

Medicinal Profile of a Sacred Drug in Ayurveda: *Crataeva religiosa*

A Review

Udaysing Hari Patil¹ and Gaikwad D.K.²

¹Department of Botany, Bhogawati Mahavidyalya Kurukali, Tal-Karveer, District- Kolhapur, Maharashtra [India]-416001

²Department of Botany, Shivaji University, Kolhapur, [MS] India-416004

Abstract

Crataeva religiosa (Hook and Frost) is one of the herbal drug in urolithiasis, belongs to the family capparidaceae. The drug is well known for its various pharmacological properties like diuretic, anti-inflammatory, laxative, antioxidant, antioxaluric, hepatoprotectant, lithonotriptic, antireumatic, antiperiodic, antimycotic, contraceptive, antipyretic, antilithitic, antihelminthic, rubifacient and vesicant properties. The bark of the *Crataeva religiosa* is useful in the urinary disorders and kidney stone remover. The crude drug contains an active principle lupeol, a triterpenoid which is mainly involved in the pharmacological activities of this plant. The present review summarizes Ethnobotanical, pharmacological and phytochemical aspects of this medicinal plant.

Key Words: Laxative, Pharmacological, Phytochemical, Rubifacient, Urolithiasis, Vesicant.

1. Botany

The name *Crataeva* is given in the honor of Crataevus, a Greek botanist, who was living in the time of Hippocrates and the name *religiosa* indicates its growth near the places of worship [1]. *Crataeva religiosa* is much branched deciduous tree belonging to the family capparidaceae, commonly called as Varuna [2]. The trade name given for this tree is three leaved capper [3]. The leaves are trifoliate, glabrous, and ovate. Flowers are whitish to milky white in colour in terminal dense corymbs [2]. Fruit is berry, globose or some times oblong with woody rind, embedding seeds in the yellow pulp [1]. The outer surface of bark is wrinkled and grey-white in colour, covered with large number of lenticells. Tree flowers and fruits in the month of Dec-May [4].

2. Distribution

Crataeva religiosa is globally distributed in India, Myanmar, Sri Lanka, Malaysia, Indonesia and China. In India, it is found in Peninsular India, Western India, Gangetic Plains, and Eastern India, up to Tripura and Manipur [2]. It is also found in Sikkim and Andman and Nicobar Island [3]. It is found mostly along the bank of the river and streams and near to temple side [5], [6].

3. Ethnobotany

The plant part used for the medicinal purpose includes Leaves, stem bark and Root bark [7],

[8], [9]. These parts of *C. nurvala* are commonly applied to regulate equilibrium among Vata, Pitta and Kapha in Ayurvedic system while the stem bark is used to promote the appetite and to decrease the secretion of the bile in unani medicines [10]. Recently Bopana and Saxena [11] critically reviewed *C. nurvala* for its ethnobotanical and pharmacological properties. Plant is used ethnopharmacologically as diuretic, laxative, lithonotriptic, antireumatic, antiperiodic, bitter tonic, rubifacient and counterirritant [7], [8]. The bark is used in the urinary disorders including kidney and bladder stones, antiemetic, and calculous affections and as an antidote in snakebite [7]. *C. religiosa* is valuable in treating vata (blood flow, waste elimination and breathing), Pitta- (fever and metabolic disorder) and Kapha (joint lubrication, skin moisture, wound healing, strength and vigour, memory loss, heart and lung weakness and weak immune system [9]. A preparation called 'Varunal' contains *Crataeva* in combination with *Eclipta*, *Picrorrhiza*, *Achillea*, *Cichorium*, *Solanum*, *Arjuna*, and *Cassia* seeds is used against hepatitis, edema, ascites, urinary stones and arthritis [12]. The bark is contraceptive and cytotoxic and useful in kidney bladder stones, fever vomiting and gastric irritation [13]. Roots and bark are laxative and lithontipic and increase appetite and biliary secretion [14]. Leaves are used as externally rubifacient and used in

rheumatism. Leaves are given internally febrifuge and tonic [15], [16].

According to Gurrero [http/www.bpi.da.gov.ph. 2009], In Philippines, leaves are useful in irregular menstruation and also in stomachic, whereas the bark is used to cure convulsions and tympanites. Sanyal and Ghose [http/www.bpi.da.gov.ph. 2009] speculated that the crushed leaves are applied in the form of paste for swelling of feet and also for a burning -sensation in the soles of feet. The bark and the leaves are pounded and applied in the form of a poultice in rheumatism. The fresh leaves bruised with little vinegar, applied to skin. Bark and roots are rubifacient and vesicant. Decoction of bark is used in the disorders of urinary organs and urinary calculi. Roots and bark in the form of decoction are used as calculus affections [http/www.bpi.da.gov.ph. 2009]. Traditionally, the plant is used as oxtotic, in rheumatic fever in kidney stones, bladder stone and as tonic [17]. It is useful as antipyretic, antilithitic, antihelminthic, demulcent, in blood and chest diseases [18]. NR-AG-I is a polyherbal formulation containing *Crataeva religiosa*, *Dolichos biflorus*, *Tribulus terrestris* and *Shilajit*. NR-AG-II is another herbal formulation containing *Crataeva religiosa*, *Boerhavia diffusa*, *Sacchaarum officinarum*. and *Butea frondosa*. Between these two, NR-AG-II is having good diuretic potential than NR-AG-I [19]. A mixture containing-*Tribulus terrestris* fruits (25%); *Zinziber officinalis* roots(10%); *Solanum xanthocarpum* whole plant (10%); *Asparagus racemosus* roots (10%); *Tephrosia purpurea* leaves (10%) and *Crataeva religiosa* bark (25%) was prepared and 4gm of mixture given to patient twice daily with water in urinary disorder [20].

Berry like globose fruits of *Crataeva* are edible and used as astringent [1] and rind of the fruit is used as mordant in dying [18]. In People living in Kango and Yurubas leaf paste in water is used for counter irritant purposes [21]. Quisumbing [22] reported that fresh leaves of this plant have rubifacient and vasicant properties. According to Corner [23], young shoots and fruits of *Crataeva religiosa* are eaten and used in curries. Fruits of this tree are used as spice because of its garlic

taste [24]. In Pallaypatty village of Tamil Nadu, people use the leaves and bark of this tree to cure jaundice, eczema, rabies [25]. The bark of this tree is useful in family planning [http://www.milliontreedream.org]. The bark is also diuretic [26]. The juice of fruit, leaves and bark is applied to cure snakebite, infected wounds and cuts. It increases appetite and controls other skin diseases [27]. The decoction of the bark is useful in the treatment of urinary organs [27] and leaves are used as vegetable and the dried leaves are smoked in caries of nasal bones, the smoke being exhaled through the nose in neurologic pains [28].

4. Phytochemistry

Lakshmi and Chuhan [29] isolated lupeol from the root bark of *C. religiosa*. It also contains lupeol acetate, varunaol, spinasterol acetate, taraxasterol and 3-epilupeol [30]. A triterpene, diosgenin and two alkaloids cadabicine and cadabcine diacetate have been isolated the bark of *Crataeva religiosa* [31]. By repeated chromatography technique, Enamul huque *et al.* [32] isolated two triterpenoids phragmalin triacetate and lupeol from the ethyl acetate fractions of stem bark of *C. religiosa*. The stem bark also found to contain Epiafzelechin 5-glucoside [33]. Chemical investigation of leaves by Gagandeep and Khadilkar [34], showed presence of four compounds- Dodecanoic anhydride, methyl pentacosanoate, Kaemferol-3-O- α -D glucoside and quercetin-3-O- α -D- glucoside. Leaves contain isovitexin, proanthocyanidins, myricetin and phenolic acids, p- hydroxyl benzoic acid vanilic acid, ferulic acid and sinapic acid [30]. Sethi *et al.* [35] reported glucocaparin from the fruits of *Crataeva religiosa*. Gagandeep and Khadilkar [36], first time reported four chemical compounds- pentadecane, octanamide, 12-tricosanone and friedelin from the fruits of *C. religiosa*.

5. Pharmacology

Sahoo *et al.* [37] studied the antimycotic activity against the *Candida albicans*, *Candida tropicalis*, *Candida krusei*, *Cryptococcus marinus*, and *Aspergillus niger*. They noticed that aqueous extract of bark

inhibited *Cryptococcus marinus* and *Aspergillus niger* whereas aqueous and ethanolic extract did not showed any effect against *Candida albicans*, *Candida tropicalis*, *Candida krusei* and *Cryptococcus marinus*. While ethanolic extract, the chloroform extract showed better results against the test fungal pathogens and indicates the presence of higher contents of phytochemicals having antifungal activity.

The pharmacology division of Central Drug Research Institute Lucknow has carried out detailed pharmacological and chemical studies on this plant. According to Varalakshmi *et al.* [38], decoction of bark also lowers the intestinal Na⁺ and K⁺-ATPase levels. Reports of Singh *et al.* [39] showed the effectiveness of *Crataeva* bark in prophylaxis of oxalate urolithiasis induced by simultaneous administration of sodium oxalate and methionine in guinea pig. Alam *et al.* [40] studied the antinociceptive effects of crude ethanolic extract of *C. religiosa* on mice by acetic analgesic test method. Crude ethanolic extract of *Crataeva religiosa* bark produced dose dependent significant antinociceptive effects against chemically induced noncicepative pain stimuli in mice. Further results of Alam *et al.* [40], suggested that the effects are peripherally and centrally mediated.

A pentacyclic triterpane, lupeol isolated from the stem bark and its ester derivative lupeol linolate were tested for their anti-inflammatory activity in Freund's adjuvant induced arthritis in rats [41]. The effect of lupeol linolate was found to be better in this respect when compared with lupeol [41]. According to Geetha and Varalakshmi [42], lupeol linolate reduces the foot-pad thickness and complement activity in arthritis in rats, was greater than unestrified lupeol and indomethacin. Shirwaikar *et al.* [43] investigated the role of lupeol in reducing the blood urea nitrogen, creatinine and lipid peroxidation with corresponding increase in glutathione and catalase activities in cisplatin induced nephrotoxicity indicating its antioxidant nature. Hippocratic screen carried out by Molone and Robichaud [44] revealed the ability of crude bark extract to minimize acetic acid induced writhing at higher doses.

According to Vidya and Varalakshmi [45], the total administration of lupeol and its analogue betulin to hyperoxaluric rats minimized tubular damage and reduced markers of crystal deposition in kidney. In this connection the lupeol was found to be effective than betulin. Anti-inflammatory, antinociceptive anti-pyretic and ulcerogenic properties of lupeol and lupeol linolate were studied by Geetha and Varalakshmi [46] in comparison with commonly used non-steroidal anti-inflammatory drug indomethacin. Lupeol and lupeol linolate caused reduction in paw-swelling in adjuvant arthritis. Singh and Kapoor [47], reported anti-urolithiatic activity of ethanolic extract of bark extract in albino rats by foreign body insertion method using glass bead. A triterpenoid compound, Lupeol isolated from bark of this plant showed prophylactic and curative activities in albino rats when studied by foreign body insertion method [48]. Lupeol also showed significant antioaxaluric [49] and anti-calciuric [50] effects in rats against hydroxyproline induced hyperoxaluria. Vidya *et al.* [51] studied the anti-oxaluric effects of number of lupeol derivatives against hyper-oxaluria in rats. The effect of bark decoction on calcium oxalate urolithiasis induced by 3% glycolic acid has been studied in rats [52]. Bark decoction significantly prevented the deposition of calcium and oxalate in the kidney by inhibiting the glycolic acid oxidase activity in liver. Sunita *et al.* [53] investigated the hepatoprotective properties of Lupeol and lupeol linolate against cadmium induced toxicity in rats. The cadmium toxicity caused elevated level of malondialdehyde and decreased level of enzymic and non- enzymic antioxidants in rat liver. Oral administration of lupeol and lupeol linolate significantly reverted the tissue redox system to normal level by scavenging free radicals and improved the antioxidant status of the liver. Lupeol linolate had better effect than lupeol on antioxidant status of the liver. Preetha *et al.*, [54] studied the effect of lupeol on aflatoxin (AFB-1) induced peroxidative hepatic damage in rats. They compared the hepatoprotection of lupeol with silymarin, a standard hepatoprotectant drug. AFB-1

treatment caused hepatic damage by increasing the level of lactate dehydrogenase, alkaline phosphatase, alanine and aspartate aminotransferase along with increase in the lipid peroxide level while enzymic and non-enzymic antioxidant levels were found to be decreased in hepatic tissue. Oral treatment of lupeol normalized the altered mechanism of the hepatic tissue system and the effect was comparable to silymarin, indicating potent hepatoprotectant [54]. In experimental model of urolithiasis, Deshpande *et al.* [55] noticed decrease in weight of kidney stone when treated with bark of the plant. He also observed that, the bladder mucosa had less edema and ulceration, and also the cellular infiltration was intense than control group not treated with *C. religiosa* bark. According to Malini *et al.* [56], lupeol administration to stone forming rats reduced the renal excretion of the oxalate, a causative agent of stone formation and reduced the stone formation in animals preventing crystal induced tissue damage to kidney eluting stone forming constituents from kidney and restricted oxalate and crystal induced peroxidative alterations to renal tissue [56]. According to Deshpande *et al.*, [55] stem bark decoction in water is useful in the treatment of prostatic hypertrophy and hypotonic bladder and positively affects the patients from incontinence, urinary frequency, pain and urine retention.

Urinary electrolytes Calcium, Sodium and magnesium play very important role in the pathology of urolithiasis. Deshpande *et al.*, [55] estimated the urinary electrolytes after treatment of bark decoction of *Crataeva religiosa* and noticed reduced excretion of urinary calcium while that of sodium and magnesium increased significantly, altered the relative proportion of urinary electrolyte responsible for kidney stone formation [55]. According to Deshpande *et al.* [55], decoction of *Crataeva religiosa* bark helps in passing out the kidney stones in crystalurea patients. 'Uriflow', a commercial herbal formulation containing *C. religiosa* bark has been found to be useful in initiating the passage of renal and bladder stones [<http://www.getridofkidneystones.com>].

Urinary tract infection includes urethritis,

cystitis, nephritis or pyelonephritis. Four day treatment with *C. religiosa* bark decoction minimized these symptoms of urinary tract [58]. A formulation patented by Oneal and White

[<http://scientific.thomsonreuters.com/media/>] contain cratavin (extract of root bark and stem bark), is used to treat the *E. coli* infection to urinary tract. Samiolla and Harish [19] studied the diuretic effects of a herbal formulation-NR-AG-II containing aqueous extract of *Crataeva nurvala* bark. When activity of NR-AG-II was compared with a loop diuretic drug frusemide, NR-AG-II increased Na, K and Cl electrolyte level in urine, urine volume. 'Renaloka' product of Himalaya herbal health care, is used in the treatment of urinary tract infection. Shukla and Nayak [56] evaluated the use of PR-2000, a polyherbal formulation, to treat patient with benign prostatic hyperplasia. PR-2000 contains *Crataeva religiosa*, *Tribulus terrestris*, *Asparagus racemosus* and *Caesalpenis*.

Chakraborty *et al.* [<http://www.Himalayhealthcare.com>] studied the potential of a polyherbal formulation Himaplasia (Himalaya herbal healthcare). Daily use of himaplasia reduced the prostate size and increased the flow rate. It also reduced the prostrate volume, postvoid residual urine volume, urinary flow time, latent period and increased the peak flow rate significantly [58]. Clinical study with 98-BDH patients 'Himaplasia' treatment relived the symptoms of BDH by increasing the urinary flow rate and reducing the postvoid residual volume through reduction in prostrate size [59], [60]. Meher *et al.* [61], studied the effect of *Tribulis terrestris* and *Crataeva religiosa* against gentamycin induced nephrotoxicity in albino rats. Aqueous extract of these drugs protected the rats from the nephrotoxicity and showed the maximum level of nephroprotective action. Lupeol and its derivative known as Lupeol-EPA is a fatty acid, lowered the increased activities of the lysosomal and glycoproteins in the rats to normal level when compared to control edomethacin treatment [62]. Possible cardioprotective effects of lupeol isolated from the *Crataeva religiosa* bark against cyclophosphamide (CP) induced

oxidative stress have been studied by Sudharsan *et al.* [63]. CP used in cancer treatment causes fatal cardiotoxicity, and increases the activities of enzymes lactate dehydrogenase, creatine phosphokinase in serum and decreases in cardiac tissue. Cyclophosphamide treatment in albino rats caused intermuscular hemorrhage in histology, increased the lipid peroxide level and decreased the enzymic and non enzymic oxidant level in hearts. Oral administration of lupeol and lupeol linolate reversed the alterations caused by cyclophosphamide induced oxidative stress [63].

High cholesterol diet caused increase in total cholesterol and triglyceride levels in plasma along with elevation in the low density protein (LDL), very low density protein (VLDL) and cholesterol content and decreased level of high density lipoprotein. The lupeol and its derivative normalized the impaired lipid profile by decreasing the lipid peroxidation levels and stabilizing the antioxidant defense system by increasing the enzymic and non enzymic antioxidant status [64]. Lupeol also posses anti-malarial potential against chloroquine resistant *Plasmodium falciparum*. Among 96 lupeol derivatives synthesized, 15 posses higher activity than lupeol, and other have potential equivalent to lupeol or nil effect against the pathogen [65]. An herbal formulation (Herbmed- constitutes Bark of *Crataeva religiosa* and stem of *Mussa paradisiaca*.) prepared by Patankar *et al.* [66] helps to dissolve the renal calculi and facilitate their passage out, thereby minimizing the pain due to renal and ureteric calculus disease. Saleem *et al.* [67] evaluated the anti-inflammatory and anticancer activities of lupeol in Benzoyl peroxide induced tumor formation in murine skin. Benzoyl peroxide administration increased the microsomal peroxidation and hydrogen peroxide generation. Activities of the antioxidant enzymes catalase, peroxidase glutathione reductase, glutathione peroxidase, and glutathione S- transferase were found to be decreased along with decrease in coetaneous glutathione level and increase in ornithin decarboxylase activity and thymidin uptake in the DNA synthesis. Administration of lupeol 1 hr. before the Benzoyl peroxide

treatment perved the oxidative damage due to Benzoyl peroxide [68].

6. Biotechnology

Walia *et al.* [69], regenerated *C. religiosa* by using seedling derived explants- cotyledonary nodes, epicotyl nodes, hypocotyls segments, first pair of leaves, cotyledons and root segments. MS medium supplemented with 0.5mg/L BAP and 0.02mg/L or 0.1mg/L was found suitable for production of multiple shoots and good rooting. Walia *et al.* [70] successfully regenerated the *C. religiosa* by using the nodal explants from the 30 year old *Crataeva religiosa*. MS medium containing 2.22 μ M of BAP successfully produced multiple shoots which elongated satisfactorily on the same medium. Sanayaima *et al.* [16] investigated the cryopreservation of *in vitro* grown axillary shoot tips. Axillary buds from 4 weak old *in vitro* cultures produced shoots on MS medium supplied with 0.1mg/L BAP. The shoots were rooted on MS medium supplied with 0.02mg/L NAA. Shirin and Maravi [71] studied the clonal propagation of *Crataeva religiosa* by using the stem node segments from axillary branches. MS medium containing 10micro M BA and 15 micro M IAA was effectively producing the shoots and rooting the plants.

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