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REVIEW ARTICLE

Phytochemistry and Pharmacological activities of *Caesalpinia crista* L: A Review

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ABSTRACT

Caesalpinia crista L. is an important medicinal plant in Ayurveda due to its applications in curing wide range of disorders. Phytochemically *C. crista* is rich in tannins, flavonoids, proteins, reducing sugars, carbohydrates, saponins, phytosterols and triterpenoids. It is the richest source of various cassane and norcassane-type of diterpenes. Various extracts derived from leaves, seeds and flowers of *C. crista* revealed antimicrobial, antioxidant, hepatoprotective, anthelmintic, cytotoxic, antimalarial, anticancer, anti-ulcer, anti-inflammatory, antidiabetic, insecticidal activities. Present paper comprehensively accounted for phytochemical diversity and various pharmacological activities of *C. crista*.

Keywords: Ayurveda, *Caesalpinia crista*, Medicinal Plant, Phytochemistry, Pharmacology

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INTRODUCTION

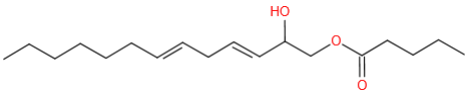
Caesalpinia crista L. is an important member of subfamily Caesalpinioideae coming under Fabaceae family. It is a prickly shrub with huge medicinal potential and commonly distributed in tropical and subtropical regions of Southeast Asia [1]. It is quite prominently scattered in Maharashtra, Kerala and West Bengal states of India [2]. In Bangladesh, it locally known as Kutum Kanta [3], while Indian trivial names are Katikaranja or Natakaranja [4], in Myanmar it locally called as "Ka-Lain", whereas "Bagore" in Indonesia [5], "Taepee" in Thai [6] and "Shirotsubu" in Japanese [7]. Phytoconstituents like phenolics and flavonoids impart several medicinal properties to many medicinal and aromatic plants. In ayurvedic preparations seeds, leaves and stem of *C. crista* are mostly used to cure constipation, gynecological disorders, piles and ulcers and skin diseases [1, 4]. Present review provides detailed insides about phytoconstituents diversity and pharmacological activities of medicinally important *C. crista* plant.

PHYTOCONSTITUENTS

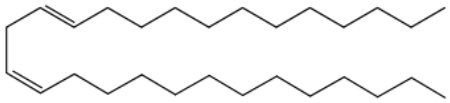
Ethanolic extract of *C. crista* seeds is rich in flavonoids, tannins, alkaloids, triterpenoids and proteins [8]. Aqueous and ethanolic extract of *C. crista* seeds tested positive for alkaloids, carbohydrates, flavonoids, phytosterols, proteins, reducing sugars, saponins, triterpenoids and tannins [9, 10]. *C. crista* seed coats methanol extract showed presence of alkaloids, steroids, flavonoids, phenols, glycosides and triterpenoids [11]. HPLC analysis documented seven polyphenolics and six flavonoids in ethyl acetate, methanol and aqueous extracts of *C. crista* leaves [12]. Aqueous extract of *C. crista* leaves reported gallic acid, gentisic acid, chlorogenic acid, protocatechuic acid, ferulic acid, *p*-coumaric acid and caffeic acid [13]. Three novel norcassane diterpenes were isolated from dichloromethane extract of *C. crista* seeds, of which norcaesalpinin A and B showed 17-norcassane skeleton whereas, norcaesalpinin C is with 16-norcassane skeleton [14]. Dichloromethane extract of *C. crista* seeds documented total twenty three diterpenes of which ten viz. caesalpinins H-P and norcaesalpinin F were new furanocassane-type diterpenes [15]. Ethanolic and dichloromethane extract of stems and roots of *C. crista* documented total fourteen diterpenes viz. ent-11b-hydroxy-rosa-5,15-diene, vinhaticoic acid, methyl vinhaticoate along with taepeenin A–I and nortaepeenin A–B which were newly recognized cassane and norcassane-type of diterpenes[15]. Acetone extract of *C. crista* seeds reported (5a,8b)-vouacapane, (5a,6b,8b)-vouacapan-6-ol, (5a)-vouacapa-8(14),9(11)-diene, taepeenin J, taepeenin K and taepeenin L. The taepeenin J was a dimer and taepeenin K and L belongs to cassane-type diterpenes [6]. Two new diterpenoids viz. 6b-cinnamoyloxy-7b-acetoxyvouacapen-5a-ol and 6b,7b-dibenzoyloxyvouacapen-5a-ol were extracted from aerial parts *C. crista* using 1:1 ratio chloroform and methanol [16]. Fresh sub-cultured callus of *C. crista* accounted maximum 61.4% of Glutamine, cultured medium showed 21.3% of Alanine and protoplast found with 45% of Arginine [17]. 17-methylvouacapane-8(14),-9(11)-diene a new marker cassane furanoditerpene was successfully extracted from n-hexane extract of *C. crista* seed kernel [18]. Cassane-type diterpenes like 2-acetoxy-3-deacetoxycaesaldekarin e, 14(17)-dehydrocaesalmin F, 7-acetoxybonducellpin C, 6-acetoxy-3-deacetoxycaesaldekarin e caesaldekarin e, caesalmin C, caesalmin E, 2-acetoxycaesaldekarin e, caesalpinin E, caesalpinin C, caesalmin B, norcaesalpinin B, along with newly isolated caesalpinins MA-ME and norcassane-type diterpenes, norcaesalpinins MA-MC were isolated from dichloromethane extract of *C. crista* seed kernels collected from Myanmar [19]. Dichloromethane extract of *C. crista* seed kernels collected from Myanmar yielded cassane-type diterpenes like 2-acetoxycaesaldekarin e, bonducellpin C, 1-deacetylcaesalmin C, caesalmin C, caesaldekarin e, 2-acetoxy-3-deacetoxycaesaldekarin e, norcaesalpinin E, 1-deacetoxy-1-oxocaesalmin C, in addition to this normal cassane-type furanoditerpenes viz. caesalpinins MO, MP and rare methyl migrated cassane-type furanoditerpenes caesalpinins MM and MN were also extracted [20]. Along with sixteen already reported cassane-type diterpenes, newly found caesalpinin MF—ML and one new norcassane-type diterpene, norcaesalpinin MD was successfully isolated from dichloromethane extract of Myanmarese *C. crista* seed kernels [21]. Neocaesalpins H and I, new cassane diterpene-acids were isolated from acetone extract of *C. crista* leaves with rare α, β-butenolide hemiacetal ring and 5-hydroxy group deficiency [7]. GC-MS and LC-MS investigations of *C. crista* leaves methanolic extract accounted twenty six and fourteen compounds respectively and HPLC analysis of methanol extract found with rutin hydrate, myricetin, sinapic acid, quercetin, *p*-coumaric acid, caffeic acid, cinnamic acid, vanillin, chlorogenic acid, kaemperol, protocatecheuic acid, catechin, epicatechin and gallic acid [22]. In addition to familiar compound 3-*O*-methylellagic acid-3'*O*-α-

rhamnopyranoside, unique compounds such as 2-hydroxytrideca-3,6-dienyl-pentanoate and octacosa-12,15-diene (Figure 1.) were isolated from methanolic extract of *C. crista* seeds [23]. Dichloromethane extract of Indonesian *C. crista* seed kernels produces new caesalpinins C-G and norcaesalpinins D and E (furanocassane-type diterpenes) and norcaesalpinins A-C along with other known eleven compounds [24]. Phangininoxys D and E, identified as new cassane-type diterpenes isolated from methanol extract of *C. crista* seeds along with caesalpinin MP, phanginin I, caesalpinista A, caesalpinilinn and caesalpinista B [25]. *C. crista* flower methanolic extract yielded four flavonoid compounds isolated first time in plants [26]. A new cassane-type diterpene named as 1α-acetoxy-5α, 7β-dihydroxycassa-11,13(15)-diene-16,12-lactone was extracted from methanol extract of *C. crista* seed kernels [27]. Caesalpinista A, caesalpinista B, caesaljapin B, caesaljapin C and caesalpinilinn were the five new cassane-type diterpenes isolated from methanolic extract of *C. crista* seeds [28]. Two cheilanthane-type tricarbocyclic sesterterpenoids viz., cristasesterterpenoic acid and cristasesterterpinol glucoside were isolated from methanolic fraction of *C. crista* leaves [29].

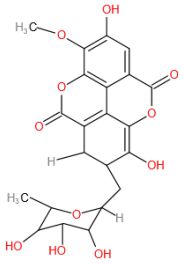
Figure 1 Structures of phytoconstituents isolated from *C. crista* [23, 25, 26, 30].



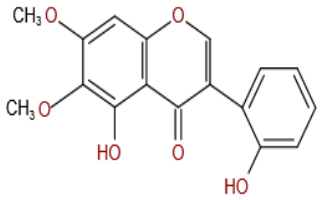
2-Hydroxytrideca-3,6-dienyl pentanoate



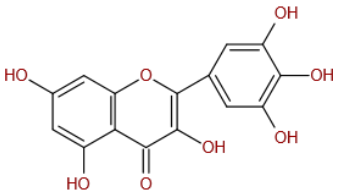
Octacosa-12,15-diene



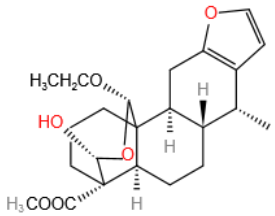
3-O-Methylellagic acid-3'O-α-rhamnopyranoside



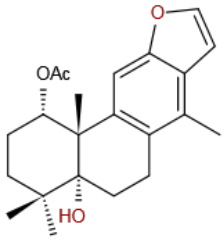
5,2'-digydroxy-6,7-dimethoxy isoflavone



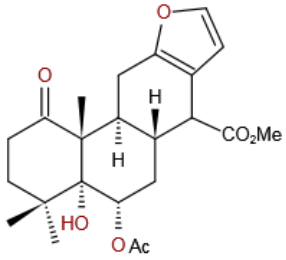
3,5,7,3',4', 5'-hexahydroxy flavone



Phangininoxys D



Caesalpinin MP



Caesalpinin F

PHARMACOLOGICAL ACTIVITIES

Antibacterial activity

C. crista leaves methanolic extract inhibited seven bacterial strains and highest antibacterial activity was recorded at 500 µg/disc against *S. aureus* and *E. coli* with 14.8 mm and 14.5 mm of zone of inhibitions respectively; on contrary chloroformic extract failed against all tested bacterial strains [31]. Against all tested bacterial strains, crude methanolic extract of *C. crista* seeds revealed most vigorous and significant antibacterial activity compared to other fractions and isolates [23]. Flavonol fraction of *C. crista* seed coat demonstrated significant antibacterial activity against *S. aureus* with 27 ± 0.14 mm zone of inhibition; however least activity was recorded towards *E.coli* having 10 ± 0.15 mm zone of inhibition [32]. All compounds derived from methanolic extract of *C. crista* flower revealed antimicrobial action against all examined strains; compound C showed maximum effect against *M. lutens* with 16.64 mm zone of inhibition [26].

Antifungal activity

Phenolic acid fraction of *C. crista* seed coat showed activity against all strains and highest antifungal potential recorded against *A. flavus* with 30 ± 0.90 mm zone of inhibition; however flavonol fraction revealed moderate activity against *C. albicans* only [32]. Three out of four compounds extracted from methanolic extract of *C. crista* flower revealed activity against all fungal strains and compound B revealed best action against *F. oxysporum* with 18.1 mm zone of inhibition [26].

Antiviral activity

Aqueous and ethanol extract of *C. crista* completely inhibited paramyxovirus and revealed substantial inhibition of orthomyxovirus (87.5% each); on the contrary chloroform extract failed to inhibit paramyxovirus and showed half efficacy (50% inhibition) against orthomyxovirus [51].

Antioxidant efficacy

In DPPH assay, methanolic extract of *C. crista* leaves revealed higher (IC_{50}= 103.7 µg/ml) free radical scavenging activity than chloroformic (IC_{50}= 201.92µg/ml) extract; In FRAP assay, methanolic extract revealed stronger (70.4 ± 0.031) antioxidant activity than chloroformic extract (35.4 ± 0.023) [31]. Ethanolic extract of *C. crista* seeds showed highest (73.9 ± 0.84% and 77.7 ± 0.05%) activity in DPPH and hydrogen peroxide assay respectively [8]. *C. crista* leaves methanol extract showed higher inhibition potential (93.01± 0.33%) as compared to aqueous extract (55.74 ± 0.09%) at 400 µg/ml concentration in DPPH assay [22]. Hydro-methanolic extract of *C. crista* leaves showed ROS scavenging activities for hydroxyl, superoxide, nitric oxide, singlet oxygen and hypochlorous acid assays and *in vivo* analysis of extract illustrated significant raise in superoxide dismutase, catalase, glutathione S-transferase, whereas glutathione level get reduced [2]. Aqueous extract of *C. crista* leaves demonstrated very high antioxidant activity in DPPH assay with IC_{50}= 24.35±1.1 µg/ml as compared to *C. asiatica* IC_{50}= 139.5±2.01 µg/ml [13]. Poor antioxidant activity was revealed by hydro-ethanolic extract of *C. crista* leaves in ABTS assay with 0.152 ± 0.002 TEAC value; also very low free radical scavenging capacity was measured in superoxide, nitric oxide, peroxynitrite, singlet oxygen and hypochlorous acid assays (IC_{50}= 139.4± 17.23; 52.21± 7.28; 4229.17± 522.79; 425.24 ± 48.27 and 410.48 ± 81.2 µg/ml respectively) as compared to other medicinal plants [33]. In DPPH method, hydro-ethanolic extract of *C. crista* seeds revealed concentration dependent antioxidant activity and highest (71.6±0.42%) inhibition was recorded at 300µg/ml concentration [34]. *C. crista* seed coat methanol extract revealed 76% of inhibition with IC_{50}= 71.89 mg/ml in DPPH assay; the extract also trim down level of $NaNO_2$ induced lipid peroxidation and protein carboxylation. In oxidative stress-induced RBCs, dose dependent usual level of superoxide dismutase and catalase was observed [11]. Ethyl acetate extract of *C. crista* leaves showed strong antioxidant activity in DPPH, ABTS methods with IC_{50}= 23.9 ± 1.8 µg GAE, 38.9 ± 1.8 µg respectively; however in hydroxyl radical scavenging assay methanol extract perform better (IC_{50}= 76.8 ± 2.4 µg/mL) than rest of the extracts [12].

Anthelmintic efficacy

Methanol extract of *C. crista* seeds revealed 70.83% of efficacy against *Ascaridia galli* infected broilers and concentration dependant vermicidal effect [37]. *C. crista* seeds extracted with methanol showed low efficacy (70.83%) as compare to oxfendazole (90.83%) against *Ascaridia galli* infected broilers [38]. Ethanol and aqueous seed extract at 15% w/v concentration recorded least time of paralysis and death for *Pheretima posthuma* and *Ascaridia galli* [39]. Aqueous-ethanol extract of *C. crista* seeds was less effective in terms of faecal egg and adult worm counts of *H. contortus*, although it showed second best (8.8%) effectiveness of drug against *H. contortus*. In the case of *T. colubriformis* it failed to control adult worm count with no effectiveness of drug [40]. Ethanolic seed extract of *C. crista* seeds showed 92.1% of effectiveness against *Haemonchus contortus* third stage larvae with 0.08% of parasitic survival rate [41]. Crude aqueous methanolic extract of *C. crista* seed kernels revealed dose as well as time-dependent anthelmintic effects by killing worms and preventing egg hatching with LC_{50} = 0.134 mg/mL; also declined (93.9 %) eggs per gram of faeces *in vivo* condition at 3.0 g/kg on day 13 of post-treatment [42]. 4% petroleum ether extracts of *C. crista* seeds showed excellent paralytic and lethal time (2.2 and 15.3 min respectively) against earthworms compared to other extracts [43].

Antimalarial activity

Two furanocassane diterpenes, caesalpinin N and norcaesalpinin F isolated from dichloromethane extract of *C. crista* seeds showed very high inhibitory action against *P. falciparum* FCR-3/A2 with IC_{50} value of 120 and 140 nM as compared to chloroquine [5]. From dichloromethane extract *C. crista* collected form Myanmar and Indonesia, cassane and norcassane-type diterpenes were isolated which showed concentration dependent manner inhibitory action against *Plasmodium falciparum* FCR-3/A2; among these, norcaesalpinin E showed most potent antimalarial activity (IC_{50} = 0.090 µM) as compared to known drug chloroquine (IC_{50}= 0.29 µM) [44]. Dichloromethane extracted compounds from *C. crista* kernels revealed dose dependent action against *P. falciparum* FCR-3/A2 and compound norcaesalpinin E showed strong activity with IC_{50} = 90 nM [24].

Anticancer activity

70% ethanol extract of *C. crista* root bark at a dose of 150mg/kg revealed reduction in tumor volume and packed cell volume (1.9±0.28 and 2.2±0.14 ml respectively) whereas, it recorded elevated mean survival time, increase life span (22±0.28 days and 62.9±0.2 % respectively) in Ehrlich ascites carcinoma bearing mice; Haematologically, *C. crista* ethanol extract at 150 mg/kg dose significantly raised RBC count and hemoglobin content whereas, it reduces WBC count as compared to EAC control [45].

Anti-ulcer activity

Although aqueous and ethanolic extracts of *C. crista* declined pylorus ligation and indomethacin induced ulcer occurrence in rats through drop off ulcer score and ulcer index, the maximum effect was recorded at 200 mg/kg b.w. dose of ethanolic extract [9].

Anti-inflammatory activity

In carrageenan induced rat paw edema assay, ethanolic extract of *C. crista* seeds revealed significant anti-inflammatory activity (74.2%) at 300mg/ml dose after 3 hours as compared to diclofenac [8]. Aqueous extract of *C. crista* leaves revealed strong inhibition of 5-lipoxygenase with IC_{50} = 23±1.1 µg/mL [13].

Analgesic activity

Ethanolic extract of *C. crista* seeds showed potent analgesic effect (71%) at 300 mg/kg dose in writhing reflexes assay while, in tail immersion assay significant activity was observed at 60 min (5.30 ±0.05 sec) at same dose. In both assays, extract showed concentration dependent activity [8].

Antidiabetic activity

In streptozotocin induced diabetic rats, aqueous as well as ethanolic extract of *C. crista* seeds significantly declined serum glucose, cholesterol and triglycerides however, it results in decreased average body weight and increased water and food intake demand. Histopathological investigation observed structural changes in islets of pancreas. Comparatively aqueous extract is more effective than ethanolic extract [10].

Anti-amyloidogenic property

Aqueous extract of *C. crista* leaves worked at three levels to reveal anti-amyloidogenic property. The aqueous extract restrains Aβ(42) aggregate formation from monomers; it also inhibits combining of Aβ(42) from oligomers and it can separate earlier developed Aβ(42) fibrils [48].

Antineoplastic activity

In MTT assay, phanginin I isolated from methanol extract of *C. crista* seeds revealed significant action against HeLa, HT-29 and KB cell lines, however it showed excellent activity against KB cell lines with IC_{50} = 17.1 ± 2.4 μM [25]. From methanol extract of *C. crista* seed kernels, newly isolated compound 1α-acetoxy-5α, 7β-dihydroxycassa-11,13(15)-diene-16,12-lactone revealed modest antiproliferative activity against T47D and DU145 cell lines with IC_{50} = 16.5 and 8.2 mg/mL respectively [27].

Antiplatelet activity

Methanol extract of *C. crista* seed coat at 150 μg concentration showed low antiplatelet activity (28 and 23% respectively) by inhibiting ADP and epinephrine agonists [11].

Antipyretic activity

Pyrexia induced in rabbits due to yeast, TAB vaccine and boiled milk was reversed with oral administration of ethanolic and aqueous extract of *C. crista* seeds at a dose of 100 mg/kg b.w. It significantly brings down body temperature to normal, however in all cases ethanolic extract proved much more significant than aqueous [53].

Cytotoxic activity

Methanolic extract of *C. crista* leaves showed stronger cytotoxic activity (LC_{50} = 2.972 and 5.794 μg/ml) than chloroformic extract in brine shrimp lethality bioassay [31]. Two new diterpenoids isolated from *C. crista* aerial parts showed significant cytotoxic activity against HL-60 (IC_{50} = 17.37 ± 0.88 and 19.77 ± 1.54 μM) and HeLa cell lines (IC_{50} = 33.41 ± 0.75 and 33.90 ± 0.66 μM) [16].

Cholinesterase inhibition

Acetylcholinesterase and butyrylcholinesterase activity of *C. crista* methanol extract showed 51.19% and 63.86% inhibition respectively [22].

Cardio-protective effect

In isoproterenol triggered myocardial infarction, aqueous and ethanol extract of *C. crista* seeds at 400 mg/kg b. w. dose significantly declined serum and heart homogenates based elevated marker enzyme levels [54].

Hepatoprotective activity

Paracetamol and carbon tetrachloride induced liver toxicity in albino rats was lowered on treatment with aqueous and ethanolic extract of *C. crista* seeds. Both extracts showed significant reduction of serum aspartate aminotransferase, alkaline phosphatase, alanine transaminase, total bilirubin and significantly enhanced total proteins in serum [35]. In excess iron induced liver toxicity, methanolic extract of *C. crista* leaves inhibit lipid peroxidation, protein oxidation and liver fibrosis by dose dependent manner and best results were observed at 200 mg/kg b.w dose; on treatment with same extract serum marker enzymes level declined, however liver antioxidant enzymes showed elevated concentrations [36].

Insecticidal activity

Methanol extract of hexane defatted *C. crista* seeds caused utmost antifeedance in *Helicoverpa armigera* (AI_{50}=0.0186%) and feeding of extract introduced abnormalities in *H. armigera* larvae, pupae and adults; extract treated larvae recorded 50% growth reduction (GI_{50}=0.0151%). The extracts proved biologically safe against predator beetle, *Coccinella septempunctata* up to nine days of treatment [49].

Inhibition of erythrocytes hemolysis

Hydrogen peroxide induce erythrocyte hemolysis was strongly inhibited by ethyl acetate, methanol and aqueous extracts of *C. crista* leaves following dose-dependent pattern, however ethyl acetate extract proved better (IC_{50}= 88.56 ± 1.88 µg) than rest of the extracts [12].

Inhibition of DNA damage

Damage caused to λ-DNA due to fenton reaction generated radicals was overcome by ethyl acetate, methanol and aqueous extracts of *C. crista* leaves. λ-DNA damaged with hydroxyl ion, significantly lower down the fluorescence intensity; however, higher fluorescence intensity 47.7, 41.98 and 45.96 was recorded on treatment with above three extracts of *C. crista* leaves [12].

Nootropic activity

In the radial arm maze model, *C. crista* seed kernels aqueous extract showed dose dependent memory retention and averagely 57.552 ± 5.768 seconds to complete three successful trials at 150 mg/kg p.o. While working with morris water maze model, aqueous extract at 150mg/kg, p.o. showed increased memory retention percentages and 22.495 ± 1.138 seconds averagely for three successful trials, very near to standard drug Piracetam [46].

Neuroprotective effect

Methanol extract of *C. crista* leaves dose dependently improve the cognitive damage occurs due to aluminum, acetylcholinesterase hyperactivity and oxidative stress in hippocampus and frontal cortex of rat brain, also extract declined aluminium triggered neuronal injury revealed by decreased neuron loss and degeneration of nucleus in certain areas of rat hippocampus [52].

Toxicology Study

Ethanol extract of *C. crista* seed kernels showed a non toxic effect on body and organ weights of mice, also no significant variation is detected in hematological analysis. During this study no mortality was observed [47].

Wound healing activity

Amongst the six fractions of *Caesalpinia crista* seed kernels, ethyl acetate fraction revealed superior wound healing activity [50].

Conflict of Interest

The authors declare no conflict of interest.

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