Biological Activity of *Cerbera manghas* L. (Apocynaceae)

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SUMMARY

Background: *Cerbera manghas* L. (*C. manghas*), is a crucial medicinal plant in various regions from Comoros and Seychelles to French Polynesia. The plant is mainly used as a biodiesel source, but despite its toxicity, it can be used as herbal medicine in small amounts. **Methods and Materials:** In July 2024, information on biological usages and pharmacological applications of *C. manghas* was obtained from Google Scholar and The Utah Valley University Library. **Results:** Different properties were identified in various studies about *C. manghas*. It is widespread in coastal habitats; utilization was compiled from nineteen studies globally. The plant has multiple uses ranging from decorative to medicinal. **Conclusion:** *C. manghas* serves diverse purposes across different populations. This paper touches on its usage as a method of self-poisoning and has biodiesel, anticancer, antioxidant, analgesic, antifungal, and antiviral properties. However, further research is necessary before it can be safely incorporated into treatment protocols.

Keywords: Medicinal Plant, *C. manghas*

INTRODUCTION

C. manghas also known as the sea mango, pink-eyed cerbera, Bintaro, blind rhino, wood octopus (English), *kanyeri white* (Bali), *bilutasi* (NTT), *wabo* (Ambon), *goro - goro guwae* (Ternate), *madangkapo* (Minangkabau), *bintan* (Malay), *lambuto* (Makassar), *rewa/ vasa* (Fiji), *leva* (Samoa), *diyakaduruin* (Sinhala), *kattuarali* (Indian Tamil), *natchuchukkaiin* (Sri Lankan Tamil)) *C. manghas* is a potent evergreen tree that thrives in Polynesia, northern Australia, and Southeast and Southern Asia [1]. *C. Manghas* is primarily utilized for landscaping and ornamental purposes because of its ability to manifest as either a tree or a shrub, boasting a height range from one to twenty meters. The leaves of *C. manghas* are arranged in spirals, forming dense clusters towards the terminal branches,

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exhibiting a distinctive, pigmented green color. Despite its toxicity and lack of scientific validation, *C. manghas* leaf juice extraction has traditionally been employed as a remedy for rheumatic diseases [1]. The stem, characterized by softwood and prominent lenticels, further contributes to the unique attributes of this species. The bright red fruits of *C. manghas*, each containing a single seed, serve as additional features to garner visual interest. Beyond its aesthetic appeal, this plant finds application in traditional medicine. It has been employed for alleviating eye pain, as an antidote for fish poisoning, and even as an anti-viral. Notably, *C. manghas* is purported to possess therapeutic properties, including its potential use in cancer treatment and as an abortifacient, as the World Health Organization documented in 1998. In addition to its traditional uses, *C. manghas* has been recognized for its diverse properties, including biodiesel production, anticancer attributes, anti-venom/poison, antioxidant capabilities, analgesic effects, antifungal properties, and antiviral potential [2]. This article aims to provide readers with an informative overview of the multifaceted properties associated with *C. manghas*.

METHODS AND MATERIALS

In July 2024, an extensive investigation was conducted utilizing various databases, notably Google Scholar and the Fulton Library at Utah Valley University. A total of seventy articles were found using the search parameters; after exclusion of non-relevant and of duplicate articles, thirty-five articles were included for a comprehensive understanding of the various applications and characteristics of *C. manghas.*

RESULTS

Description: *C. manghas* is part of the *Apocyanaceae* family, native to Melanesia and the Tuamotus. It grows best along the seashore in beach thickets. It also flourishes in dense forests or within reeds in open areas. The plant is commonly found in coastal habitats and mangrove forests. Its leaves are spirally arranged with an ovoid shape and clusters at the end of the branches. The leaves have a shiny, glossy covering and the blades are glossy green which grow to be about eight to twenty-five centimeters long. The petiole grows to be about one to five centimeters long. The flowers grow to be about twenty-five to forty millimeters long and are fragrant, white, and tubular with a pinkish throat. There are five stamens, and the ovary is placed above the other parts. *C. manghas* produces fruits that grow to be up to ten meters long. The fruit starts with a greenish color and ultimately transitions to a vibrant red when fully matured [3].

Habitat & classification: *C. manghas* is commonly found in rain forests of Melanesia, Samoa, Hawaii, Fiji, Australia, East Africa, Australia, and Indonesia [4]. It is also cultivated in Madagascar, Seychelles, Mauritius, Southeast Asia, and other parts of the South Pacific. However, the reported locations of *C. manghas* differ across various journals and articles. The most common areas where it is also found are by the seashores and tidal banks in Southeast Asia and Southern China [1]. *The taxonomic hierarchy of C. manghas is as follows: it belongs to the Kingdom Plantae, falls under the Phylum Magnoliophyta, is classified within the Class Eudicots, is ordered under Gentianales, is a part of the Family Apocynaceae, and is a member of the Genus Cerbera, with the specific species being C. mangha.* [1]. *C. manghas* is common along the shoreline and coastal areas. It is also common in beach thickets, open or dense forests, and reeds in open areas. It also flourishes in the lowland tropics such as lowland swamp forests. The plant prefers full sunlight and fertile, moist soil. *C. manghas* can grow to a hundred fifty meters in the dry deciduous forests of Madagascar. Stems are collected in the wild primarily around the flowering period but can be collected throughout the year. These stems are collected about four times a year and when collected they must be kept in moist, cool conditions. Its flowering period is between April through August and the fruiting period is from July to December [3]. The plant produces fruits that contain cardiac glycoside which is extremely toxic. These fruits are common in Tamil, Nadu, Kerala, and in the Eastern parts of Sri Lanka [1].

Chemical components: The chemical constituents from the *C. manghas* leaves were isolated by chromatography and elucidated by physiochemical constants. Nine compounds were found including p-hydroxybenzaldehyde, benzamide, n-hexadecane acid monoglyceride, loliolide, β-sitosterol, cerberin, neriifolin, cerleaside, and daucosterol [5]. Two new compounds along with others were isolated from the bark including 1,3-bis(*m-carboxylphenyl*)-propan-2-one and 2-(*m-carboxylphenyl*)-3-(*m-carboxylbenzyl*) succinic acid [6]. The other compounds found included tanghinin and deacetyltanghinin [7]. The seeds contain glycosides such as those listed above. The plant's latex is comprised of cardenolides, in addition to cerebroside, a compound recognized for its cardiotoxic properties. Interestingly, the potent compound Cerberin, despite being derived from the plant's toxic seeds, can be harnessed in small quantities for medicinal purposes [8]. The Apocynaceae family is notorious for being poisonous and this plant is no different especially seen in how the seeds are used for self-poisoning

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[1]. *C. manghas* also contain secondary metabolites such as polyphenols, terpenoids, saponins, and alkaloids [2].

Toxicity activity: *C. manghas* has been used as a method for self-poisoning in Eastern parts of Sri Lanka. Examination of the treatment and outcome of patients who use *C. manghas* to poison themselves occurred [1]. This plant is common in coastal regions of Sri Lanka. The latex contains cardenolides including cerberin, neriifolin, and cerebroside which cause cardiac dysrhythmias, vomiting, and hyperkalemia. The patient population was studied for two years in a tertiary care hospital in Eastern Sri Lanka. Out of the 583 cases of poisoning, forty-eight of the causes were due to *C. manghas* self-poisoning from the cardenolides [1]. Below is a diagram that shows the results of the self-poisoning cases in Eastern Sri Lanka. Most subjects were male and Tamil, with the main group of patients between sixteen and thirty years of age. Twenty-four cases ingested half a seed which is ten grams since one seed is about twenty grams. Most of them suffered from vomiting, dizziness, restlessness, drowsiness, and abdominal pain. The patients were treated with activated charcoal but many of them suffered from cardiac toxicity and did not have a great recovery causing an either immediate or slow death. Those with hyperkalemia were treated with insulin-dextrose. Patients with severe symptoms of toxicity such as vomiting, abdominal pain, and hyperkalemia had a significantly higher risk of death. However, the risk of cardiac toxicity was higher in patients who ingested less or half the number of seeds [1]. Selladurai concluded that *C. manghas* had the second highest plant poisoning in Eastern Sri Lanka following yellow oleander poisoning [1]. The seeds produce cardenolide poisoning causing vomiting, cardiac dysrhythmias, and hyperkalemia. Patients with cardiac arrhythmias and persistent hyperkalemia were important in that these symptoms predict the mortality risk. These patients did not recover from the poisoning. Most of the deaths occurred with patients who only ingested less or half the number of seeds. This was because patients who ingested more than half of the amount of the seeds ended up vomiting, removing the seeds from their bodies [1]. Another fatal injury was recorded in Eastern Sri Lanka regarding the cardenolide seeds. An analysis of the severity behind the fruits of this plant in South Asia took place. Like the above article, the yellow oleander seeds cause the most deaths with self-poisoning. However, in Eastern Sri Lanka, it was noted that many cases involved the sea mango seeds. All cases were recorded in the Batticaloa Teaching Hospital for two years. Intentional self-harm was the main cause for these cases. *C. manghas* was responsible for seven deaths due to cardenolide poisoning causing cardiac dysrhythmias and hyperkalemia [9]. It was concluded that this self-poisoning method accounts for twenty percent of self-harm with plants in just one hospital in Sri Lanka. Deaths due to self-poisoning were recorded in Sri Lanka Hospitals. However, there have been some cases reported in Kerala and Tamil Nadu in South India. It can only be imagined how many deaths take place from the poisoning of these seeds in Asia as a whole and other parts of the world that still haven't been identified or recorded. This article also establishes a need for better resources to save these precious lives. It is a means for emphasizing the need for affordable antitoxin, a treatment option for plant cardenolide poisoning in these areas [9]. *C. manghas* is an extremely dangerous plant to ingest due to the potent cardiac glycoside cerberin [8]. In Sri Lanka, the lack of resources contributes greatly to the death of self-poisoning patients. This is why such articles and studies are important because they help spread awareness of different plants and their potential threat to society.

Traditional usage: In addition to the self-poisoning usage, *C. manghas* has several other medicinal applications. In Madagascar, the plant is used to treat cardiac disorders. Some of the cardenolides are used to treat human colon, breast, lung cancer, and epidermoid carcinoma. In several Asian countries, the seeds are used in the treatment as a hair tonic, or in the treatment of lice/scabies. The bark is used to treat constipation, dysuria, and ringworm. The flowers are used to treat hemorrhoids. The wood is used for moldings, trimmings, clogs, charcoal, etc. *C. manghas* is planted as an ornamental tree and in some areas made as flower arrangements. Ligands were found and derived from olivil and monoternoids such as cerberidol. The ethanolic extracts from this plant also help against the vesicular stomatis virus. The olivil, carinol, and cycloolivil help with antioxidant activities. *C. manghas* is not traded on the international level, instead found in local markets in Madagascar. The wood is exported from Madagascar, Papa New Guinea, and the Solomon Islands to other parts of the world [10]. The oil from *C. manghas* is burned in lamps for light in various parts of the world [11].

Food usage: *C. manghas* is a non-edible plant [12]. The fruit is not edible at high doses as it contains cerberin, which is highly toxic and causes poisoning.

Biodiesel activity: Biodiesel properties in *C. manghas* have been studied to reduce fossil fuels without impeding food crop availability. This plant is studied for its potential renewable fuel in Indonesia. The study's concept was to find out if this plant can replace pure petroleum and palm oil biodiesel. It was

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found that *C. manghas* biodiesel fuel has lower characteristics in density, viscosity, sulfur content, color, water content, etc. than that compared to normal petroleum diesel. However, there was a higher flash point and cetane index in the sea mango [13].

Further analysis occurred of the biodiesel effect from *C. manghas* in a single-cylinder engine versus pure petroleum and palm oil diesel. It was found that *C. manghas* had enhanced engine performance compared to the other two types of biodiesels. Engine performance was based on fuel consumption, brake means effective pressure, torque, power, and thermal efficiency. *C. manghas* could potentially replace and become an alternative diesel fuel without impeding food availability. It was also stated that no additional changes must be made to the existing diesel engine for *C. manghas* to work efficiently which is another perk of using it as an alternative diesel choice [13]. *C. manghas* has the potential to develop into a renewable raw material source. The *C. manghas* oil contains toxic compounds, making it a non-edible vegetable oil. It can also be used as a biofuel because of the high oxygen atoms, viscosity, freezing point, low heating value, and thermal instability. The analysis of the effect of different reaction temperatures on the hydrocracking of this plant, which is used to produce biofuel occurred. The experiment was conducted under hydrogen initial pressure in a 600 ml bath reactor. Fruits were obtained and dried in the sun. The seeds would change color when exposed to air from white to black. *C. manghas* was found to have high amounts of unsaturated carboxylic acids which contain mostly trioleic. The GC-MS spectra of this oil and biofuel showed a retention time between ten and eighteen minutes. It was concluded that the Co-Ni/HZSM-5 catalyst is effective when producing biofuel by hydrocracking this oil including n-paraffin which is the most abundant of the hydrocarbons [14]. Keute found important lignans related to olivil from *C. manghas* [15]. From the plant, cardenolide glycosides were isolated for further analysis utilizing NMR and TLC. The stems were percolated with methanol and then diluted with water. The process continued with other chemical compounds, filters, etc. Chromatography occurred on silica gel and then analyzed. The same process occurred with the leaves [12]. Olivil, cyclolivil, and dimers of olivil were found in the stem and leaves of *C. manghas* which could potentially be used for biofuel and possess antibacterial, antimicrobial, and cytotoxic properties. Some have unique chemical structures that could potentially have anticancer properties [15].

Briquette activity: *C. manghas* grown in Indonesia is known to have one of the strongest roots which are used for decorating in the house and on the roadside. The plant has been used for shade, but the falling leaves have left a ton of waste products behind. Instead of becoming waste, this study accumulates the leaves and analyzes its potential use as a solid fuel alternative in the form of briquettes. It was tested at different temperatures to analyze if the biomass briquettes of *C. manghas* leaves waste could be made using tapioca as a binder [12]. Since natural resources are limited in supply, newer advances are being made to use other compounds for energy to fulfill human needs for fuel and electricity. Biomass is one of the most common forms of renewable energy, especially in third-world countries. Biomass can be produced from agricultural crops, seaweed, algae, and so much more such as *C. manghas* leaves. Indonesia has become a top coal exporter and has many different resources such as oil. However, the government pushes a green policy where every city should plant more trees to not only reduce global warming but counteract vehicle pollution emission. With each tree planted comes tons of waste, especially solid waste from *C. manghas*. These leaves have been used as biodiesel in the past and analyzed the potential use as a biomass briquette. From the chemicals section above, the leaves of *C. manghas* contain many different compounds such as neriifolin and cerberin which conclude it's a non-edible plant. Instead, the waste leaves were tested for different properties such as proximate, ultimate, heating value, and binding abilities. The waste leaves that had fallen from the tree and were sun-dried for three days. After testing the biomass briquette from the *C. manghas* waste, at 100 percent, *C. manghas* waste leaves were 4287.53 Kcal/Kg, and the heating of tapioca was 3574.47 Kcal/Kg. The greater amount of tapioca causes a lower heating value of biomass briquettes from *C. manghas* leaves was concluded. The highest heating value is when ninety percent *C. manghas* and ten percent tapioca mixtures. This is the perfect combination of temperature and cost to create the biomass briquette. It was concluded that the leaves can indeed be used as an energy source. The higher heating values of *C. manghas* and ten percent tapioca mixtures are a prime combination for optimal composition.

Anticancer activity: *C. manghas* has been medicinally used for human colon, lung, and breast cancer. Two new cardenolides called 14-hydroxy-3β-(3-O-methyl-6-deoxy-α-L-rhamnosyl)-11α,12α-epoxy-(5β,14β,17βH)-card-20(22)-enolide, 14-hydroxy-3β-(3-O-methyl-6-deoxy-α-L-glucopyranosyl)-11α,12α-epoxy-(5β,14β,17βH)-card-20(22)-enolide,and neriifolin were isolated from the roots [10]. Bioassay-guided fractionation was used with Ishikawa (human endometrial

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cells) antiestrogenic assay [15]. Antiestrogens are drugs that prevent estrogens from doing their job properly in the body. These antiestrogens block the estrogen receptor from suppressing or inhibiting estrogen production. This type of activity is found with a decrease in phosphatase activity when cells are treated with different compounds when estrogen is present [16]. Here however, these compounds have antiproliferative and antiestrogenic properties against human colon cancer and the Ishikawa cell line [10]. Lower estrogen levels can occur by blocking estrogen receptors with antiestrogens. These compounds can block the receptors which helps with the treatment of hormone-dependent tu**mors such as breast cancer [17].**

Antioxidant activity: Several compounds help with antioxidant activity in the leaves of *C. manghas.* Antioxidant activities of the ethanol leaves were investigated. Collection of the *C. manghas* leaves occurred in Bangladesh and was put under shade to prevent any photochemical degradation [8]. Phytochemical screening occurred with the crude ethanol extract. Reducing sugars, alkaloids, glycosides, steroids, flavonoids, and tannins were found by the phytochemical analysis of the extract [8]. The phytochemical screening is shown below. Anything with a positive sign shows that it is there and anything with a negative sign is absent. Gums and saponins are the only two phytochemical groups that are absent in this test [8]. In the in vitro antioxidant activity test, free radical DPPH occurred. The antioxidant activity of the ethanol leaves was analyzed both quantitatively, through the prediction of the antioxidant ethanol extract potential, and qualitatively, through thin-layer chromatography used to observe the radical. Another statistical analysis was used to find any contrast between the test and control groups [8]. The results showed that the ethanol extract did indeed convert the free radical DPPH into DPPH-H. This happened by donating an electron. The tannins and flavonoids in the extract were found could be responsible for antioxidant properties. The conversion of the DPPH is like that of the standard antioxidant ascorbic acid. This in turn, shows how this plant does have antioxidant activity and could further be researched to help with heart disease, cancer, and other diseases [8].

Analgesic activity: The ethanol extract of *C. manghas* is noted to have analgesic activity. Acetic acid-induced writing was used in mice for further analysis. The mice were divided into four test groups including control, positive group, test I, and test II groups. Each group was treated with different doses of chemicals such as diclofenac sodium. Thirty-minute intervals were given to ensure proper absorption of these treatments occurred. To calculate the analgesic activity, the percent inhibition was recorded and compared to the control group [8]. With ethanolic extract present, there is an analgesic effect in acetic acid-induced writing mice. The extract produced high counts of inhibition compared to that of diclofenac sodium. The extract produced 17.75 percent and 30.64 percent at 250 and 500 mg/kg- body weight which is comparable to the diclofenac at a lower dosage of twenty-five mg/kg-body weight. Phytochemical tests were run to observe if any phytochemicals were present in the extract. Observations found many different phytochemicals which are responsible for analgesic activity. Each of the alkaloids, glycosides, etc. is responsible for analgesic activity. It was concluded that the ethanol leaf extract of *C. manghas* showed potential analgesic activity and needs further research to develop these compounds into a drug that is available for all [8].

Anti-Inflammatory Activity: *C. manghas* is used medicinally to help treat inflammatory diseases and hypertension. Research was conducted to understand the molecular and cellular mechanisms which are not fully understood yet. More information is being analyzed and researched to understand the ethnopharmaceutical uses of this plant [18]. However, more compounds are being analyzed to form pharmaceutical drugs for different diseases. To understand the compounds, different tests were conducted on laboratory mice incubated with various diseases. To analyze the compounds from the methanol extract that produces these inflammatory mediator receptors, lipopolysaccharide (LPS) treated macrophages were used in vitro. The inhibitory effects of Cm-ME were also tested by LPS/D-galactosamine-induced hepatitis and LPS-induced peritonitis mouse models in vitro as well. In conclusion, *C. manghas* does help with inflammatory diseases. The Cm-ME helps with inflammatory actions on the LPS macrophages and in mouse models with acute inflammatory disease [18].

Antifungal activity: C. manghas has many different bioactive constituents that help antifungal activities. Sukmawati analyzes the diverse yeast species associated with the leaves [2]. A sampling of sixteen leaves from four different *C. manghas* plants from Bekasi West Java were collected first. The isolation of yeast from the leaves occurred through the washing technique. In this technique, leaves are weighed and sliced into smaller pieces. The leaves are washed with sterile compounds and vortexed for ten minutes. Once washed, the leaves were placed on agar plates and kept at twenty-seven to twenty-eight degrees Celsius for three days. The colonies were

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purified two times on yeast malt extract agar, maintained on potato dextrose agar, and kept at twenty degrees Celsius [2]. The next step in the process was the antagonism test technique. Here, early screenings were carried out by using yeast isolate from the fresh leaves. Thirty-six yeast and mold isolates were found. This was shown through a change in colors and textures. A variety of colors and textures of yeasts on the leaves were found [2]. Another screening antagonism of the yeast from *C. manghas* was done with Aspergillus and Penicillium. The same screening method took place with incubation lasting three days. The phylloplane yeast isolates from the leaves were a potential antagonism mechanism inhibited in *Aspergillus* and *Penicillium*. It was concluded that the yeast isolates from *C. manghas* leaves showed antagonism activity [2]. Testing of the *C. manghas* with the mold Aspergillus with a three-day incubation period at twenty-seven degrees Celsius temperature. The second testing of *C. manghas* with Penicillium on the same three-day incubation period at the same temperature. It was concluded that the two antagonistic yeasts were successfully able to inhibit the growth of both *Aspergillus* and *Penicillium* [2].

Antiviral activity: *C. manghas*, one of the plants used in Malaysian Indigenous medicine, was tested for both antiviral and cytotoxic activities. Mammalian cell culture systems make it easier to test compounds for these activities. Sixty-one plant species were tested and analyzed for antiviral and cytotoxic activities including *C. manghas* [19]. Taxol was found and recorded as one of the most notable examples of these compounds that exhibit antiviral and anticancer activities. An ethnopharmacological approach was taken instead of random selection because it would yield higher biological activity. The ethanolic extracts were tested for vesicular stomatitis (RNA) and herpes simplex type-1 (DNA) using Vero cells and cytotoxicity was tested using a human cervical carcinoma cell line [19]. The plants were collected in Malaysia and samples of each leaf and fruit from *C. manghas* were sliced into smaller pieces and put in ethanol for a week. The pieces were then filtered and evaporated. Residues were stored. The Vero and HeLa cells were obtained from Japan. Herpes simplex virus type-1 and vesicular stomatitis virus were obtained from the University of Minnesota [19]. The antiviral activity was tested by plaque reduction assay. After undergoing the test, the activity was analyzed. The analysis occurred by being scored from the inverted microscope that showed inhibitory concentration. The cytotoxic activity was also tested. However, a microtitration assay was used instead. After undergoing the test, the inverted microscope detected the concentration of plant extract with reduced cell number. This indicated activity and was compared to the control group [19]. Out of the sixty-one plants, thirty-three of them tested positive for either activity or both. Below is a diagram showcasing how many plants showed activity for Hela cells, herpes simplex virus, and vesicular stomatitis. Five co-existing activities with the HSV and VSV were observed and recorded. Three plants were found to have all these activities. Twenty-eight plants tested negative and did not show any of these activities. Twenty-six species showed antiviral activity and eighteen species expressed cytotoxicity activity. Each of these are shown in the diagram below [19]. Eleven plant extracts possessed antiviral activity including *C. manghas. C. manghas* also tested positive for cytotoxicity activity. It recorded the strongest cytotoxic activity from its fruits. The fruits expressed cytotoxic activity twenty times stronger and anti-VSV activity than its leaves. This solidifies the toxicity and antiviral effects of *C. manghas* [19].

Future potential uses: As reviewed above, *C. manghas* has many different biological and pharmacological activities. There is a potential drug target for anti-inflammatory activity. There is potential for anticancer, antifungal, and antiviral targets as well. This is due to the different compounds and chemicals that C. manghas contains. More research needs to be done to turn these compounds into medical drugs that could be sufficient for therapy of these health issues. There is also potential to turn *C. manghas* into a household name as an energy source such as biodiesel. There have been some studies, however, more needs to be done to understand all that this plant has to offer.

CONCLUSION

Each part of *C. manghas* is used for different biological and pharmacological activities. This paper concludes how much of a threat the fruits of this plant can be with self-poisoning in other parts of the world. It is important to understand and educate the surrounding community, especially children about the toxicity of such a plant. It can also effectively be used as biomass briquettes which are utilized as an alternative to coal and charcoal. It is important to understand all the chemical compounds in this plant to potentially create more pharmaceutical drugs that could help treat many different diseases. Overall, there needs to be more clinical studies of this plant to predict future treatment plans/ cures for different diseases. It should also serve as a warning sign to people trying to ingest the toxic seeds.

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LIST OF ABBREVIATIONS

C. manghas- Cerbera manghas

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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