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A REVIEW ON – PHARMACOLOGICAL EFFECT OF *CARISSA CARANDAS* L.

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ABSTRACT

Carissa carandas (Karonda), a fruit of dryland which is a widely grown indigenous shrub in India and is able to flourish in marginal and wasteland where other crops of commercial importance are unsuitable. Collection, conservation and evaluation, a process of crop improvement for characterization and selection of elite plants, are being successfully performed in different parts of India and standardized its vegetative technique of propagation. Its fruits have been utilized in processed products such as in the preparation of jam, jelly, squash, syrup and chutney and is in great demand in the international market. *Carissa* speciesare traditionally used to treat various diseases, such as chest pain, headaches, gonorrhoea, rheumatism, syphilis, oedema, rabies, stomach pain, hepatitis, cardiac diseases, and asthma. The pharmacological studies on *Carissa* species revealed its antioxidant, antimicrobial, anticancer, cardioprotective, antipyretic, analgesic, wound healing, anticonvulsant, antiarthritic, adaptogenic, anti-inflammatory, and antidiabetic activities, thus validating its use in indigenous medicine systems.

INTRODUCTION

Carissa carandas growing shrub of the genus carissa also known as Karonda. Karonda is a perennial evergreen plant also used as a spiny ornamental plant that can grow in the tropic Mediterranean or subtropic climate. Karonda is a species of flowering shrub in the dogbane family, Apocynaceae. Carissa carandas has good nutrition value. It is rich in iron, the fruits contain vitamin C and it is antiscorbutic and very useful for the cure of anemia.[1]

India has a rich culture of medicinal plants, which includes about more than two thousands of

species and has a huge geographical region with highly possible abilities for Ayurvedic, Unani, Siddha traditional medicines. Human beings have used plants for the treatment of various diseases for thousands of years. Rural areas of many developing countries still depend on traditional medicine for their primary health care requirements and have found a place in day-to-day life. These medicines are comparatively safer and cheaper than synthetic or modern medicine.

Carissa carandas is an evergreen thorny shrub belongs to Apocynaceae family, which is commonly known as karonda. It has small berry-shaped fruits, used as additive in many pickles or as a spice in northern India. It is drought-resistant plant that can be grown in a wide range of different types of soils. Approximately more than 25 species of genus *Carissa* are known, out of which five species are native to India. It is commonly used to make ledge for orchards. It has been found that the fruit is the richest source of iron, vitamin C and pectin.

Even it is used as an ingredient in most of the edible preparations such as jam, jelly, squash and syrup. The demand of the plant has been increased tremendously in the market as it contains antiscorbutic property and found very beneficiary effect in the treatment of anaemia. It has been utilised in many ayurvedic preparations. Root extract is used in chest pain. The leaf extracts are used in the treatment of fever. The fruits are richest source of thiamine, riboflavin, pantothenic acid, pyridoxine, biotin and folic acid.[2]

Taxonomic classification[3]

Scientific name	carissa carandas
Kingdom:	Plantae
Class:	Angiosperm
Subclass:	Eudicots
Order:	Gentianales
Family:	Apocynaceae
Genus	Carissa
Species:	C. carandas

Synonymes: Zingiberis, Ginger, Sonth.

Names in regional language[2]

Sanskrit	Krsnapakphala
Gujarati	Karamadan
Bengali	Karamach
Malayalam	Karimkar
Hindi	Karaunda
Kannada	Karimkar
Punjabi	Garna
Tamil	Kalakke
Urdu	Karaunda

Macroscopic Properties[4]

Plant Part	Colour	Test	Size
Leaves	Green	tart, sourish-sweet	4-6 inch long and 2-3inch wid
Bark	Grey	Tart	-
Fruit	Red	Sour, tart, Sweetness	1-3 inch
Flower	White	better	3-6 mm

Description and distribution

In India, apart from higher altitudes it grows very well in other parts such as Bihar, West Bengal, Maharashtra, Karnataka, Rajasthan, Gujarat and Uttar Pradesh states. It is also found naturally in Malaysia and South Africa. The plant can be grown successfully in tropical and subtropical climate regions. It grows well in acrid climate at higher temperature. It requires optimum range of pH from 5.0 to 8.0 for their better growth. They were ready for planting after 6–7 months of this process. The plant start bearing flowers in December–March, and the fruit gets matured in the month of April– June.[2][5][6]

Chemical constituents

The presence of different phytochemical constituents, for example alkaloids, carbohydrates,

phenolic compounds, gums and mucilage, saponins, proteins and fats.[7][5] The analysis of methanol extract of dried fruits of *C. carandas* showed myo-inositol, 4-c-methyl, 2*R*-acetoxymethyl-1,3,3-trimethyl-4t-(3-methyl-2-buten-1-yl)-1t-cyclohexanol, dichloroacetic acid, 2-ethylhexyl ester, 12-oleanen-3-yl acetate, (3-alpha), other minor compounds like 1-pentatriacontanol, *β*-amyrin, Z,Z-6,28-heptatriactontadien-2-one, 1-methoxy-25-methyl heptacosan-1-ol, and 2,4,4-trimethyl-3 hydroxymethyl-5a-(3-methyl-but-2-enyl)-cyclohexene.[8]

Pharmacological activity

Antidiabetic activity

Investigated the methanol extract and its fractions were screened for antidiabeticactivity in alloxan induced diabetic rats. The polyphenolic, flavonoid and flavanone contents of methanolic extract and its fractions were also determined and correlated with its antidiabetic activity. the experimental data indicated that the methanol extract and its ethyl acetate soluble fraction has significantly lowered the elevated blood glucose levels by 48% ($p<0.001$) and 64.5% ($p<0.001$) respectively at dose level of 400mg/kg per oral after 24h as compared to diabetic control. In order to assess the role of polyphenolic components in the relevant activity, polyphenolic and flavonoid contents were determined. The polyphenolic and flavonoid content of methanol extract and its ethyl acetate soluble fraction were found to be 15.8 ± 1.2mg and 18.55 ± 0.34 mg (gallic acid equivalent/g extract) and flavonoid content 2.92 ± 0.03 mg and 1.534 ± 0.30 mg (rutin equivalent/g extract) respectively. the increased antidiabetic potential of ethyl acetate fraction over methanol extract is due to its partial purification achieved by fractionation which resulted in increase in degree of polymerization and segregation of secondary metabolites.[9]

In investigated, hexane, chloroform, ethyl acetate, methanol and aqueous extracts ofCC fruit were examined for hypoglycemic activity in healthy Wistar rats. Aqueous Extract of CC (AECC) was most active and showed fall of 67.08% in fasting blood glucose from 0 to 1hin glucose tolerance test (GTT). The ED_{50} of AECC was 300mg/kgbw in streptozotocin induced diabetic rats. Treatment of diabetic rats with ED_{50} of AECC for 28 days significantly reduced post prandial glucose (PPG) by 33.65% ($p<0.01$), glycosylated hemoglobin (HbA1c) by 45.79% ($p<0.01$) and increased insulin level by 69.7% ($p<0.05$). The results indicated that increase in insulin secretion may be partly responsible for antidiabetic effect of AECC. To assess the mechanism of secretagogues activity, AECC was

incubated with isolated pancreatic islets of healthy Wistar rats at basal (3.3mM) and high (16.7mM) level of glucose in presence or absence of Diazoxide (K-ATP channel opener), Nimodipine (Ca^{2+} Channel blocker) and Calphostin-C (PKC inhibitor). AECC induced insulin secretion at 16.7mM of glucose was significantly ($p<0.01$) reduced by Diazoxide and Nimodipine but non significantly ($p>0.05$) by Calphostin-C. The study indicated that the phytochemicals present in AECC may be inducing insulin secretion by closing K-ATP channels in β-cells of pancreatic islets.[10]

Anti-convulsant activity

Reported the anticonvulsant activity of root bark extract of Carissa edulis. the median lethal dose (LD50) of Carissa edulis extract was determined using Lork's method (1983). The anticonvulsant activity of the extract was assessed in pentylensetetrazole (PTZ)- induced convulsion in mice and maximal electroshock test (MEST) in chicks, with benzodiazepine and phenytoin as standard drugs, respectively. While mechanistic studies were conducted using both flumazenil, a GABA (A)-benzodiazepine receptor complex site antagonist and naloxone a non-specific opioid receptor antagonist. the median lethal dose (LD50) of Carissa edulis was 282.8mg/kg and over 5000mg/kg following intraperitoneal and oral administration, respectively. Carissa edulis produced 40% and 20% protection against convulsion at 5 and 20mg/kg, respectively, compared with 100% protection with benzodiazepine. The mean onset and percentage protection against convulsion in Carissa edulis extract-treated mice were reduced by flumazenil and naloxone. Carissa edulis exhibited dose-dependent inhibition of the convulsion induced by MEST with (20mg/kg) providing 90% protection while phenytoin (20mg/kg) produced 100% protection. these results suggest that Carissa edulis possesses biologically active constituent(s) that have anticonvulsant activity.[11]

Evaluated the anticonvulsant effect of the ethanolic extract of the roots of Carissa carandas (ERCC) on electrically and chemically induced seizures. Methods: The ethanolic extract of the roots of C. carandas (100, 200 and 400 mg/kg, i.p.) was studied for its anticonvulsant effect on maximal electroshock-induced seizures and pentylenetetrazol-, picrotoxin-, bicuculline-and N-methyl-dl-aspartic acid-induced seizures in mice. The latency of tonic convulsions and the number of animals protected from tonic convulsions were noted. Results: ERCC (100-400 mg/kg) significantly reduced the duration of seizures induced by maximal electroshock (MES). However, only 200 and 400mg/kg of the extract conferred protection

(25 and 50%, respectively) on the mice. The same doses also protected animals from pentylenetetrazol-induced tonic seizures and significantly delayed the onset of tonic seizures produced by picrotoxin and N-methyl-dl-aspartic acid. The extract had no effect on bicuculline-induced seizures. Conclusion: The data suggest that the ethanolic root extract of C. carandas may produce its anticonvulsant effects via non-specific mechanisms since it reduced the duration of seizures produced by maximal electroshock as well as delayed the latency of seizures produced by pentylenetetrazol and picrotoxin.[12]

Reported the anticonvulsant activities of aqueous fraction of ethanol root bark extract of *Carissa edulis* (RAF) and sub-fractions (S1 and S2) in animal models. evaluatedthe acute toxicity of the RAF, S1 and S2, and the anticonvulsant activity using pentylenetetrazole (PTZ), picrotoxin, strychnine, *N*-methyl-D-aspartate (NMDA), isoniazid (INH), and aminophylline-induced seizures in mice. Their effects on maximal electroshock (MES) and kindling-induced seizures were studied in chicks and in rats, respectively, and in the electrophysiological study. The doses used for RAF were 150, 300, and 600 mg/kg while S1 and S2 were 250, 500, and 1000 mg/kg. Both RAF and sub-fractions were administered once during the experiment. the intraperitoneal LD_{50} of the RAF was estimated to be 2222.61 mg/kg and that of the S1 and S2 were above 5000 mg/kg. RAF protected the mice by 50% while sub-fractions by 16.67% against PTZ-induced seizures. RAF offered 33.33 and 16.67% protection against strychnine and NMDA models, respectively. However, RAF offered 66.67–33.33% protections against aminophylline-induced seizures at doses of 150 and 600 mg/kg, but RAF, S1, and S2 had no effect on MES-induced seizures. this results validate the use of the plant traditionally in the management of epilepsy.[13]

Anti-depressant activity

Evaluated the antidepressant-like effect of different fractions of the root bark in rodents and the possible underlying mechanisms in rats. A 70% ethanol extract of the root bark was successively fractionated with n-butanol, ethyl acetate, and water. Animals of both sexes received 2% Tween 80, imipramine (30 mg/kg), or various doses (50, 100, 200 mg/kg) of the fractions. Duration of immobility was determined using the tail suspension test and the forced swim test. Locomotor activity was evaluated in the open field test. Serum corticosterone levels, total phenols, flavonoids, and alkaloids were determined. Preliminary mechanistic studies were also performed to explore possible mechanisms of action of the active fraction. All fractions but the aqueous fraction significantly ($p<0.001$) decreased the duration of

immobility in both tests, with the ethyl acetate fraction being the most active. The locomotor test revealed that the activity was not due to non-specific psycho-stimulant effects. Serum corticosterone levels were reduced by both fractions, with the ethyl acetate fraction again being the most effective. Mechanistic studies showed the involvement of multiple neurotransmission systems, including adrenergic, dopaminergic and cholinergic as well as L-Arginine-NO-cGMP pathway. Higher contents of phenols (42.42 vs 29.8 mgGAE/g), flavonoids (12.43 vs 2.07 mgQE/g), and alkaloids (0.17 vs 0.07 mgATE/g) were found in the ethyl acetate than in the n-butanol fraction. the evaluated findings collectively indicate that the ethyl acetate and n-butanol fractions are endowed with antidepressant-like activity due to the presence of phenols, flavonoids, and alkaloids, which are medium polar in nature.[14]

Anti-inflammatory activity

Investigated the screening different solvents extract of Carissa carandas fruit for their phytochemical and pharmacological activity especially the anti-inflammatory activity of the fruits at 3 different stages of maturation. The n-hexane and chloroform extracts of immature, mature and ripe fruits showed positive tests for steroids and triterpenoids, whereas acetone extract showed positive tests for steroids, triterpenoids, alkaloids, tannins, sugar, saponins except for triterpenoids in immature fruits. The hydroalcoholic extract showed presence of alkaloids, tannins, sugars, saponin and flavonoids. The highest concentration of phenol, flavonoids and ascorbic acid were found to be more in acetone extract of mature fruits and of carbohydrates in ripe fruits. The hydroalcoholic extract also exhibited similar pattern. The anti-inflammatory property was evaluated by using different models like carrageenan induced paw edema in Wistar rats and cotton pellets induced granuloma. There was a consistent increase in % inhibition of inflammation at concentrations of 100 and 200 mg/kg up to 3 h. The highest activity was at 3 h with 200 mg/kg dose. Thus the present work has clearly proved that the acetone extract of mature fruits have considerable anti- inflammatory activity.[15]

Evaluated the potential of *Carissa carandas* Linn. as a natural anti-aging, antioxidant, and skin whitening agent was studied. Various parts of *C. carandas*, including fruit, leaf, seed, and pulp were sequentially extracted by maceration using *n*-hexane, ethyl acetate, and ethanol, respectively. High-performance liquid chromatography, Folin– Ciocalteu, and Dowd method were used to investigate their chemical compositions. The inhibitory activities of oxidation process, matrix metalloproteinases (MMPs), elastase, hyaluronidase, and tyrosinase

were analyzed. Cytotoxicity was determined by 3-(4,5- dimethylthiazol-2-yl)-2,5 diphenyl tetrazolium bromide assay in a human epidermal keratinocyte line (HaCaT). The results exhibited that ethyl acetate could extract the most ursolic acid from *C. carandas*, while ethanol could extract the most phenolics and flavonoids. The leaf extract had the highest content of ursolic acid, phenolics, and flavonoids. The leaf extracted with ethyl acetate (AL) had the highest ursolic acid content (411.8 mg/g extract) and inhibited MMP-1, NF-kappa B, and tyrosinase activity the most. Ursolic acid has been proposed as a key component in these biological activities. Although several *C. carandas* extracts are beneficial to human skin, AL has been proposed for use in cosmetics and cosmeceuticals due to its superior anti-wrinkle, anti-inflammation, and whitening properties.[16]

Evaluated the total phenolic content, antioxidant capacity (DPPH, ABTS, and FRAP), and the bioactive compounds present in the various extracts of *C. edulis* (HEC, MEC, AEC, and PC). An HPLC analysis determined the different compounds present in the extracts. High concentration of total phenolic content was observed in aqueous and methanolic extracts more than in the hydroethanolic extract though not significantly different. Flavonoids were higher in the hydroethanolic and methanolic extracts, respectively, with 14.84 mg RE/g extract and 12.02 mg RE/g extract. Tannins were also found in large amounts in the same two extracts with 26.76 mg TAE/g extract and 34.67 mg TEE/g extract. The percentage radical scavenging activity DPPH ranged between 58.63% and 94.67% for aqueous extract and for ABTS between 51.39% and 94.12% for the methanolic extract. The highest FRAP was obtained in the methanolic extract (6.73 g AAE/100 g extract). HPLC analysis revealed the presence of quercetin, rutin, and gallic acid in the different extracts. *C. edulis* represents a potential source of bioactive components with antioxidant capacity.[17]

There is a clear trend towards increasing consumption of juices as they can reduce imbalance of redox potential and provide necessary health benefits to consumers. Levels of karwanda (*Carissa congesta* Wight) and vegetable juices were varied to prepare nine different formulations of ash gourd-karwanda (AgK) and bottle gourd-karwanda blends (BgK) of higher nutritive, sensory qualities and storability. Total polyphenols (TP), antioxidant activity (AOA), total soluble solids and acidity were increased significantly($p \leq 0.05$) with addition of karwanda. AgK blend (35:35) and BgK blend (35:30) were selected based on their higher overall acceptability, TP and AOA. AgK blends had higher α- amylase (31%) while BgK blends had higher α-glucosidase (43%) inhibitory activities. Concentration of TP and

anthocyanins decreased significantly ($p < 0.05$), AOA remained unchanged and anti-inflammatory activities decreased (33–38%) in AgK and BgK blends during accelerated storage at 50 °C for 12 days. Addition of sugar in BgK blend decreased stability of TP (11%), flavonoids (31%) and anthocyanins (8%). During in vitro gastrointestinal digestion, TP, flavonoids and anthocyanins reduction rate was significantly higher for BgK blend with sugar.[18]

Reported the total phenolic content (TPC), antioxidation, antiaging, and antibacterialactivities of *Carissa carandas* Linn., and aims at the novel plant sources which is utilized for their cosmeceutical applications. The two conditions (fresh and dried) and three stages (unripe, ripe, and fully ripe) of *C. carandas* were extracted by ethanolic maceration. Folin– Ciocalteu assay was used for determining the TPC. 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assays were used for estimating antioxidant activity. The inhibitory tyrosinase activities were measured using the modified dopachrome assay. Antiaging was evaluated by inhibition of collagenase and elastase, and antibacterial activities. The result of six extracts from *C. carandas* showed that the highest phenolic content and elastase inhibition of the fresh fruit in fully ripe stage were 100.31 ± 2.64 mg GAE/g extract and 14.11% ± 0.95%, respectively. The fresh fruit in the unripe stage showed that the strongest percentage of DPPH IC_{50} and collagenase inhibitory activity were 29.11 ± 0.23 µg/mL and 85.94% ± 2.21%, respectively. The ethanolic extract ofunripe dried fruit exhibited the highest antioxidant activity in the of ABTS assay, with anIC_{50} of 0.17 ± 0.01 µg/mL. The MBC displayed the dried fruit ripe stage anti *Cutibacterium acnes, Staphylococcus epidermidis,* and *Staphylococcus aureus* strains were 25.0, 25.0, and 16.25 mg/mL, respectively. The fresh fruit in the ripe stage showed that the strongest inhibition tyrosinase was 93.88% ± 5.64%. The conclusion of this research indicates that the fresh fruit of *C. carandas* fruit extracts has high potential as a novel cosmeceuticals' applications to antiaging and skin whitening. The dried fruit in ripe stage extract has the most effective ingredient for antiacne products.[19]

Antiulcer activity

Investigated the antiulcer as well as antioxidant activity from natural origin has also been increased due to having certain side effects, adverse effects, drug interaction of allopathic drugs. The main objective of the present study includes investigation of antiulcer and antioxidant activities of 60 % ethanolic leaves extract of Carissa carandas Linn. Antiulcer

activity was investigated using ethanolic acid induced gastric ulcer model. Carissa carandas Linn. Showed protection index of 42.45%, 47.17 % and 64.15 % at the dose of 100, 200 and 400 mg/kg respectively while standard drug omeprazole also showed a protection index of 73.59 % which were statistically more significant. The antioxidant activity was investigated using DPPH free radical scavenging assay. The IC50 values of extract as well as ascorbic acid were 15.01 µg/ml as well as 3.56 µg/ml respectively. Further studies can be carried out for identification and isolation of compounds of Carissa carandas Linn. which are responsilble for such activities.[20]

Wound healing Activity

Investigated in vivo wound healing and antimicrobial properties of methanolic extract of Carissa spinarum. the effect of methanolic extract of Carissa spinarum root extracted by cold maceration was evaluated on burn wound model in mice. The wound healing activity of 1% and 2.5% (w/w) extract was assessed by the rate of wound contraction, period of epithelization and hydroxyproline content. Histological study of the granulation tissue was carried out to know the extent of collagen formation in the wound tissue. The antimicrobial activity of extract was also studied against the bacterial and fungal strain using agar dilution method. the results showed that Carissa spinarum root extract has significant wound healing activity as evident from the rate of wound contraction and epithelization. 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. this study provides a scientific rationale for the traditional use of Carissa spinarum in the management of wounds.[21]

Investigated the methanolic (1% and 2.5%) extract of *C. spinarum* root extract against a burn wound mice model and observed wound contraction and epithelisation, therefore proving the significant wound healing potential of the root extract. Subsequently, the in vivo toxicity (acute as well as subacute) of the root extract of *C. spinarum* in Swiss albino mice was evaluated by Gebrehiwot. According to the researchers, the hydro- methanolic and chloroform extracts at a 5000 mg/kg dose did not produce significant physical and behaviour changes, and no death was recorded. Whereas, in sub-acute toxicity studies, the extracts showed an insignificant change ($p > 0.05$) of haematological and physical parameters in the treated groups when associated with the control groups. Shamim also studied the acute, subacute, and sub-chronic toxicological studies of the ethanolic extracts of

C. carandas leaves. The authors reported that the extracts at 1750 and 5000 mg/kg did not exhibit any mortality in the acute toxicity evaluation, whereas subacute toxicity exhibited no signs of toxicity and mortality in the treated group, contrary to the control ones at 5000 mg/kg. On the other hand, chronic toxicity (5000 mg/kg) showed some changes in the histological parameters. The ethanolic extract of *C. spinarum* roots at 2000 mg/kg exhibited no toxicity or behavioural changes in Wistar albino rats during 14 days of treatment. They have an important regulatory role and are therefore seen as therapeutic goals of *Carissa* species to control the wound healing processes in the future.[22]

Anthelmintic activity

Evaluated the in-vitro anthelmintic potency of the petroleum ether (60-80), chloroform and ethanolic unripe fruits extract of Carissa carandas Linn using Indian earthworms (Pheretima posthuma). The various concentrations (50, 100, and 150 mg/ml) of the different solvent extract were tested in in-vitro for anthelmintic potency by determination of time of paralysis and time of death of worm. Piperazine citrate (15mg/ml) used as standarddrugs. The result of present study indicates that the unripe fruits extract of Carissa carandas Linn Potentiate to paralyze earthworm and also caused its death after some time. The shortesttime of paralysis was observed at higher dose (150 mg/ml) of ethanolic extract (EECC), chloroform extract (CECC) and pet. ether extract (PEECC) i.e., found to 56.35 min, 40 min and 22.35 min respectively. The result showed that EECC took less time to cause paralysis of the earthworm than that of other unripe fruits extract of Carissa carandas Linn due to the availability of some important phytoconstituents. Thus the present studies demonstrate that the unripe fruits extract of Carissa carandas Linn having an anthelmintic has been confirm on Pheretima posthuma.[23]

Anthelmintic activity

Reported the anthelmintic activity of the Imethanolic extract of the root bark of *Carissa carandas* was evaluated on adult Indian earthworm (Pheretima posthuma) using albendazole as a reference standard. The extract caused paralysis followed by the death of worm at the tested dose level. The extract at the highest tested concentration has anthelmintic activity comparable with that of standard drug albendazole.[24]

CONCLUSIONS

This review article concludes that crude extracts from different parts of *Carissa* species possess significant anti-inflammatory, antiarthritic, adaptogenic, antidiabetic, antimalarial,

antispasmodic, anticonvulsant, and antiviral activities in in vitro as well as in vivo conditions. However, the mechanism of action of extracts/phytocompounds for their antioxidant, antimicrobial, anticancer, and cardioprotective potential using different model systems is still required.

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