



Carissa carandas: A multi-faceted approach to health, wellness, and commerce

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ABSTRACT

Carissa carandas (*C. carandas*), an Apocynaceae family member, fruit bearing crop is locally known as karonda in Asia, grown wild has gained attention owing to impressive nutritional composition and health benefits. A 100–200 g serving size of *C. carandas* meets 100 % recommended dietary allowance (RDA) of iron, zinc, manganese, copper, chromium, and vitamin C in all age groups, making it a promising candidate for addressing nutrient deficiencies across all age groups. Other than that it also contains significant amount of carbohydrates (61–67 %) sugars (4.7–13 % mainly reducing), fats (4.5–19 % mainly PUFA_s), and protein (1.6–3.2 %) despite remaining underutilized. *C. carandas* extracts reported to have antioxidant, anti-inflammatory, antimicrobial, and anti-tyrosinase potential comparable to the commercially available synthetic drugs. Therefore, this review aims to consolidate current knowledge on the nutritional profile and bioactive components of *C. carandas*, and to explore its importance in food technology sector. The study provides novel insights about the potential of *C. carandas* to address micronutrient deficiencies, boost local economies, and provide income for farmers. It also highlights its potential for sustainable agriculture, functional food development, and innovative products due to its antioxidant, antimicrobial, and anti-inflammatory properties.

1. Introduction

Carissa carandas (*C. carandas*) belongs to the Apocynaceae family and is an evergreen shrub that remained an underprivileged plant with significant economic, commercial, clinical, and nutritional potential [1]. It is also known as “Crane berry” (English), Karonda (Devanagari), Karonda (Hindi), Karamcha (Bengali), and Ci-Huang-Guo (Chinese). It is found to be widely distributed in tropical and subtropical regions of Pakistan, India, Sri Lanka, Myanmar, Bangladesh, and Nepal [2]. This plant has rhombus and conical leaves, white-colored flowers, and clusters (3–10) containing berry-like fruits [3]. The unripe fruit is pinkish white, which turns red to dark purplish when completely ripened. Fresh juice from ripened fruits is rich in vitamin C and iron so combats scurvy and iron deficiency [4]. The berry-sized fruits look attractive and are

usually an additive of condiments in pickles and spices in India. *C. carandas* fruit contains an appreciable number of macro- and micro-nutrients, organic acids, and pectin making this an ideal candidate in developing beverages, jams, jellies, and curries [5].

Traditionally, it is reported to cure upset stomach, neurological impairments, cardiogenic, anthelmintic, and anti-hypertensive [6,7]. Fruits of *C. carandas* known to have potential to treat piles, appetite loss, and calming nervous disorder (as a nervine), edema, colic, splenomegaly, hepatomegaly, amenorrhea, CVDs, brain anorexia in humans, and in treating fever [8–10]. It is used to treat epilepsy, diarrhea, dog bites, myopathic spasms, cough and colds, leprosy, itches, inflammation, malaria, and skin infections [4,5,9,11]. It is also known to restore female libido, fight microbial infections, and intestinal worms, recover liver functioning, and counter blood putrefaction and rheumatoid arthritis [4,

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[11]. Likewise, its leaves are reported to cure diarrhea, fever, ear, syphilitic ache, and snake poisoning [8,9]. The root portion improves digestion, cures scabies, intestinal worms, stomach disorders, diabetes, pruritis, and ulcers, and controls hypertension [10].

C. carandas an underutilized and neglected berry fruit contains an appreciable number of micro- (zinc, copper, manganese) and macro- (carbohydrates, protein, fat, fiber) nutrients [5]. In depth nutritional compositional analysis revealed that taking 100–200 g *C. carandas* fruit can meet 100 % recommended daily allowance of iron, zinc, copper, manganese, and vitamin C for all age groups. On the other hand, mentioned micronutrients i.e., iron and zinc deficiency is a major problem for public health throughout Asia. Nearly half of pregnant women and 40 % of preschoolers in Southeast Asia suffer from iron deficiency resulting anemia and zinc deficiency affects over 30 % of the population in South and Southeast Asia [12–15]. Despite 5538 food crops estimated worldwide, only 12 plants and 5 animal species produce 75 % of the world's food and 3 plant species provide more than 50 % of its food-energy needs. Continued crop variety loss in agricultural production systems makes global food systems insecure. Smallholder systems, which preserve locally adapted, climate-resilient varieties and breeds, are more vulnerable to shocks [16], compromising their role in feeding the globe sustainably. Bringing crop diversity in agricultural production by introducing neglected and underutilized crops can improve global food systems, more options for farming communities for addressing the evolving needs of households and markets, and ultimately a decline can be observed in nutrient deficiencies [16]. Moreover, *C. carandas* traditional medicinal claims are well supported by pharmacological evidences as discussed in detail in section 3 wherein its various extracts including methanol, ethanol, and water outlined biological potential comparable to the synthetic drugs. Therefore, present review aimed to raise awareness to increase *C. carandas* consumption and demand, promote dietary diversity by incorporating this neglected species into diets, which can contribute to overall nutritional well-being and food security. The current analysis gives novel insights into *C. carandas* for addressing micronutrient deficiencies, which are a major public health problem in impoverished nations. The assessment also noted how *C. carandas* may be a beneficial crop for sustainable agriculture, boosting local economies and providing a source of income for farmers, thereby driving further research and investment in its production and commercialization. This study provides novel insights to utilize this neglected berry in the development of functional foods, natural preservatives, and innovative food products owing to its great antioxidant, antimicrobial, anti-tyrosinase and anti-inflammatory properties and potential for sustainable harvesting.

2. Nutritional composition and phytochemical contents

C. carandas fruit contains an appreciable amount of carbohydrates, fat, minerals, and vitamin C but moderate source of protein and fiber contents (Table 1). Carbohydrates, fat, protein, fiber, ash and total sugars on fresh and dry weight basis (f.w. and d.w.) were found to be 61 %–67 % f.w. and 16 %–28 % d.w., 4.5 %–19 % f.w. and 2.5 %–6.6 % d.w., 2 %–6.5 % d.w. 1.6 %–3.2 % f.w. 1.3 %–15 % d.w. and 0.6 %–1.4 %, 0.5 %–4.5 % d.w. and 0.5 %–1.8 % f.w., 8 %–9 % d.w., and 4.7 %–13 % f.w. respectively. Vitamin C contents were between 6.9 mg/100 g to 72 mg/100 g on a fresh weight basis. Moreover, a notable amount of macro- and micro minerals was also reported in *C. carandas* fruit [17–20].

C. carandas fruit intake can fulfill the RDA of certain minerals and vitamin C. The adequate intake (AI) of chromium for men and women (19–30 years) is 0.035 mg/day and 0.025 mg/day respectively. One serving (1 g) of *C. carandas* contains 0.0462 mg of chromium fulfilling almost 100 % daily need. AI of chromium for pregnant women aged (19–30) is 0.030 mg/day [21] which can be obtained from 1 g *C. carandas* fruit on d.w. basis. Copper, another important mineral, is also present in considerable amounts. Copper deficiency onsets defects in connective tissues that lead to vascular and skeletal problems, anemia

Table 1
Nutritional profile of *C. carandas* fruit.

Nutrient	Amount d.w.	Amount f.w.	Reference
Primary metabolites			
Carbohydrates	67 %	–	[5]
Carbohydrates	–	35 %	[17]
Carbohydrates	61 %	16 %	[18]
Carbohydrates	–	13 %	[19]
Carbohydrates	–	28 %	[17]
Carbohydrates	19 mg/100 g	–	[20]
Protein	2 %	–	[5]
Protein	5.6 g	–	[4]
Protein	2.07 %	–	[18]
Protein	–	3.5 g	[4]
Protein	–	3.2 %	[19]
Protein	–	1.68 %	[18]
Fat	10 %	–	[5]
Fat	4.47 %	–	[18]
Fat	19 %	–	[17]
Fat	7.5 %	–	[4]
Fat	–	1.94 %	[18]
Fat	–	6.62 %	[4]
Fat	–	2.5 %	[17]
Fiber	1.81 %	–	[5]
Fiber	4.9 %	–	[17]
Fiber	1.9 %	–	[18]
Fiber	1.31 %	–	[4]
Fiber	15 %	–	[20]
Fiber	–	1.4 %	[18]
Fiber	–	0.6 %	[4]
Fiber	–	1.01 %	[17]
Ash	0.78 %	–	[5]
Ash	4.9 %	–	[17]
Ash	0.53 %	–	[4]
Ash	2.12 %	–	[18]
Ash	–	0.51 %	[4]
Ash	–	1.32 %	[18]
Ash	–	1.8 %	[17]
Total sugars	11.58 %	–	[5]
Total sugars	9.0 %	–	[18]
Total sugars	8.05 %	–	[17]
Total sugars	2.2 %	–	[4]
Total sugars	–	13 %	[18]
Total sugars	–	1.7 %	[4]
Total sugars	–	4.9 %	[17]
Minerals			
Calcium	160 mg/100 g	–	[5]
Calcium	261 mg/kg	–	[4]
Calcium	2.6 mg/kg	–	[17]
Calcium	–	16mg/100 g	[3]
Calcium	–	11 mg/g	[1]
Calcium	–	24 mg/kg	[17]
Iron	3.14 mg/kg	–	[17]
Iron	39 mg/100 g	–	[5]
Iron	150 mg/kg	–	[4]
Iron	–	42 mg/kg	[17]
Iron	–	6.24 mg/100 g	[3]
Phosphorus	1095 mg/kg	–	[4]
Phosphorus	–	2845 mg/g	[1]
Phosphorus	–	24 mg/100 g	[3]
Sodium	777 mg/kg	–	[4]
Sodium	–	827 mg/g	[1]
Magnesium	1057 mg/kg	–	[4]
Magnesium	–	260 mg/g	[1]
Potassium	5863 mg/kg	–	[4]
Potassium	–	2662 mg/g	[1]
Potassium	–	79 mg/kg	[17]
Manganese	17 mg/kg	–	[4]
Manganese	257 mg/kg	–	[17]
Manganese	–	0.9 mg/g	[1]
Manganese	–	533 mg/kg	[17]
Zinc	44 mg/kg	–	[4]
Zinc	133 mg/kg d.w.	–	[17]
Zinc	–	17 mg/g	[1]
Zinc	–	413 mg/kg	[17]
Copper	15 mg/kg	–	[4]
Copper	–	3.31 mg/g	[3]

(continued on next page)

Table 1 (continued)

Nutrient	Amount d.w.	Amount f.w.	Reference
Chromium	–	0.46 mg/g	[1]
Vitamin C	16 mg/100 g	–	[4]
Vitamin C	49 mg/100 g	–	[3]
Vitamin C	–	20 mg/100 g	[17]
Vitamin C	–	6.9 mg/100 g	[4]
Vitamin C	–	72 mg/100 g	[17]

d.w. dry weight, f.w. Fresh weight.

associated with defective iron utilization, and possibly specific aspects of CNS dysfunction [22,23].

Evidence suggested that immune and cardiac dysfunction occurs in experimental copper deficiency and the development of such signs of deficiency has been demonstrated in infants [24,25]. Osteoporosis was observed in copper-deficient infants and growing children. The RDA of copper for adults (19–50) is 700 µg/day (0.7 mg/day) and for lactating mothers (19–30 years) 1 mg/day. While 100 g of *C. carandas* powder contains 0.3 mg copper meeting about 50 % and 35 % RDA in adults and lactating mothers respectively. Similarly, the RDA of iron for all age groups of men and postmenopausal women is 8 mg/day, necessary for physical growth, neurological development, cellular functioning, and synthesis of some hormones [26,27]. A 50 g *C. carandas* fruit powder fulfills about 100 % of the dietary needs of iron in males (19–50 years) and 50 % in females. Moreover, the RDA of iron for pregnant women aged (19–30 years) is 22 mg/day. About 100g of *C. Carandas* adequately satisfies approximately 65 % of the RDA of iron in pregnant women. Likewise, manganese is a cofactor for many enzymes, including manganese superoxide dismutase, arginase, and pyruvate carboxylase [28, 29]. It is involved in the formation of bone and amino acids, lipid, and carbohydrate metabolism. The AI of manganese for male adults is 2.3 mg/day and 1.8 mg/day respectively. About 100 g of *C. carandas* provides 1.7 mg of manganese meeting a substantial portion of daily need. Zinc is involved in many aspects of cellular metabolism. It is required for the catalytic activity of many enzymes and plays a role in enhancing immune function, protein and DNA synthesis, wound healing, and cell signaling and division [30–32]. The RDA for zinc is 11 mg/day for males (31–50 years) 8 mg/day for females (31–50 years) and 9.5 mg/day for pregnant women (19–30 years) [21]. 100 g of *C. carandas* powder can provide 13.36 mg of zinc, which is enough to overcome zinc deficiency. The National Institution of Health (NIH) recommends about 400 mg/day magnesium, for males and 310 mg/day for females. *C. carandas* powder contains 65.6 mg/100g which can fulfil about 12 % of the dietary needs of magnesium. In addition to the minerals, *C. carandas* fruit is also a good source of Vitamin C, required for the maintenance of normal connective tissue and wound healing. Vitamin C also is needed for bone remodeling because of the presence of collagen in the organic matrix [33]. The NIH suggests RDA for Vitamin C as 90 mg/day for males and 75 mg/day for females. Hundred grams of *C. carandas* contains 72 mg of vitamin C and can satisfy more than half of the required dietary need for vitamin C in adults.

The phytochemical analysis of *C. caranda*'s anatomical parts revealed the presence of valuable secondary metabolites (Table 2). *C. carandas* are reported to contain a wide array of bioactive secondary metabolites that do not participate in the normal growth, development, or reproduction of plants but play a critical role in plant defense, interaction with the environment, and provide notable medicinal advantages. Table 2 provides a concise overview of the secondary metabolites that have been found in several components of *C. carandas*, including the leaves, roots, flowers, and fruit. The table classifies these metabolites into many categories, emphasizing the varied chemical characteristics and probable biological functions of these molecules. This classification offers a thorough summary of the many secondary metabolites found in said neglected berry fruit, which might be valuable for researchers studying phytochemistry and pharmacology. In detail,

Table 2

Phytochemical analysis of *C. carandas* anatomical parts.

Plant Part	Class/name of the Compound	References
Leaves	Organic compounds: Isobenzofuran, ethylbenzene, Benzenoids: o-Xylene, 1,2,4-trimethylbenzene, 4-hydroxybenzoic acid Steroids: Card-20(22)-enolide, Stigmasterol, β -Asarone, 24-Noroleana-3,12-diene, Lupeol, β -sitosterol-3-O- β -D-glucopyranoside Fatty acid (esters): Methyl 4-O-methyl-D-arabinopyranoside, n-Decanoic acid, 4-O-Methylmannose, Hexadecanal, Hexadecanoic acid, 8,11,14-Docosatrienoic acid, 9,12,15-Octadecatrienoic acid, (Z, Z, Z)-, 6-Octadecenoic acid, methyl ester, (Z), 9,12,15-Octadecatrienoic acid, 2-[[trimethylsilyl]oxy]-1-[[trimethylsilyl]oxy]methyl] ethyl ester, (Z, Z, Z)-, 5,8,11,14-Eicosatetraenoic acid, methyl ester (all-Z)-, 9,12-Octadecadienoic acid (Z, Z)-, Pentadecanoic acid, 14-methyl-, methyl ester, Prop-2-enyl Octadecanoate Ketone Esters: Hexanoic acid, 3-oxo-, ethyl ester Terpenoids: Carandinol, ursolic acid- γ -lactone, 27-O-Z-p-coumaroyl ursolic acid, 23-hydroxy ursolic acid, uvaol, ursolic aldehyde, triterpene, betulinic acid, oleanolic acid, ursolic acid, β -Sitosterol Isoprenoids: Phytol, Squalene Aldehydes: Pyrazole[4,5-b] imidazole, 1-formyl-3-ethyl-6- β -D-ribofuranosyl Bicyclohexyl Ketone: [1,1'-Bicyclohexyl]-2-one, 1'-hydroxy Cyclohexanones: Cyclohexanone, 2-cyclohexylidene, Cyclohexanone Phthalates: Bis(2-ethylhexyl) phthalate Siloxanes: Octasiloxane Flavanone: Naringin	[46]; [65]; [2]; [57]
Flowers	Terpenes and Terpenoids: Myrcene, limonene, camphene, carene, dipentene, farnesol, nerolidol, α -terpeneol, citronellal, β -ionone, linalool, and geranyl acetate	[34]
Root	Ketones: 2-Acetyl phenol, acetophenone Phenols: Phenol, 2-methoxy-4-(2-propenyl) phenol, 2,4-bis(1,1-dimethyl ethyl)phenol Hydrocarbons/Alkanes: n-Eicosane, n-octane, 2,4-dimethyl hexane, n-nonane, n-decane, n-undecane, n-dodecane, n-tetradecane, n-tetrasocane, n-hexatriacontane, n-heneicosane, n-heptadecane, n-pentadecane, n-nanodecane, hexadecane, 1,1-bis (dodecyloxy)- Ester & Fatty Alcohols: 7,9-Di-test-butyl-1-oxaspiro (4,5)deca-6,9-diene-2,8-diene, 1-(+)-ascorbic acid 2,6-dihexa decanoate, 2-H,8-H, benzo[1,2-b:5,4-b]dipyran-2-one,8,6 dimethyl, 2-H-1-benzopyran-2-one, 7-methoxy-6-(3-methyl-2-butyl) 4-pyrimidinecarboxylic acid, 2,6 bis [(tet-butyl dimethylsilyl)oxy] Fatty Acids: Stearic acid, 9-octadecenoic acid, 9,12-octadecanoic acid, 6-octadecenoic acid (Z)-, methyl ester, 7-octadecadienoic acid, hexadecanoic acid, hyristic acid Terpenoids: β -Sitosterol glycoside, α -amyrin 16 β -hydroxybetulinic acid, lupeol, sesquiterpenes (carissone, carindone), β -sitosterol, β -viscol, oleanolic acid, carinol Steroids: γ -Sitosterol, β -amyrin, stigmasterol Coumarins: Scopoletin	[34,35,55]
Fruit	Anthocyanins: Cyanidin-3-galactoside, cyanidin-3-glucoside, 5-carboxypyranopelargonidin-3-O-beta-glucopyranoside, delphinidin-3-rutinoside, peonidin-3-arabinoside, delphinidin, delphinidin-3-galactoside, delphinidin-3-glucoside Phenolic acids/Acids: Protocatechuic acid, dichloroacetic acid, malic acid, decanoic acid, quinic acid.	[36]; [34,37,38, 60,62]

(continued on next page)

Table 2 (continued)

Plant Part	Class/name of the Compound	References
	Flavonoid: Quercetin	
	Esters: 2-Ethylhexyl ester, 12-oleanen-3-yl acetate (3- α)	
	Fatty Acid Esters: Hexadecanoic acid methyl ester, <i>cis</i> -10-nonadecenoic acid methyl ester, methyl stearate, methyl 3-hydroxytetradecenoate	
	Aldehydes: Octadecanal, octacosanal, eicosanal, 2-furancarboxaldehyde, decanal, trifluoroacetyl-lavandulol	
	Ketones: Z, Z-6,28-Heptatriactontadien-2-one, 2-pyrrolidinone, citronellol epoxide, semicarbazone	
	Alcohols: Heptacosanoic acid, 1-methoxy-25-methyl heptacosan-1-ol, methyl ester, 1-pentatriacontanol, cyclohexanol, 1,2,3,5-cyclohexanetetrol	
	Alkenes: 2,4,4-Trimethyl-3-hydroxymethyl-5a-(3-methyl-but-2-enyl)-cyclohexene	
	Terpenoids: 2R-Acetoxymethyl-1,3,3-trimethyl-4t-(3-methyl-2-buten-1-yl)-1t-cyclohexanol, methyl 13-octadecenoate, β -amyrin, carisol, linalool, β -caryophyllene, carissone, carissic acid, carindone, ursolic acid, carinol, lupeol, β -sitosterol	

roots of *C. carandas* contain a diverse group of compounds like ketones, flavonoids, terpenoids, alkaloids, alkanes, fatty alcohols, and fatty acids [34,35]. Moreover, the identified compounds found in the *C. carandas* fruit were anthocyanins, phenolic acids, flavonoids, esters, alkenes, and terpenoids [34,36–38]. Similarly, leaf extracts of *C. carandas* were identified to contain organic compounds, fatty acids, terpenoids, and flavanones whereas geranyl acetate was isolated from the flowering part of *C. carandas*. Aforementioned group of secondary metabolites are reported to offer a wide array of health benefits. The plant remained an underutilized commodity with such diverse composition, supposed to be a promising niche as a functional and nutraceutical food ingredient. Future research is still needed to evaluate its comprehensive composition, therapeutic and industrial aspects, and safety concerns.

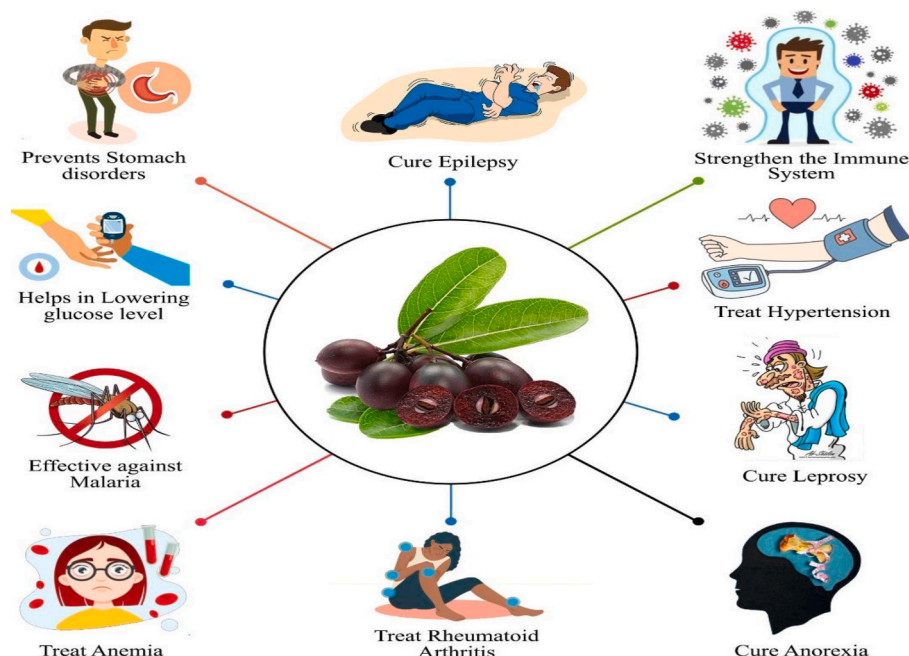
3. Pharmacological potential

The World Health Organization (WHO) has estimated that 80 % of the earth's inhabitants rely on traditional medicine for their primary

healthcare needs, and most of this therapy involves the use of plant extracts and their active components [39]. *C. carandas* fruit, leaves, stem, and pomace extracts exhibited the excellent potential to inhibit the generation of free radicals, inflammation, growth of cancer cells, pathogenic bacteria, diabetes, tyrosinase, diabetes, and many other ailments that confirm its claims in ancient medicinal systems (Fig. 1). The documented pharmacological activities of *C. carandas*. are reviewed in the proceeding sections.

3.1. Antioxidant activity

When endogenous antioxidant potency is imbalanced by ROS_s, the onset of oxidative stress starts, which eventually incepts the ailments [39]. ROS_s contains chemically reactive oxygen, which encounters signaling and homeostasis pathways, consequently putting oxidative stress and cell damage underway. Antioxidants are inevitable to protect a physiological system from ROS_s, various infections, and degeneration [40]. *C. carandas* seeds and pulp ethanol extracts were reported to have antioxidant potential in the DPPH assay at 183 mg Trolox equivalent (TE)/g and 17 mg TE/g, respectively. Total phenolic contents in seed ethanol extract were also notably higher (52 mg gallic acid equivalent (GAE)/g) as compared to ethanol pulp extract (16 mg GAE/g) [41]. *C. carandas* root powder was extracted with various solvents based on increasing polarity (petroleum ether, petroleum ether + chloroform, chloroform, chloroform + ethyl acetate, ethyl acetate, ethanol, and methanol) and evaluated for total phenolics, total flavonoids, and antioxidant potential. Methanol extract was observed to have maximum phytochemical potential and antioxidant activity in the DPPH (IC₅₀ 46 mg/mL) assay and inhibition of linoleic acid oxidation (72 %) followed by ethanol extract, and ethyl acetate extract [35]. The methanol extract of *C. carandas* fruit, carrying total phenolic contents of 188.75 μ g GAE/g, exhibited antioxidant activity with an IC₅₀ of 27.4 μ g/mL against a stable free radical, i.e., DPPH [20]. Flavonol-rich fractions of *C. carandas* fruit methanol extract showed 61 % inhibition, followed by phenolic acid > anthocyanins > flavanol-rich fractions in the β -carotene-linoleic acid assay. A similar trend was observed in the reducing power assay, wherein the flavonol fraction at 50 ppm outlined higher activity at 1.86 as compared to other fractions. In the DPPH assay, the anthocyanin fraction showed inhibition of 70 %, followed by the phenolic acid, flavonol, and flavonol fractions at 20 ppm [42]. *C. carandas* fruits of two

Fig. 1. Pharmacological potential of *C. carandas*.

different types (T1, T4) were extracted with methanol to evaluate the radical scavenging potential, and T1 was recorded to offer better activity in DPPH (34 % inhibition), FRAP (90 mg/100 g), and ABTS (95 % inhibition) assays than T4 in all assays and the potential was comparable with the standard ascorbic acid in all assays [43]. Lately, *C. carandas* anatomical parts (fruit, leaves, seeds) were extracted with various solvents (hexane, ethyl acetate, ethanol) wherein fruit and leaves ethanol and hexane extracts outlined significant antioxidant activity in DPPH, FRAP, and ABTS assays [44]. Ethanol fruit extract of *C. carandas* was found to be a notable carrier of total phenolic (14 mg GAE/g) and total flavonoids (2.2 mg CE/g) and showed higher antioxidant activity in DPPH (IC_{50} 195 μ g/mL) and nitric oxide (IC_{50} 219 μ g/mL) as compared to ethanol root, chloroform fruit, and chloroform root extracts [45]. The DPPH and ABTS assays revealed the antioxidant activity of the methanol extract of *C. carandas* leaves, with IC_{50} of 10.5 and 1.75 μ g/mL [46]. *C. carandas* leaves AgNPs showed stable free radical scavenging activity (90 % inhibition) more than butylated hydroxyanisole (68 % inhibition) [47a]. Similarly, at all the tested concentrations between 50 and 300 μ g/mL *C. carandas* leaves ethanol extract AgNP outlined higher inhibition in DPPH, FRAP, and ABTS assays as compared to basic extract [48, 47b]. In another study, AgNPs fabricated from the *C. carandas* fruit methanol extract bestowed antioxidant activity in DPPH assay more than *C. carandas* fruit methanol extract and comparable to the standard ascorbic acid [49]. Nexus to the above it can be suggested that *C. carandas* fruit extracts having significant antioxidants can serve as natural preservatives, extending the shelf life of perishable items like meats, dairy, and baked goods. It can also enhance health benefits and antioxidant intake in functional foods and beverages. It can stabilize

flavors, improve bakery products' nutritional profiles, and prevent lipid oxidation in meat and fish products.

3.2. Anti-inflammatory activity

The overproduction of free radicals by activated inflammatory leukocytes, particularly in cases of prolonged inflammation, is believed to play a significant role in the development of various pathological conditions (Fig. 2). The epithelial layer of tissue is damaged by carcinogenic stimuli, which in turn activate immune cells. These cells emit proinflammatory cytokines, which induce blood vessel constriction and facilitate the migration of platelets and neutrophils to the site of inflammation. This migration results in the destruction of necrotic cells and organisms. Mutagenicity, abnormal cell proliferation, hyperplasia, dysplasia, and tumour formation are all potential consequences of chronic inflammation. This uncontrolled growth is facilitated by angiogenesis. Numerous studies have shown that polyphenols may help treat conditions linked to inflammation by targeting specific sites as shown in Fig. 2 [50,51]. Carrageenan induces inflammation in a biphasic manner, releasing histamine and serotonin during the initial phase, and prostaglandin, lysozyme, followed by bradykinin in the second phase [52,53]. Steroidal and non-steroidal drugs usually play a role during the second phase. Likewise, *C. carandas* roots, leaves, and fruit extracts also reduced the inflammation during the second phase by averting the release of proinflammatory cytokines and the reduction is almost comparable with the standard drugs used. In this regard, *C. carandas* is a well-reputed medicinal plant with anti-inflammatory potential. Decades earlier a study aimed to investigate the analgesic, anti-inflammatory, and antipyretic potential of ethanol and aqueous

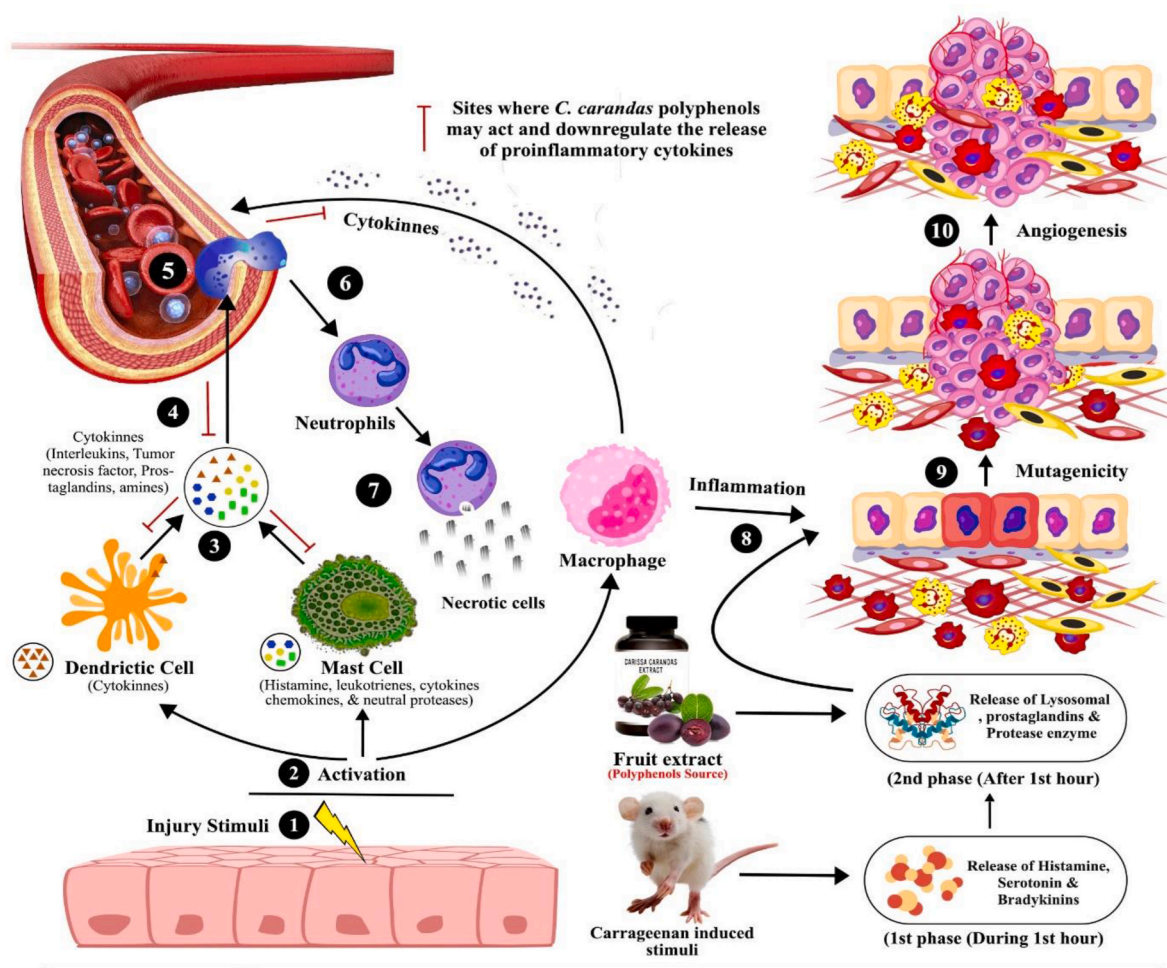


Fig. 2. Inflammatory mechanism and targeted sites of *C. carandas* polyphenols.

extracts of *C. carandas* roots. Results showed that ethanol and aqueous extracts exhibited significant analgesic effects against acetic acid-induced abdominal writhing, anti-inflammatory against carrageenan-induced paw edema, and antipyretic activities at 200 mg/kg b.w [54]. *C. carandas* roots methanol extract reported to downregulate the release of proinflammatory mediators i.e., TNF- α , IL-1 β , and nitric oxide (NO) with IC₅₀ of 21, 29, and 48 mg/mL, respectively. Bioassay-guided fractionation of the same extract resulted in two fractions (B1 and B2), which further purification identified with 5 compounds named scopoletin, carissone, oleanolic acid, lupeol, and stigmasterol. Added that, carissone and scopoletin were found to reduce the NO production with an IC₅₀ of 20 and 24.6 μ g/mL comparable to standard NO down regulator (L-NAME; IC₅₀ 19.82 μ g/mL). Carissone and scopoletin also decreased the production of TNF- α , and IL-1 β up to 41 % and 53 % at 30 μ M without inducing any toxicity [55]. Similarly, *C. carandas* fruit methanol extract inhibited the release of proinflammatory cytokines i.e., NF- κ B, IL-6, and TNF- α more than ursolic acid and standard drug indomethacin.

C. carandas pulp ethyl acetate extract also outlined notable inhibition of these cytokines followed by ethanol extract [44]. Defatted methanol extract of *C. carandas* fruit at doses of 100, 200, and 400 mg/kg body weight exhibited 33.70, 60.95, and 76.12 % inhibition of carrageenan-induced paw edema volume when compared with control at 2 h in a dose-dependent manner. GC-MS analysis identified 11 compounds wherein terpenoids were found in abundance followed by fatty acids, esters, and ketones [36]. *C. carandas* fruit of varying stages was subjected to extraction using different solvents i.e., *n*-hexane, chloroform, and hydroalcoholic, and screened for phytochemicals. The higher contents of ascorbic acid, flavonoids, and phenols were recorded in the acetone and hydroalcoholic extract of mature fruit. Hydroalcoholic extract mature fruit showed the highest activity against carrageenan-induced paw edema at a dose of 200 mg/kg at 3 h followed by the same extract of immature fruit [56]. *C. carandas* leaves methanol extract at 200 mg/kg b.w. exhibited maximum inhibition of inflammation, i.e., 71.8 %, 3.00 %, and 72.1 % at the end of 3 h in carrageenan, histamine, and dextran-induced hind paw edema models, respectively and results were comparable with the standard drug i.e., diclofenac dispensed at the rate of 10 mg/kg. Moreover, the doses of 100 and 200 mg/kg p.o. showed a significant reduction in yeast-induced elevated temperature in a dose-dependent manner, and the effect also extended up to 4 h after the drug administration [12]. *C. carandas* leaves methanol extract-fabricated AgNPs (CCL-AgNPs) demonstrated a significant anti-inflammatory effect in rats treated with a carcinogen named diethylnitrosamine. To be precise, rats in the control group were given 30 mg/kg b.w. of CCL-AgNPs, which decreased the proinflammatory cytokine levels (Pg/mL) of 750 (TNF- α), 780 (IL-1 β), 2000 (IL-6), and 1600 (NF- κ B) to 300, 250, 1200, and 600 Pg/mL, respectively [47]. Naringenin was purified from the *C. carandas* methanol extract and tested against carrageenan-induced paw edema inflammation. Standard indomethacin bestowed 48 % inhibition at 20 mg/kg whereas naringenin 53 % at 50 mg/kg after 4 h of injection [57]. *C. carandas* leaves and seed hexane extracts also outlined notable inhibition of 5 % against NF- κ B [44]. *C. carandas* stem methanol extract was subjected to anti-inflammatory and anti-pyretic analysis and showed notable inhibition as compared to standard wherein the phytochemical screening indicated the presence of steroids, glycosides, flavonoids, tannins, and terpenoids [58]. *C. carandas* extracts have potential applications in food technology, as it can be used in functional foods and beverages to manage chronic inflammatory conditions, reduce inflammation-related spoilage in nutraceutical products, and in specialized foods for athletes and individuals with high physical stress, providing health benefits and faster recovery.

3.3. Anticancer activity

C. carandas fruit aqueous ethanol fruit extract showed better cytotoxicity at 800 μ g/mL against HeLa cancer cells wherein cell viability

reduced to 65 % as compared to 1000 μ g/mL and 1200 μ g/mL [59]. Hydro-ethanol extract of *C. carandas* leaves bestowed higher cytotoxic effects against cultured human hepatocellular carcinoma (HepG2) cells (cell viability reduced to 67 %) as compared to fully ripe and unripe fruit extracts at 200 μ g/mL. The activity was consistent with their respective total phenolic contents and antioxidant activity [60]. *C. carandas* pomace aqueous methanol extract detected with notable amounts of alkaloids, flavonoids, tannins, and saponins was reported to have anticancer potential against various cancer cell lines including cervical (IC₅₀ 58.62 μ g/mL), breast (IC₅₀ 56.72 μ g/mL), hepatocellular carcinomas (IC₅₀ 56.81 μ g/mL), and bone sarcoma (IC₅₀ 82.90 μ g/mL) [61]. In another study, ethanol fruit extract of *C. carandas* reported to show inhibitory activity against breast cancer (MCF-7) in a dose-dependent manner wherein cell viability reduced to 20 % at 200 μ g/mL with an IC₅₀ of 86.73 μ g/mL [62]. Bioassay-guided fractionation of *C. carandas* fruit methanol extract highlighted that chloroform fraction exhibited significant activity against MCF-7, HT-29, and A-549 with IC₅₀ values of 3.98 μ g/mL, 1.28 μ g/mL, and 1.48 μ g/mL, respectively. Further investigation on this fraction led to the isolation of carissic acid that outlined notable activity with IC₅₀ of 3.47 μ M, 2.65 μ M, and 13.58 μ M against A-549, HT-29, and MCF-7 cells. Carissic acid caused chromatin condensation with a decrease in mitochondrial membrane potential and also confirmed cell death via reactive oxygen species (ROS) generation and significantly decreased colony formation in a dose-dependent manner [63]. *C. carandas* unripe-fruit (*n*-hexane) and leaves (chloroform) were found effective against human ovarian carcinoma and lung cancer with an EC₅₀ of 2.9 μ g/mL and 7.7 μ g/mL, respectively [64]. In the following study the triterpene carandinol was isolated from *C. carandas* leaves methanol extract and found to exhibit notable cytotoxicity against HeLa and PC-3 with IC₅₀ 6.8 μ M and 12.6 μ M, respectively [2]. Methanol extract of *C. carandas* leaves (MELC) was reported to reduce the viability of adenocarcinoma cells including SW-480 and SW-48 in a dose-dependent manner (*in vitro*) and also resulted in a significant decrease in viable EAC cell count thereby increasing the life span of the EAC cell bearing mice. Moreover, treatment with MELC induced apoptosis of EAC cells as observed in fluorescence microscopic view of DAPI (4,6-diamidino-2-phenylindole) stained cells and also increased p53 gene expression MELC-treated cells in respect to untreated EAC control. Restoration of hematological parameters such as red blood cells (RBC), hemoglobin, and white blood cells (WBC) to normal levels in MELC-treated mice was also observed [46]. Six natural compounds (1–6) were isolated from the fresh leaves of *C. carandas* including ursolic acid (1), ursolic acid-*c*-lactone (2), 27-*O*-*Z*-*p*-coumaroyl ursolic acid (3), 23-hydroxy ursolic acid (4), uvaol (5) and ursolic aldehyde (6) and evaluated for anticancer activity against lung (NCI-H460), oral (CAL-27), and human cervical cancer (HeLa) cell lines. Compounds 3 and 4 outlined potent activity against lung and cervical cancer cell lines with an IC₅₀ of 18.6 μ M and 12.8 μ M, compound 4 was recorded to have IC₅₀ of 28.7 μ M against oral cancer, compound 1 and 4 exhibited IC₅₀ of 13 μ M and 21 μ M against cervical cancer cell lines [65]. β -sitosterol-3-*O*- β -D-glucopyranoside isolated from the *C. carandas* leaves methanol extract was found to have higher activity against oral cancer with an IC₅₀ of 18.69 μ M as compared to the cytotoxic effects against lung cancer with an IC₅₀ of 63.34 μ M but found to have no cytotoxicity against normal cells [66].

3.4. Antimicrobial activity

This very plant may be referred to as a medicinal and food homologue (MFH) plant offering a microbial infection cure. Literature has highlighted that *C. carandas* anatomical parts have shown significant antibacterial activity and effectively manage infectious diseases (Table 3). Aqueous ethanol fruit extract of *C. carandas* has antibacterial activity against *K. pneumoniae* and *S. aureus* with MIC of 0.312 mg/mL followed by *E. faecalis* and *E. coli* [59]. Phenolics-rich fraction of aqueous ethanol from *C. carandas* fruit has a notable antibacterial

Table 3
Health-promoting activities of *C. carandas* anatomical parts.

Plant part	Solvent	Dosage	Findings	References
Anti-inflammatory				
Roots	Ethanol	100 mg/kg	Reduced carrageenan-induced inflammation by 63.83 % after 3 h in rats	[54]
Roots	Water	100 mg/kg	Reduced carrageenan-induced inflammation by 49.6 % after 3 h in rats	[54]
Roots	Methanol	–	Inhibition of pro-inflammatory mediators with an IC ₅₀ (µg/mL) of 21.75, 29.30, and 48.52 against NO, TNF-α, and IL-1β (<i>in vitro</i>)	[55]
Fruit	Methanol	400 mg/kg	Reduced carrageenan-induced inflammation was 76 % after 2 h in rats as compared to 80 % inhibition of standard Indomethacin	[36]
Unripe Fruit	Methanol	200 mg/kg	Reduced carrageenan-induced inflammation by 58 % as compared to standard drug inhibition of 78 % at the end of 3 h in rats	[56]
Ripe Fruit	Methanol	100 mg/kg	Reduced carrageenan-induced inflammation by 66 % as compared to standard inhibition of 78 % at the end of 3 h in rats	[56]
Fruit	Ethanol	–	Inhibited proinflammatory cytokines i.e., NF-κB, IL-6, TNF-α by 95 %, 25 %, and 20 %, respectively more than ursolic acid and standard indomethacin (<i>in vitro</i>)	[44]
Pulp	Ethyl acetate	–	Inhibited proinflammatory cytokines i.e., NF-κB, IL-6, TNF-α by 85 %, 25 %, and 30 %, respectively more than ursolic acid and standard indomethacin (<i>in vitro</i>)	[44]
Roots	Ethanol	100 mg/kg	Reduced pyretic activity by 1.19 % after 3 h in rats	[54]
Roots	Water	100 mg/kg	Reduced pyretic activity by 1.77 % after 3 h in rats	[54]
Leaf	Methanol	200 mg/kg	Reduced pyretic activity comparable to standard in rats	[12]
Stem	Ethanol	300 mg/kg	Reduced pyretic activity comparable to the standard drug (10 mg/kg) i.e., diclofenac sodium in rats	[58]
Leaf	Methanol	200 mg/kg	Reduced histamine-induced inflammation by 72 % as compared to standard diclofenac (10 mg/kg) exhibited 79.9 % inhibition after 3 h in rats	[12]
Leaf	Methanol	200 mg/kg	Reduced histamine-induced inflammation by 3 % as compared to standard diclofenac (10 mg/kg) exhibited 4 % inhibition after 3 h in rats	[12]
Leaf	Methanol	200 mg/kg	Reduced carrageenan-induced inflammation by 71 % as compared to standard diclofenac (10 mg/kg) exhibited 79 % inhibition after 4 h in rats	[12]
Leaf	Methanol	50 mg/kg naringenin	Reduced carrageenan-induced inflammation by 53 % as compared to standard indomethacin (20 mg/kg) exhibited 43 % inhibition after 4 h in rats	[57]
Stem	Ethanol	300 mg/kg	Reduced carrageenan-induced inflammation by 60.88 % after 2 h in rats	[58]
Roots	Ethanol	100 mg/kg	Reduced acetic acid-induced abdominal writhing 72.67 % in mice	[54]
Roots	Water	100 mg/kg	Reduced acetic acid-induced abdominal writhing at 71.68 % in mice	[54]
Antioxidant				
Pulp	Ethanol	1 g/20 mL	Stable free radical i.e., DPPH scavenging activity was recorded as 16.86 mg TE/g	[41]
Fruit	Methanol	1 mg/mL	DPPH radical scavenging activity obtained with an IC ₅₀ of 27.4 µg/mL	[20]
Pulp	Ethanol	1 mg/mL	DPPH radical scavenging activity obtained with an IC ₅₀ of 224 µg/mL as compared to gallic acid and quercetin IC ₅₀ of 1 µg/mL and 4.4 µg/mL, respectively	[44]
Fruit	Methanol	20 ppm	Anthocyanins-rich fraction obtained from methanol extract outlined the highest DPPH radical scavenging activity (62 % inhibition) as compared to standard BHT (89 % inhibition)	[42]
Fruit	Methanol	0.25 g/mL	Type 1 of <i>C. carandas</i> outlined 34 % inhibition of stable free radical i.e., DPPH followed by type 4 with 33 % inhibition	[43]
Fruit	Ethanol	300 µg/mL	DPPH radical scavenging activity obtained with an IC ₅₀ of 195.8 µg/mL as compared to standard BHT IC ₅₀ of 64.2 µg/mL	[45]
Fruit	Chloroform	300 µg/mL	DPPH radical scavenging activity obtained with an IC ₅₀ of 237.4 µg/mL compared to standard BHT IC ₅₀ of 64.2 µg/mL	[45]
Seed	Ethanol	1 g/20 mL	Stable free radical i.e., The DPPH scavenging activity was recorded as 182.7 mg TE/g	[41]
Seed	Ethanol	1 mg/mL	DPPH radical scavenging activity obtained with an IC ₅₀ of 16 µg/mL as compared to quercetin exhibited 4.4 µg/mL	[44]
Roots	Methanol	10 mg/mL	DPPH radical scavenging activity obtained with an IC ₅₀ of 46.1 µg/mL as compared to an IC ₅₀ of 12 µg/mL of standard BHT	[35]
Roots	Ethanol	10 mg/mL	DPPH radical scavenging activity was obtained with an IC ₅₀ of 49.1 µg/mL as compared to an IC ₅₀ of 12 µg/mL of standard BHT	[35]
Roots	Ethanol	300 µg/mL	DPPH radical scavenging activity obtained with an IC ₅₀ of 216 µg/mL	[45]
Roots	Chloroform	300 µg/mL	DPPH radical scavenging activity obtained with an IC ₅₀ of 259.5 µg/mL	[45]
Fruit	Methanol	20 ppm	Anthocyanins-rich fraction obtained from methanol extract outlined the highest inhibition (61 %) of β-carotene oxidation in the linolenic emulsion system	[42]
Roots	Methanol	10 mg/mL	Inhibition of linoleic acid oxidation was recorded as 72 % as compared to BHT exhibited 89 %	[35]
Roots	Ethanol	10 mg/mL	Inhibition of linoleic acid oxidation was recorded as 72 % as compared to BHT exhibited 89 %	[35]
Fruit	Methanol	0.25 g/mL	Type 1 of <i>C. carandas</i> outlined 95 % inhibition of ABTS followed by Type 4 with 75 % inhibition	[43]
Fruit	<i>n</i> -Hexane	1 mg/mL	15.1 TEAC (µM Trolox/g Extract) more than standard gallic acid and quercetin	[44]
Leaves	Ethanol	3.75 µg/mL	An IC ₅₀ of 1.75 µg/mL was observed in the ABTS assay	[46]
Leaves	<i>n</i> -Hexane	1 mg/mL	Antioxidant activity was 22.2 µM TE/g which is more than standard gallic acid (25 µM TE/g) and quercetin (58.1 µM TE/g) in the TEAC assay	[44]
Leaves	Ethanol	37.5 µg/mL	An IC ₅₀ of 10.5 µg/mL was observed in the DPPH assay	[46]
Leaves	Ethanol	1 mg/mL	An IC ₅₀ of 16.4 µg/mL was observed in the DPPH assay	[44]
Fruit	Methanol	0.25 µg/mL	Type 1 of <i>C. carandas</i> outlined FRAP potential as 90 mg/100 g followed by type 4 with 87 mg/100 g	[43]
Anticancer				
Fruit	Aqueous ethanol	800 µg/mL	Significantly reduced the cervical (HeLa) cancer cell viability up to 65 %	[59]
Leaf	Chloroform	100 µg/mL	Potent EC ₅₀ of 7.70 µg/mL was observed against ovarian cancer cells	[64]
Unripe fruit	<i>n</i> -Hexane	100 µg/mL	Potent EC ₅₀ of 2.94 µg/mL was observed against lung cancer cells	[64]
Leave	Ethanol	200 µg/mL	Reduced the hepatocellular carcinoma (HepG2) cell viability to 67 % in a significant manner	[60]
Pomace	Aqueous methanol	100 µg/mL	Inhibited the cervical cancer (IC ₅₀ 58.62 µg/mL), breast cancer (IC ₅₀ 56.72 µg/mL), hepatocellular cancer (IC ₅₀ 56.81 µg/mL), bone sarcoma (IC ₅₀ 82.9 µg/mL) in notable manner	[61]

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Table 3 (continued)

Plant part	Solvent	Dosage	Findings	References
Leaves	Methanol	–	Triterpene carandin isolated from leaves methanol extract had significant anticancer activity against HeLa (IC ₅₀ 6.8 µM) and PC-3 (IC ₅₀ 12.6 µM) as compared to standard doxorubicin caused potent activity against HeLa (IC ₅₀ 3.10 µM) and PC-3 (IC ₅₀ 0.91 µM)	[2]
Fruits	Ethanol	200 µg/mL	Good anticancer activity observed against breast cancer (IC ₅₀ of 86 µg/mL)	[62]
Leaves	Methanol		27-O-Z-p-coumaroyl ursolic acid isolated from leaves methanol extract showed significant activity with an IC ₅₀ of 12.8 µM against lung cancer	[65]
			23-hydroxy ursolic acid showed significant inhibition with an IC₅₀ of 12.8 µM against lung and cervical cancer cell lines	
			23-hydroxy ursolic acid showed good activity with an IC ₅₀ of 28.7 µM and 21 µM against oral and cervical cancer cell lines ursolic acid outlined significant inhibition with an IC ₅₀ of 12 µM against cervical cancer	
Leaves	Methanol		β-sitosterol-3-O-β-D-glucopyranoside had IC ₅₀ of 18.69 µM and 63.34 µM against oral and lung cancer, respectively.	[66]
Fruit	Methanol		Chloroform fraction of methanol extract showed potent anticancer activity with an IC ₅₀ of 3.98 µg/mL, 1.28 µg/mL, and 1.48 µg/mL against MCF-7 (breast), HT-29 (human colorectal), and A-549 (human alveolar) cancer cell lines, respectively	[63]
			Chloroform fraction isolated carissic acid potent anticancer activity with an IC ₅₀ of 13.58 µM, 2.65 µM, and 3.47 µM against MCF-7 (breast), HT-29 (human colorectal), and A-549 (human alveolar) cancer cell lines, respectively	
Antimicrobial				
Leaves	Methanol	500 mg/mL	<i>Escherichia coli</i> (ZOI 19.5 mm) Tetracycline (ZOI 16.1 mm) <i>Pseudomonas aeruginosa</i> (ZOI 15.0 mm) Tetracycline (ZOI 14.0 mm) <i>Staphylococcus aureus</i> (ZOI 23.5 mm) Tetracycline (ZOI 17.1 mm)	[11]
Fruit	Ethanol	2.5 mg/mL	<i>Streptococcus mutans</i> (ZOI 10.8 mm) Erythromycin (ZOI 26.6 mm) <i>Streptococcus aureus</i> (ZOI 9.2 mm) Erythromycin (ZOI 26 mm)	[69]
Fruit	Ethanol	–	<i>Cutibacterium</i> (ZOI 6.67 mm) Clindamycin (ZOI 26.3 mm) <i>Staphylococcus epidermidis</i> (ZOI 7.0 mm) Ampicillin (ZOI 9.0 mm) <i>Staphylococcus aureus</i> (ZOI 6.6 mm) Ampicillin (ZOI 21 mm)	[68]
Fruit	Water	100 mg/mL	<i>Staphylococcus aureus</i> (ZOI 20.3 mm) <i>Aeomonas hydrophila</i> (ZOI 19.3 mm) <i>Pseudomonas fluorescens</i> (ZOI 18.3 mm) <i>Escherichia coli</i> (ZOI 17.0 mm)	[70]
Fruit	Aqueous methanol	10 mg/mL	<i>Klebsiella pneumoniae</i> and <i>Staphylococcus aureus</i> with MIC of 0.312 mg/mL	[59]
Fruit	Methanol	–	<i>B. subtilis</i> (ZOI 20.0 mm) <i>Staphylococcus aureus</i> (ZOI 27.0 mm) <i>Staphylococcus epidermidis</i> (ZOI 24.0 mm) <i>Klebsiella pneumonia</i> (ZOI 26.0 mm)	[67]
Fruit	Methanol	250 AgNPs (mg/mL)	<i>Escherichia coli</i> (ZOI 10.0 mm) <i>Staphylococcus aureus</i> (ZOI 11.0 mm)	[49]
Leaves	Methanol	100 mg/mL	<i>Staphylococcus aureus</i> (ZOI 10.0 mm) <i>Streptococcus mutans</i> (ZOI 6.0 mm) <i>Mycobacterium smegmatis</i> (ZOI 10.0 mm) <i>Salmonella typhi</i> (ZOI 7.0 mm)	[72]
Leaves	Ethanol	250 mg/mL	<i>Staphylococcus aureus</i> (ZOI 10 mm)	[71]
Antidiabetic				
Fruit	Methanol	1.25–10 mg/mL	β-glucosidase inhibition was 82 % in Type 1 <i>C. carandas</i> and 81 % in Type 2 <i>C. carandas</i> (<i>in vitro</i>) α-amylase inhibition was 34 % in Type 1 <i>C. carandas</i> and 30 % in Type 2 <i>C. carandas</i> (<i>in vitro</i>)	[43]
Pomace	Aqueous methanol	200 mg/mL	IC ₅₀ of 29.66 mg/mL against α-amylase inhibition (<i>in vitro</i>)	[61]
Unripe fruit	Methanol	400 mg/kg b.w.	Reduced alloxan-induced diabetes from 97 % to 85 % comparable to the standard metformin in rats	[79]
Fruit	Water	400 mg/kg b.w.	67.08 % decrease in fasting blood glucose level in rats in the GTT test	[82]
Fruit	Water	300 mg/kg b.w.	Altered elevated postprandial glucose and glycosylated hemoglobin level 33.65 % and 45.79 % But increased insulin level up to 69.7 % in rats	[82]
Fruit	Water	400 mg/kg b.w.	44 % reduction in blood glucose concentrations among diabetic rats as compared to metformin caused 43 % reduction	[83]
Root	Ethanol	100 µg/mL	Attained potent effects <i>in vitro</i> α-amylase inhibitory activity of 71.16 % as compared to the standard drug i.e., acarbose	[80]
Juice	Ethanol	100 mg/mL	98.7 % and 50.86 % inhibition of α-amylase and α-glucosidase as compared to standard acarbose showed 100 % inhibition at 50 µg/mL	[81]
Residue	Ethanol	100 mg/mL	50.34 % and 18.30 % inhibition of α-amylase and α-glucosidase, respectively as compared to standard acarbose showed 100 % inhibition at 50 µg/mL	[81]
Anti-tyrosinase				
Fruit	Ethanol	1 mg/mL	Tyrosinase inhibition 25.32 mg kE/g	[41]
seed	Ethanol	1 mg/mL	Tyrosinase Inhibition 18.77 mg kE/g	[41]
Fruits	Ethanol	0.10 mg/mL	Tyrosinase inhibition 36.90 %	[84]
Fruit	Ethanol	20 mg/mL	Tyrosinase inhibition 77.65 %	[84]
Fruit	Ethyl acetate	20 mg/mL	Tyrosinase inhibition 47 % as compared to standard Kojic acid inhibition of 50 %	[44]
Seed	Ethyl acetate	20 mg/mL	Tyrosinase inhibition 40 % as compared to standard Kojic acid inhibition of 50 %	[44]

(continued on next page)

Table 3 (continued)

Plant part	Solvent	Dosage	Findings	References
Pulp	Ethyl acetate	20 mg/mL	Tyrosinase inhibition 48.9 % as compared to standard Kojic acid inhibition of 50 %	[44]
Leaves	Ethyl acetate	20 mg/mL	Tyrosinase inhibition 47 % as compared to standard Kojic acid inhibition of 50 %	[44]

DPPH: α -diphenyl- β -picrylhydrazyl, NO: Nitric oxide, TNF- α : Tumor necrosis factor alpha, IL-1 β : Interleukin-1-beta, NF- κ B: Nuclear factor kappa light chain enhancer of activated B, BHT: Butylated hydroxytoluene, MST: Mean Survival Time, ILS: Increase in Life Span, ZOI: Zone of inhibition, MIC: Minimum Inhibitory Concentration. TE/g: Trolox equivalent/gram, TEAC: Trolox equivalent antioxidant capacity, ABTS: ,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonate) radical cation, FRAP: Ferric Reducing antioxidant power.

activity against tested strains like *B. subtilis*, *S. aureus*, *S. epidermidis*, and *K. pneumoniae* followed by flavonols and flavonoids-rich fractions while no activity was shown by anthocyanins rich fraction [67]. Dried *C. carandas* ethanolic fruit extract has a lower minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) against *C. acnes*, *S. epidermidis*, and *S. aureus* compared to fresh ethanolic fruit extract. The activity of both extracts (dried and fresh) was more pronounced against *C. acnes*. The activity is accredited to alkaloids, flavonoids, glycosides, tannins, and saponins presence [68]. Dichloromethane and methanolic extracts of ripe fruit inhibited the growth of tested strains including *S. aureus*, *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *A. baumannii*, and *E. faecalis* at MIC between 12.5-50 and 25-50 mg/mL, respectively as compared to unripe *C. carandas* fruit extracts [69]. Aqueous extract has shown a concentration-dependent inhibition against pathogenic bacterial strains like *S. aureus*, *A. hydrophila*, *P. fluorescens*, and *E. coli* with the highest activity acquired at 100 mg/mL [70]. Recently, silver nanoparticles (Ag-NPs) at 25-250 μ g/mL concentrations were prepared using *C. carandas* fruit aqueous extract, stabilized by flavonoids, have notable antibacterial activity against both gram-negative and gram-positive bacteria i.e., *E. coli* and *S. aureus*, respectively [49,71]. Methanolic extract of *C. carandas* leaves inhibited the growth of pathogenic bacteria (*P. aeruginosa*, *S. aureus*, and *E. coli*) at 500 mg/mL more efficiently than the standard tetracycline [11]. Aqueous-methanolic leaves extract were reported for zone inhibition against *M. smegmatis*, *S. mutans*, and *S. aureus* at 100 mg/mL followed by methanol and hexane extracts in comparison to standard treatment i.e., Kanamycin drug [72]. *C. carandas* leaves ethanol extract (300 mg/mL) has shown significant inhibition of bacteria (*P. acnes* and *S. epidermis*) primarily due to flavonoids, terpenoids, steroids, tannins, and saponins [73]. Silver nanoparticles increased the antibacterial potential of fruit and leaf extracts. Recently, a comparative study revealed that the antibacterial activity of *C. carandas* leaf extract and its Ag-NPs inhibited growth zone (6-7 mm) of *E. faecalis*, *Gonococci* spp., *S. Typhi*, *Citrobacter* spp., and *S. flexneri* using [47b]. Green synthesis of Ag-NPs using *C. carandas* leaf extract exhibited excellent antibacterial activity against *S. aureus* and *P. aeruginosa*, with Ag-NPs coated urinary catheters showing the highest biofilm inhibition, making them a potential treatment niche for urinary tract infections (UTI) and nosocomial infections [74]. *C. carandas* derived-nitrogen-doped carbon dots (N-CDs) were proved effective (100 μ g/mL) against human pathogenic strains (*S. aureus* and *K. pneumoniae*) while tested using the disk diffusion method [75]. *C. carandas* leaf extract-mediated synthesized Ag-NPs was reported to enhance the antibiofilm effects of antibiotics against biofilm-producing organisms including *S. aureus*, *E. coli*, and *P. aeruginosa*, paving the way towards controlling UTI [74]. *C. carandas* extracts possess antibacterial qualities that can be utilized as natural preservatives. This can help prolong the shelf-life of perishable goods and decrease the need for synthetic preservatives, which are typically met with growing consumer doubt.

3.5. Antidiabetic activity

Diabetes mellitus (DM), a global concern affected half a billion people in 2021, with adults being affected might reach 800 million by 2045 [76]. Type-II diabetes mellitus (T2D), which is more prevalent presents disordered metabolism of carbohydrates, protein, and lipids

with deficient or insufficient insulin secretion, utilization, and resistance [77]. This chronic disorder may lead to neuro-, retino-, angio-, and nephropathy [78]. Among management and curing approaches, the inhibition of α - and β -amylase (carbohydrate digesting enzymes) in the gastrointestinal tract (GIT) to limit postprandial sugar (glucose) concentration is primarily looked for [79]. *C. carandas* fruit of two types i.e., T1 and T2 were extracted with methanol and observed to inhibit the β -glucosidase and α -amylase enzymes in a notable manner. β -glucosidase inhibition was 82 % in T1 and 81 % in T2. Alpha-amylase inhibition was 34 % in T1 and 30 % in T2 [43]. *C. carandas* root ethanolic extract (100 μ g/mL) exhibited 71.6 % α -amylase inhibition with an IC₅₀ of 41.42 μ g/mL which is more potent than standard drug acarbose which exhibited IC₅₀ of 84.42 μ g/mL [80]. Similarly, freeze-dried *C. carandas* crude juice powder at 100 μ g/mL demonstrated 98.7 % α -amylase and 50.86 % alpha-glucosidase inhibition, whereas its residues powder revealed 50.34 % α -amylase and 18.30 % α -glucosidase inhibition and results in all assays were comparable to the standard acarbose [81]. More importantly, *C. carandas* fruit methanol extract (CCFME) was recorded to reduce alloxan-induced diabetes in a dose-dependent manner and comparable to the standard metformin. CCFME reduced the blood glucose concentration from 97 % (control) to 85 % when dispensed at the rate of 400 mg/kg b.w. after 120 h in rats. The activity was believed to be due to the presence of total polyphenols, flavanols, and flavanones [79]. Furthermore, *C. carandas* fruit aqueous extract (CCFEE) caused a 67.08 % (0-1 h) decrease in fasting blood glucose level assessed using glucose tolerance test (GTT) in healthy rats. While in streptozotocin-induced diabetic rats a dose of 300 mg/kg f.w., reduced 70 % blood glucose, 33.65 % postprandial glucose, 45.79 % decline in glycosylated hemoglobin, and increased 69.7 % insulin level. CCFEE antidiabetic potential was comparable to the standard drug glibenclamide (10 mg/kg b.w.) [82]. The glucose uptakes of cells treated with the various concentrations of *C. carandas* aqueous fruit extract (CCAFE) between 100 and 400 μ g/mL + lipopolysaccharide (LPS) significantly increased by 29.3 %, 27.3 %, and 38.5 %, respectively, when compared with LPS-treated T3-L1 adipocytes, an indicative of anti-insulin resistance effects. Remarkably, administration of the CCAFE extract at doses of 200 and 400 mg/kg b.w, successfully decreased the fasting plasma glucose as -34 % and -44 %, respectively, as compared to 43 % inhibition of metformin among rats. Moreover, HOMA-IR and glucose intolerance were also significantly improved in diabetic rats [83]. The aforementioned results pave way to utilize to *C. carandas* in the development of functional foods aimed at managing blood sugar levels, catering to the growing population of health-conscious consumers and individuals with diabetes.

3.5.1. Anti-tyrosinase activity

Ethanol extract of *C. carandas* fruit and seed inhibited tyrosinase (25.32 mg kE/g and 18.77 mg kE/g, respectively) [41]. Similarly, ethanol fruit extract has shown 36.90 % tyrosine inhibition [84]. Within this context, *C. carandas* fruit ethanol extract manifested 77.65 % tyrosinase inhibition [85]. Likewise, ethyl acetate extract of *C. carandas* fruit, seed, pulp, and leaves revealed comparable tyrosinase inhibition as 47.3 %, 40.3 %, 48.9 %, and 47.7 %, which was 48.4 % in Kojic acid (standard treatment) [44]. Furthermore, the ability of *C. carandas* to inhibit tyrosinase activity suggests potential use in cosmetic foods and beverages, specifically addressing the growing market for beauty and

wellness products that enhance skin health.

4. Value addition and possible industrial applications

The literature has highlighted a significant insight for both the food industry and consumers, emphasizing *C. carandas*'s potential as a valuable source of carbohydrates, fats, sugars, minerals, vitamin C, and bioactive metabolites. Nutritional profiling with inherent shorter shelf stability of *C. carandas* signifies its value-addition thus reducing post-harvest loss, promoting consumption of this indigenous fruit, and enhancing food security [17]. For instance, *C. carandas* pulp-added yogurt made with 20 % supplementation has shown a higher consumer preference despite higher prices. The supplemented product had similar protein and antioxidant levels with higher fat than the standard [86]. Likewise, yogurt made with 20 % *C. carandas* pulp was reported to have a higher nutritional profile and phytochemical content when assessed against standard recipes. Interestingly, lactic acid bacteria remained above 8 log CFU/g during the 3-week storage period and received higher hedonic responses than regular yogurt [87]. The addition of *C. carandas* juice squeezed from 1000 g fruit, 100 g sugar, and 2 g stevia in ice cream showed a higher total phenolic (2–176 µg GAE/g), antioxidant potential (93–96 µg TE/g) and color appearance comparative to standard treatment suggesting the development of functional frozen desserts [88]. Lately, Rafique et al. (2023) developed different jam formulations using 100 % *C. carandas* pulp (T₁), 75 % *C. carandas* pulp+25 % apple pulp (T₂), 50 % *C. carandas* pulp+50 % apple pulp (T₃), and 25 % *C. carandas* pulp+75 % apple pulp (T₄). The product made from 100 % *C. carandas* pulp (T₁) had the minimum ash, vitamin C, total phenolic, total flavonoid, total anthocyanins, and antioxidant activity after 120 days of storage. The product made from 50 % *C. carandas* pulp had the maximum acceptability based on the taste and color profile using hedonic responses [17]. Ripe fruits are highly perishable and represent an option to retain bioactive components via fermentation [89]. The study analyzed the properties of *C. carandas* fruit-made wine, revealing a typical alcohol content, aroma-contributing volatile compounds (3-methyl-1-butanol, butanoic acid, butyrolactone, phenyl ethyl alcohol, butanedioic acid, benzene ethanol, 2-propenyl ester) low heavy metal (Pb, As, Cu, Cd) and methanol levels (12.50 %), high antioxidant activity (DPPH, IC₅₀ 0.84 %; ABTS, IC₅₀ 3.28 %), and total phenolic content (746 mg GAE/100 mL), suggesting its potential usage in fermented beverages with similar characteristics to other wines [90]. In another investigation, fermentation was performed to harness the polyphenolic contents using two distinct genotypes i.e., white with pinkish blush and green with purple blush of *C. carandas* fruit. The alcoholic contents of fermented beverages varied between 4.5 and 5.5 % and retained higher levels of ascorbic acid, phenolics, and antioxidants with acceptable sensory liking suggesting the potential of *C. carandas* in the fermentation industry to ensure food and nutritional security [89]. Similarly, ready-to-serve (RTS) functional beverage with 10 % *C. carandas* fruit juice had notable reducing sugars (9.8 %), total sugars (12.1 %), iron (3.39 mg/kg), anthocyanins (17 mg/L), phenol (228 mg GAE/100 mL), total flavonoid (43 mg EC/100 mL), and antioxidant activity as 14 and 19 µmol TE/g in FRAP and CUPRAC assay. Storage analysis (180 days) revealed enhanced total soluble solids (TSS), reducing sugars, and total sugars while declining polyphenolic contents and radical scavenging potential [91]. *C. carandas* juice was mixed with guava, papaya, and pineapple juices at varying concentrations to develop an RTS drink. A combination of 25 % *C. carandas* juice with 75 % pineapple juice had the highest organoleptic score and cost-benefit ratio [92]. *C. carandas* fermented whey beverage (CFWB) was fed to the rats as 10 %, 20 %, and 30 % and observed to impart positive effects on kidney and liver function. In detail, CFWB decreased the levels of creatinine, SGOT, SGPT, and also triglycerides as compared to the normal group. CFWB had no substantial impact on protein and cholesterol levels [93]. Methanolic and petroleum ether extracts of *C. carandas* stabilized corn oil in terms of peroxide value when tested with BHT,

which had the highest stabilization potential. Both extracts had stabilizing effects to some extent, indicating further research to unveil their potential as natural antioxidants [35].

5. Conclusions

C. carandas a neglected and underutilized berry fruit that has been ignored and not used enough, outlines a compelling case for its inclusion in dietary regimens and agricultural practices due to its exceptional nutritional and therapeutic benefits. *C. carandas* potential to fulfill 100 % of the recommended dietary allowance (RDA) for essential nutrients such as iron, zinc, and vitamin C for all age groups makes it a powerful ally in combating nutrient deficiencies across diverse populations. In addition to wonderful nutritional profile, *C. carandas* exhibited notable medicinal potential including antioxidant, anti-inflammatory, antimicrobial, and anti-tyrosinase activities comparable to those of commercially available synthetic drugs. These features show that *C. carandas* could be useful not only as a food supplement but also as a natural medicine. The inherent antioxidant and antimicrobial characteristics of *C. carandas* can be utilized to create functional foods that have longer shelf lives and with no synthetic antioxidant or preservatives.

It can be concluded that adding *C. carandas* to farming systems can help increase the variety of crops, ensure food security, improve food availability, and nutrition while promoting sustainable farming methods by growing this nutrient-dense berry. The reintroduction and valorization of *C. carandas* can thus play a crucial role in addressing both micronutrient deficiencies and the challenges of food security, making it a promising candidate for future food and health strategies.

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CRedit authorship contribution statement

Wisha Saeed: Writing – original draft, Visualization, Investigation. **Tariq Ismail:** Writing – review & editing, Project administration, Conceptualization. **Muhammad Qamar:** Writing – review & editing, Visualization, Validation, Project administration, Conceptualization. **Muhammad Zulqarnain Khan:** Software. **Naveed Ahmad:** Writing – review & editing. **Mohammad S. Mubarak:** Writing – review & editing. **Tuba Esatbeyoglu:** Writing – review & editing, Validation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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References

- [1] G. Thiyagarajan, S. Rajasekaran, S. Balamurugan, S. Karthikeyan, Studies on the effect of phytochemical and mineral analysis of kalakai (*Carissa carandas* L.) fruit, Int. J. Curr. Res. 12 (10) (2020) 14066–14072, <https://doi.org/10.24941/ijcr.39772.10.2020>.
- [2] S. Begum, S.A. Syed, B.S. Siddiqui, S.A. Sattar, M.I. Choudhary, Carandinol: first isohopane triterpene from the leaves of *Carissa carandas* L. and its cytotoxicity

- against cancer cell lines, *Phytochem. Lett.* 6 (1) (2013) 91–95, <https://doi.org/10.1016/j.phytol.2012.11.005>.
- [3] R.P. Dalal, N.A. Thakur, A. Singh, Nutritional value of Karonda (*Carissa carandas* Linn.). A non-conventional fruit under semi-arid condition of Punjab, *Indian J. Agrofor.* 12 (2010) 102104.
 - [4] M. Mahajan, H.K. Bons, G.K. Dhillon, P.A. Sachdeva, Unlocking the impact of drying methods on quality attributes of an unexploited fruit, karonda (*Carissa carandas* L.): a step towards food and nutritional security, *South Afr. J. Bot.* 145 (2022) 473–480, <https://doi.org/10.1016/j.sajb.2022.03.008>.
 - [5] K. Jayakumar, B. Muthuraman, Traditional uses and nutrient status of Indian native plant fruit (*Carissa carandas* Linn.), *WSN.* 96 (2018) 217–224.
 - [6] Y. BinteSadek, N. Choudhury, M. Shahriar, Biological investigations of the leaf extracts of *Carissa carandas*, *Int. J. Pharm. Res. Technol.* 5 (2013) 97–105, <https://www.researchgate.net/publication/259331804>.
 - [7] N.B.F. Food, N. Board, Institute of Medicine, Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium and Carotenoids, 2000.
 - [8] S.V.S. Verma, H.S. Chaudhary, Effect of *Carissa carandas* against clinically pathogenic bacterial strains, *J. Pharm. Res.* 4 (10) (2012) 3769–3771, <https://doi.org/10.1016/j.jlwt.2018.04.012>.
 - [9] S. Rajaram, G. Ashvin, Comparative studies of phytochemical screening of *Carissa carandas* L., *Asian J. Plant Sci.* 3 (2013) 21–25, <https://hal.science/hal-03696386>.
 - [10] K. Verma, D. Shrivastava, G. Kumar, Antioxidant activity and DNA damage inhibition in vitro by a methanolic extract of *Carissa carandas* (Apocynaceae) leaves, *J. Taibah Univ. Sci.* 9 (2015) 34–40, <https://doi.org/10.1016/j.jtusi.2014.07.001>.
 - [11] T. Agarwal, R. Singh, A.D. Shukla, I. Waris, *In vitro* study of antibacterial activity of *Carissa carandas* Leaf extracts, *Asian J. Plant Sci. Res.* 2 (2012) 36–40.
 - [12] S. Sundararajan, H. Rabe, Prevention of iron deficiency anemia in infants and toddlers, *Pediatric res* 89 (2021) 63–73, <https://www.nature.com/articles/s41390-020-0907-5>.
 - [13] Institute of Medicine, Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc, 2001.
 - [14] Z.A. Bhutta, J.K. Das, A. Rizvi, M.F. Gaffey, N. Walker, S. Horton, R.E. Black, Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost? The Lancet 382 (2013) 452–477, [https://doi.org/10.1016/S0140-6736\(13\)60996-4](https://doi.org/10.1016/S0140-6736(13)60996-4).
 - [15] International Zinc Nutrition Consultative Group (IZiNCG), Assessment of the Risk of Zinc Deficiency in Populations and Options for its Control, 2004.
 - [16] FAO, Save and Grow: A Policymaker's Guide to the Sustainable Intensification of Smallholder Crop Production, Rome, 2011 (also available at: <http://www.fao.org/3/I2215E/i2215e.pdf>).
 - [17] N. Rafique, T. Mamoon, N. Ashraf, S. Hussain, F. Ahmed, T.A. Shah, M. Bourhia, Exploring the nutritional and sensory potential of karonda fruit: physicochemical properties, jam production, and quality evaluation, *Food Sci. Nutr.* 11 (11) (2023) 6931–6944, <https://doi.org/10.1002/fsn3.3619>.
 - [18] R. Meti, B. Sunita, Physico-chemical properties and proximate analysis of fresh and dried karonda (*Carrisa carandas*), *J. Postharvest Technol.* 11 (2) (2023) 29–35.
 - [19] P.A. Patra, U. Basak, Nutritional and antinutritional properties of *Carissa carandas* and *Cordia dichotoma*, two medicinally important wild edible fruits of odisha, *J. Basic Appl. Sci. Res.* 7 (2017) 1–12.
 - [20] A. Sarma, P. Sarmah, D. Kashyap, S. Dutta, M. Mahanta, Antioxidant activity and nutraceutical property of the fruits of an ethno-medicinal plant: *Carissa carandas* L. found in Brahmaputra valley agro-climatic condition, *Int. J. Pharm. Sci.* 7 (2) (2015) 55–57.
 - [21] Institute of Medicine (US, Standing committee on the scientific evaluation of dietary reference intakes. Using dietary reference intakes for nutrient assessment of individuals, in: *DRI Dietary Reference Intakes: Applications in Dietary Assessment*. NAP. (US), 2000.
 - [22] E.D. Harris, Copper homeostasis: the role of cellular transporters, *Nutr. Rev.* 59 (9) (2001) 281–285, <https://doi.org/10.1111/j.1753-4887.2001.tb07017.x>.
 - [23] J.R. Turnlund, W.R. Keyes, S.K. Kim, J.M. Domek, Long-term high copper intake: effects on copper absorption, retention, and homeostasis in men, *Am. J. Clin. Nutr.* 81 (4) (2005) 822–828, <https://doi.org/10.1093/ajcn/81.4.822>.
 - [24] G.G. Graham, A. Cordan, Copper depletion and deficiency in the malnourished infant, *Johns Hopkins Med. J.* 124 (1969) 139–150, <https://www.cabidigitallibrary.org/doi/full/10.5555/19701401168>.
 - [25] R. Uauy, M. Olivares, M. Gonzalez, Essentiality of copper in humans, *Am. J. Clin. Nutr.* 67 (5) (1998) 952–959, <https://doi.org/10.1093/ajcn/67.5.952S>.
 - [26] P.J. Aggett, J. Hathcock, D. Jukes, D.P. Richardson, P.C. Calder, H. Bischoff-Ferrari, T. Nicklas, S. Mühlebach, O. Kwon, J. Lewis, M.J.F. Lugard, P. Prock, Nutrition issues in Codex: health claims, nutrient reference values and WTO agreements: a conference report, *Eur. J. Nutr.* 51 (2012) 1–7, <https://doi.org/10.1007/s00394-012-0306-8>.
 - [27] P.M. Coates, J.M. Betz, M.R. Blackman, G.M. Cragg, M. Levine, J. Moss, J.D. White, *Encyclopedia of Dietary Supplements*, CRC press., 2010.
 - [28] P. Chen, J. Bornhorst, M.A. Aschner, Manganese metabolism in humans, *Front. Biosci. (Online)* 23 (2018) 1655–1679, <https://doi.org/10.3389/fpsyg.2015.00766>.
 - [29] F.H. Nielsen, Manganese, Molybdenum, Boron, Chromium, and Other Trace Elements, *Present Knowledge in Nutr.* 2012, pp. 586–607, <https://doi.org/10.1002/9781119946045>.
 - [30] M.S. Ryu, A.T.B. Aydemir, in: B.P. Marriott, D.F. Birt, V.A. Stallings, A.S. Yates (Eds.), *Zinc. Present Knowledge in Nutrition*, 2020, pp. 393–408.
 - [31] J.C. King, Zinc: an essential but elusive nutrient, *Am. J. Clin. Nutr.* 94 (2) (2011) 679–684, <https://doi.org/10.3945/ajcn.110.005744>.
 - [32] R.S. MacDonald, The role of zinc in growth and cell proliferation, *J. Nutr.* 130 (5) (2000) 1500–1508, <https://doi.org/10.1093/jn/130.5.1500S>.
 - [33] F. Durré, B. Baron, Vitamin C: is supplementation necessary for optimal health? *J. Alternative Compl. Med.* 14 (10) (2008) 1291–1298, <https://doi.org/10.1089/acm.2008.0165>.
 - [34] S.V. Bhosale, R.V. Shete, V.S. Adak, K. Murthy, A review on *Carissa carandas*: traditional use, phytochemical constituents, and pharmacological properties, *JDDT* 10 (6-s) (2020) 145–150, <https://doi.org/10.22270/jddt.v10i6-s.4443>.
 - [35] F. Aslam, N. Rasool, M. Riaz, M. Zubair, K. Rizwan, M. Abbas, I.H. Bukhari, Antioxidant, haemolytic activities, and GC-MS profiling of *Carissa carandas* roots, *Int. J. Phytomed.* 3 (2011) 567–578, <http://www.arjournals.org/index.php/ijpm/index>.
 - [36] N. Anupama, G. Madhumitha, K.S. Rajesh, Role of dried fruits of *Carissa carandas* as anti-inflammatory agents and the analysis of phytochemical constituents by GC-MS, *BioMed Res. Int.* 2014 (2014), <https://doi.org/10.1155/2014/512369>.
 - [37] R. Sarkar, A. Kundu, K. Banerjee, S. Saha, Anthocyanin composition and potential bioactivity of karonda (*Carissa carandas* L.) fruit: an Indian source of biocolorant, *Lebensm. Wiss. Technol.* 93 (2018) 673–678, <https://doi.org/10.1016/j.lwt.2018.04.012>.
 - [38] S. Verma, A.K.S. Rawat, M.V. Ramana, S. Dhaneeshwar, Gas chromatographic-mass spectrometric profile of non-polar fraction and high-performance thin-layer chromatographic analysis of methanolic fraction with simultaneous quantifications of protocatechuic acid and Quercetin in *Carissa carandas* L. fruits, *J. Planar Chromatogr. Mod. TLC* 32 (2019) 237–241, <https://doi.org/10.1556/1006.2019.32.3.9>.
 - [39] W.J. Craig, Health-promoting properties of common herbs, *American J. Clin. Nutr.* (Phila.) 70 (3) (1999) 491–499, <https://doi.org/10.1093/ajcn/70.3.491s>.
 - [40] M. Suleman, A. Khan, A. Baqi, M.S. Kakar, M. Ayub, Z. Antioxidants, its role in preventing free radicals and infectious diseases in human body, *PAB (Pesqui. Agropecu. Bras.)* 8 (1) (2019) 380–388, <https://doi.org/10.19045/bspab.2018.700197>.
 - [41] N. Thitilertdech, P. Pintathong, The antioxidant and anti-tyrosinase activities of *Carissa carandas* linn. Fruit extracts and their applications in cosmetics, *Indian J. Pharmaceut. Sci.* 84 (5) (2022) 1218–1226.
 - [42] R. Siddiqi, S. Naz, S.A. Sayeed, S. Ishteyaque, M.S. Haider, O.M. Tarar, K. Jamil, Antioxidant potential of polyphenolics in *Grewia asiatica*, *Eugenia jambolana* and *Carissa carandas*, *J. Agric. Sci.* 5 (3) (2013) 217, <https://doi.org/10.5539/jas.v5n3p217>.
 - [43] S. Madhuri, S.E. Neelagund, Antioxidant, anti-diabetic activity and DNA damage inhibition activity of *Carissa carandas* fruit, *Int. J. Adv. Res. Dev.* 4 (2019) 75–82, <https://www.researchgate.net/publication/330873243>.
 - [44] W. Neimkhum, S. Anuchapreeda, W.C. Lin, S.C. Lue, K.H. Lee, W. Chaiyana, Effects of *Carissa carandas* Linn. Fruit, pulp, leaf, and seed on oxidation, inflammation, tyrosinase, matrix metalloproteinase, elastase, and hyaluronidase inhibition, *Antioxidants* 10 (9) (2021) 1345, <https://doi.org/10.3390/antiox10091345>.
 - [45] C.K. Mishra, D. Sasmal, D. Kumar, *In vitro* antioxidant activity of chloroform and ethanolic fruit and root extracts of *carissa carandas* linn., *J. Pharm. Innov.* 1 (1) (2017) 41–45.
 - [46] M. Khatun, M.R. Habib, M.A. Rabbi, R. Amin, M.F. Islam, M. Nurujjaman, M. H. Rahman, Antioxidant, cytotoxic and antineoplastic effects of *Carissa carandas* Linn. Leaves, *Exp. Toxicol. Pathol.* 69 (7) (2017) 469–476, <https://doi.org/10.1016/j.etp.2017.03.008>.
 - [47] D. Singh, D. Chaudhary, V. Kumar, A. Verma, Amelioration of diethylnitrosamine (DEN) induced renal oxidative stress and inflammation by *Carissa carandas* embedded silver nanoparticles in rodents, *Toxicol Rep* 8 (2021) 636–645, <https://doi.org/10.1016/j.toxrep.2021.03.014>.
 - [48] D. Singh, V. Kumar, E. Yadav, N. Falls, M. Singh, U. Komal, A. Verma, One-pot green synthesis and structural characterisation of silver nanoparticles using aqueous leaves extract of *Carissa carandas*: antioxidant, anticancer and antibacterial activities, *J. Nanobiotechnol.* 12 (6) (2018) 748–756, <https://doi.org/10.1049/iet-nbt.2017.0261>.
 - [49] A.B. Daphedar, T. Basavaprabhu, V. Nilagar, A. Waddar, *Carissa carandas* L. fruit mediated in vitro synthesis of silver nanoparticles and their antioxidant and antibacterial activities, *BJEPS* 2 (2) (2023) 53–60, <https://doi.org/10.55810/2312-5721.1019>.
 - [50] M. Qamar, S. Akhtar, T. Ismail, P. Sestili, A. Tawab, N. Ahmed, Anticancer and anti-inflammatory perspectives of Pakistan's indigenous berry *Grewia asiatica* Linn (Phalsa), *J. Berry Res.* 10 (1) (2020) 115–131, <https://doi.org/10.3233/JBR-190459>.
 - [51] Z. Abbas, A.L. Manoharan, G. Jagadeesan, G. Nataraj, K. Muniyandi, S. Sathyanarayana, P. Thangaraj, Evaluation of an edible polyherbal formulation against urinary tract infection pathogens, its antioxidant and anti-inflammatory potential, *Biocatal. Agric. Biotechnol.* 35 (2021) 102104, <https://doi.org/10.1016/j.bcab.2021.102104>.
 - [52] P. Crunkhorn, S.C.R. Meacock, Mediators of the inflammation induced in the rat paw by carrageenan, *Br. J. Pharmacol.* 42 (3) (1971) 392–402, <https://doi.org/10.1111/j.1476-5381.1971.tb07124.x>.
 - [53] A. Vysakh, M. Ratheesh, T.P. Rajmohan, C. Pramod, S. Premal, P.I. Sibi, Polyphenolics isolated from virgin coconut oil inhibits adjuvant induced arthritis in rats through antioxidant and anti-inflammatory action, *Int. Immunopharm.* 20 (1) (2014) 124–130, <https://doi.org/10.1016/j.intimp.2014.02.026>.
 - [54] V.H. Bhaskar, N. Balakrishnan, Analgesic, anti-inflammatory and antipyretic activities of *Pergularia daemia* and *Carissa carandas*, *Daru* 7 (3) (2009) 168–174.
 - [55] S. Galipalli, N.K. Patel, K. Prasanna, K.K. Bhutani, Activity-guided investigation of *Carissa carandas* (L.) roots for anti-inflammatory constituents, *Nat. Prod. Res.* 29 (17) (2015) 1670–1672, <https://doi.org/10.1080/14786419.2014.989846>.

- [56] S. Saher, S. Narnawre, J. Patil, Evaluation of phytochemical and pharmacological activity of *Carissa carandas* L. fruits at three different stages of maturation, *Drug Res.* 70 (02/03) (2020) 80–85, <https://doi.org/10.1055/a-0815-4832>.
- [57] A.H. El-Desoky, R.F. Abdel-Rahman, O.K. Ahmed, H.S. El-Beltagi, M. Hattori, Anti-inflammatory and antioxidant activities of naringin isolated from *Carissa carandas* L.: *In vitro* and *in vivo* evidence, *Phytomedicine* 42 (2018) 126–134, <https://doi.org/10.1016/j.phymed.2018.03.051>.
- [58] V. Singh, To determine the anti-inflammatory and anti-pyretic activity on the stem of *carissa carandas* linn, *J. Pharm. Negat. Results* 13 (2022), <https://doi.org/10.47750/pnr.2022.13.S05.174>.
- [59] M. David, G. Karekalammanavar, Spectrographic analysis and *in vitro* study of antibacterial, anticancer activity of aqueous ethanolic fruit extract of *Carissa carandas* L, *J. Adv. Sci. Res.* 6 (3) (2015) 10–13, <https://scisage.info/index.php/JASR/article/view/235>.
- [60] W. Pewlong, S. Sajjabut, J. Eamsiri, S. Chookaew, Evaluation of antioxidant activities, anthocyanins, total phenolic content, vitamin C content and cytotoxicity of *Carissa carandas* Linn, *CMUJ. Nat. Sci.* 13 (1) (2014) 509–517, <https://doi.org/10.12982/cmujns.2014.0053>.
- [61] P. Gupta, I. Bhatnagar, S.K. Kim, A.K. Verma, A. Sharma, *In-vitro* cancer cell cytotoxicity and alpha amylase inhibition effect of seven tropical fruit residues, *Asian Pac. J. Trop. Biomed.* 4 (2014) 665–671, <https://doi.org/10.12980/APJTB.4.2014B433>.
- [62] S. Kiruthika, P.S. Lakshmi, A. Praveena, Screening of novel lead compound from *Carissa carandas* against breast cancer using *in-vitro* and *in-silico* methods, *Int. J. Pharm. Biol. Sci.* 9 (2019) 1046–1052, <https://doi.org/10.21276/ijpbs.2019.9.2.126>.
- [63] N. Kour, A. Qayum, B.A. Lone, S.K. Singh, V. Sharma, P. Gupta, A novel carissic acid from fruits of *Carissa carandas* induced apoptotic cell death in A-549 cells following the activation of caspases, *Nat. Prod. Res.* (2023) 1–11, <https://doi.org/10.1080/14786419.2023.2232082>.
- [64] S.F. Sulaiman, S.T. Wong, K.L. Ooi, S.R. Yusof, T. Muhammad, T. Sifzizul, Anticancer Study of *Carissa Carandas* Extracts, Project Report. USM, 2008, pp. 1–6.
- [65] Z. Bano, S. Begum, S.S. Ali, Z. Kiran, B.S. Siddiqui, A. Ahmed, S. Khawaja, F. Fatima, A. Jabeen, Phytochemicals from *Carissa carandas* with potent cytotoxic and anti-inflammatory activities, *Nat. Prod. Res.* 36 (6) (2022) 1587–1592, <https://doi.org/10.1080/14786419.2021.1886101>.
- [66] Z. Bano, S. Begum, S.S. Ali, Z. Kiran, B.S. Siddiqui, S. Khawaja, A. Ahmed, Novel ursane-type triterpene from the fresh leaves of *Carissa carandas* and evaluation of cytotoxicity, *J. Asian Nat. Prod. Res.* 23 (9) (2021) 892–898, <https://doi.org/10.1080/10286020.2020.1791098>.
- [67] R. Siddiqi, S. Naz, S. Ahmad, S.A. Sayeed, Antimicrobial activity of the polyphenolic fractions derived from *Grewia asiatica*, *Eugenia jambolana* and *Carissa carandas*, *J. Food Sci. Technol.* 46 (2) (2011) 250–256, <https://doi.org/10.1111/j.1365-2621.2010.02480.x>.
- [68] M. Khuaneekaphan, W. Khobjai, C. Noysang, N. Wisidsri, S. Thungmungmee, Bioactivities of Karanda (*Carissa carandas* Linn.) fruit extracts for novel cosmeceutical applications, "J. Adv. Pharm. Technol. Research" (JAPTR) 12 (2) (2021) 162–168, https://doi.org/10.4103/2Fjaptr.JAPTR_254_20.
- [69] Y. Sudjaroen, *In vitro* antioxidant, antibacterial, and cytotoxicity activities from Karanda (*Carissa carandas* L.) fruit extracts, *IJGP.* 11 (1) (2017).
- [70] K. Pilasombut, C. Laosinwattana, T.K.T. Nguyen, N. Ngamyeeesoon, M. Teerarak, Antimicrobial properties of extracts from *Carissa carandas* L. fruits and its application in chilled and frozen ground pork, *Int. J. Agric. Technol.* (2019) 91–102.
- [71] S. Shifa, T. Begum, F. Afroze, M.K. Shraboni, Preliminary phytochemical screening, antibacterial activity and cytotoxic activity of leaves extract of *Carissa carandas* Linn, *J. Pharmacogn. Phytochem.* 8 (4) (2019) 801–804.
- [72] G. Pathak, S. Singh, M. Singhal, J. Singh, Y. Hussain, M. Gupta, A. Meena, P. Gupta, P.K. Rout, Pharmacology of *Carissa carandas* leaf extract: anti-proliferative, antioxidant and antimicrobial investigation, *Plant Biosyst.* 155 (3) (2021) 543–556, <https://doi.org/10.1080/11263504.2020.1762787>.
- [73] V.E. Kaban, N. Nasri, H.D. Syahputra, M.F. Lubis, D. Satria, Uji Aktivitas Antibakteri Ekstrak Daun Karenda (*Carissa carandas* Linn.) Terhadap Bakteri *Propionibacterium acne* dan *Staphylococcus epidermidis*, *JPHSR* 4 (1) (2023) 91–96, <https://doi.org/10.47065/jpharma.v4i1.3181>.
- [74] H.B.H. Rahuman, R. Dhandapani, V. Palanivel, S. Thangavelu, R. Paramasivam, S. Muthupandian, Bioengineered phytomolecules-capped silver nanoparticles using *Carissa carandas* leaf extract to embed on to urinary catheter to combat UTI pathogens, *PLoS One* 16 (9) (2021) e0256748, <https://doi.org/10.1371/journal.pone.0256748>.
- [75] S. Rajapandi, V. Kandasamy, D. Govindaraj, P. Chandrasekaran, G.N. Kousalya, *In-Vitro Bio-Medical Applications of Novel Carissa Carandoss Derived Nitrogen Doped Carbon Dots*, 2023, <https://doi.org/10.2139/ssrn.4377413>. SSRN.
- [76] H. Sun, P. Saeedi, S. Karuranga, M. Pinkepank, K. Ogurtsova, B.B. Duncan, C. Stein, A. Basit, J.C. Chan, J.C. Mbanya, M.E. Pavkov, IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045, *Diabetes Res. Clin. Pract.* 183 (2022) 109119, <https://doi.org/10.1016/j.diabres.2021.109119>.
- [77] K.G.M.M. Alberti, P.Z. Zimmet, Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation, *Diabet. Med.* 15 (7) (1998) 539–553, [https://doi.org/10.1002/\(SICI\)1096-9136\(199807\)15:7<539::AID-DIA668>3.0.CO;2-S](https://doi.org/10.1002/(SICI)1096-9136(199807)15:7<539::AID-DIA668>3.0.CO;2-S).
- [78] R.R. Holman, S.K. Paul, M.A. Bethel, D.R. Matthews, H.A.W. Neil, 10-year follow-up of intensive glucose control in type 2 diabetes, *NEJM* 359 (15) (2008) 1577–1589, <https://doi.org/10.1056/NEJMoa0806470>.
- [79] P.R. Itankar, S.J. Lokhande, P.R. Verma, S.K. Arora, R.A. Sahu, A.T. Patil, Antidiabetic potential of unripe *Carissa carandas* Linn. fruit extract, *J. Ethnopharmacol.* 135 (2) (2011) 430–433, <https://doi.org/10.1016/j.jep.2011.03.036>.
- [80] S. Singh, Antidiabetic activity (In vitro alpha amylase inhibitory) of ethanol extract of *Carissa carandas* Linn. Roots, *Int. J. Pharmacol. Res.* 12 (3) (2020), <https://doi.org/10.31838/ijpr/2020.12.03.002>.
- [81] M.S.A. Owatworakitb, N. Siri Wongd, Antioxidant, antidiabetic and Antiproliferative activities of juice extract and residue powder from Karanda (*Carissa carandas* L.), *JFHB.* 16 (1) (2023) 9–16.
- [82] R. Singh, M. Shrivastava, P. Sharma, Antidiabetic effect of *Carissa carandas* in rats and the possible mechanism of its insulin secretagogues activity in isolated pancreatic islets, *J. Biomed. Therm. Sci.* 6 (1) (2019) 1–7.
- [83] M. Lailerd, T.W. Linn, N. Lailerd, D. Amornlerdpison, A. Imsumran, Assessment of antidiabetic and anti-inflammatory activities of *Carissa carandas* Linn extract: *in vitro* and *in vivo* study, *Appl. Sci.* 13 (11) (2023) 6454, <https://doi.org/10.3390/app13116454>.
- [84] T. Anunthawan, T. Rimluduan, Antioxidant activity, anti-tyrosinase activity, and lipstick pigments of *Oryza sativa* Linn. and *Carissa carandas* Linn. Extracts, *J. Appl. Pharmaceut. Sci.* 13 (10) (2023) 217–224, <https://doi.org/10.7324/JAPS.2023.145623>.
- [85] J. Khunchalee, The study of free radical scavenging, total phenolic contents and tyrosinase inhibition activity of crude extract from *Carissa carandas* Linn, *Cre. Sci.* 11 (1) (2019) 26–34, <https://ph01.tci-thaijo.org/index.php/snrjournal/article/view/149566>.
- [86] P. Olakit, Formulation and Characterization of Karanda (*Carissa carandas*) Yogurt, 2018.
- [87] N. Chomsri, Characteristics of yogurt supplemented with different concentrations of *Carissa carandas* L, *JAST.* 1 (1) (2020) 18–25, <https://doi.org/10.14456/jsat.2020.3>.
- [88] N. Lapsongphon, S. Changso, Development of reduced calories *Carissa carandas* sherbet by substitution sugar with stevia extract, *Food Appl. Biosci.* 7 (3) (2019) 162–171, <https://li01.tci-thaijo.org/index.php/fabjournal/article/view/176797>.
- [89] R. Arora, H.K. Bons, G.S. Kocher, Fermentative processing of unexploited fruit, karonda (*Carissa carandas* L.) into alcoholic beverages, *South Afr. J. Bot.* 158 (2023) 73–79, <https://doi.org/10.1016/j.sajb.2023.04.052>.
- [90] K. Rumjuankiat, N. Sonhom, K. Showpanish, A. Somsri, K. Pilasombut, *In vitro* antioxidant activities and volatile compounds from Karanda (*Carissa carandas* L) fruit wine, *Int. J. Agric. Technol.* 14 (7) (2018) 1843–1860, <http://www.ijat-aatsea.com>.
- [91] V.S. Khandare, D.P. Waskar, B.M. Kalalbandi, N.M. Navsare, Studies on preparation of functional beverages from karonda (*Carissa carandas* L.), *J. Agric. Res. Technol.* 40 (2) (2015) 239.
- [92] S.K. Shaheel, D.V. Swami, B.P. Kumar, K.U. Krishna, Effect of blending of karonda (*Carissa carandas* L.) juice with guava, papaya and pineapple juices on its quality and organoleptic evaluation, *Plant Arch.* 15 (1) (2015) 187–192.
- [93] P.J. Sawant, D.C. Rai, S.P. Yadav, Assessment of impact of feeding fermented karonda (*Carissa carandas*) whey beverage on biochemical parameters of albino rats, *Indian J. Anim. Res.* 52 (8) (2018) 1162–1166, <https://doi.org/10.18805/ijar.B-3336>.