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Review Article

CARISSA EDULIS PHYTOCHEMICAL AND PHARMACOLOGICAL STUDIES: A REVIEW ARTICLE

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Abstract

Background: *Carissa edulis* is a plant of Apocynaceae family that is used in many countries of Africa, Asia, and Oceania. The plant has been employed and used in traditional medicine for various ailments. The diversified utilizations, widely acclaimed and proven efficacy of preparations of *C. edulis* in traditional medicine have led researchers to take an interest in phytochemical and pharmacological properties of this plant. **Objective**: The purpose of this review isto provide updated information about therapeutic effects of *C. edulis* and improve our future experimental and clinical research plan. **Methods**: This review covers articles between 1975 and 2020. The available information was collected via electronic search (Pubmed, SciFinder, Google Scholar, ResearchGate) and a library search for articles published in peer-reviewed journals, using ''Carissa *edulis*'' as search term (''all fields'') and with no specific time frame set for search. No restrictions regarding the language of publication were imposed. **Results**: Studies have shown that extracts of *C. edulis* may contain biologically active principles with diuretic, analgesic, antimicrobial, antidiabetic and anticancer effects. It's a plant with many properties that is rich in flavonoids, phenolic compounds, chlorogenic acid derivatives, lignans, sesquiterpene, sterols, triterpenes, coumarins, cardiac glycosides and miscellaneous compounds. Though short term used of the plant doesn't have any toxic effect, its long term used can alter hepatic, renal and haematopoietic functions of the organism. **Conclusion**: Although the mechanisms of action are not very clear, there is enough evidence of *C. edulis* efficacy in the treatment of many diseases. However, it's necessary to do more well-designed animal and randomized clinical studies with sufficient sample sizes, to collect more objective data and confirm traditional effects of this plant. Exploring other fields of research such as the effect of the plant on cardiovascular disease would also be interesting.

Keywords: *Carissa edulis*, traditional medicine, therapeutic effects.

INTRODUCTION

The art of herbal medicine is extremely ancient, probably as old as humanity itself (Tyler, 2000). *Carissa* L. is a genus of the family Apocynaceae, with about 36 species as evergreen shrubs or small trees native to tropical and subtropical regions of Africa, Asia, and Oceania. Most of Carissa plants have been employed and used in traditional medicine for various ailments, such as headache, chest complains, rheumatism, edema, gonorrhea, syphilis, rabies. (Kaunda and Zhang, 2017). This genus is a rich source of different natural classes of compounds such as sesquiterpenes, cardiac glycosides, phenolic compounds, flavonoids, lignans, chlorogenic acid derivatives (Al-Youssef and Hassan, 2012; Kirira *et al.,* 2006; Pal *et al.,* 1975; Wangteeraprasert and Likhitwitayawuid, 2009). *Carissa edulis* (Forssk) Vahl (syn. *Carissa spinarum* L.) is a perennial thorny shrub widespread in Africa, Australia, Vietnam, Yemen and India. It is one of the secondary advantage plants grown in dry-hot valleys, which can survive under stress conditions of high temperature and extreme low humidity (Zhang *et al.,* 2010).The plant bears sweet edible fruits, while its pungent root and leaf is used locally for a variety of medicinal purposes. These include the treatment of HIV/AIDS symptoms, tuberculosis, chest complaints, rheumatism, headache, gonorrhea, syphilis, rabies, as diuretic, snake bite, evil eye, malaria, epilepsy (Kebamo, 2015). It has also been reported to treat fever, hernia, sickle cellanemia, ulcer, worm infestation, pain, inflammation (Fanta Yadang *et al.,* 2019) and hypertension (Olou *et al.,* 2018).

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This review may be useful in increasing our knowledge on *C. edulis* therapeutic effects and in improving our future experimental and clinical research plan.

METHODS

This review covers articles between 1975 and 2019. The available information was collected via electronic search (Pubmed, SciFinder, Google Scholar, ResearchGate) and a library search for articles published in peer-reviewed journals, using ''*Carissa edulis*'' as search term (''all fields'') and with no specific time frame set for search. No restrictions regarding the language of publication were imposed.

RESULTS

Taxonomy and morphology (Table 1) (Ansari and Patil, 2018)

Common names: Currant Bush, Conker berry, Bush Plum, Burrum Bush, Wild Karaunda.

Ethno pharmacological relevance: *C. edulis* is a plant which is used in many countries in the world. The diversified utilizations, widely acclaimed and proven efficacy of preparations of *C. edulis* in traditional medicine have led researchers to take an interest in the pharmacological properties of this plant.

Pharmacological studies: Studies have shown that extracts of *C. edulis* may contain biologically active principles with potential diuretic (Nedi *et al.,* 2004), analgesic (Ibrahim *et al.,* 2007), antimicrobial (Ibrahim *et al.,* 2005), antidiabetic

Table 1. Taxonomy and morphology of Carissa (Ansari and Patil, 2018)

Kingdom: Plantae Subkingdom: Viridaeplantae Phylum: Tracheophyta Class: Magnoliopsida Subclass: Asteridae Order: Gentianales Family: Apocynaceae Genus: Carissa Species: Spinarum.	- Plant: Thorny shrub, with forked branches, - Height: 2–3 m, - Wood: Very hard, - Bark: Light brown to green, - Thorns: 3.2 cm long, at the base brown to greenish and toward the tip deep brown colored, - Leaves: Ovate, 4.5 cm long, 2.5 cm broad, leathery, venation, reticulate pinnate; margin, entire; petiole 3 mm long; leaves exuding a white latex, when plucked from the stem, -Flowers: Short-stalked, sweetly scented, bisexual, complete, and white colored, - Fruit: An ovoid berry, 5–12 mm in length, 6 mm in diameter, green when unripe, and shining black when completely ripe.

Fig. 1. *Carissa edulis* http://themeforest.net/ user/GoodLayers

(El-Fiky *et al.,* 1996), sedative, anticonvulsant, and anxiolytic properties (Yau, 2007; Ya'u *et al.,* 2010, 2008), antiplasmodial, antiviral and hypoglycemic activity (Alodeani, 2016). *C. edulis* has also developed a mechanism to accommodate heat and drought stress by protecting the photosynthesis apparatus by induction of many different types of small HSPs and Rubisco activates (RCA) (Zhang *et al.,* 2010). The coregulation pattern of large amounts of different small Heat Shock Proteins (sHSPs) may render the cells more susceptible to aggregation and denaturation caused by heat and dehydration (Zhang *et al.,* 2010).

Wound healing and antimicrobial potential: The effect of methanolic extract of *C. edulis* root extracted by cold maceration was evaluated by (Sanwal and Chaudhary, 2011)on burn wound model in mice. Results of their studies have shown that *C. edulis* root extract has significant wound healing activity as evident from the rate of wound contraction and epithelization. In addition, Hydroxyproline expressions and histological parameters were also well correlated with the healing pattern observed. Methanolic extract also exhibited significant antimicrobial activity against all the tested microorganisms (Sanwal and Chaudhary, 2011).

Antioxidant capacity: Oxidative stress is considered as a major contributor to many chronic diseases. To reduce the excess of reactive oxygen species (ROS) and suppress oxidative damage, an antioxidant intake is needed. Aqueous extract of *C. edulis* leaves has percentage radical scavenging activity DPPH ranged between 58.63% and 94.67%,and the methanolic extract have ABTS between 51.39% and 94.12% and FRAP 6.73 g AAE/100 g extract (Fanta Yadang *et al.,* 2019).

Antiviral activity: Tolo et al. have studied antiviral activity of C. *edulis*. Their work showed that *C. edulis* aqueous root bark extract contains potential agents with activity against Herpes simplex virus (HSV). The extract was evaluated for in vitro and in vivo anti-HSV activity. The results have shown that both the wild and resistant strains of HSV were sensitive to the extract. The resistant strains were even more sensitive to the extract than the wild strains. The virus yield reduction assay which simulates an in vivo environment of infection, demonstrated that the extract had a virucidal activity, further supporting the potency of the extract. The virus yield reduction assay also confirmed the observations of the plaque inhibition assay on anti-HSV activity (Tolo *et al.,* 2006).

Antidiabetic activity: Oral administration of C.*edulis* leaves extract (2 g/kg body weight) to diabetic rats lowered the blood glucose level after 3 h of treatment. C.*edulis* were found to exhibit a hypoglycemic activity in streptozotocin (STZ) diabetic rats (El-Fiky *et al.,* 1996).Further, pharmacological investigations must be carrying out to elucidate the mechanism of this hypoglycemic effect.

Antinociceptive activity: Mworia et al. showed in their study that the acetone leaves extract of C.*edulis* have a significant anti-nociceptive effect by reducing formalin paw- licking time in mice compared to the reference drug diclofenac sodium. The acetone leaves extracts tested at different dose levels lowered paw licking time in a dose dependant manner. This suggests both central and peripheral antinociceptive effects (Mworia *et al.,* 2015)

Hematological effect: Dichloromethane-methanolic (DCM-MeOH) leaves extract of *C. edulis* induced general increase in

the levels of red blood cells, Hemoglobin and related parameter profiles across the different dose levels. Administration of DCM-MeOH leaf extract of *C. edulis* led to significant increase in the levels of white blood cells, platelets and all related indices in normal rats. This shows that the DCM-MeOH extracts of *C. edulis* may have immune boosting properties and contain compounds and phytochemicals that may have stimulated thrombopoietic process in normal rats.(H Jorum and M Piero, 2016).

Anti-cancer potential: It was also found that aqueous extract of *Carissa edulis* stem and its n-butanol fraction have anti-cancer potential. Both inhibited cell proliferation of human cancer cell linesHL-60. Cells treated with n-butanol fraction showed maximum growth inhibition having an inhibitory concentration (IC_{50}) value of 34.58± 0.91 µg/ml. This provides valuable insight into the pro-apoptotic nature of *C. edulis* (Sehar *et al.,* 2011).

Hepatoprotective effect: Ethanol extract of *Carissa edulis* leaveshas effect against dimethoate-induced hepatotoxicity in male guinea pigs that can be beneficial to overcome the toxicity and side effect associated with liver disorder due to pesticide intoxication (Al-Awthan and Salem Baha, 2019). Similar studies were conducted by Hegde and Joshi. But instead of leaves, they selected roots for screening their potential hepatoprotective effect. Ethanolic extracts of *C. edulis* roots were evaluated again chloroform (CCl4)-induced and Paracetamol-induced hepatotoxicity. Results showed significant elevation in the levels of serum marker enzymes incontrol group such as SGOT, SGPT, and SALP content of CCl4/PCM intoxicated animals. Animals pre-treated with extract (100, 200, and 400 mg/kg) as well as a standard drug (silymarin) demonstrated significant protective effect by decreasing serum marker enzymes in a dose-dependent manner (Hegde and Joshi, 2010).

Phyto and physicochemical properties of fruits: *C. edulis* fruits are fleshy, ovoid, 6–11 mm in diameter, red to purplish black berries and two- to four-seeded. They have phenolic, antioxidant and physicochemical properties that are affected by ripening stages. Significant variability was observed for physicochemical (color, total solid solubility and pH) antioxidant and phenolic properties among all three stages of ripening of *C. edulis* fruit. Although ripe *C. edulis* berries are generally more edible at the final stage of ripening, greater antioxidant activity was observed at the first stage of ripening while total flavonoid content increased with progression in ripening (Makumbele *et al.,* 2019).

***Carissa edulis* fruits capped nanoparticles:** Use plant extract to synthesize nanoparticle has been considered as one of the eco-friendly methods. Studies have shown that secondary metabolites extract of *C. edulis* fruits by microwave assisted have a good reducing property to form zinc oxide nanoparticles. The ZnO NPs are capable to degrade Congo red compound with respect to time (Fowsiya *et al.,* 2016).

Chemical constituents

A literature search for the phytoconstituents of *Carissa edulis* indicated the isolation of flavonoids, phenolic compounds, chlorogenic acid derivatives, lignans, sesquiterpene, sterols, triterpenes, coumarins, cardiac glycosides, miscellaneous compounds (Al-Youssef and Hassan, 2017). A total of 19 compounds (14 phenolics, 1 organic and 4 unknown compounds) were identified in *C. edulis* berries. The identified polyphenolic compounds are mainly phenolic acids and flavonoid groups. Citric acid was the organic acid identified in fruit samples with the other unknown compounds (Makumbele *et al.,* 2019).

Volatile compounds

The root oil of *Carissa edulis* from Benin was analyzed by GC/MS and six components were identified. The main constituent was 2-acetylphenol (92.7%) with lesser amounts of limonene (1.2%), y-eudesmol (1.2%), a-pinene (0.3%), sabinene (0.3%) and myrcene (0.8%) (Moudachirou *et al.,* 1998).

Sesquiterpenes

Sesquiterpenes are known to possess antimicrobial, antimalarial, anticancer and anti-inflammatory activity (Al-Youssef and Hassan, 2014). Nine eudesmane-type sesquiterpenes and two germacrane-type sesquiterpene were isolated from the methanolic extract of the root of *Carissa edulis* they include carissone, cryptomeridiol, β-eudesmol,6α-carissanol, 6β-carissanol, 2α-carissano,4-Epi-Aubergenone, dehydrocarissone, germacrenol (Achenbach *et al.,* 1985, 1983). Petroleum ether extract of *C. edulis* stem yielded a new germacrane sesquiterpene named carenone (Jagadeeshwar Rao *et al.,* 2005).

Lignans

From the stems of C. *edulis*, 8 lignans named (-)-Nortrachelogenin, (-)-Secoisolaricirestinol, (-)-Carissanol, (-)-Carinol, (-) olivil, (+)-Cycloolivil, (+)-8-hydroxypinoresinol, (+) Pinoresinol were isolated (Wangteeraprasert *et al.,* 2012) and (+)-lariciresinol were isolated from root (Achenbach *et al.,* 1983). (-) Nortrachelogenin showed antiplasmodium activity at a dose of 14.50µg/ml (Kebenei *et al.,* 2011) and (+)-Nortrachelogenin, the enantiomer of (-)-Nortrachelogenin, has been proved to process antitumor activity.

Flavonoids

Flavonoids present in *C. edulis* are mainly in the form of their glycosyl derivatives. The most common sugar moieties include *β*-D-glucose and α-L-rhamnose and the glycosides are usually –O- glycosides in which the sugar moiety bound generally to the hydroxyl group of the aglycone at C-3. Aglycones (the forms lacking the sugar moieties) occur less frequently. Ethyl acetate extract of areal part of *C. edulis* afforded four known flavonol glucosides including kaempferol 3-O- *β*-D-glucopyranoside, quercetin 3-O- *β*-D-glucopyranoside, rhamnetin3-O- *β*-D-glucopyranoside and isorhamnetin 3-O- *β*-D-glucopyranoside and, butanol extract as isorhamnetin-3-O-β-D-glucopyranoside(2"→1")-L-rhamnopyranoside,1-{1-[2-(2 hydroxypropoxy) propoxy] propan-2-yloxy} propan-2-ol, (+) butyl-O-a-L-rhamnoside(Al-Youssef and Hassan, 2017).

Carissa edulosides

Ten previously undescribed glycosides, carissaedulosides A–J (**1–10**) referring to six apiosylated phenylpropanoids (**1–6**), one coumarin-secoiridoid hybrid (7), and three furofuran lignans (**8–10**) were isolated from the root barks of Carissa *edulis* (Fig.2).

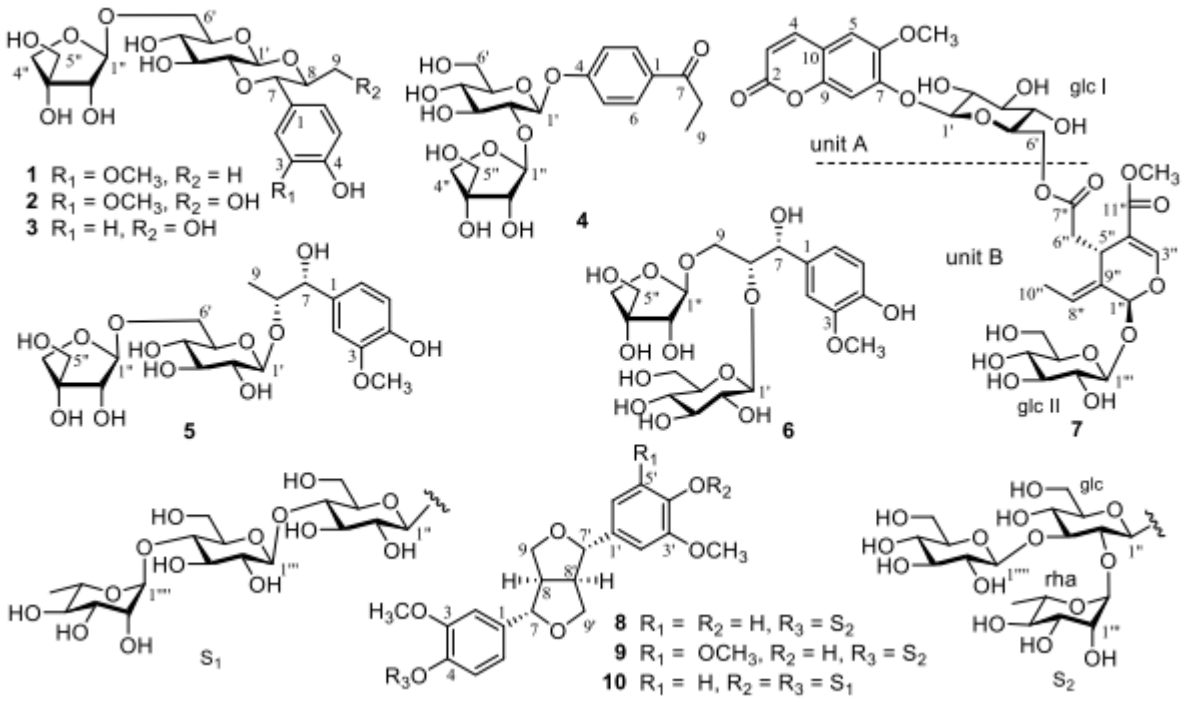

Fig. 2. Structures of new compounds, 1–10, isolated from *C. edulis* (Kaunda *et al.,* 2020)

Their structures were elucidated by spectroscopic analysis, electronic circular dichroism (ECD) computational methods, and chemical derivations for configurations of sugar moieties. The new lignan bisdesmoside, **10**, exhibited significant cytotoxicity against A549 and MCF-7 cell lines. The half maximal inhibitory concentration is respectively (IC_{50} = 3.87 ± 0.03 μM) and (IC_{50} = 9.231 ± 0.290 μM) (Kaunda *et al.,* 2020).

Phenolic compounds

It was found that the root of *Carissa edulis* contain phenolic compounds, 2-hydroxyacetophenone (Bentley and Brackett, 1984).Soluble phenolics, insoluble pro anthocyanidins (Reed, 1986). Identified phenolic acids in *C. edulis* fruits were quinic acid, protocatechuoyl-hexose, neochlorogenic acid, chlorogenic acid, cryptochlorogenic acid and dicaffeoylquinic acid. Identified flavonoids included rutin, catechin, procyanidin dimer, procyanidintrimer, quercetin-3-O-glucosyl-xyloside, quercetin-3-O-robinobioside,quercetin-3-O-glucoside andquercetin-3-OH-3-methylglutaryl-glucoside (Makumbele *et al.,* 2019).

Toxicity studies

Acute toxicity

C. edulis root bark did not present lethal effects after the oral administration of the standardized ethanol extract at doses of 1600, 2900 and5000 mg/kg. No behavioral changes were observed. The oral LD_{50} of the extract was estimated to be greater than 5000 mg/kg (Ya'u *et al.,* 2013). The aqueous extract of the leaves of *C. edulis* was found to have no toxic effect at the dose of 2000mg/kg (Osseni *et al.,* 2016).

Sub-acute toxicity

Sub-acute treatment (28 days) with the standardized extract of *C. edulis* root bark, did not affect hematopoiesis and leucopoiesis in rats.

The orally administrated doses of the extract were non-toxic and did not interfere with the production of circulating red blood cells, white blood cells, and platelets (Ya'u *et al.,* 2013). 28-days sub-acute oral ingestion of the aqueous extract of *C. edulis* showed the normal architecture of the rat's histological structure. Nodetrimental changes of livers and kidney were observed in treated group compared to the control one (Osseni *et al.,* 2016).

Sub-chronic toxicity

Evaluation of sub-chronic toxicity of C.*edulis* was done by Osseni *et al.* Their study did not show any death after 90 days treatment. But long time used of *C. edulis* could alter some functions of the organism, especially the hepatic, renal and hematopoietic functions. Lipid profile parameters were significantly affected especially total cholesterol, triglyceride, and low-density lipid. The relative organ weights analysis showed a significant reduction of liver and kidneys weights treated with the extract in all groups as compared to control. Biochemical analysis of the treated and control rats showed that there were significant differences in the levels of transaminases especially at the middle of the treatment (day 45), but the values were physiologically normalized at the end of the study. The haematological analysis revealedan increase in erythrocytes count, haemoglobin, haematocrit (polyerythrocythemia) associated with an increase of MGV level (macrocytosis) (Osseni *et al.,* 2017).

Conclusion

Pharmacopoeia and traditional medicine are significant alternatives for health coverage. *C. edulis* is present in many countries of Africa, Asia, and Oceania.The plant is used in day to day live because ofhis various pharmacological activities. This review updated information about pharmacological, and chemical effect of C. *edulis*. The plant is rich in flavonoids, phenolic compounds, chlorogenic acid derivatives, lignans, sesquiterpene, sterols, triterpenes, coumarins, cardiac

glycosides, miscellaneous compounds. Though short term used of the plant (28 days successively) does not have any toxic effect, its long termused (90 days successively) can alter hepatic, renal and haematopoietic functions of the organism. Fruits, leaves, stem, bark have many activities such as antidiabetic, sedative, antiplasmodial, antiviral, hypoglycemic. However, well-designed animal and randomized clinical studies with sufficient sample sizes are essential to investigate their exact mechanisms of action. Although multidirectional approach to the herbal research is not easy to pursue, it is essential to consider all approaches so that remedies that are developed from *C. edulis* be grounded in solid scientific evidence.

Conflicts of interest: The authors declare that there are no conflicts of interest regarding the publication of this paper.

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