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TREATMENT OF VARIOUS DISEASES BY *CARISSA SPINARUM* L. - A PROMISING SHRUB

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ABSTRACT: *Carissa spinarum* L. is a small spinous evergreen shrub growing throughout India in dry regions. The plant used locally in Indian and Chinese system of medicines to cure various diseases. *Carissa spinarum* has also been used in the Ayurvedic medical system because of its therapeutic effects against liver disease, epileptic disease, microbial disease, cytotoxic, viral diseases. The isolated metabolites and crude extract have exhibited a wide of *in vitro* and *in vivo* pharmacological effect, including antioxidant, antimicrobial, antiviral, anticonvulsant, anticancer, antiarthritic, antihelminthic, cytotoxic activity. A chemical study of this plant was then initiated, and this led to the isolation of 12 compounds, including a coumarin, two cardiac glycosides and nine lignans. These isolated compounds were evaluated for several biological activities, including antihyperthermic, cytotoxic, antioxidant and antibacterial effects. A shrub, *Carissa spinarum* have emerged as a good source of the traditional medicines for the treatment of inflammation, arthritis, microbial infection, epilepsy, viral infection, cancer disease. Pharmacological results have validated the use of this species in the traditional medicines. Some bioassays are difficult reproduce because the plant materials used have not been well identified; therefore analytical protocol and standardization of extracts should be established prior to biological evaluation. Root, stem and leaf of this shrub should receive more attention. Expansion of research materials would provide more opportunities for the discovery of new bioactive principles from the *Carissa spinarum*.

INTRODUCTION: Plants and their secondary metabolic constituents have a long history of use in modern medicine and in certain systems of traditional medicine, and are the sources of important drugs such as atropine, codeine, digoxin, morphine, quinine and vincristine¹.

India is sitting on a gold mine of well-recorded and well-practiced knowledge of traditional herbal medicine. But, unlike China, India has not been able to capitalize on this herbal wealth by promoting its use in the developed world despite their renewed interest in herbal medicines².

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Plant-derived substances have recently become of great interest owing to their versatile applications. Medicinal plants are the richest bio resource of drug of traditional systems of medicine, modern medicines, nutraceuticals, food supplements, folk medicines, pharmaceutical intermediates, and chemical entities for synthetic drug³.

Plant profile:

Synonyms: *C. diffusa* Roxb, *C. ovata*, *C. brownii*, *C. edulis*, *C. opaca*.

Family: Apocynaceae – the oleander family

Common names: Currant Bush, Conker berry, Bush Plum, Burrum Bush, Wild Karaunda ⁴.

Taxonomical Hierarchy ⁵:

Kingdom	:	<i>Plantae</i>
Subkingdom	:	<i>Viridiaeplantae</i>
Phylum	:	<i>Tracheophyta</i>
Class	:	<i>Magnoliopsida</i>
Subclass	:	<i>Asteridae</i>
Order	:	<i>Gentianales</i>
Family	:	<i>Apocynaceae</i>
Genus	:	<i>Carissa</i>
Species	:	<i>Spinarum</i>

Vernacular names ^{6,7}:

Andhra Pradesh:	<i>Vaka, kalivi, kalli;</i>	
Bengal	:	<i>Karamacha;</i>
Gujarat	:	<i>Karmarda;</i>
Karnataka	:	<i>Karekayi, garji, kavali;</i>
Maharashtra	:	<i>karavada, karanda, karwant;</i>
Himachal Pradesh:	<i>karondhu, garna, kharnu;</i>	
Hindi	:	<i>Karunda;</i>
Sanskrit	:	<i>Karamarda, avighna;</i>
Tamil Nadu	:	<i>Kalakkay, kalachedi.</i>

Botanical studies:

Distribution: Thorny bushes of *C. spinarum* L. are found commonly growing in the forests and wastelands up to elevations of 1,500 meters. They are highly drought-resistant. They bear small fruits which are eaten by all and are also offered for sale at many places.

This shrub is found wild in most parts of India, especially in the dry foothills of the Punjab, the sub-Himalayan tract up to 4,000 feet in the trans-Indus territory and also on the coast of the southern Andaman (**Fig. 1**) *Carissa spinarum* L. ⁸.



FIG: 1 *CARISSA SPINARUM* L.

Morphology: An erect thorny shrub, with forked branches, 2-3 meters in height; wood, very hard; bark, light brown to green, can be stripped off longitudinally by hand, exposing the white to light-green wood underneath; thorns, 3.2 cm long, brown to greenish at the base and deep brown towards the tip.

Leaves ovate, 4.5 cm long, 2.5 cm broad, leathery, venation, reticulate pinnate; margin, entire; petiole 3 mm long; leaves exuding white latex, when plucked from the stem.

Flowers, short-stalked, sweetly scented, bisexual, complete, bracteates, cyclic, actinomorphic, their color varying between white and camellia rose 622; inflorescence, terminal or a corymbs cymes, with about 10 flowers; calyx, polysepalous, with 5 sepals, green, companulate, 2 to 3 mm, long; corolla, tubular at the base, dilated at the top, five-lobed, glabrous, white, the dilation of corolla 8 to 9 mm; androecium, with 5 stamens, each 2 to 3 mm long, inserted near the neck of the tubular portion of the corolla; gynoecium, one, superior, 7 to 8 mm long, with a spindle-shaped stigma. Fruit, an ovoid berry, 9 mm in length, 6 mm in diameter, 642 mg in weight, 586 microlitres in volume; fruit color, hyacinth blue 40; pulp, scarlet 19/2; juice, shrimp red 616/3.

Seeds lanceolate, 5 to 6 mm in length, 4 mm in diameter, black, each 28 mg in weight, 42 microlitres in volume⁸.

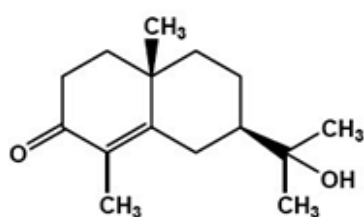
The flowering and fruiting season: Generally, the flowering takes place during April and May. In some cases, it might start even by the end of July. The peak flowering season, however, was observed to occur by the middle of May. The small fruits take a lot of time to develop and mature. They start ripening from November and continue to do so till the end of January. Mature fruits were also observed on some bushes as late as April. These fruits were, probably, the outcome of the July blossoming⁸.

Yield: The average yield of medium-sized bush is *C. spinarum* L. was found to be 272 grams.

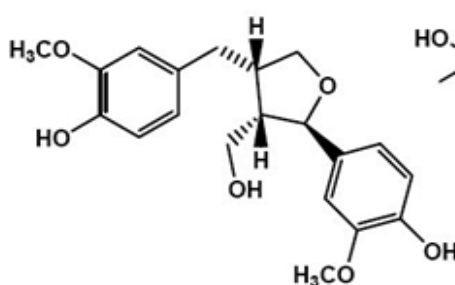
Chemical Constituents:

Chemical composition of the fruit: The fresh fruits contain acids, sugars, reducing sugars, non-reducing sugars, tannins, pectin and vitamin C. carissol (an epimer of α -amyrin), lupeol, oxalic, tartaric, citric, malic, malonic and glycolic acids, glycine, alanine, phenyl alkaline, cerine, glucose and galactose.

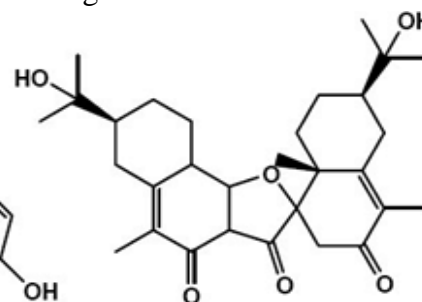
Chemical composition of the Root: Carissone, carindone, carinol, odoroside H, digitoxigenin, glucose and D- digitalose.



CARISSONE



CARINOL



CARINDONE

Chemical composition of the Seed: Fatty acids, viz., palmitic, stearic, oleic, arachidic, linoleic acids.

Chemical composition of the Leave: Triterpene alcohol, ursolic acid.

Chemical composition of the Flower: myrcene, limonene, camphene, canene, dipentene, farnesol, nerolidol, dihydrojasnone, α -terpeneol, citronellal, β -ionone, nerylacetate, linalool and geranyl acetate⁹.

Medicinal properties: The roots of *C. spinarum* L. are reported to be many medicinal uses. They are ground and put into the wounds of cattle to kill

worms. It is also used in combination with the roots of some other medicinal plants to treat rheumatism by the *mundas* (a tribe) of Chhota Nagpur. It is a strong purgative and is used as one of the ingredients in some purgative preparations. A large dose of the roots of *C. spinarum* L. may even prove fatal owing to profuse purging. The roots also act as a repellent in the case of snakes, when the roughly ground powder of the roots mixed with water is poured into the holes of snakes⁸.

The medicinal uses, commercial uses, edible uses and other uses of *C. Spinarum* whole plant are given in **Table 1**.¹⁰

TABLE 1: THE MEDICINAL USES, COMMERCIAL USES, EDIBLE USES AND OTHER USES OF *C. SPINARUM* WHOLE PLANT

Description	Form of application	Use
Medicinal Uses	Root extract	Purgative, Wounds in animals
	Glycosidal extract	Cardio tonic
Commercial Uses	leaves and fruits	Garlands
	Fruit	Pickles
	Leaf	Syrup, Jelly, Preserves
	Plant	Fodder for goats, Fodder for sheep
Edible Uses	Raw	Tanning industry
	Ripe	Hedge plant, Fragrant flower, Cover crop in dry rocky areas
	Fresh flower	Pickles
Other Uses		Syrup, Jelly, Preserves
		Personal adornment

Dessert quality: The fruits are eaten along with the seeds. They are sweet in taste and of fairly good quality.

Utilization: As stated earlier, the small fruits of *C. spinarum* L. are commonly eaten and are also offered for sale at certain places. As it is evident from the chemical composition of the fruit, it is highly nutritious and is a very good source of protein. The content of total soluble solids is very high and indicates the possibility of this wild fruit being dehydrated and processed. Research should be taken up in this direction.

The bushes of this wild plant are thorny and are very effective as a fence and are mainly used in the villages for this purpose. These bushes are very hardy and drought-resistant and can grow even on very poor and rocky soils. Therefore they can be used for afforestation in soil conservation. The leaves are fairly rich in tannins (9-15 per cent) and constitute a promising tanning material, particularly in combination with other tanning stuffs, such as the twigs and bark of *Embllica officinalis* Gaertn⁸.

Family Apocynaceae: Trees, shrubs, or vines, rarely sub shrubs or herbs, with latex or rarely watery juice. The Leaves simple, opposite, rarely whorled or alternate, pinnately veined; stipules absent or rarely present. Inflorescences cymose, terminal or auxiliary, with bracteoles. Flowers are bisexual, 5- [or 4]-merous, actinomorphic. Calyx 5- or rarely 4-partite, quincuncial, basal glands usually present. Corolla 5- or rarely 4-lobed, salver form, funnel form, urceolate, or rarely rotate, lobes overlapping to right or left, rarely valvate.

Stamens 5 or rarely 4; filaments short; anthers mostly sagittate, free or connivent into a cone adherent to pistil head, dehiscent longitudinally, base rounded, cordate, sagittate, or prolonged into an empty spur; pollen granular; disc ring like or cup-shaped, 2-5-lobed, or absent. Ovaries superior, rarely half-inferior, connate or distinct, 1- or 2-locular; ovules (1 or) 2-numerous per locule Style 1; pistil head capitate, conical, or lampshade – shaped, base stigmatic, apex 2-cleft and not stigmatic.

Fruit a berry, drupe, capsule, or follicle. Seeds with or without coma; endosperm thick and often horny, scanty but sometimes absent; embryo straight or nearly so, cotyledons often large, radical teretes.

Fruit type is highly diversified in the family, and it is diagnostic of many genera. Genera 1-4 produce 1, 2-celled berries from a flower; genus 5 produces 2, 1-celled berries from a flower; 6 and 7 produce mostly fleshy follicles containing deeply indented seeds with ruminant endosperm; 8 has follicles and winged seeds; 9 produces follicles and seeds with 2 comas; 10-12 have follicles with globose seeds; 13-18 have drupes mostly with fleshy mesocarp; 19 has samaroid fruit; 20 has spiny capsules with seeds winged all around; and 21-44 have free or fused follicles and comose seeds. Double flowers are known only from cultivated forms of *Nerium oleander*, *Tabernaemontana divaricata*, and *Wrightia religiosa*.

Plants of the Apocynaceae are often poisonous and are rich in alkaloids or glycosides, especially in the seeds and latex. Some species are valuable sources of medicine, insecticides, fibers, and rubber. About 155 genera and 2000 species distributed primarily in the tropics and subtropics, poorly represented in the temperate regions. Of the 44 genera and 145 species present in China, one genus and 38 species are endemic, and nearly 95% of the taxa grow in the southern in the southern and southwestern portions of the country¹¹.

Genus Carissa: Shrubs are climbers, or small trees, mostly spiny, branches dichotomous. Leaves opposite; petiole 2-3 mm. Cymes terminal or auxiliary, dichotomous, pedunculate, usually many flowered. Flowers are 5- [or 4]-merous, Calyx without gland or rarely with many basal gland inside. Corolla salver form, tube cylindrical, dilated at stamina insertion, lobes overlapping to left or to right. Stamens included in throat; anthers lanceolate, obtuse or apiculate, base not appendage; disc absent. Ovary are 2-loculed; ovules 1-4 in each locule, rarely numerous, biseriate. Style are fili form; pistil head narrowly oblong or fusi form, apex shortly 2-cleft. Berries are 1- [or 2]-loculed. Seeds are 2 or more, peltate; endosperm fleshy; cotyledons ovate, radicle inferior. About 30 species: tropics and subtropics of Africa, Asia, and Australia; four species in China¹².

Species spinarum: A bushy shrub or tree with rigid spreading branches armed with straight thorns. This evergreen plant found throughout the hotter parts of India and sub-Himalayan region. It is also observed in Andaman Islands.

Light grey fibrous barks, white or pink fragrant flowers in clusters. Berries dark purple or black. It can be cultivated in gardens, mostly as hedges for its fragrant flowers and edible berries. Berries make good tarts, syrups, jellies or a cooked preserve. Flowers are used for personal adornment.

Leaves are used in tanning industry and as fodder for sheep and goats. It is also suitable for rock gardens and fencing¹⁰.

Pharmacological studies done so far on *Carissa spinarum* L.: The pharmacological studies done so far on *Carissa spinarum* L. are given in **Table 2**.

TABLE 2: THE PHARMACOLOGICAL STUDIES DONE SO FAR ON *CARISSA SPINARUM* L.

S. No.	Pharmacological Activity	Plant part/ Extract	Model/ Dose	Standard Drug	Result	References
1.	Antiarthritic activity	Root/ Ethanolic extract	Freund's adjuvant induced-polyarthritis (100,200 and 400 mg/kg,p.o.)	Phenylbutazone	The extract of <i>C. spinarum</i> possesses anti-arthritic properties.	13
2.1.	Anticonvulsant	Root/ Ethanolic extract	MES, PTZ & PC - induced seizures (100, 200 and 400 mg/kg, p.o.)	Diazepam and phenobarbitone	The <i>C. spinarum</i> may possess significant anticonvulsant activity via non-specific mechanisms.	14
2.2.	Anticonvulsant	Root bark/ Ethanolic extract	MEST & PTZ (5, 20 mg/kg)	Benzodiazepine	The <i>C. edulis</i> extract possesses biologically active constituent that has anticonvulsant activity.	15
3.1.	Hepatoprotective	Root/ Ethanolic extract	CCl ₄ and PCM-induced (100, 200 and 400 mg/kg)	Silymarin	The extract of <i>C. spinarum</i> was confirmed the Hepatoprotective activity by the decrease in liver wet weight and histopathological examination.	16
3.2.	Hepatoprotective	Leaves/ Methanolic extract	CCl ₄ induced (200 mg/kg)	Silymarin	The extract of <i>C. spinarum</i> was significant protective effect against CCl ₄ induced hepatotoxicity in rats.	17
4.1.	Antioxidant	Fruit/ chloroform and aqueous fractions	DPPH, (25-250 µg/ml)	Ascorbic acid	The chloroform and aqueous fractions have strong antioxidant activities.	18
4.2.	Antioxidant	Root/ Ethanolic extract	CCl ₄ and PCM-induced (100, 200 and 400 mg/kg)	Silymarin	The <i>C. spinarum</i> possesses strong antioxidant activity.	16
4.3.	Antioxidant	Stem/ Chloroform extract	DPPH (47.03 µg/ml)	-----	The chloroform extract of <i>C. spinarum</i> displayed strong antioxidant activity.	19
5.	Anthelmintic	Root/ Methanolic and chloroform extract	Indian adult earthworms <i>Pheretima posthuma</i> (100 mg/ml) and (50 and 100 mg/ml)	Piperazine citrate	The <i>C. spinarum</i> extract showed anthelmintic activity on <i>Pheretima posthuma</i> .	20
6.	Wound healing	Root/ Methanolic extract	Burn wound model 1% and 2.5% (w/w)	Plain ointment base	The <i>C. spinarum</i> extract has significant wound healing activity as evident from the rate of wound contraction and epithelization.	21
7.1.	Antimicrobial	Root/ Methanolic extract	Agar dilution method (125, 512, 110, 165 and 256 µg/ml)	Silver sulfadiazine	The <i>C. spinarum</i> extract has significant antimicrobial activity against all the tested microorganisms.	21
7.2.	Antimicrobial	Fruit/ ethanolic extract	Disc diffusion assay (15±1mm, 14±1mm and 13±1mm)	Silver sulfadiazine	The <i>C. opaca</i> extract have considerable efficacy against various pathogenic bacteria.	22
7.3.	Antimicrobial	Leaves and fruits/ Aqueous extract	Cup plate method (3, 4% w/v)	Silver sulfadiazine	The <i>C. edulis</i> extract justify the use of the plant in the treatment of microbial infections in ethno medicine.	23

8.	Diuretic effect	Root bark/ Methanol extract	Urinary electrolyte excretion induced (1000mg/kg)	Hydrochlorothi azide	The result support the ethnomedical use of <i>C. edulis</i> extract as a diuretic agent.	24
9.	Antidiabetic	Leaves/ ethanolic extract	STZ induced (2000mg/kg)	Glibenclamide	The <i>C. edulis</i> extract to diabetic rats lowered the blood glucose level after 3 h of treatment.	25
10.	Antibacterial	Leaves/ Methanol extract	Agar well diffusion method (200mg/kg)	Cefotaxime	The <i>C. opaca</i> extract contain a large proportion of hydroxy acetophenone along with other chemical compound which might be responsible for antibacterial activity.	26
11.1.	Antiviral	Roots/ Aqueous extract	Murine model (250mg/kg)	Acyclovir	The <i>C. edulis</i> extract suggest that this herbal extract has potent anti- viral agent against herpes simplex viruses.	27
11.2.	Antiviral	Stem, Root bark/ Aqueous extract	Plaque inhibition assay (40 to 80 $\mu\text{g/ml}$)	Gancyclovir	The <i>C. edulis</i> extract have potential anti-viral activities.	28
11.3.	Antiviral	Root bark/ diethylether and methanol	HSV-1 infection model (2.98- 4.2 $\mu\text{g/ml}$)	Acyclovir	The <i>C. edulis</i> indicate promising antiviral activity of lupeol.	29
12.	Anti-plasmodial	Root bark/ Methanol	chloroquin-sensitive (D6) strains (14.53 $\mu\text{g/ml}$)	chloroquine diphosphate	The <i>C. edulis</i> showed anti- plasmodium activity.	30
13.	Erythropoietic effect	Root bark/ Etanol	Phenylhydrazine- induced anemic (100, 300 and 1000 mg/kg)	Bioferon	The <i>C. edulis</i> has erythropoietic activity with normocytosis.	31

Toxicity: There was no mortality amongst the graded dose groups of animals and they did not show any toxicity of behavioral changes at a dose level of 2000mg/kg. This finding suggests that the ERCS is safe in or non-toxic to rats and hence doses of 100, 200 and 400 mg/kg, p.o were selected for study^{13, 14, 16}.

The evaluation of acute toxicity for the *Carissa edulis* extract at the therapeutic oral dose of 250 mg/kg in uninfected male and female Balb/C mice. The results indicate that there was no significant difference in the mean weights of mice given an oral dose of extract at 250mg/kg and the control that were given no drug in both sexes of mice²⁷.

The median lethal dose (LD₅₀) of the *Carissa edulis* extract in mice was found to be 282.8 mg/kg body weight administered intraperitoneally. At 1000 mg/kg dose there was 100% mortality and the minimum dose that killed a rodent was 100 mg/kg. The oral LD₅₀ value for *Carissa edulis* was above 5000 mg/kg¹⁵.

CONCLUSION: The present review discusses the pharmacological aspect of the shrub *C. spinarum* and especially provides a detail analysis of the literature published since the year 1771. Glycosides, flavonoids, saponins, triterpenoids, steroids, tannins and other phenolic compounds are commonly occurred in this species. Pharmacological studies carried out on crude extracts and pure metabolites provided pragmatic documents for its traditional uses, and have revealed this shrub to be a valuable source for medicinally important molecules.

Throughout our literature review, we observed that *C. spinarum* were inclined to dissimilar pharmacological functions. The *C. spinarum* possesses potent antimicrobial and nutritional evaluation. The *C. spinarum* is good treatment of Hepatoprotective, helminthic and cytotoxic diseases. The toxicity of *C. spinarum* shows no mortality amongst the dosed group of animals and they did not show any toxicity or behavioral changes at a dose level of 2000mg/kg. This finding probably suggests that the *C. spinarum* is relatively safe in or non-toxic.

Expansion of research materials would provide more chances for discovery of new bioactive principle from the *C. spinarum*.

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