**Caesalpinia crista**: A coastal woody climber with promising therapeutic values

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**ABSTRACT**

*Caesalpinia crista* L. is a scrambling coastal woody climber of the family Caesalpiniaceae. Leaves of *C. crista* are bipinnate with the rachis armed with spines beneath. Flowers are yellow and fragrant, bearing 5 petals. Pods are flat and have a beaked tip. Diterpenoids of the cassane and norcassane types are the major compounds isolated from *C. crista*. Seeds of *C. crista* yielded cassane diterpenoids such as caesalpinins and caesalmins, and norcassane diterpenoids such as norcaesalpinins. From the stems, roots and seeds, cassane diterpenoids (e.g. taepeenins A–L), and norcassane diterpenoids (e.g. nortaepenins A & B) have been isolated. Flavonoids such as derivatives of flavones and flavanones have been isolated from aerial parts and flowers. Phenolic acids such as caffeic acid, chlorogenic acid, p-coumaric acid, ferulic acid and gallic acid have been identified from leaves. Pharmacological properties of *C. crista* include antioxidant, antibacterial, antiviral, anti-malarial, anticancer, anti-inflammatory, analgesic, hepatoprotective, cardioprotective, anti-amyloidogenic, nootropic, wound healing, anthelmintic, insecticidal, antipyretic and antulcer activities. In conclusion, properties of *C. crista* exhibit potential benefits to be used for pharmacological purposes.

**INTRODUCTION**

The genus *Caesalpinia* consists of ~200 species of shrubs, trees and climbers, mostly armed with spines, hooks or thorns (Khatun and Rahman, 2006; Dickson et al., 2011). Leaves are bipinnate with few to many opposite leaflets. Inflorescences are multi-flowered bearing yellow, red or variegated flowers that are bisexual, showy and medium to large. Flowers have 5 sepals, 5 petals and 10 stamens. Pods are flat and thorny. Diterpenoids of the cassane and norcassane types are the major compounds isolated from *C. crista*. Of the genus, 14 species notably *C. decapetala* and *C. sappan* have long been used in Chinese traditional medicine for the treatment of rheumatism and inflammatory diseases (Wu et al., 2011). Leaves, barks and roots of *C. pulcherrima* have been used to alleviate fungal infection and fever (Pranithanchai et al., 2009).

Plants of *Caesalpinia* species have been employed in folkloric medicine to treat ailments such as skin diseases, malaria, cancer, infections, erectile dysfunction, pain and wounds (Dickson et al., 2011). Of the genus, 14 species notably *C. decapetala* and *C. sappan* have long been used in Chinese traditional medicine for the treatment of rheumatism and inflammatory diseases (Wu et al., 2011). Leaves, barks and roots of *C. pulcherrima* have been used to alleviate fungal infection and fever (Pranithanchai et al., 2009).

The chemical constituents and biological activities of *Caesalpinia* species have been reviewed by Wu et al. (2011) and Zanin et al. (2012), respectively. *Caesalpinia* species are a rich source of cassane and norcassane diterpenoids (Wu et al., 2011). Other compounds include triterpenes, flavonoids, phenolic acids, sterols, aromatic phenols, etc. To date, a total 280 compounds have been reported in the genus. Pharmacologically, these species exhibit potential therapeutic values to be used for medicinal purposes.
immunomodulatory, immunosuppressive, antidiabetic, anti-inflammatory and anti-rheumatic activities, among others (Zanin et al., 2012).

In this overview, we updated the current knowledge of phytochemical compounds isolated or identified from *Caesalpinia crista* including reported biological properties of compounds and extracts from this species. Endowed with cassane and norcassane diterpenoids, the species is known to have beneficial pharmacological properties such as anti-malarial, cytotoxic and anti-diabetic activities. To date, there are only two reviews on the traditional uses, and on the medicinal and pharmacological properties of *C. crista* (Suryawanshi and Patel, 2011; Al-Snaï, 2015). As an update, this review is therefore timely and appropriate.

**BOTANY AND USES**

*Caesalpinia crista* L. is a scrambling woody climber of the family Caesalpiniaceae. According to The Plant List (2013), synonyms of *C. crista* are *Caesalpinia nuga*, *C. paniculata*, *Guilandina paniculata* and *G. semina*. Recent reviews on *C. crista* have included *C. bonduc* and *C. bonducible* as synonyms (Al-Snaï, 2015) and vice versa (Moon et al., 2010).

Botanical features of *C. crista* described here are derived from the following references (Khatun and Rahman, 2006; Giesen et al., 2007; Neli and Kalita 2013). Leaves of *C. crista* are bipinnate with the rachis (10–30 cm) armed with stout, sharp, hooked or recurved spines beneath. The pinnae (6–8 pairs) bear 2–3 pairs of leaflets that are opposite, ovate-elliptic to lanceolate-ovate and obtuse to shortly acute at the apex. Flowers are yellow and fragrant, bearing 5 petals. The standard petal is deep orange with red stripes. Pods are flat, rhombic-elliptic, 5–7 cm in length and have a beaked tip. Each pod contains one or two seeds that are large, rounded to ovate, hard and lustrous grey. Flowers, leaves, pods and seed of *C. crista* are shown in Figure 1.

![Fig. 1: Yellow fragrant flowers (left), leaves and pods (middle), and excised pod showing the seed (right) of *Caesalpinia crista*.](image)

In Guangdong, China, flowering and fruiting occur from February to March and from September to October, respectively (Li et al., 2004). Flowers are bisexual and protogynous, i.e. the stigma become receptive before the anthers dehisced. Anthesis was observed at 0700–0800 in the morning and flowers can last 4–5 days. Hand-pollination of flowers revealed that the species has a self-incompatible breeding system, suggesting that only cross-pollinated flowers will set fruits. Bees are the main pollinators, and peak visitation is from 1000–1500 h (Neli and Kalita, 2013). Geographically, *C. crista* is found in South, Southeast and East Asia including the Ryukyu Islands of Japan (Giesen et al., 2007).

The species has also been reported in Queensland and New Caledonia. It grows in coastal areas landward of sandy beaches and mangrove shores.

The leaves, roots and fruits of *C. crista* are used as tonic and antiperiodic (Cheenpracha et al., 2005). In India, Indonesia and Myanmar, its seeds have been used as an anthelmintic, antipyretic, anti-inflammatory and antimalarial drug (Banskota et al., 2003; Kalauni et al., 2006; Ramesh et al., 2010). In Assam, India, the leaves and seeds are traditionally used to treat malarial fever (Zaman et al., 2017). A root decoction has been used for the treatment of rheumatism and backache (Linn et al., 2005; Awale et al., 2006). In Perak, Malaysia, an indigenous tribe consumes the seeds of *C. crista* as condiment after crushing and mixing with fermented shrimp paste (Samuel et al., 2010).

**PHYTOCHEMISTRY**

Diterpenoids of the cassane and norcassane types are the major chemical constituents isolated from *C. crista*. From the seeds, cassane diterpenoids such as caesalpinins and caesalmins, (Kalauni et al., 2004; 2005a; 2005b) and norcassane diterpenoids such as norcaesalpinins (Banskota et al., 2003; Kalauni et al., 2004) have been identified. Caesalpinins also included cassane furanoditerpenoids (Linn et al., 2005; Kalauni et al., 2005b). Five new cassane diterpenes were isolated from seeds of *C. crista* (Kalauni et al., 2004). They were caesalpins MA–MD with caesalpinin ME having a cleaved furan ring and with a bridge from C-7 to C-17. Cassane diterpenoids (taepeenins A–L) and norcassane diterpenoids (nortaepenins A & B) have been isolated from the stems, roots and seeds of *C. crista* (Cheenpracha et al., 2005; 2006). ent-11β-Hydroxy-rosa-5,15-diene was the only rosane diterpenoid isolated. Leaves of *C. crista* yielded
neocaesalpins H & I or cassane diterpene acids (Kinoshita et al., 2005) and sesterterpenoids identified as cristastesterterpenoic acid and cristastesterterpinol glucoside (Zaman et al., 2017). Flavonoids such as derivatives of flavones and flavanones have been isolated from aerial parts (Das et al., 2010) and flowers (Satnami and Yadava, 2011) of C. crista. Phenolic acids such as caffeeic acid, chlorogenic acid, p-coumaric acid, ferulic acid and gallic acid have been identified from leaves of C. crista (Ramesh et al., 2014). Amongst them, gallic acid and ferulic acid were dominant. 

The basic cassane skeleton is characterized by a tricyclic diterpenoid with three cyclohexane rings A, B and C, a substitution of ethyl group at C-13 and one methyl group at C-14 (Maurya et al., 2012). Norcassane diterpenoids have one carbon less, either at C-16 or C-17 (Figure 2). Among Caesalpinia species, the cassane diterpenoids are tetracyclic with ring C fused to a furan ring D at C-12 and C-13 (Dickson et al., 2011; Maurya et al., 2012) (Figure 3). Ring C may sometimes be aromatic and has a methyl group at C-14. However, not all cassane diterpenoids have the furan ring. Cassane diterpenoids of Caesalpinia species can be classified into five basic skeleton types (Wu et al., 2011). They are: i) tricyclic fused to a furan ring; ii) tricyclic fused with an α,β-butenolide; iii) tricyclic with cleavage of the furan ring; iv) rearranged furanoditerpenoids with migration of the Me group from C-4 to C-3; and v) furanoditerpenoid lactones constructed from ring closure involving the O-atoms bridged to C-7 and C-17. 

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 (Singhal, 2007).

**PHARMACOLOGY**

Extracts of C. crista possess pharmacological properties, which include antioxidant, antibacterial, antiviral, anti-malarial, anti-tumour, anticancer, anti-diabetic, anti-inflammatory, analgesic, hepatoprotective, cardioprotective, anti-amylolodigenic, nootropic, wound healing, anthelmintic, insecticidal, antipyretic and anti-ulcer activities. Among the different plant parts, the seeds of C. crista are noteworthy.

**Antioxidant**

Antioxidant properties of leaf and seed extracts of C. crista have been studied. The 70% methanol leaf extract...
was assayed using different assays for phenolic contents and antioxidant activities (Mandal et al., 2011). 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. IC₅₀ 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 (Mandal et al., 2011). At 300 µg/ml, the ethanol seed extract of C. crista exhibited DPPH and H₂O₂ radical scavenging activities of 74% and 78%, as compared to 87% and 80% of ascorbic acid used as control, respectively (Gill et al., 2012). Leaf extracts of C. crista possessed antioxidants that are able to induce protection against DNA and membrane damage (Kumar et al., 2017).

### Antibacterial and antiviral

Phytochemical study on the methanol leaf extract of C. crista afforded 2-hydroxytrideca-3,6-dienyl-pentanoate, octacosa-12,15-diene, along with 3-O-methylellagic acid 3’-O-α-rhamnopyranoside and β-sitosterol (Kumar et al., 2014). 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 and mithicillin-resistant S. aureus with MIC ranging from 64–512 µg/ml. Against paramyxovirus and orthomyxovirus, significant or complete inhibition was exhibited by aqueous, ethanol and methanol extracts of C. crista (Patil and Sharma, 2012).

### Anti-malarial

A preliminary study on the dichloromethane extract of C. crista seeds from Indonesia showed significant in vivo anti-malarial activity against the growth of Plasmodium bergi in mice (Banskota et al., 2003). Consequently, cassane and norcassane diterpenoids isolated from the same extract of C. crista seeds from Indonesia (Linn et al., 2005) and Myanmar (Kalauni et al., 2006) exhibited significant dose-dependent inhibitory effects on the growth of Plasmodium falciparum (FCR-3/A2) in vitro. Four compounds (norcaesalpinin E, 2-acetoxy-3-deacetoxycaesaldekarin e, 14(17)-dehydrocaesalpin F and norcaesalpinin B) were found to be more potent than the well-known anti-malarial drug, chloroquine (Linn et al., 2005). Eight compounds were more potent than chloroquine, with IC₅₀ value 0.29 µM (Kalauni et al., 2006). The most potent inhibitory activity was observed in norcaesalpinin E (0.09 µM), 2-acetoxy-3-deacetoxycaesaldekarin e (0.10 µM), bonducellin (0.12 µM) and norcaesalpinin F (0.14 µM). The molecular structures of norcaesalpinin E and 2-acetoxy-3-deacetoxycaesaldekarin e are shown in Figure 4. Kalauni et al. (2006) concluded that the presence of an acetoxy 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. Of 14 compounds isolated from stems and roots of C. crista and tested for anti-malarial activity, only ent-11β-hydroxy-rosa-5,15-diene exhibited significant activity with ED₅₀ value of 4.1 µg/ml (Cheenpracha et al., 2005). Anti-malarial activity has also been reported in other Caesalpinia species such as C. volkensii (Kuria et al., 2001), C. pluviosa (Kayano et al., 2011), C. minax (Ma et al., 2014) C. bonduc (Ogunlana and Ogunlana, 2015) and C. sappan (Ma et al., 2015).

### Anti-tumour and anticancer

The ethanol root bark extract of C. crista was found to have significant anti-tumour activities in the Ehrlich ascites carcinoma-bearing mice (Bodakhe et al., 2011). 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. Cassane-type diterpenoids isolated from C. crista have been reported to possess cytotoxic activity towards human cancer cell lines. Two cassane diterpenoids (6β-cinnamoyloxy-7β-acetoxycouacapen-5α-ol and 6β,7β-dibenzyloxyxycouacapen-5α-ol) isolated from the aerial parts of C. crista were reported to display moderate cytotoxic activity towards human cancer cell lines (Das et al., 2010). Against HL-60 and HeLa cancer cells, their IC₅₀ values were 17.4 and 33.4 µM, and 19.8 and 33.9 µM, respectively. Another cassane diterpene (1α-acetoxy-5α,7β-dihydroxycass-11,13(15)-diene-16,12-lactone) isolated from C. crista, was reported to show significant inhibitory activities against human T47D and DU145 cancer cells (Tian et al., 2013). Taepenin D, isolated from the roots and stems of C. crista (Cheenpracha et al., 2005; 2006), was found to have significant cytotoxicity against PANC1 and DU145 cancer cells, and to inhibit the Hedgehog signalling pathway (Rifai et al., 2010; Nakazawa et al., 2016).
The pathway controls cell growth and proliferation, and abnormal activation of Hedgehog signalling has been implicated in the development of certain types of cancer (Abidi, 2014). Recently, two fragments of taepin D have been synthesised for study of the structure–activity relationships and subsequently for total synthesis (Nakazawa et al., 2016). Anticancer activity has also been reported in other Caesalpinia species such as C. pulcherrima (Das et al., 2010), C. sappan (Ma et al., 2015) and C. mimosoides (Palasap et al., 2013).

**Anti-diabetic**

The antidiabetic activity of ethanol and aqueous seed extracts of C. crista was evaluated in streptozotocin-induced diabetic mice (Gupta et al., 2013). Both the extracts showed antidiabetic activity. There was a significant decrease in serum glucose, cholesterol and triglyceride when compared with the diabetic untreated group after 3 weeks of treatment. Treatment with the extracts also affected physical parameters such as decrease in body weight, and increase in food and water intake.

**Anti-inflammatory and analgesic**

Seeds of C. crista have been reported to possess anti-inflammatory and analgesic properties (Gill et al., 2012). Using the carrageenan-induced paw oedema method, the ethanol seed extract showed maximum inhibition of 74% at 300 mg/kg. Diclofenac, the standard, had a value of 88% at 13 mg/kg. The extract at 300 μg/ml concentration showed potent analgesic activity of 71% based on writhing reflexes in mice and 5.3 sec tail withdrawal latency using the tail immersion method. The aqueous extract of C. crista leaves was reported to inhibit 5-lipoxygenase with an IC₅₀ value of 23 μg/ml compared to nordihydroguaiaretic acid used as the control which had an IC₅₀ value of 8.6 μg/ml (Ramesh et al., 2014). 5-Lipoxygenase is a key enzyme in the biosynthesis of leukotriens, which are implicated in inflammatory and allergic reactions.

**Hepatoprotective**

The ameliorative effect the aqueous methanol leaf extract of C. crista on iron-overload-induced liver injury has been reported (Sarkar et al., 2012). The extract attenuated the increase in liver iron and serum ferritin levels, and also showed inhibition of lipid peroxidation, protein oxidation and liver fibrosis. Enhanced levels of liver antioxidant enzymes were detected in the treated group, which also had significantly increase in the release of ferritin iron. The extract exhibited DPPH radical scavenging and protection against Fe²⁺-mediated oxidative DNA damage. A recent publication reaffirmed the hepatoprotective properties of C. crista (Gupta et al., 2014). Results of the study 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 (CCL₃) and paracetamol intoxication.

**Cardioprotective**

The alcohol and aqueous seed extracts of C. crista was evaluated for their protective effects on against isoprotenerol-induced myocardial infarction in albino rats (Kumar et al., 2013). The induced heart damage resulted in elevated levels of enzymes in the serum with increased lipid peroxide and reduced glutathione content in the heart homogenate. Pre-treatment with the extracts at a dose of 400 mg/kg, orally for 30 days, reduced significantly the elevated enzyme levels in the serum and heart homogenate. Histopathological examination also showed marked protection by the extract against myocardial necrotic damage.

**Anti-amyloidogenic and nootropic**

Alzheimer’s disease, characterized by loss of memory, cognitive dysfunction and alterations in behaviour, is widely believed to be driven by the production and deposition of amyloid beta (Aβ) peptides (Selkoe, 2001; Murphy and LeVine III, 2010). The self-assembling monitoring of Aβ in vitro provides an opportunity to screen drugs for anti-amyloidogenic properties. A study on the effects of C. crista aqueous leaf extract on the formation of oligomers and aggregates from monomers, and on the formation of fibrils from oligomers has been conducted using the thioflavin-T assay and transmission electron microscopy (Ramesh et al., 2010). Results showed that the extract was able to inhibit Aβ(42) aggregation from monomers and oligomers, and to dis-aggregate pre-formed fibrils. The aqueous seed extract of C. crista has been examined as a learning and memory enhancer (a nootropic drug) in mice with scopolamine-induced amnesia using the radial arm maze and the Morris water maze (Kshirsagar et al., 2011). Mice treated with 50 and 150 mg/kg of the extract was found to have memory retention of 33% and 45% compared to 26% of the amnesic group in the arm maze. Learning performance based on average time taken for three successful trials was 65 and 58 sec compared to 113 sec of the amnesic group. In the arm maze, memory retention was 39% and 52% compared to 15% of the amnesic group while learning performance was 33 and 23 sec compared to 38 sec of the amnesic group.

**Wound healing**

The wound healing activity of different extracts and fractions of seeds of C. crista has been studied using the excision, incision and dead space wound models in albino rats (Patil, 2005). Results showed that the group orally administered with the ethyl acetate fraction was the most effective. Closure of excision was 21% at day 4 and 100% at day 20. 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.

**Anthelmintic**

The anthelmintic activity of the aqueous methanol extract of C. crista seeds has been demonstrated in vitro against the sheep nematode Haemonchus contortus using the adult motility assay and the egg hatch test (Jabbar et al., 2007). In the adult motility assay, all the worms were found dead after 6 h of exposure to different concentrations of the extract. In the egg hatch test, the extract had a LC₅₀ value of 0.13 mg/ml. In vivo, the maximum reduction in nematode eggs per gram of sheep faeces was recorded as 94% at 3.0 g/kg on day 13. The seed powder of C. crista was serially extracted with different solvents and tested for in vitro anthelmintic activity against earthworms (Singhal, 2007). 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. Ranking of anthelminthic activity was of the order: petroleum ether extract > benzene extract > alcohol extract. Recently, a similar study reported anthelminthic activity of different seed extracts (petroleum ether, ethyl acetate, ethanol and aqueous) of *C. crista* using earthworms *Pheretima posthuma* and roundworms *Ascardia galli* (Bhardwaj et al., 2016). Results showed that all the extracts displayed anthelminthic activity based on the time of paralysis and death. Notably were values of the ethanol and aqueous extracts at 15% w/v, which were comparable to piperazine citrate used as the control.

**Insecticidal**

The insecticidal effects of *C. crista* seed extracts against *Helicoverpa armigera* (Lepidoptera) and its predator, *Coccinella septumpunctata* (Coleoptera) have been reported (Nathala and Dhingra, 2006). 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.

**Antipyretic**

Ethanol and aqueous extracts of *C. crista* seeds have antipyretic or fever reduction effects on experimental animals (Ishan et al., 2013). The extracts were tested on Brewer’s yeast-induced pyrexia in rats, on typhoid and paratyphoid A & B vaccine-induced pyrexia in rabbits and on boiled milk-induced pyrexia in rabbits. In all three models, there was decline in the rectal temperature of the animals following administration of the extracts. The ethanol extract showed antipyretic activity comparable to that of paracetamol, the standard drug.

**Antiulcer**

The extracts of *C. crista* seeds exhibited significant anti-ulcer activity in rats using the pylorus ligation and indomethacin-induced ulcer models (Chauhan et al., 2015). Oral administration of the ethanol extract at 200 mg/kg dose had maximum effects with ulcer score and ulcer index of 0.52 and 3.44 compared to the control of 4.16 and 11.1, respectively. Its ulcer protection index of 69% was comparable to 85% of Ranitidine used as the reference standard drug. In addition, there was decrease in the volume of gastric juice, free acidity and total acidity in the animals treated with the extracts.

**CONCLUSION**

Diterpenoids of the cassane and norcassane types are the major compounds isolated from *C. crista*. These diterpenoids are of interest due to their structural diversity and their broad spectrum of pharmacological properties, which include antioxidant, antibacterial, antiviral, anti-malarial, anti-tumour, anticancer, anti-diabetic, anti-inflammatory, analgesic, hepatoprotective, cardioprotective, anti-amyloidoigenc, nootropic, wound healing, anthelmintic, insecticidal, antipyretic and antiulcer activities. Further studies are needed to identify the bioactive compounds responsible and their roles for each of the pharmacological properties.

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