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

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 nurvala*.

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.

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Figure 1 – Some chemical constituents of *Crataeva nurvala* (“Varuna”) extract
urethra, and they are classified as
the kidneys, ureters, bladder and
isoquercetin, have been isolated from
bark. Flavonoids, rutin, quercetin, and
(13), have been identified in the stem
isothiocyanate glucoside, glucocapparin
(–)-epicatechin-5-glucoside, and
diacetate (11), flavonoids, (–)-catechin,
(10), are also present in the root bark.

Other major constituents of
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, β-taraxasterol,
β-sitosterol acetate (3,4).

Lupenone (3,4), β-sitosterol acetate
(3,4), and a pentacyclic triterpene
alcohol, [Lup-21,20 (29) diene-3β-ol] (10),
are also present in the root bark.
Alkaloids, cadabarine and cadabarine
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
antiurinoilthic 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
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,
bladder capacity was 766 before the operation.

C. nurvala operated cases of hypotonic bladder, the mean total (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. nurvala 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 recti 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 Freund’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 alkylationing 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 a decoction of C. nurvala.

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

<table>
<thead>
<tr>
<th>Actives (per effervescent tablet)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Crataevina * (Crataeva nurvala extract)</td>
<td>400 mg</td>
</tr>
<tr>
<td>Lactospora ** (15 billion count/g)</td>
<td>20 mg</td>
</tr>
<tr>
<td>Olive leaf Extract (20% oleuropein)</td>
<td>50 mg</td>
</tr>
<tr>
<td>Cranberry juice solids</td>
<td>530 mg</td>
</tr>
</tbody>
</table>

| Total Active            | 1000 mg       |

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**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 crystalluria (a disease that increases the tendency for developing urinary stones) within 1-4 weeks of treatment.

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).

**APPLICATIONS**

**Cratavine®,** 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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