvala* treatment, 28 passed stones, while 18 experienced symptomatic relief. The majority of the *C. nurvala*-treated patients passed their stones within 1-4 weeks of treatment. Spontaneous passing of stones is a well-known phenomenon in 10-33% of cases (21,22). However, the results observed in the present study could not be attributed to the spontaneous passing of stones, alone. In the study, 50% (28 of 47 patients) of the patients taking *C. nurvala* spontaneously passed stones. It is speculated that *C. nurvala* caused the passage of stones by means of its tonic, contractile action on the smooth muscle of the stomach (14).

Urinary Tract Infection

The benefits of *C. nurvala* in the management of urinary tract infections have also been reported. In chronic urinary infection cases, 17% of patients who received a 4-week treatment of *C. nurvala* were symptom free and their urine was devoid of microorganisms and pus cells. The authors concluded that the anti-inflammatory of *C. nurvala* and tonic effect on the smooth muscle helps to evacuate the bladder of urine; and that if proper drainage is maintained for a long period of time, infection may be mitigated (14).

POTENTIAL HEALTH APPLICATIONS

Cratavin®, is thus beneficial as an adjuvant to Saw palmetto and other natural extracts in prostate health support, and can be used with cranberry juice solids/extract and other natural agents in the management of urinary tract infections. The extract also offers anti-inflammatory benefits in joint health and cardiovascular support formulations. Topically, the extract would help to reduce the appearance of wrinkles and is useful in "anti-aging" support formulations.

Formulation

As effervescent tablets (Table I) with suitable inactive ingredients.
100 g of the effervescent mix would yield about 20 tablets (servings). Each tablet would disperse in 200 ml water to produce an effervescent beverage

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