The chemical constituents and therapeutic importance of *Cressa* cretica- A review

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Abstract: *Cressa cretica* contained many biologically active constituents including coumarins, sterols, alkaloids, tannins, glycosides (cardiac glycoside, anthraquinone glycoside), protein, carbohydrate, flavonoids, unidentified sugars and high salt content. The pharmacological studies of *Cressa cretica* revealed that the plant possessed bronchodilatory, antitussive, reproductive, nootropic, antidiabetic antibacterial, antifungal, antioxidant, anti-inflammatory, antipyretic, and analgesic effects. This review will highlight the chemical constituents and medical importance of *Cressa cretica*.

Keywords: constituents, pharmacology, Cressa cretica.

I. INTRODUCTION

A large and increasing number of patients in the world use medicinal plants and herbs for health purpose. Therefore, scientific scrutiny of their therapeutic potential, biological properties, and safety will be useful in making wise decisions about their use⁽¹⁾. Recent reviews showed that plants produce many secondary metabolites which are bio-synthetically derived from primary metabolites and constitute an important source of many drugs ⁽²⁻⁴⁰⁾. *Cressa cretica* contained many biologically active constituents including coumarins, sterols, alkaloids, tannins, glycosides (cardiac glycoside, anthraquinone glycoside), protein, carbohydrate, flavonoids, unidentified sugars and high salt content. The pharmacological studies of *Cressa cretica* revealed that the plant possessed bronchodilatory, antitussive, reproductive, nootropic, antidiabetic antibacterial, antifungal, antioxidant, anti-inflammatory, antipyretic, and analgesic effects. This review will highlight the chemical constituents and medical importance of *Cressa cretica*.

II. PLANT PROFILE

Synonyms: Cressa loscosii Tremols and Cressa villosa Hoffmanns & Link⁽⁴¹⁾. Taxonomic classification: Kingdom: Plantae : Phylum: Angiosperms: Class: Magnoliatae: Subclass: A

Kingdom: Plantae ; Phylum: Angiosperms; Class: Magnoliatae; Subclass: Asteridae; Order: Polemoniales; Family: Convolvulaceae; Genus: Cressa; Species: Cressa cretica⁽¹⁾. Common names:

Arabic: Molleih, Nadewa; **Bengali**: Rudravanti; **English:** Alkali weed, Rosin weed, Cressa; **French**: Cresse de Crète, Cresse à feuilles d'herniaire; **Hindi**: Rudravanti; **Poland:** Erva molhada⁽⁴²⁻⁴⁵⁾.

Distribution

This species occurs from the Mediterranean east through western, central and south east Asia, south to northern and central Africa, south America and Australia. However, it was distributed in Afghanistan; Albania; Algeria; Angola (Angola); Australia (new south Wales, northern Territory, Queensland, south Australia, Victoria, western Australia); Bahrain; Bulgaria; Cyprus; Egypt; Ethiopia; France; Greece; Guinea-Bissau; India; Indonesia; Iran, Iraq, Palestine; Italy; Jordan; Kenya; Lebanon; Libya; Madagascar; Malta; Mauritania; Morocco; Mozambique; Oman; Pakistan; Portugal; Senegal; Somalia; Spain; Sri Lanka; Sudan; Syria; Tunisia and Yemen^(41, 45).

Description:

Cressa cretica is an erect, small, dwarf shrub upto 38cm height. Roots are horizontal, geminate, with lateral branches leading upward to produce above-ground parts. It is a perennial sub shrub or herb, usually muchbranched. Stems are at first erect and then become decumbent, apparently short-lived, gray appressed pilose to sericeous. Leaves on main branches are often larger than those on branchlets, the blade 1-12 mm long, lanceolate, ovate or elliptic- to scalelike, sessile, Peduncle lengths, stamen lengths, filament pubescence and ranges distinguish. Flowers are solitary, white or pink, axillary, 5-8 mm long, sessile or on short peduncles, bracteates, in spicate to head-like clusters at tips of branchlets, bracteoles unequal in length. Sepals ovate to obovate imbricate. Corolla salver form, the limb 5-lobed, the lobes mostly ovate, imbricate, spreading to reflexed. Stamens exserted; filaments filiform; styles exserted. Ovary 2- locular, 4-ovulate; styles 2, distinct to the base; stigmas capitate. Fruit is capsular, ovoid, unilocular, 2-4-valved, and usually one-seeded. Seeds are 3-4 mm long, glabrous and smooth, and shining to reticulate, dark brown⁽⁴⁵⁻⁴⁶⁾.

Traditional uses:

The plant was used traditionally as anthelmintic, stomachic, tonic, aphrodisiac, for constipation, leprosy, asthma and urinary discharges. In Senegal a maceration of the whole plant (together with the barks of *Vitex cuneata* Thonn and *Faidherbia albida* (Delile) A.Chev) was drunk against bronchitis. In Sudan a maceration of the aerial parts was drunk as a tonic. A decoction of the stems (together with leaves of *Vitex doniana* Sweet) was applied topically against skin eruptions as in smallpox. In Sudan crushed dry leaves with sugar were taken as an emetic ^(41, 46-47).

Physicochemical parameters:

Total ash 5.23 (% w/w), acid soluble ash 1.24 (% w/w), water soluble ash 0.87 (% w/w), sulphated ash 3.12 (% w/w), extractive values: hexane 3.390 (%), ethyl acetate 7.6-8.621(%), methanol 4.440- 14.4 (%), petroleum ether 1.5%, chloroform 4.8%, n-butanol 3.2% and water 27.2% $^{(48-49)}$.

Chemical constituents:

The plant contained coumarins, sterols, alkaloids, tannins, glycosides (cardiac glycoside, anthraquinone glycoside), protein, carbohydrate, flavonoids, unidentified sugars and high salt content⁽⁴⁹⁻⁵³⁾.

Creticane, cressatetracosanoate, cressanonacontanoic acid, cressatetratriacontanoic acid, cressatriacontanone, cressatriacontanone, cressanyl ester A, B, C, D, E, F and G were isolated from the aerial parts of the $plant^{(54-56)}$.

Chloroform soluble fraction of *Cressa cretica* produced seven compounds: triacontanoic acid, 24-hydroxy-4 octacosanone, 24-nor-12-ursene, β -amyrin, stigmasterol, ursolic acid and stigmasterol 3-O- β -D-glucoside^(46, 57). It also contained syringaresinol- β -d-deglucoside, triacontanoic acid, β -amyrin, edible fixed oil, quercetin, n-octacosanol, scopoletin and umbelliferone⁽⁴⁶⁾.

Sunita and Jha isolated nine compounds included three coumarins, four flavonoids along with two phytosterols from *Cressa cretica*. Their structure established as coumarin, umbelliferone, daphnetin, quercetin, kaempferol, quercetin 3-O-b-D-glucoside, quercetin-3-O-a-L-rhamno- $(1\rightarrow 6)$ -b-D-glucoside, stigmasterol and b-sitosterol⁽⁵⁸⁾.

Cresoside, a new coumaranochromone glycoside was isolated from fruits of *Cressa cretica*⁽⁵⁹⁾. Syringaresinolbeta-D-glucoside was also isolated from *Cressa cretica*⁽⁶⁰⁾.

The extract of Cressa cretica was also shown to have high phenolic content, 99.09±0.10 µg/mg⁽⁶¹⁾.

The aerial parts of *Cressa cretica* yielded five flavonoids that were identified as quercetin, quercetin-3-*O*-glucoside, kampferol-3-*O*-rhamnoglucoside, and rutin⁽⁶²⁾.

It was also reported the fruits of *Cressa cretica* was a potential source of edible oil. The oil of *C cretica* was free from any undesirable components and could safely be recommended for human consumption⁽⁶³⁾. However, saturated /un-saturated fatty acid fractions (%) constituents of *Cressa cretica* oil were: total saturated were 35.76% [dodecanoic acid methyl ester (lauric) 0.00, tetradecanoic acid methyl ester (myristic) 0.00, pentadecanoic acid methyl ester 0.00, hexadecanoic acid methyl ester (palmitic) 25.75 ± 7.82 , octadecanoic acid methyl ester (stearic) 8.267 ± 0.16 , non-adecanoic acid methyl ester 0.00, eicosanoic acid methyl ester (arachdic) 1.19 ± 0.03 , heneicosanoic acid methyl ester 0.00, docosanoic acid methyl ester (behenic) 0.287 ± 0.01 , tricosanoic acid methyl ester 0.00, tetracosanoic acid methyl ester (lignoceric) 0.287 ± 0.05 and hexacosanoic acid methyl ester (cerotic) 0.00]; while total unsaturated were 63.45 [9-hexadecenoic acid methyl ester (palmitoleic) 0.127 ± 0.01 , 7-hexadecenoic acid methyl ester (palmitoleic) 0.00, 8, 11-octadecadienoic acid methyl ester (linoleic) 62.707 ± 0.87 and 11-eicosanoic acid methyl ester (gadoleic) 0.637 ± 0.01]⁽⁶⁴⁾.

The concentration of *Cressa cretica* seeds minerals (N, P, K, Ca, Mg and S) were 2.48, 0.38, 0.71, 3.19, 0.21 and 0.18 (%) respectively, while that of (Na, Fe, Mn, Zn and Cu) were 310, 1526, 80, 46 and 157 (ppm) respectively⁽⁶⁴⁾.

Pharmacological effects: Bronchodilatory effect:

The effect of ethylacetate fraction (Fr-Et) and methanolic fraction (Fr-Me) obtained from *Cressa cretica* were evaluated in experimental models for bronchodilatory activity and mast cell stabilising activity. The effect of Fr-Et and Fr-Me were studied on acetylcholine and histamine aerosol-induced broncospasm using guinea pigs as an experimental animals. Also, the effects of these fractions were evaluated on the isolated guinea pig tracheal preparations. Besides this, mast cell degranulation effect was assessed using egg albumin and compound 48/80 on rat peritoneal mast cells. Significant increase in preconvulsion time was observed due to pretreatment with the fractions when guinea pigs were exposed to histamine and acetylcholine aerosol. Fr-Et

and Fr-Me significantly increased the preconvulsion in a dose depended manner that suggestive of bronchodilating activity. Fr-Et and Fr-Me exhibited a significant concentration dependant relaxant effect on guinea pig trachea pre-contracted with CCh, K^+ and histamine. The results revealed that Fr-Et was more potent than Fr-Me in relaxing histamine, K^+ and calcium induced contraction than CCh induced contractions. In styding the effect of the fractions in protecting mast cell degranulation, which were elicited by the egg albumin as well as synthetic compound 48/80 revealed that both fractions significantly protect the mast cell degranulation, which release mediators such as histamine and proinflammatory cytokines through various stimuli, in a dose depended manner⁽⁶⁵⁾.

Antitussive effect:

The antitussive effect of the plant was evaluated in two different experimental models. The antitussive effect of aerosols of two different concentrations (2.5%, 5% w/v) of methanolic extract of *Cressa cretica* (CME), codeine (0.03g/ml), and normal saline were tested by counting the numbers of coughs produced due to aerosols of citric acid 10 min after exposing the male guinea pigs to aerosols of different plant aerosols. In another set of experiment CME was investigated for its therapeutic efficacy on a cough model induced by sulfur dioxide gas in mice. The results showed significant reduction of cough number obtained in the presence of both concentrations of CME and codeine. The antitussive effect of higher concentration of CME in guinea pigs was significantly (p<0.01) greater than those of lower concentration and the prototype antitussive agent codeine phosphate (p<0.01). It also exhibited significant antitussive activity as that of codeine phosphate, in sulfur dioxide gas induced cough model. The extract at 100, 200 and 400 mg/kg orally, showed inhibition of cough by 22.1, 34.35 and 55.44 % within 90 min of performing the experiment⁽⁶⁶⁾.

Effects on Reproductive systems: Oral administration of a methanolic extract of *Cressa cretica* (whole plant) at a dose level of 100 mg/kg/day for a period of 60 days led to a significant decrease in the weight of testis, epididymis, seminal vesicle, and ventral prostate. *Cressa cretica* reduced the fertility of male rats by 100%. There was a marked reduction in the number of primary spermatocytes, secondary spermatocyte, and spermatids. Sertoli cell counts were significantly decreased. Leydig cell nuclear area and the number of mature Leydig cells were also significantly decreased. The protein, sialic acid, glycogen, and cholesterol content of the testis, the fructose in the seminal vesicle, and protein and sialic acid in the epididymis were significantly decreased. Serum testosterone levels were also reduced after *Cressa cretica* treatment. The RBC and WBC counts, hemoglobin, hematocrit, blood sugar, serum cholesterol, phospholipids, triglyceride, and HDL-cholesterol were within the normal range⁽⁵³⁾.

The various fractions (FrI 75:25 CHCl₃:CH₃OH, FrII 50:50 CHCl₃:CH₃OH and FrIII 25:75 CHCl₃:CH₃OH) of the *Cressa cretica* whole plant methanol extract were isolated by column chromatography on silica gel. These fractions were used to evaluate their effects on the reproductive functions in male albino rats. Oral administration of fractions I, II and III to male rats (50mg/rat/day) for a period of 60 days did not cause body weight loss, whereas the weight of testes and accessory sex organs were decreased significantly (P \leq 0.001). Sperm counts of testes and cauda epididymis as well as cauda epididymal sperm motility was also declined significantly (P \leq 0.001) in comparison to control rats. The serum testosterone production was reduced in treated male rats. The fertility was decreased by 90% in FrI, 100% in FrII and FrIII treated male rats. Total protein, sialic acid, glycogen content of testes and seminal vesicular fructose content were reduced significantly, whereas testicular cholesterol level was increased significantly. The seminiferous tubular diameter and Leydig cell nuclear area were reduced significantly. The population of spermatogenic cells (spermatogonia, preleptotene, pachytene, secondary spermatocytes and round spermatids) were also reduced significantly in comparison to controls⁽⁶⁷⁾.

Cressa cretica was evaluated for male contraceptive activity due to their rich amount of flavonoids (rutin and scopoletin). After 60 days oral administration of *Cressa* constituents, results showed 100% antifertility activity in male rats with the reduction in testosterone levels and spermatogenic elements⁽⁶⁸⁾.

Nootropic effect:

The effects of *Cressa cretica* was evaluated in learning and memory in mice. Elevated plus maze and passive avoidance paradigm were utilized to test learning and memory. Two doses (200 and 400 mg/kg, po) of ethanolic extract were administered for 28 successive days in separate group of animals. The dose of 400 mg/kg po, of *Cressa cretica* extract (CCE) significantly improved learning and memory of mice. Furthermore, this dose significantly reversed the amnesia induced by scopolamine (0.4 mg/kg, ip). To find out the mechanism by which CCE exerted nootropic activity, the effect of CCE on whole brain AChE activity was also estimated. CCE decreased whole brain acetyl cholinesterase activity and reduced whole brain MDA and NO levels. The

antioxidant properties and the presence of flavonoids in *Cressa cretica* may be contributing to memory enhancement effect. Accordigly, *Cressa cretica* was a potent candidate for enhancing learning and memory and it would be beneficial for the treatment of amnesia and Alzheimer's disease⁽⁶⁹⁻⁷⁰⁾.

Antidiabetic effect:

The antidiabetic activity of *Cressa cretica* was evaluated in alloxan induced diabetes in rats. The maximum glucose lowering effect of (11.86%) was observed at 12 hour after the administration of 300mg/Kg. Repeated oral treatment with ethanolic extract of *Cressa cretica* (EECC) (300mg/Kg/day) for two weeks significantly reduced blood glucose, serum cholesterol and improved HDL-cholesterol and albumin as compared to diabetic control group⁽⁷¹⁾.

The antidiabetic potential of methanolic extract of *Cressa cretica* was studied in streptozotocin induced diabetic rats. The methanolic extract of *Cressa cretica* was administered orally at a dose of 100 mg/kg for 15 days to streptozotocin induced diabetic rats. Methanolic extract of *Cressa cretica* produced a significant reduction in fasting blood glucose level in diabetic rats. Significant differences were also observed in body weight in methnolic extract treated diabetic rats, when compared with diabetic control, normal control and standard drug treated rats. The authors postulated that phenolic compounds and flavonoids were responsible for antidiabetic activity⁽⁷²⁾.

Antibacterial and antifungal effects:

Antibacterial activity of various extracts of *Cressa cretica* and the crude alkaloid solution was tested against four micro organisms (*E. coli, Staphylococcus aureus, Proteus* Spp and *Pseudomonas* spp.). Antibacterial analysis revealed considerable antibacterial activity exerted by all the extracts except hexane extract and in the case of *Proteus* spp the extracts showed greater activity compared to the control. All extracts showed maximum activity against *E. coli*⁽⁷³⁾.

The antibacterial effect of the different fractions (hexane, ethylacetate and methanol) of the whole methanolic extract of *Cressa cretica* were studied against wide ranges of bacteria (both positive and negative strain) and five fungi *Candida albicans, Candida tropicalis, Aspergillus fumigatus, Aspergillus niger* and *Fusarium oxysporum* by agar disc diffusion method. Among the three fractions, the ethylacetate fraction of *Cressa cretica* showed the highest activity, but among the pathogens highest activity was revealed against *Escherichia coli, Klebsiella pneumoniae* (zone of inhibition diameter was found to be 26 and 31mm, respectively). The ethylacetate fraction was active against both gram positive and gram negative bacterias. *Cressa cretica* showed higher inhibitory activity against the *Aspergillus fumigates, Aspergillus niger* (zone of inhibition diameter was found to be 26 and 22mm, respectively) than the *Candida albicans* and *Candida tropicalis* and, the least activity was recorded against *Fusarium oxysporum*⁽⁷⁴⁾.

The antibacterial and antifungal activity of methanolic extract of *Cressa cretica* was studied by cup plate method against various organisms like *E. coli, S aureus, S. typhi, B. subtilis,* and *C. albicans.* 200-800µg/ml of the ethanolic extract showed dose dependent antimicrobial activity, the diameter of zone of growth inhibition (mm) was 25-30 against *E. coli,* 15-25 against *S. aureus,* 20-30 against *S. typhi,* 20-25 against *B subtilis,* and 20-25 against *C. albican⁽⁴⁹⁾.*

Antifungal activity was exerted by ethanol extract of *Cressa cretica* against *Penicillium citrinum* (32.2 mm) and *Candida albicans* (25.7 mm)⁽⁷⁵⁾.

The antifungal activity of crude solvent extract of *Cressa cretica* against the dermatophytic fungi *Aspergillus niger*, *Aspergillus flavus*, *Paecilomyces varioti*, *Microsporum gypseum* and *Trichophyton rubrum* was investigated. The various crude solvent extracts were found to be effective against the test organisms, the chloroform and aqueous extracts appeared to be the most effective antifungal extracts, compared to the ethanol, methanol and ethyl acetate extracts⁽⁷⁶⁾.

Anti-inflammatory, antipyretic and analgesic effects:

The methanolic (Fr-Me) and ethyl acetate fraction (Fr-Et) obtained from the aerial parts of *Cressa cretica* exhibited inhibitory effect against acute and chronic models of inflammation (carrageenan-induced paw edema, cotton pellet granuloma, carrageenan air pouch inflammation, vascular permeability and Freuds complete adjuvant induced arthritis models). The fractions also inhibited arachidonic acid and other mediator (histamine, serotonin, prostaglandin E2)-induced paw edema in rats in a dose dependent manner. Moreover, Fr-Me and Fr-Et significantly increased plasma superoxide dismutase, catalase, glutathione and glutathione peroxidase activities. On the contrary, the malonaldehyde (as a measure of lipid peroxidation) level was significantly decreased in comparison with the control group. Also, it was found that Fr-Et reduced the inflammation and revealed the antioxidant activity more significantly than Fr-Me⁽⁶³⁾.

The analgesic and antipyretic activities of methanolic extract of *Cressa cretica* at different doses (100, 150 and 200 mg/kg) was studied using hot plate, acetic acid induced writhing and yeast induced hyperthermia methods. Methanolic extract of *Cressa cretica* showed significant analgesic and antipyretic activities at the dose of 200 mg/kg in all models studied⁽⁷⁷⁾.

Antioxidant effect:

n-Butanol extracts of nine medicinal plants, *Cressa cretica, Ziziphus spinachrist, Acacia tortilis, Tephrosia haussknechti, Aristolochiae bracteolata, Citrullus colocynthis, Teucrium mascatense, Rhazya stricta and Nerium oleander,* were screened for their antioxidant activity using phosphomolybdenum complex assays and their radical scavenging activity using DPPH assays. *Cressa cretica* showed high level of DPPH scavenging activities 87.7%⁽⁷⁸⁾.

The free radical scavenging activity of *Cressa cretica* was studied on *in vitro* antioxidant models. The antioxidant activity was evaluated by determining the activity of hydrogen peroxide (H_2O_2) radicals scavenging and 1,1-diphenyl-2-picryl hydrazyl (DPPH) assay. In all these models, a significant correlation existed between concentrations of the extract and percentage inhibition of free radicals⁽⁶¹⁾.

The methanolic (Fr-Me) and ethyl acetate fraction (Fr-Et) obtained from the aerial parts of *Cressa cretica* significantly increased plasma superoxide dismutase, catalase, glutathione and glutathione peroxidase activities. On the other hand, the malonaldehyde (as a measure of lipid peroxidation) level was significantly decreased in comparison with the control group⁽⁶³⁾.

III. CONCLUSION

This review discuss the chemical constituent, pharmacological and therapeutic effects of *Cressa cretica* as promising herbal drug because of its safety and effectiveness.

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