Review Article

# A Review on Phytopharmacological Properties of *Caesalpinia Crista*

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***Caesalpinia crista*** **belonging to family Caesalpiniaceae is found in the hotter parts of India. It is common in West Bengal and South India. It often grows as a hedge plant. It is commonly known as Fever nut or Latakaranja. Various parts of the plant like seeds, leaves, bark, flowers, root and oils are used in traditional system of medicine to treat fever, malaria, skin diseases and inflammation. It also possesses antidiarrheal, anthelmintic, antifertility, antidiabetic, analgesic, anticonvulsant, hepatoprotective, antioxidant, antitumour, wound healing, antipyretic and antiulcer activities. The major constituents isolated are diterpenoids of the cassane and norcassane types. The extracts also show the presence of flavonoids, tannins, alkaloids, saponins, coumarins, proteins, carbohydrates, reducing sugars, triterpenoids and fatty acids.**

**Key words: *Caesalpinia crista*, fever nut, chemical constituents, pharmacology**

Medicinal plants are nature's gift to human beings owing to their useful applications for the treatment of various diseases. The herbal products promise safety as compared to the synthetics that are considered as dangerous to human and environment[1]. Thus there is revival of interest in studying traditional plant derived drugs. Medicinal plant is any plant from which valuable drugs can be synthesized as it contains constituents that can be used for medicinal purposes[2]. The envisioned study's primary objective was to review and compile the available data about *Caesalpinia crista* (*C. crista*) to carry out the isolation and characterisation of phytoconstituents from the seed extracts of *C. crista*, and to perform its phytochemical investigation and pharmacological screening and thus predicting a better lead molecule responsible for biological activity.

*C. crista* belongs to family Caesalpiniaceae and is a popular traditional medicinal plant which is widely distributed throughout the tropical and subtropical regions of southeast Asia[3]. It is found throughout the hotter parts of India and is common in West Bengal and South India. It is a woody climber often grown as a hedge plant[4]. The taxonomic hierarchy[4] and common names[5-11] of *C. crista* are shown in Table 1 and Table 2.

## TRADITIONAL/AYURVEDIC USES

*C. crista* is used in treating a vast range of diseases. Different parts of the plant like leaves, flowers, fruit, root, bark, seeds and seed oil were used medicinally[6]. Roots were used in the treatment of tumour, small pox, colic fever, malaria, menstrual complaints, pulmonary tuberculosis, uterine disorders, diabetes and asthma[12]. They were used as diuretic and anticalculus. The seeds were considered febrifugal, periodic, tonic and vesicant. They are used to treat colic, convulsions, leprosy and palsy. The oil from the seeds is said to soften the skin and remove pimples[11]. The seeds have been used as an anthelmintic, antipyretic, anti-inflammatory and antimalarial drug[13-16]. The bark is antiperiodic, rubefacient and used to counteract toothache. The leaf decoction is used as collyrium[17,18]. Fruits were used as aphrodisiac, astringent, anthelmintic, cures urinary diseases, leucorrhoea, piles, wounds and ulcers[19]. Also the leaves and seeds were traditionally used to treat malarial fever in Assam region[20]. A

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root decoction has been used for the treatment of rheumatism and backache[21,22].

In Ayurveda the powder of roasted seeds of *C. crista* with ghee mitigates and relieves the abdominal pain. Thus it is the best remedy for abdominal pain due to flatulence, as it effectively alleviates the vata dosha. The roasted seed powder, asafoetida, ghee and little amount of salt eliminate the abdominal pain during postpartum period. The seed's powder, given along with milk helps control diarrhoea. The skin of the seed is extremely beneficial in the treatment of leucorrhoea. Having astringent properties, the seed's skin is also used as a medicament for treating diarrhoea, dysentery and colitis. The juice of its leaves or powder of its roasted seeds is given along with palasa, amra and haridrai to treat worm infestations. The leaves fried in ghee, eliminate vata and relieve constipation, hence valuable in piles[5,23].

Latakaranja (combination of roasted seeds powder of *C. crista* and pippali (1:1) with honey) is the best medication for malarial fever. Another combination recommended for treating malaria is the powders of marica and latakaranja (Sakra vati). The splenic enlargement due to malaria, responds well to latakaranja[5,23].

The seeds are stimulant to the uterus, thus improve the menstrual discharge in oligomenorrhea and reduce the pain in lower abdominal region. They also render contraceptive activity. Latakaranja is used as a bitter tonic. It is also a useful remedy for cough and asthma, as it alleviates the kapha dosha. For this purpose, the tender leaves (fresh juice) are given along with the honey to ward off the mucous

**TABLE 1: SCIENTIFIC CLASSIFICATION OF *Caesalpinia crista***

| Taxonomic Hierarchy | |
|---|---|
| Kingdom | Plantae |
| Phylum | Magnoliophyta |
| Class | Angiospermae |
| Order | Fabales |
| Family | Caesalpiniaceae |
| Genus | *Caesalpinia* |
| Species | crista |

**TABLE 2: COMMON NAMES OF *Caesalpinia crista***

| Language | Common name |
|---|---|
| Arabic | Bunduc Hindi |
| Bengali | Lata karancha |
| English | Fever Nut, Bonduc Nut, Nikkar Nut and Nicker seed |
| Gujarati | Kanchaki, Kankachia |
| Hindi | Kantkarej, Kantikaranja, Sagar Gota |
| Kannada | Gajjiga, Kiri Gejjuga, Gajikekayi |
| Konkani | Vakeri |
| Malayalam | Ban-karetti, Kakamoullou, Kazhanji, Kalanci, Kajanchikkur |
| Marathi | Sagargoti, Gajra, Kanchak |
| Persian | Khayahe-i-iblas |
| Sanskrit | Latakaranja, Kakachika, Kantakikaranja, Kantakini, Karanja, Krakachika, Kuberaksah, Kuberakshi, Kuberaksi, Prakiriya, Prakirnah, Putikah, Putikaranja, Putikaranjah, Putikaranji, Tinagachhika, Tirini, Valli, Varini, Vitapakaranja |
| Tamil | Kalarci ver, Kalarcik Koluntu, Kalarcip paruppu, Kazharchikkaai, Kalachikai, Kalichikai, Kazarci |
| Telugu | Mulluthige,Gaccakayai |
| Unani | Karanjwaa |
| Urdu | Akitmakit |

secretions. The oil prepared from the leaves, is a valuable nervine tonic[5,23].

Also in India, various parts of *C. crista* have been used therapeutically, for example, as an adaptogenic, antimicrobial, antiproliferative, antidiabetic, anti-filarial, enhanced uterine contractility, hepatoprotective, antitumor and antioxidant[9,23]. In Iraq, the seeds were used as antipyretic and febrifuge and the leaves were used in treating the disorders of the liver[24]. In Perak, Malaysia, an indigenous tribe consumes the seeds of *C. crista* as condiment after crushing and mixing with fermented shrimp paste[25].

## PHYTOCHEMICAL PROPERTIES

The preliminary phytochemical screening of the ethanolic and aqueous extracts of *C. crista* showed the presence of flavonoids, tannins, proteins, alkaloids, carbohydrates reducing sugars, phytosterols, saponins, coumarins and triterpenoids[26,27]. The literature has revealed that seeds and leaves of *C. crista* contain around fourteen compounds of which diterpenoids of the cassane and norcassane types are the major chemical constituents isolated[16].

From the seeds, cassane diterpenoids such as caesalpinins and caesalmins[14,28,29] and norcassane diterpenoids such as norcaesalpinins A-F[6,13,14] have been identified. Caesalpinins also included cassane-furano-diterpenoids (caesalpinin C-P)[6,21,29]. Five new cassane diterpenes were isolated from seeds of *C. crista*[14]. They were caesalpinins MA-MD with caesalpinin ME having a cleaved furan ring and with a bridge from C-7 to C-17. Neo-cassane diterpenes (neocaesalpins H and I), characterized by α and β-butenolide hemiacetal ring that is rare in nature, while they lack 5-hydorxy group which distinguishes them from cassane diterpenes (caesalpins) were also identified. Nine new cassane-type diterpenes (taepeenin A-I) were also isolated from the plant[6,11,30,31].

It has also been mentioned that the seeds of the plant contained bonducin, proteins, saponin, starch, sucrose, enzymes, two phytosterols namely sitosterol and hepatsane, fatty acids such as palmitic acid, stearic acid, lognoceric, oleic, linolenic acid, as well as furanoditerpenes[11,32].

The cold macerated methanolic seed extract showed the presence of triterpenoids such as lupeol acetate, ß-amyrin and α-amyrin[11,19].

From the methanolic extract of seed kernels of *C. crista* from Myanmar, five new cassane-type diterpenes, caesalpinins MA-ME, and three new norcassane-type diterpenes, norcaesalpinin MA-MC have been isolated, together with 12 known cassane-type diterpenes, 14(17)-dehydrocaesalmin F, caesaldekarin E, caesalmin B, caesalmin C, caesalmin E, 2-acetoxy-3-deacetoxycaesaldekarine, 2-acetoxycaesaldekarine, caesalpinin C, 7-acetoxybonducellpin C, caesalpinin E, norcaesalpinin B, and 6-acetoxy-3-deacetoxycaesaldekarine[5,33].

The seed kernels of *C. crista* contained protein which varies from 7.4 % to 25.3 %. They contained the following amino acids *viz*., aspartic acid 9.5 %, lysine 7.9 %, glycine 6.9 %, leucine 6.3 histidine 5.1%, isoleucine 5.1%, serine 3.8%, r-aminobutyric acid 3.7 %, tyrosine 3.7 %, citrulline 3.6 %, glutamic acid 3.6 %, threonine 3.6 %, arginine 3.4 %, proline 3.3 %, L-alanine 2.5 %, methionine 2.1 %, phenyl alanine 1.4 %, cysteine 1.2 %, valine 1.2 % and tryptophan 0.8 %.The non-protein amino acids detected in the seed were r-ethylidene glutamic acid, r-methylene glutamic acid, r-ethyl glutamic acid and traces of r-OH-r-methyl glutamic acid and β-OH r-methylglutamic acid, accumulation of r-methyl glutamic acid being extremely large[6,11,34]. It also contains diterpine δ-caesalpin[35,36]. The seeds also contained 49 % carbohydrates including pentoan (16.8 %), starch (6.1 %) 54 and water soluble mucilage (4.4 %). 4-o-methyl myoinositol hydrate was isolated from *C. crista* grown in China[6,34,37].

The leaves of *C. crista* yielded neocaesalpins H and I or cassane diterpene acids[38] and cheilanthane-type tricarboxylic sesterterpenoids identified as cristasesterterpenoic acid and cristasesterterpinol glucoside[20]. The HPLC fingerprinting of leaf extracts show the presence of gallic acid, protocatechuic acid, catechin, chlorogenic acid, epicatechin, caffeic acid, vanillin, p-coumaric acid, sinapic acid, rutin hydrate, myricitin, cinnamic acid, quercetin, and kaempferol[39].

The leaves also contain pinitol (4.1 %), glucose and minerals like calcium (2 %) and phosphorous (0.3 %). Bonducin, waxy material and an amorphous bitter principle ($C_{20}H_{32}O_8$, mp 119.12 C, yield 0.35 %) have been isolated from the leaves. The waxy material yields mysteric acid and an alcohol[40,41]. Phenolic acids such as caffeic acid, chlorogenic acid, p-coumaric acid, ferulic acid and gallic acid have been identified from leaves of C. crista[42]. Amongst

them, gallic acid and ferulic acid were dominant.

Flavonoids such as derivatives of flavones and flavanones have been isolated from aerial parts[3] and flowers[43] of C. crista. Stem and root contained peltogynoids, pulcherrimin, 6-methoxypulcherrimin, homoisoflavonoid, 8-methoxybonducellin, and the known compounds bonducellin, 2,6-dimethoxybenzoquinone, 2',4',4-trihydroxychalcone and 2',4-dihydroxy-4'- methoxychalcone[26,33,44-46]. Root also contains cassane furano-diterpene, caesalpinin, caesaldekarins F and G, caesaldekarin A, Bonducellpins A, B, C and D, steroidal saponin like Diosgenin[12,47].

Bark contains 6-o-methylcaesalpinianone, caesalpinianone, hematoxylol, 6-o-acetylloganic acid, 4-o-acetylloganic acid and 2-o-glucosyloxy-4-methoxybenzenepropanoic acid[48]. Phytochemical study on the methanolic extract of *C. crista* also showed the presence of two novel compounds, 2-hydroxytrideca-3,6-dienyl-pentanoate and octacosa-12,15-diene along with known compounds 3-O-methylellagic acid 3′O-α-rhamnopyranoside, β-sitosterol and sucrose[49]. The chromatographic analysis of the seed oil of *C. crista* showed the presence of methyl esters with dodec-9-enoate (16.8 %), palmitate (13.3 %), oleate (12.3 %), linoleate (11.5 %), 7-palmitoleate (10.3 %) and caproliate (10.1 %) as major components[16,50]. The structures of some of the phytoconstituents present in *C. crista* are shown in fig. 1.

## PHARMACOLOGY

The extracts of *C. crista* have profound medicinal use and reported to have antimalarial, anthelmintic, adaptogenic, anti-inflammatory, antipyretic and analgesic, anti-amyloidogenic, nootropic/memory enhancer, hepatoprotective, antioxidant, anticonvulsant, anxiolytic, antidiabetic, cardioprotective, antiulcer, antibacterial and

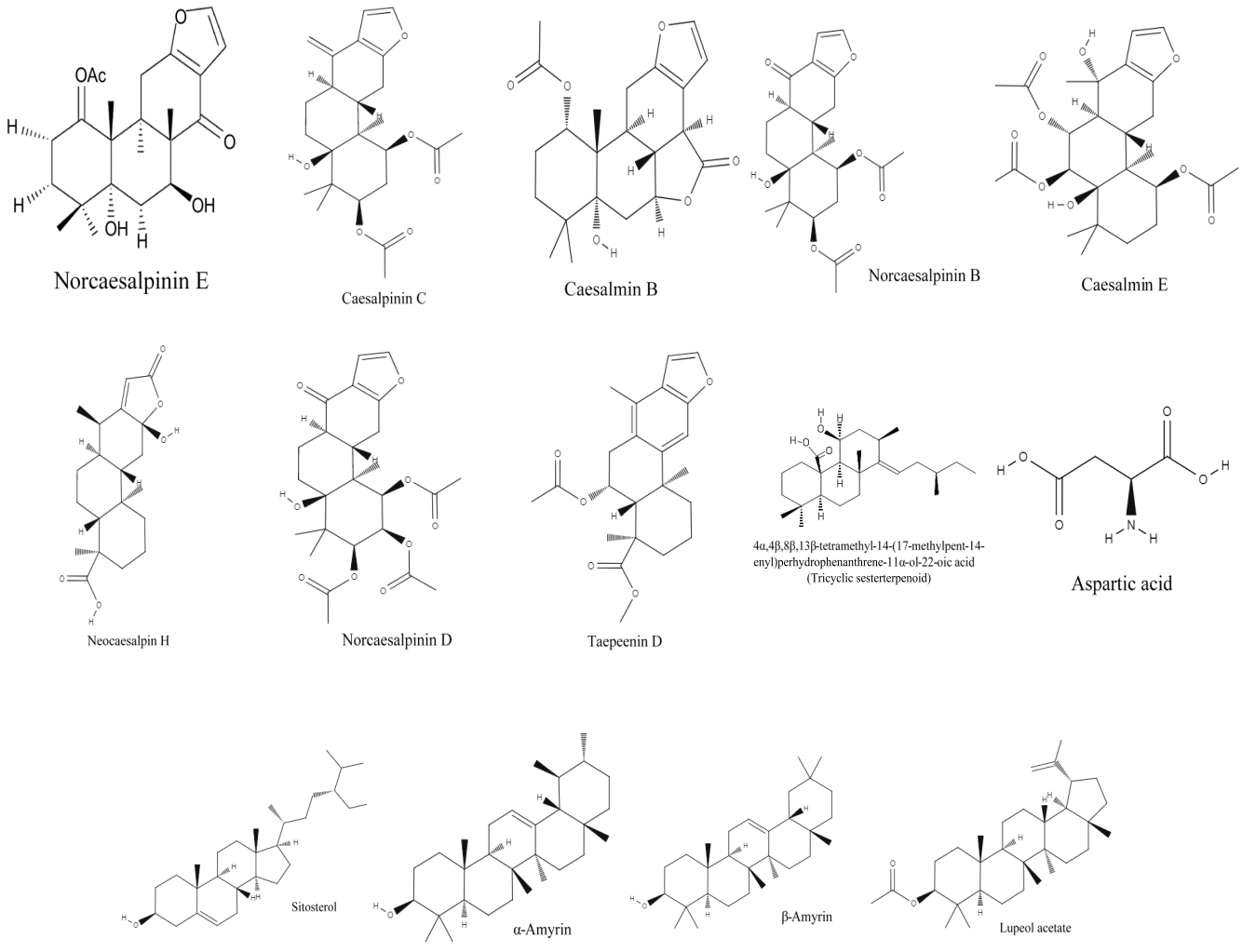


**Fig. 2: Structures of some of the phytoconstituents present in *Caesalpinia crista***

antiviral, anti-inflammatory antitumour, wound healing, insecticidal and toxicity effects.

**Antimalarial activity:**

Dichloromethane extract of *C. crista* seeds from Indonesia was studied and it showed significant *in vivo* antimalarial activity against the growth of *Plasmodium bergi* in mice[13]. 44-cassane- and norcassane-type diterpenes from *C. crista* were isolated and evaluated for their antimalarial activity against the malarial parasite *Plasmodium falciparum* (FCR-3/A2 clone) *in vitro*. Most of the tested diterpenes showed antimalarial activity, and norcaesalpinin E showed the most potent activity with half minimal inhibitory concerntration ($IC_{50}$) value of 0.090 µM, more potent than the clinically used standard chloroquine ($IC_{50}$, 0.29 µM). He concluded that the presence of an acetoxyl group at C-1 and a hydroxyl group at C-7, including the type of substituents on ring C, are important for the antimalarial activity[51].

14 compounds were isolated from stems and roots of *C. crista* and tested for anti-malarial activity but only ent-11β-hydroxy-rosa-5,15-diene exhibited significant activity with Effective Dose $ED_{50}$ value of 4.1 µg/ml[30].

In a study, caesalpinins C-G and norcaesalpinins A-E showed significant inhibitory effects on *Plasmodium falciparum*[34].

**Anthelmintic activity:**

Antiascarid activity of *C. crista* seeds was evaluated in chickens of the Fumi breed, suffering from artificially induced *Ascaridia galli* infection. Eggs Per Gram (EPG) counts were determined in the droppings of chickens prior and after treatment with powdered *C. crista* at doses of 30, 40 and 50 mg/kg of body weight along with its extracts in water and methanol in amounts representing 50 mg/kg of crude powder. The crude drug at the dose rates of 40 and 50 mg/kg and its methanol extract induced a significant ($p<0.001$) effect on 10$^{th}$ and 15$^{th}$ d post-treatment while the 30 mg/kg dose was efficacious ($p<0.05$) on day 15$^{th}$ d only. However, the aqueous extract did not show significant results. These results suggested that a 50 mg/kg dose of *C. crista* seed powder, its equivalent methanolic extract and piperazine (200 mg/kg) are equi-effective in treating the ascarid infection of poultry. The crude *C. crista* powder appears to be potent and safer than its methanol extract on the basis of the observed side effects[52].

*In vitro* anthelmintic activity of crude Aqueous Methanolic Extract (AME) of *C. crista* (L.) was studied using mature *Haemonchus contortus* and their eggs in adult motility assay and egg hatch test, respectively. *In vivo* anthelmintic activity was evaluated in sheep naturally infected with mixed species of gastrointestinal nematodes by administering Crude Powder (CP) and AME in increasing doses (1.0-3.0 g/kg). *C. crista* exhibited dose- and time-dependent anthelmintic effects by causing mortality of worms and inhibition of egg hatching ($LC_{50}$ value of 0.13 mg/ml). *In vivo*, the maximum reduction in nematode eggs per gram of sheep faeces was recorded as 93.9 % at 3.0 g/kg on 13$^{th}$ d. Thus *C. crista* (L.) showed anthelmintic activity both *in vitro* and *in vivo* against trichostrongylid nematodes of sheep, supporting its traditional use in Pakistan[53].

Seed powder of *C. crista* was serially extracted with different solvents and tested for *in vitro* anthelmintic activity against earthworms. Results indicated that the anthelmintic activity of petroleum ether extract was good with lethal time of 15 and 22 min at 4 % and 2 % concentration, respectively[50].

A study reported a similar study about the anthelmintic activity of different seed extracts (petroleum ether, ethyl acetate, ethanol and aqueous) of *C. crista* using earthworms *Pheretima posthuma* and roundworms *Ascardia galli*. The results showed that all the extracts displayed anthelmintic activity based on the time of paralysis and death[54].

Antiplasmodial activity of the seed extracts of *C. crista* was investigated against rodent malaria infections in chloroquine sensitive *Plasmodium falcipuram* strain. The study revealed significant and dose dependent decrease in parasitaemia in the parasitized groups treated with varying doses of the extract (50-200 mg/kg p.o.) in both suppressive and curative tests. There was also significant decrease in parasitaemia density in the chloroquine treated group. Thus the authors concluded that seed extracts of *C. crista* extract possesses potent antiplasmodial activity and may therefore, serve as potential sources of new antimalarial agents[55].

**Adaptogenic activity:**

*C. crista* seed extracts were screened for adaptogenic activity using cold stress and swim endurance models. An oral dose of 300 mg/kg of the seed coat

as well as kernel extracts significantly increased the swim endurance time. The extracts also corrected hyperglycaemia, the depletion in serum cortisol level, increased total leukocyte count, and controlling the hyperlipidaemia condition associated with cold stress[56].

**Effects on muscle contraction:**

Effects of *C. crista* extract on gallamine-induced relaxation in rat tibial muscle contractility *via* measurement of isometric-tension-anesthetized, 10-12 w old, male rats as studied. When administered intravenously, the extract increased twitch contractions in a dose-dependent manner. The authors concluded that *C. crista* extract stimulates the muscle contractile activity *via* activation of the cholinergic mechanism[57].

Calcium dependency and the cholinergic effect of the leaf extract of *C. crista* were studied in isolated pregnant rat myometrium preparations. Their findings referred to the existence of cholinergic receptors sensitive to the leaf extract of *C. crista* which could influence the influx of calcium (phasic contraction) and mobilization of calcium from cellular stores (tonic contraction), both of which are responsible for the increase of contractile activity and development of the contracture of uterine smooth muscle[58].

*C. crista* extract also caused concentration-dependent inhibition of spontaneous and high $K^+$ (80 mM)-induced contractions of isolated rabbit jejunum preparations, similar to that caused by verapamil[59].

**Analgesic/antipyretic/anti-Inflammatory activity:**

Various scientists reported the anti-inflammatory effects and the analgesic activity of the ethanolic seed extract of *C. crista*. Using carrageenan induced paw oedema method the extract showed maximum inhibition of 74.2 % at 300 mg/kg as compared to standard diclofenac. The extract at 300 µg/ml showed potent analgesic activity of 71 % based on writhing reflexes in mice and 5.3±0.05 s tail withdrawal latency using the tail immersion method.

The anti-inflammatory activity was studied in rats using the formalin arthritis and granuloma pouch methods. The extract at 250 mg/kg was found to be effective in the granuloma pouch model and at an oral dose of 1000 mg/kg, the seeds showed a 50 % inhibitory activity against carrageenan induced oedema in the rat hind paw, when given 24 h and 1 h prior to carrageenan injection.

The seed coat *C. crista* extracted by 95 % ethanol was also screened for anti-inflammatory and analgesic activity using carrageenan-induced paw oedema, egg albumin-induced paw oedema, Eddy's hot plate test and tail immersion method and it showed the ability to decrease the induced inflammation at varied doses in carrageenan and egg albumin model in rats. Thus the anti-nociceptive results indicated that the extract has the ability to increase the pain threshold of the animals, reduce the pain factor and induce analgesia[60-66].

Antipyretic or fever reduction effects of ethanol and aqueous extracts of *C. crista* seeds on experimental animals were investigated. The extracts were tested on Brewer's yeast induced pyrexia in rats, on typhoid and paratyphoid A and B vaccine-induced pyrexia in rabbits and on boiled milk-induced pyrexia in rabbits. There was decline in the rectal temperature of the animals following administration of the extracts, in all three models. The antipyretic activity of ethanolic extract was comparable to that of paracetamol, the standard drug[27].

**Anti-amyloidogenic activity:**

The major etiological factor implicated in Alzheimer's disease is the production and deposition of Amyloid Beta (Aβ) peptides[67,68]. The ability of *C. crista* leaf aqueous extract on the prevention of the formation of oligomers and aggregates from monomers; the formation of fibrils from oligomers and disaggregation of preformed fibrils using thioflavin-T assay and Transmission Electron Microscope (TEM) was studied. The results showed that *C. crista* leaf aqueous extract was able to inhibit the Aβ aggregation and was also able to disaggregate the preformed fibrils[15,68].

The leaf extract fractions were screened to study the action of *C. crista* from non-polar to polar solvents towards inhibition of oxidative stress, cholinergic and amyloidosis. The result showed that among all extracts, *C. crista* methanolic extract was found to inhibit the oligomers, fibrillation of $\alpha\beta_{42}$ with good defibrillation of amyloid cascading properties and thus is a promising option in treating Alzheimer's disease[39].

**Nootropic/Memory Enhancer:**

Dried seed kernels of *C. crista* aqueous extract was evaluated as learning and memory enhancer in mice against scopolamine induced amnesia using the radial

arm maze task performance. Results suggested that *C. crista* can be beneficial in improving cognition in disorders like dementia and other neurodegenerative disorders[69].

**Hepatoprotective activity:**

Ameliorating effect of *C. crista* Linn. (CCME) extract was evaluated on iron-overload induced liver injury, induced by intraperitoneal administration of iron dextran into mice. CCME attenuated the percentage increase in liver iron and serum ferritin levels when compared to control group and also showed a dose dependent inhibition of lipid peroxidation, protein oxidation and liver fibrosis. Thus the study confirmed the hepatoprotective effect of CCME against the model hepatotoxicant iron overload and the activity was likely related to its potent antioxidant and iron-chelating property[70].

The hepatoprotective properties of *C. crista* were reaffirmed in a study and the results showed that the ethanol extract of *C. crista* seeds at 100 and 200 mg/kg was able to normalise the biochemical levels in the serum and histopathological changes in the liver of albino rats, altered by carbon tetrachloride ($CCl_4$) and paracetamol intoxication[71].

**Antioxidant activity:**

Antioxidant properties of leaf and seed extracts of *C. crista* was studied where 70 % methanol leaf extract was assayed using different assays for phenolic contents and antioxidant activities. Total phenolic content was 50 mg GAE/ml while total flavonoid content was 107 QE/ml. Total antioxidant activity based on Trolox Equivalent Antioxidant Capacity (TEAC) was 0.6. $IC_{50}$ values of scavenging were 0.4, 25, 34, 61 and 170 µg/ml for ROS of hydroxyl, superoxide, nitric oxide, singlet oxygen and hypochlorous acid, respectively. For *in vivo* experiments, oral administration of the leaf extract to normal mice for a week significantly enhanced the activity of antioxidant enzymes[72].

Antioxidant effects of ethanolic seed extract of *C. crista* was studied using 1,1-diphenyl-2-picrylhydrazyl (DPPH) and hydrogen peroxide ($H_2O_2$) methods. The seed extract at 300 µg/ml, exhibited DPPH and $H_2O_2$ radical scavenging activities of 73.9 % and 77.7 %, as compared to 87 % and 80 % of ascorbic acid used as control, respectively[60].

The potential antioxidant activity of chloroformic and methanolic leaf extracts of *C. crista* was elucidated in different established *in vitro* experimental methods. The chloroformic and methanolic extract of *C. crista* leaf showed $IC_{50}$ value of 201.92 and 103.7 µg/ml, respectively in DPPH assay. Reducing power increased in a concentration-dependent manner while significant total antioxidant capacity of 70.4 µM Fe(II)/g and 35.4 µM Fe(II)/g was observed in methanolic and chloroformic extract, respectively using ferric reducing ability of plasma assay[73].

Antioxidants present in *C. crista* were evaluated against free radical induced DNA and erythrocyte damage. Result showed that *C. crista* extracts are rich in polyphenols that act through several mechanisms to quench free radicals in many different systems. They exhibited protective role against oxidative stress-induced DNA and erythrocyte membrane damage. *C. crista* could be used as a source of therapeutic or nutraceutical product to be incorporated in herbal medicine[74].

**Anticonvulsant activity:**

Anticonvulsive effect of seed extract of *C. crista* was investigated by pentylenetetrazole (PTZ), maximal electro shock strychnine- and picrotoxin-induced convulsions models. Petroleum ether, ethanol, methanol and water were used for successive extraction of powdered seed kernels. Diazepam was used as a standard reference for all models except maximal electro shock model, wherein phenytoin was used as standard reference. In all the experiments, the extracts were administered as suspension in 2 % gum acacia. In PTZ, maximal electro shock, strychnine- and picrotoxin-induced convulsion models, the medium and high doses (600 and 800mg/kg) of the extract showed significant anticonvulsant activity as compared against standard[75].

**Anxiolytic activity:**

The anxiolytic activities of seed extract of *C. crista* was studied in experimental animals, mice and rats by stair-case model. Three doses (400, 600 and 800 mg/kg) showed a significant and dose dependent anxiolytic activity by increasing the number of steps climbed, without any significant effect on rearings by all the three doses. Similarly in elevated plus maze, hole-board, mirror-chamber and open-field test models medium and high doses 600 mg/kg and 800 mg/kg, but not the low dose 400 mg/kg had more significant effect. However in laboratory developed test model, high doses 800 mg/kg had significantly

exhibited anxiolytic activity by increasing time spent, number of crossings in light compartment and decreased the time spent in dark compartment and decreased the number of rearings in both light and dark compartments. These result confirmed the anxiolytic activity of *C. crista* [76].

**Antidiabetic activity:**

Antidiabetic activity of ethanol and aqueous extracts of *C. crista* seed was studied in streptozotocin-induced diabetes in 2 d old pup's model. Both extracts of *C. crista* showed antidiabetic activity but the aqueous extract showed more significant effect as compared to the ethanol extract. Both the seed extracts caused significant decrease in serum glucose, cholesterol and triglyceride levels when compared with diabetic untreated group after 3 w treatments. Treatment with the both seed extracts also affected the physical parameters-decreased body weight, increase demand of food and water intake; when compared with diabetic untreated group[77].

**Cardioprotective activity:**

Alcoholic and aqueous seed extracts of *C. crista* were evaluated for their protective effects against isoproterenol-induced myocardial infarction in albino rats. The induced heart damage resulted in elevated levels of marker enzymes like Creatine Kinase-isoenzyme (CK-MB), Lactate Dehydrogenase (LDH), Serum Glutamate Oxaloacetic Transaminase (SGOT) and Serum Glutamate Pyruvate Transaminase (SGPT) in the serum with increased lipid peroxide and reduced glutathione content in the heart homogenates. Pre-treatment with both the extracts at a dose of 400 mg/kg, orally for 30 d, reduced significantly the elevated marker enzyme levels in the serum and heart homogenate. Histopathological examination also showed marked protection by the extract against myocardial necrotic damage[78].

**Antiulcer activity:**

Anti-ulcer activity of ethanolic and aqueous extracts of seeds of *C. crista* Linn. were evaluated on pylorus ligation and indomethacine- induced gastric lesions in albino rats. Ranitidine (20 mg/kg i.p) was used as a standard drug in both the models. Percentage yield of ethanolic and aqueous extracts was found to be 8.7 and 13.3 which reflected reduced ulcer incidence in both ethanolic and aqueous extracts. There was decrease in ulcer score and ulcer index in both the groups but the maximum effect was shown by the ethanolic extract. Also there was decrease in gastric volume and reduction in free and total acidity, pH in the animals treated with extracts[79].

**Antibacterial and antiviral activity:**

The methanol extract and isolated four triterpenoids (lupeol, lupeol acetate, ß-amyrin and α-amyrin) from the seeds of *C. crista* were evaluated that showed a wide range of inhibiting activity against both Gram-positive and Gram-negative bacteria[27].

The phytochemistry of the methanol leaf extract of *C. crista* was studied that afforded 2-hydroxytrideca-3,6-dienylpentanoate, octacosa-12,15-diene, along with 3-O-methylellagic acid, 3'-O-α- rhamnopyranoside and β-sitosterol. All the isolated compounds, extract and fractions were evaluated for *in vitro* antibacterial activity against various Gram-positive and Gram-negative bacteria. They were found to be significantly active against *Staphylococcus aureus* (*S. aureus*) and methicillin-resistant *S. aureus* with MIC ranging from 64-512 µg/ml[49].

A study was carried out to elucidate the potential antibacterial activity of chloroformic and methanolic leaf extracts of *C. crista* in different established *in vitro* experimental methods. Methanolic leaf extract produced zone of inhibition ranged between 7.6 and 11.5 and 11 to 14.8 mm, at the doses of 250 and 500 µg/disc, respectively against seven bacterial strains. Methanol extract at 500 µg/disc showed the highest antibacterial activity against *S. aureus* and *Escherichia coli*. However, the chloroformic leaf extract failed to demonstrate any significant zone of inhibition against all the tested bacterial strains. Result showed that the methanolic leaf extract exhibited significant antibacterial activity against all Gram positive bacterial strains and two Gram negative bacterial strains[73].

The effect of *C. crista* crude extracts, the drug mentioned in Ayurvedic literature for krimighna activity was studied where using various solvents like aqueous, methanol, ethanol and chloroform, crude extracts were prepared. Antiviral activity was tested against paramyxovirus and orthomyxovirus isolates recovered from disease outbreaks in poultry birds. Against paramyxovirus and orthomyxovirus, complete or significant inhibition was exhibited by aqueous, ethanol and methanol extracts of C. crista[80].

The hydroalcoholic extracts of *C. crista* seed kernel and seed coat were injected subcutaneously

in *Pseudomonas aeruginosa* infected animals. The control groups were treated with cortisone and saline. Two weeks after challenge with *Pseudomonas aeruginosa*, the *C. crista* treated animals showed a significant bacterial clearance from the lungs ($p<0.04$), with less severe incidence of lung abscess ($p<0.05$)[81]. Ethanolic extract of the root and stem of *C. crista* was reported exhibited activity against the vaccinia virus[82].

**Anti-inflammatory activity:**

Ramesh *et al.*[42], reported that the aqueous extract of *C. crista* leaves inhibit 5-lipoxygenase with an $IC_{50}$ value of 23 µg/ml compared to nordihydroguaiaretic acid used as the control which had an $IC_{50}$ value of 8.6 µg/ml. 5-Lipoxygense is a key enzyme in the biosynthesis of leukotriens, which are implicated in inflammatory and allergic reactions. Results demonstrated that *C. crista* extract had better potential to inhibit 5-lipoxygenase activity and these effects may be attributed to the polyphenols present in the extracts[42].

**Antitumour activity:**

Cassane-type diterpenoids isolated from *C. crista* were reported to possess cytotoxic activity towards human cancer cell lines. Two cassane diterpenoids (6β-cinnamoyloxy-7β-acetoxyvouacapen-5α-ol and 6β,7β-dibenzoyloxyvouacapen-5α-ol) isolated from the aerial parts of *C. crista* were reported to display moderate cytotoxic activity towards human cancer cell lines. Against HL-60 and HeLa cancer cells, their $IC_{50}$ values were 17.4 and 33.4 µM, and 19.8 and 33.9 µM, respectively[3].

Ethanolic root bark extract of *C. crista* was found to have significant anti-tumour activities in the Ehrlich ascites carcinoma-bearing mice. At 150 mg/kg dose, the extract increased the life span of the mice by decreasing the nutritional fluid volume and arresting the tumour growth[83].

A new cassane-type diterpene (1α-acetoxy-5α, 7β-dihydroxycassa-11,13(15)-diene-16,12-lactone) isolated from *C. crista* was evaluated for antitumor activity against T47D and DU145 cell lines, it showed significant inhibitory activities[84]. Taepeenin D isolated from the roots and stems of *C. crista* was found to possess significant cytotoxicity against PANC1 and DU145 cancer cells[18,30].

**Wound healing activity:**

The wound healing activity of different extracts of seed kernels of *C. crista* was investigated using excision, incision and dead space wound models in albino rats. Result showed that ethyl acetate fraction showed better wound healing activity in all models as compared to alcoholic extract and ether fraction. Closure of excision was 21 % at 4$^{th}$ d and 100 % at 20$^{th}$ d. Values of the control group were 12 % and 77 % for the same duration. Tensile strength of the healing incision and dead space wounds was 285 g and 305 g, compared to the control group of 144 g and 157 g, respectively. Petroleum ether extract, butanol fraction and butanone fraction has shown the least effective wound healing activity[85].

**Insecticidal activity:**

The insecticidal effects of *C. crista* seed extracts were reported against *Helicoverpa armigera* (Lepidoptera) and its predator, *Coccinella septumpunctata* (Coleoptera). The extracts exhibited strong anti-feedant and growth disruption activity of *H. armigera*. Toxic symptoms were mortality and weight reduction of larvae and pupae, and malformation of adults. Against *C. septumpunctata*, there was no mortality of adults up to nine days after treatment[86].

**Toxicity effects:**

Acute and sub-acute toxicity of ethanolic extract of *C. crista* (Linn.) was evaluated in albino mice. The limit dose for acute toxicity studies was 2000 mg/kg. Observations were recorded after treatment at 2 h, 4 h, 8 h and then for seven days regularly for respiration rate, heart rate, and behavioural signs (like apathy, reduced locomotor activity as well as licking). No acute toxicological effects were recorded.

In sub-acute toxicity, animals received 200 or 400 mg/kg of ethanolic extracts every 24 h orally for 28 d. No toxic effects of the ethanolic extract were observed on body and organ weights between the control and the treated groups after 28 d of treatment. No significant variation was found in the haematological and blood chemistry parameters. No mortality was recorded during the study[87].

## CONCLUSIONS

*C. crista* is a traditional plant with wide range of chemical constituents which exerted many pharmacological effects. Diterpenoids of the cassane and norcassane types are the major compounds isolated and these are of interest

due to their structural diversity and their broad spectrum of pharmacological properties, which include antimalarial, anthelmintic, adaptogenic, anti-inflammatory, antipyretic and analgesic, anti-amyloidogenic, nootropic/memory enhancer, hepatoprotective, antioxidant, anticonvulsant, anxiolytic, antidiabetic, cardioprotective, antiulcer, antibacterial and antiviral, anti-inflammatory antitumour, wound healing, insecticidal activities. The different extracts of *C. crista* have shown notable potential for their use in traditional medicine. Results demand further studies to isolate and identify the bioactive compounds responsible for these pharmacological properties. There is a great promise for development of novel drugs from *C. crista* to treat many human diseases as a result of its effectiveness and safety.

**Conflict of interest:**

The authors declared no conflict of interests.

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