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Review Article:

The Phytochemical Ingredients and Therapeutic Potential of *Cynara scolymus* L.

Priyanka Sharma[1], Pawan Kumar Verma[1*], Nrip Kishore Pankaj[1], Sanjay Agarwal[2]

1. Department of Veterinary Pharmacology and Toxicology, Faculty of Veterinary Sciences and Animal Husbandry, Sher-e-Kashmir University of Agricultural Sciences and Technology of Jammu, RS Pura, Jammu & Kashmir, India.
2. Department of Veterinary Gynaecology and Obstetrics, Faculty of Veterinary Sciences and Animal Husbandry, Sher-e-Kashmir University of Agricultural Sciences and Technology of Jammu RS Pura, Jammu & Kashmir, India.

*** Corresponding Author:**
Pawan Kumar Verma, PhD.
Address: Department of Veterinary Pharmacology and Toxicology, Faculty of Veterinary Sciences and Animal Husbandry, Sher-e-Kashmir University of Agricultural Sciences and Technology of Jammu, RS Pura, Jammu & Kashmir, India.
Phone:+91 (1923) 251901
E-mail: drpawankv@yahoo.co.in

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ABSTRACT

Background: Medicinal herbs remain a vital source of new chemical entities, instead of the attempt of pharmaceutical companies using combinatorial and synthetic chemistry techniques for developing new drugs.

Objectives: The primary aim of review is to highlight the different phytochemcial ingredients and their therapeutic potential in Cynara scolymus

Methods: *Cynara scolymus*, commonly known as artichoke is a rich source of polyphenolic compounds, mainly caffeoylquinic acids and flavonoids, isolated in the polar extracts of the plant, together with the polysaccharide inulin. The worldwide scientific databases were comprehensively and systematically reviewed and summarized.

Results: The beneficial effects of artichoke in experimental studies include antidiabetic, anti-obesity, anti-inflammatory, anti-hypercholesterolemic, hepatoprotective, nephroprotective, gastrointestinal protectant, reproductive, and anticancer properties. Studies with artichoke conducted in experimental animals reported no mortality or significant toxicity. Increasing attention is being paid to developing herbal medicines as a newly emerging treatment for the welfare of the patients in the last few decades.

Conclusion: The present review detailed the versatile therapeutic efficiency and diverse application of *C. scolymus*. This medicinal herb has been appropriately used in conventional medicine for a long and helps cure various ailments.

Introduction

Nature has been an essential source of medicinal compounds for centuries. Moreover, multiple modern drugs have been derived and developed from natural resources. Many of these isolations of bioactive agents have been based on their uses in conventional medicine. A large proportion of

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medicinal plants have been discovered with the help of ethnobotanical knowledge of their traditional uses. The rich knowledge of researchers, based on the ayurvedic heritage of some countries, like India. Medicinal plants and healthcare have led to the keen interest of various pharmaceutical companies to use this knowledge as a source for further developing programs in the pursuit of discovering novel drugs [1]. Traditionally, numerous medicinal plants and their aerial parts, including leaves, flowers were used as an alternative remedy for treating various diseases. One such plant, widely cultivated for its nutritional potential, is *Cynara scolymus* L. The variable nutritional and therapeutic actions can be attributed to the plant; possibly due to the presence of various bioactive components which generate synergistic pharmacological effects. *C. scolymus* is a perennial plant native to the Mediterranean region [2], and commonly known as an artichoke. The globe artichoke is a thistle species variety, i.e., cultivated as food in numerous parts of the world. The flower buds prior to flower blooming constitute the edible part of the plant. The blooming flower is coarse and hardly edible.

Global artichoke production totaled 1.7M tones in 2018, remaining constant increased against the previous year. The total output volume increased at an average annual rate of+1.1% from 2009 to 2018; the trend pattern remained relatively stable. Countries with the highest volumes of artichoke consumption in 2018 were Italy (394K tones), Egypt (319K tones), and Spain (196K tones); together comprising 54% of global consumption. Peru, Algeria, Argentina, and China lagged somewhat behind, together accounting for a further 28%. In value terms, the largest artichoke markets worldwide included Italy ($608M), Peru ($421M), and Egypt ($341M), with a combined 54% share of the global market. Spain, Argentina, Algeria, and China lagged somewhat behind, together accounting for a further 26%. The countries with the highest levels of artichoke per capita consumption in 2018 were Italy (6.62 kg per person), Peru (4.75 kg per person), and Spain (4.20 kg per person). In India, the total volume of Artichoke export around the world in 2018 equaled 966090. The figures suggest the great potential for the Indian exporters of the artichoke to increase their participation in global trading. The top 5 trading partners of India are the USA (USD 1.37 million), United Arab Emirates (USD 0.15 million), United Kingdom (USD 0.07 million), France (USD 0.05 million), and Germany (USD 0.05 million). The total export value of Artichoke in these countries was measured to be USD 1.69 million from India. These top 5 countries account for >92.35% of the total artichoke export from India. The USA is the largest market for artichoke export from India. In 2019-2020, the USA imported USD 1.37 million worth of artichoke from India [3].

Materials and Methods

The required data for the comprehensive study were obtained from a worldwide accepted scientific database *viz*. Science Direct (http://www.sciencedirect.com), PubMed (http://ncbi.nih.gov/pubmed), Springerlink (http://www.springer.co.in), and abstracts, journals account for botanical description, pharmacological properties, and ethnobotanical uses of different parts of *Cynara scolymus* L. (artichoke). The present review comprehensively highlighted the botanical description, traditional uses, phytochemical constituents present in a different part of *Cynara scolymus* L., and their pharmacological properties.

Botanical description: Artichoke plants feature deeply toothed large leave that grows up to 3 feet long and

Table 1. Taxonomic features and vernacular names used for the *Cynara scolymus*

Taxonomic Features		Vernacular Names	
Kingdom	Plantae	**Language**	**Vernacular Name**
Division	Magnoliophyta	German	Artischoke
Class	Magnoliopsida	French	Artichaut
Order	Asterales	India	Artichoke
Family	Asteraceae	Hindi	Hanthi chak
Genus	Cynara	United State	Green Artichoke
Species	Scolymus	Ancient Greeks	Koktos

Figure 1. The growing mature plant of *Cynara scolymus* L.

dies each year after flowers are formed. The plants produce rosettes of sturdy branched flower stalks with purple flower heads. The plant exists in wild and cultivated forms. In North America, it is found in the wild regions. Globe artichokes may be grown as vegetables. Buds are harvested before flowering. For consumption, the bud is first steamed until the bracts are easily removed. Bracts are then individually removed with the fleshy edible base on each bract, i.e., eaten. Figure 1 showing growing mature plant and Figure 2 shows mature flower of Cynara scolymus. As a vegetable, it grows to 140-200 cm tall, with arched and deeply lobed, shiny, and glaucous green leaves of 50-80 cm long. The seeds of *C. scolymus* were found during the excavation of Roman-period Mons Claudianus in Egypt [4]. The plant species is hermaphrodite (which has male and female organs) and is pollinated by bees and Lepidoptera (Moths & Butterflies). The plant is then renewed by planting the divisions of the rosette crown or rooted offshoots. The mature flower heads produce seeds; however, the seedlings do not necessarily resemble the variety of the parent plant. Thus, vegetative propagation is preferred. Plant growth is suitable in light (sandy), medium (loamy), and heavy (clay) soils, and prefers well-drained soil. The plant can best grow in acidic, neutral, and basic (alkaline) soils. Artichoke can also grow in saline soils. Regardless of culinary value, this plant provides excellent interest to mixed borders, vegetable gardens, and Mediterranean gardens

Figure 2. The mature flower of the *Cynara scolymus* L. plant

for its ornamental foliage and flowers. The taxonomic feature and vernacular names used for *C. scolymus* are presented in Table 1.

Traditional uses: Artichoke is cultivated worldwide, owing to its nutritional benefits and medicinal properties [5]. The plant had been traditionally used as food and medicine among the ancient Egyptians, Greeks, and Romans. Since the fourth century AD, the Greek Theophrastus was the pioneer to describe the plant in detail. Thereafter, Egyptian king Ptolemy Euergetes, recommended his army to consume artichoke, as they were considered a source of strength and braveness. Earlier, this plant was used as an appetizer and digestive aid by the aristocracy of the Roman Empire until the 16th century. It was when the medicinal use of artichoke for problems, like jaundice, was initiated. Since ancient times, artichoke has been cited as a drug in traditional medicine, globally. In 1850, a French physician first used the extract of artichoke leaves for treating a boy who encountered jaundice [6]. This plant presents various beneficial effects related to the diseases of the biliary tract, digestive action, scurvy, anemia, and so on [7]. In the 16th century in Europe, it was considered a "noble" vegetable meant for the royal and the rich. It is not only a healthy food known for its pleasant bitter taste but also possesses the qualities of an herbal drug. The leaf extracts of this plant are widely used alone or in combination with other herbs for embittering alcoholic and soft drinks; they are also used to prepare herbal teas or herbal medicinal products [7, 8]. In the first half of the 20th century, French scientists initiated modern research into these traditional medicinal uses of the artichoke plant. In Persian medicine, the plant parts are commonly used for managing functional dysphoria. They suggested its various other beneficial effects, such as stimulating kidney and gall bladder, and so on. From the 1950s to 1980s the synthetic cynarin preparations were used as a drug to stimulate the liver and gall bladder, also to treat elevated cholesterol, and so on.

Phytochemical ingredients

Plants are rich sources of diverse phytochemical ingredients; these ingredient concentrations vary with environmental conditions, genetic characteristics, stress, plant age, harvest time, agrochemical process, the analyzed part of artichoke (leaves, flower, root, stem, pomace, etc.), as well as different drying methods [9]. Artichoke is a rich source of polyphenolic compounds, mainly caffeoylquinic acids and flavonoids, isolated in the polar extracts of the plant, together with the polysaccharide inulin. Table 2 enlisted the major phytochemical ingredients present in the artichoke seeds.

Concerning the lipophilic fraction, it is composed of fatty acids, triterpenes, and sesquiterpenes, as major metabolites [9]. The quantification of phenolic compounds from artichoke reviled 22 major compounds, 11 caffeoylquinic acids, and 8 flavonoids. The main phenolic compounds include caffeic acid derivatives which include caffeoylquinic acid derivatives. Flavonoids, together with anthocyanins, are minor constituents of artichoke, representing <10% of the total phenolic compounds. However, the phenolic content of artichoke varies depending on the plant age. In general, immature heads have higher phenol contents than mature heads; where total polyphenols, detected in different cultivars of *C. scolymus*, increased from external to internal parts [10].

Among flavonoids, Apigenin 7-O-glucuronide was found to be the major flavonoid. Besides, 1,5-Di-O-caffeoylquinic acid represented the major hydroxy-cinnamic acid in the pomace; however, in the juice, 1,3-di-O-caffeoylquinic acid (cynarin) was predominant, due to the isomerization during processing. Total phenolic contents of approximately 12 g/kg on a dry matter basis revealed that artichoke pomace is a promising source of phenolic compounds that might be recovered and used as natural antioxidants or functional food ingredients [11]. The artichoke leaves are found to be a rich source of polyphenolic compounds, including a combination of

Table 2. The major phytochemical composition of artichoke seeds

Ingredients	Frequency (%)
Crude proteins	21.6
Crude fibers	17.1
Crude oil	24.05
Ash	3.8

Table 3. Various pharmacological activities of isolated ingredients from the *Cynara scolymus*

Major Group	Active Compounds	Activity	Reference
Caffeoylquinic acid	Chlorogenic acid (3-O-caffeoylquinic acid)	Hepatoprotective potential	[18]
		Antioxidant potential	[19]
		Anti-carcinogenic activity	[20]
		Hepatoprotective activity	[16]
	Cynarin (1,3-Dicaffeoylquinic acid)	Antioxidant potential	[21]
		Cholorectic and diuretic	[22]
	3,4-Dicaffeoylquinic acid	Anti-influenza viral activity	[23]
	3,5-Dicaffeoylquinic acid	Antioxidant and anti-apoptotic	[24]
		Astrocytes protection	[25]
	1,5-Dicaffeoylquinic acid	Prevention of neuron apoptosis in Alzheimer's disease	[26]
		Anti-carcinogenic	[27]
		Antioxidant	[19]
Flavonoids	Luteolin	Anticholestatic, choleric	[22]
		Antioxidant potential	[28]
		Antimicrobial activity	[29]
		Vasorelaxant activity	[30]
	Cynaroside (luteolin 7-O-glucoside)	Hepato-protective, anticholestatic, cholerectic	[31]
	Scolymoside (luteolin 7-O-rutinoside)	Anti-hyperlipidemic	[32]
	Apigenin	Vasorelaxant potential	[30]
		Antioxidant potential	[19]
		Chemo-preventive agent	[33]

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quinic acid, caffeic acid, sesquiterpene B (selinene and caryophyllene), and so on [12, 13]. These also possess the essential antioxidant compounds; cynarin and chlorogenic acid, by the combination of 1,3 quinic acid with the two molecules of caffeic acid 1, 3-di-o-quinic acid (cynarin), as well as 5-o-caffeoyl quinic acid (cryogenic acid). The biological compound of artichoke leaf extract has a low content of fat and high levels of minerals (potassium, sodium, & phosphorous), vitamin C, fibers, polyphenols, flavones, inulin, hydroxycinnamates, and caffeoylquinic acid derivatives [10, 14].

Its flower heads have a high content of vitamin C (10 mg/100 mg flower weight) and minerals (potassium, calcium, etc.) [15]. Its leaf extract possesses various activities, such as antioxidative, antibacterial, hepatoprotective, and choleretic properties, cholesterol biosynthesis inhibition, Low-Density Lipoprotein (LDL) oxidation, and so on [16].

According to the International Union of Pure and Applied Chemistry (IUPAC) nomenclature, 5-O-caffeoylquinic acid (chlorogenic acid) is the most abundant single substance (39%), followed by 1,5-O-dicaffeoylquinic acid (21%) and 3,4-O-dicaffeoylquinic acid (11%), based on the total caffeoylquinic acid content [17]. These phenolic compounds possess scavenging activity against free radicals and act as a shield against oxidative damage to biological molecules, such as proteins, lipids,

and DNA [14]. Other phenolic compounds, like flavones 5,7-dihydroxy-2-(4-hydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one (apigenin) and 2-(3,4-dihydroxyphenyl)-5,7 dihydroxy-4-chromenone (luteolin), as well as the anthocyanidins, such as 2-(3,4-dihydroxyphenyl) chromenylum-3,5,7-triol (cyanidin), 2-(4-hydroxy-3 methoxy phenyl) chromenylium-3,5,7-triol (peonidin), and 2-(3,4,5-trihydroxyphenyl) chromenylium-3,5,7-triol (delphinidin) were only isolated the in heads of artichoke [17]. Flavones (apigenin & luteolin) were identified in the leaves and heads of the plant in the form of glucosides and rutinosides; anthocyanin pigments are present only in the head in the form of glucosides and sophorosides [5]. The major phytochemical ingredients and their corresponding pharmacological activities in different experimental models are presented in Table 3.

Pharmacological properties

Various experimental studies explored different extracts of *C. scolymus*; they concluded that it possesses a wide range of pharmacological properties. Due to its potent pharmacological properties, it can be used for the therapeutic purposes of various ailments in the future in animals as well as humans. These pharmacological properties are as follows:

Antioxidant potential: Extant studies indicated that the phytochemical present in the different parts of the plant possess strong antioxidant potential *in vitro* assay includes *in vitro* free radical scavenging assays, superoxide radical scavenging assay, nitric oxide scavenging assay, reducing power, and metal chelating potential along with *in vivo* studies. Gebhardt [34] assessed the antioxidative and protective potential of water-soluble extracts of artichoke leaves exposing primary rat hepatocyte culture to tertiary-butyl hydroxide or cumene hydro-peroxide. They reported that the addition of artichoke extracts did not affect the basal Malondialdehyde (MDA) production; however, it prevented the hydroperoxides increase of MDA formation when presented prior to peroxides. Wang et al. [16] purified the antioxidative components from the aqueous methanolic extractions of artichoke heads and leaves. Seven active polyphenolic compounds were purified from artichoke and apigenin-7-rutinoside and narirutin were found to be unique to artichoke heads. Goni et al. [35] reported that artichoke modifies bacterial enzymatic activities and antioxidant status in rat caecum.

This is achieved by modifying colonic bacterial enzymatic activities (increased beta-glucosidase and nitroreductase activities with reduced nitrate reductase and azo-reductase activities. This enhances the capacity of microbial enzymes to metabolize glycosides and nitro compounds. Free radical quenching ability and reducing efficacy were significantly higher in the group fed with artichoke, compared to the control group. Juzyszyn et al. [36] studied the effect of the extract of *C. scolymus* on induced reactive oxygen species generation in cultured Human Umbilical Endothelial Cells and its reductive properties. It was suggested that *C. scolymus* be used as endothelium protective agents. Skarpanska et al. [37] demonstrated that consuming artichoke leaf extract, a natural vegetable preparation of high antioxidant potential resulted in higher plasma total antioxidant capacity than placebo; however, it did not limit the oxidative damage to erythrocytes in athletes subjected to strenuous training. Jacociunas et al. [38] documented the modulatory effect of *C. scolymus* on mutagenicity due to the presence of its constitutive antioxidant compounds.

Baali et al. [39] also reported the antioxidant and protective effects of another plant of this genus *C. cardunculus* against paracetamol-induced liver mitochondrial oxidative stress; the protective effect was primarily due to its free radical scavenging activity and the enhancement of mitochondrial antioxidant reserve. Goni et al. [35] studied the antioxidant activity produced by main polyphenols present in edible artichoke heads. They found that artichoke manifested higher antioxidant activity than the individual phenols, even after *in vitro* gastrointestinal digestion. Additionally, *in vitro* digestion did not modify the antioxidant activity of artichoke polyphenols, except for 1,5-O-dicaffeoylquinic acid, which proved to be the least active. Magieise et al. [40] explored the antioxidant activity of a quantified leaf extract of *C. scolymus*. Accordingly, they observed decreased oxidative stress and MDA and 8-OH deoxyguanosine levels and increased erythrocyte glutathione levels.

Abu-Reidah et al. [41] evaluated the phenolic compounds of *C. scolymus* using HPLC; the observation reviled plant was a rich source of antioxidant phenolic compounds. Claus et al. [42] examined the chemical characterization and use of artichoke parts for protection from oxidative stress in canola oil. They found that artichoke spikes may have industrial applications as natural antioxidant additives to foods, like canola oil. Mustafa et al. [43] evaluated the protective effect of *C. scolymus* and co-enzymes Q10 in doxorubicin-induced toxicity; they observed the up-regulation of favorable protective enzymes and the down-regulation of oxidative stress.

Ergezer and Serdaroglu, [44] studied the antioxidant potential of artichoke byproducts extract in raw beef pat-

ties during refrigerated storage; subsequently, they found it to substantially inhibit lipid and protein oxidation in raw beef patties to a much greater extent, compared to Butylated Hydroxy Toluene (BHT). Similarly, Ben Salem [45] assessed the chemical composition, antioxidant potential, and enzymes inhibitory properties of globe artichoke by products. Consequently, they found it as a promising source of natural health promoting compounds, with potential applications in food and pharmaceutical industries.

Anti-hypercholesterolemic effect: Pittler et al. [46] found the available evidence regarding the hypocholesterolemic activity of artichoke leaf extract not convincingly sufficient for its recommendation as an option for treating hypercholesterolemia. He claimed that the hypocholesterolemic effects of artichoke leaf extract were found among *in vitro* and animal-based studies; therefore, advocated for clinical trials to evaluate greater samples size, for the extended durations of treatment especially among patients with high cholesterol level to establish artichoke leaf extract as an effective and safe treatment option for patients with hypercholesterolemia. Shimoda et al. [32] found lipid-lowering sesquiterpene, such as Cynaropicrin, Aguerine, and Grosheimin in the methanolic extract of artichoke leaves; it suppressed serum triglyceride level in 2 h after olive oil administration. Rangboo et al. [47] assessed the hypolipidemic activity of artichoke leaf extract 2700mg; accordingly, among 30 patients for two months, they found a favorable improvement in the liver enzymes and lipid profiles of triglycerides, as well as total cholesterol, compared to the placebo group.

Gebhardt [22, 48] studied the effects of artichoke leaf extract. They suggested that *C. scolymus* extract reduced blood lipids by directly influencing the biosynthesis of cholesterol and the production and secretion of bile from the liver. Luteolin is among the constituents of artichoke leaf extract that interfere with the fresh synthesis of cholesterol and facilitate biliary secretion from the liver. Reduced triglycerides levels are attributed to improved glycemic control and reduced glucose instead of fat. Acetyl COA yield from pyruvic acid enters Krebs cycle; this condition leads to the metabolism of glucose completely, instead of triglycerides biosynthesis.

Cynaropicrin was found most crucial among these sesquiterpene, responsible for lipid-lowering effect in experimental trials [32]. These lipid lowering activities were also found directly correlated with their gastrointestinal evacuation suppression abilities, as well. Besides, the flavone glycosides, such as luteolin 7-O-b-d-glucopyranoside and luteolin 7-O-b-d-rutinoside were reported for their moderate hypolipidemic activities [32]. Shimoda et al. explored structure-activity relationships; accordingly, they found that the functional group, e.g. oxygen and exo-methylene moiety in the a-methylene-g-butyrolactone ring were indispensable for the anti-hyperlipidemic activity of sesquiterpene [32].

Ben Salem et al., [49] reported that artichoke leaf extract treatment inhibited lipase activity in the plasma, in high-fat diet rats; it reduced serum total cholesterol, low-density lipoprotein, and triglycerides levels and significantly declined the calculated atherogenic index. Consequently, it demonstrated an increase in HDL and a decrease in body and liver weight, like an anti-obesity action. Therefore, administrating artichoke leaf extract treatment for two months at the doses of 200 mg/kg and 400 mg/kg body weight repressed the fat accumulation, confirmed by histological findings of the liver in the high fat diet-fed rats.

Magied et al. [50] studied the effects of artichoke leaves (of green globe variety) extract on total cholesterol, LDL, HDL, and triglycerides levels in rats; they recorded superior anti-hypercholesterolemic activities, compared to violet artichoke leaves extract at the dose rate of 1.5gm per days for 6 weeks. Heidarian and Soofiniya [51] also substantiated in agreement and noticed a significant dose-dependent decline in the elevated levels of total cholesterol and triglycerides among streptozotocin-induced diabetic rats, placed on the treatment of artichoke leaf extract. Kusk-Kiraz et al. [52] reported a significant decrease in the levels of total cholesterol and triglyceride among rats fed on hypercholesterolemic ration and simultaneously treated with artichoke leaves extract at doses of 1.5 gm/kg b wt for two weeks.

Joy and Haber [53] reported that artichoke significantly reduced serum cholesterol in hypercholesterolemic subjects. Heidarian et al. [54] studied the lipid-lowering effects of artichoke on liver Phosphatidate Phosphohydrolase (PAP) and plasma lipids in hyperlipidemic rats. They found that artichoke can be useful for the reduction of PAP activity and liver triglycerides. Artichoke also presented beneficial effects in controlling hyperlipidemia, abnormalities in lipid profile, and oxidative stress in hyperlipidemic regimes. Fallah et al. [55] found the fiber-free extract of *C. scolymus* to be a safe anti-hypercholesterolemic agent; however, it failed to improve glycemic control among hypercholesterolemic type 2 diabetic patients in a double-blind placebo-controlled clinical trial in humans.

Berroukche et al. [56] investigated the effects of *C. cardunculus* leaf and stem decoctions on metabolic disorders. They detected complementary mitigating and more beneficial effects on blood glucose, total cholesterol, cholesterol-HDL, and triglycerides in high fat-fed male rats, compared to the group with vitamin C supplementation. The decoctions of *C. cardunculus* stem and leave manifested hypoglycemic and hypocholesterolemic activities, respectively.

Küskü-Kiraz et al. [52] studied the effects of artichoke leaf extract at the dose rate of 1.5 gm/kg/day to the rats on the high-calorie fat diet; subsequently, they found it to reduce LDL and VLDL levels. This lipid-lowering action depends on caffeoylquinic acids and flavonoids present in artichoke leaf extract; it ultimately interfered with the development of atherogenesis and reduced MDA and diene conjugate levels in rat serum. Furthermore, the tilt of balance of oxidant-antioxidant equilibrium appears restored. Küçükgergin et al. [57] stated that artichoke leaf extract is rich in antioxidants and has a cholesterol-lowering effect; therefore, interferes with atherosclerosis, as hypercholesterolemia and lipid peroxidation play complementary roles in the genesis of atherosclerosis.

Mocelin et al. [58] examined the effects of *C. scolymus* in cholesterol-fed rats. They reported that hypolipidemic and antiatherogenic properties could be linked with existing polar components in the aqueous extract of *C. scolymus*. Ahmed et al. [59] studied the anti-atherogenic properties of Egyptian artichoke leaf extract in hypercholesterolemic rats. Accordingly, they noticed that it decreased the concentration of serum cholesterol, triglycerides, and LDL-C in hypercholesterolemic rats; thus, it facilitated the elimination of cardiovascular ailments.

Anti-inflammatory effect: Various experimental studies indicated that artichoke administration reduces the expression of inflammatory cytokines and lipopolysaccharide-induced inflammation in animals [60]. The ethanolic extract of artichoke leaves at a dose of 400 mg/kg/body weight exhibited a maximum inhibition of inflammation induced by Carrageenin-induced paw oedema for 3 and 5 hours, compared to the reference group of indomethacin [45]. The anti-inflammatory effects of an extract from *Cynara scolymus* L. and its pharmacologically effective compound cynaropicrin, a sesquiterpene lactone, on Human Gingival Fibroblasts (HGFs) stimulated by LPS and the potential anti-osteoclastogenic effects on RAW264.7 cells induced by Receptor Activator of NF-κB Ligand (RANKL). Cynaropicrin inhibited IL-8, IL-6 mRNA, and protein synthesis in LPS-stimulated HGFs in a dose-dependent manner [60]. The study indicated that cynaropicrin's of artichoke inhibition of LPS-induced IL-8 and IL-6 expression may be attributed to the inhibition of the NF-κB pathway [60]. Artichoke processed abundantly bioactive compounds, including cynaropicrins may be considered a functional remedy for treating diseases associated with chronic inflammation, without adverse effects, pending the validation of a larger sample size and multicenter human study.

Anti-obesity: Zaru et al. [61] investigated the effects of the combination of *Phaseolus vulgaris* and *C. scolymus* extracts in an experimental model; they found it to possess anti-overweight and anti-obesity properties. The combination of the extracts of *P. vulgaris* and *C. scolymus* exerted hypoglycemic activities in rats even when subjected to starch bolus feeding [62]. This hypoglycemic impact of the extract combination was the sum of the effect of every single extract to induce anorexia. Interestingly, Rondanelli et al. [63] conducted a double-blind, placebo-controlled clinical study using 2-month supplementation, comprising of extracts of *P. vulgaris* and *C. scolymus*; they found the augmentation of the satiation score in apparently healthy, overweight, and obese subjects [63].

The reversal in the level of the obesity biomarkers viz. serum cholesterol, triglyceride, glucose, and gain in body weight, as well as the micro-architectural features of liver steatosis in the concurrent administration of *C. cardunculus* extract at 10 mg/kg and 20 mg/kg body weight for over 4 weeks, in a dose-dependent manner [64]. The *C. cardunculus* extract 20 mg/kg was correlated with a greater expression of carnitine-associated transporters $OCTN_1$ and $OCTN_2$. Thus, the extract contributed via the carnitine system; thus, it presented protective effects in diet-induced hyperlipidemia, insulin resistance, and non-alcoholic fatty liver disease. Rondanelli et al. [65] evaluated the efficacy of *C. scolymus* on glucose patterns in patients; they found a decline in neurometabolic parameters among overweight subjects with impaired glycemia. Contrarily, insulin levels remained unchanged following treatment with artichoke extract. Ben Salem et al. [49] studied artichoke concerning preventing kidney dysfunction against high fat-induced obesity in rats. They found that the oral administration of ethanolic extract of artichoke declines the organ weight and kidney marker levels; it also decreased oxidative stress. Therefore, the ethanolic extract of artichoke leaves exerts antioxidant effects in high-fat obese rats.

Antidiabetic effect: Nomikos et al. [66] studied the impact of wild artichoke meals on postprandial glucose and insulin levels in patients with metabolic syndrome

and healthy subjects. They concluded that boiled artichoke could not improve postprandial glycemic profile in subjects with metabolic syndrome; however, its hypoglycemic effects could protect healthy subjects from the noxious consequences of postprandial hyperglycemia. Fantini et al. [67] studied the evidence of blood glucose-lowering effect by *C. scolymus* extract in healthy Wistar rats and obese Zucker rats. Subsequently, they observed a significant decrease in postprandial blood glucose in both rat strains. Similarly, Heidarian and Soofiniya [51] explored the hypolipidemic and hypoglycemic effects of the aerial part of *C. scolymus* in streptozotocin-induced diabetic rats. They found the beneficial reducing effects of artichoke leaf extract on serum total cholesterol, triglycerides, low-density lipoprotein cholesterol, glucose levels, and plasma malondialdehyde levels.

Eid and Haddad [68] explored the effects of artichoke leaf extract on adipogenesis in 3T3-L1 cells and glucose-6-phosphatase activity in H4IIE hepatocytes. They noticed that the extract pointedly induced adipogenesis in 3T3-L1 adipocytes by 4 times; however, rosiglitazone stimulated adipogenesis by 7.8 times. The artichoke extract also inhibited glucose-6-phosphatase activity by 30% in H4IIE hepatocytes, compared to 60% for insulin. Although the results of this study were less than that of the respective positive control, this suggested the antidiabetic potential of artichoke. Loi et al. [62] examined the effects of a combination of *Phaseolus vulgaris* and *C. scolymus* extracts on food intake and blood glucose level in rats. They found that a mixture of *P. vulgaris* and *C. scolymus* is preferable over each extract. This is because it combines the anorectic effect of *P. vulgaris* extract with the hypoglycemic effects of both extracts. These extracts also supported its clinical use in the control of appetite and postprandial blood glucose levels.

Salem et al. [45] studied the protective effects of ethanolic extract of *C. scolymus* leaves on metabolic disorders and oxidative stress in alloxan-diabetic rats. Accordingly, they found its anti-hyperglycemic properties, at least partly mediated by antioxidant and hypolipidemic effects. Turkiewicz et al. [69] found certain cultivars of *C. scolymus* to be better in antidiabetic, anticholinesterase, and antioxidant activities; although all cultivars were found to be effective inhibitors of neurodegenerative enzymes. Kuczmannová et al. [70] noticed a significant decline in blood glucose levels following the administration of the water extract of *C. cardunculus* after oral daily administration for 5 weeks in streptozotocin-induced hyperglycemic rats. Xiao et al. [26] indicated the dose-dependent neuroprotective mechanism of this compound on amyloid b 1-42 that induces apoptosis on neuronal culture.

Hepatoprotective effects: The liver is the main visceral organ where biotransformation processes take place. During this process, the liver may be damaged, i.e., induced by exogenous/endogenous compounds by the formation of toxic metabolites leading to organ dysfunction and even death. Artichoke leaf has been recognized as a popular herbal remedy in traditional medicine with its most beneficial effects on the liver. Sumer et al. [71] studied the comparative biochemical and histopathological evaluations; they found that receptacle is the most effective part of *C. scolymus* against liver damage. Histopathological examination and biochemical tests also revealed that the receptacle and stem extracts of the artichoke were the most effective parts by improving experimentally-induced pathology in the liver.

Several *in vitro* and animal studies assessed the antioxidative and free radical quenching potential of artichoke extracts in the protection of hepatocytes from oxidative stress induced by chemical/drug-induced hepatotoxicity [72, 73]. Gebhardt [34] noticed that primary rat hepatocyte culture, exposed to various hydroperoxides, when subjected to pre and or real-time addition of *C. scolymus* extract, exhibited dose-dependent declines in induced MDA level. He further noticed that the level of cellular glutathione remained unaffected, rather the loss of glutathione (GSH) was reduced. Miccadei et al. [74] demonstrated that the extract of the edible part of *C. scolymus* has pronounced antioxidative and apoptotic activity. When the human hepatoma cell line, i.e., HepG2 cells, was subjected to treatment and pretreatment with 1 mM artichoke extract, followed by exposure to the H_2O_2, presented protective effects. The artichoke extract prevented the toxicity of H_2O_2 by 55%. However, artichoke extract provided no inhibitory effect on glucose oxidase activity and, consequently, on H_2O_2 production.

Ben Salem et al. [75] studied that high-fat diet-induced hepatotoxicity in rats, i.e., restored by *C. scolymus* leaf extract treatment as evidenced by the restoration of hepatic enzymes viz. serum AST, ALT, LDH, ALP, and Ornithine Carbamoyl Transferase (OCT) levels. The artichoke leaf extract (200-400 mg/kg b wt) also improved the elevated oxidative stress parameters, i.e., TBARS, Advanced Oxidation Protein Product (AOPP), liver reactive oxygen species (ROS), reduced glutathione (GSH), superoxide dismutase (SOD) and glutathione peroxidase (GPx). The hepatoprotective activities of artichoke leaves extract were further histologically supported owing to reduced fatty deposition in hepatic

lobules in high-fat diet models. These findings also suggested that *C. scolymus* exert anti-obesity and antioxidant effects in high-fat diet-induced obese rats.

The modulatory effects of artichoke leaf extract against oxidative stress and hepatic TNF-α gene expression in acute diazinon-induced liver injury in rats were also reported [76]. They found that artichoke extract treatment resulted in declined serum ALP, AST, ALT, MDA, TNF-α, and protein carbonyl levels, improved hepatic CAT and SOD activities, and micro-architectural alterations, compared to the diazinon alone treated group. The study concluded that artichoke leaf extracts down-regulated the oxidative stress in acute diazinon-induced liver injury in rats; thereby, it has hepatoprotective effects. Al-Ahab [77] induced acute hepatotoxicity by carbon tetrachloride (CCl_4) in rats; they observed alterations in the levels of SOD, GPx, and CAT activity in tissue, i.e., ameliorated by the aqueous extracts of artichoke leaves and pulp. There was also partial mitigation of histopathological lesions owing to toxicity induced by CCl_4 in the liver. Colak et al. [78] studied the hepato-curative effects of *C. scolymus* leaf extract in rats owing to CCl_4-induced oxidative stress and hepatic injury in rats. They found reduced lipid peroxidation and the restoration of the antioxidant system towards the normal range. It also presented positive effects on the pathway of regulatory mechanisms allowing the repair of DNA damage due to CCl_4-induced hepatotoxicity.

Rangboo et al. [47] took the basic and clinical study to evaluate the artichoke leaf extract for its hepatoprotective and hypolipidemic activities. They found the investigation in an affirmative direction and attributed it to be due to the antioxidant ingredients in artichoke extract which included mono- and dicaffeoylquinic acid (cynarin & chlorogenic acid), caffeic acid and flavonoids, the glycosides luteolin-7-β-rutinoside (scolymoside), luteolin-7-β-D-glucoside, and luteolin-4-β-D-glucoside [11, 79, 80]. Rangboo et al. [47] also observed improvement in lipid profile in the group that received *C. scolymus* extract, compared to the placebo group. Such effects were attributed to cynarin and chlorogenic acid. However, Gebhardt [81] stated that chlorogenic acid is the most active antioxidant in artichoke extract. These compounds reduced cholesterol by inhibiting HMG-COA reductase and having a hypolipidemic influence, lowering blood cholesterol.

Mehmetcik et al. [82] stated that artichoke leaf extract considerably increased choleresis and acted as an antioxidant with hepatoprotective effects; accordingly, they observed that the rats pretreated with *C. scolymus* extract, manifested significant decline in plasma ALT and AST activities and restoration in CCl_4-exposed histopathological alterations in the liver. Simultaneously, the hepatic MDA and diene conjugate levels decreased; however, GSH levels and GPx activities increased without any changes in other antioxidant system parameters. Speroni et al. [83] found that the artichoke extract with greater caffeoylquinic acids derivatives (caffeic acid, dihydrocaffeic acid, ferulic acid, & dihydroferulic acid) was more effective in restoring the MDA level of the liver as well as plasma AST and ALT levels, along with the restoration of histopathological findings of the liver. Aktay et al. [84], administered *C. scolymus* extract to rats subjected to single-dose CCl_4 injury and found similar hepatoprotective activities. Moreover, the extract improved the level of glutathione peroxidase [35]. The artichoke extract administered before CCl_4 treatment improved the enzyme's activity along with the glutathione content. The hepatoprotective effects of *C. scolymus* leaf extract were associated with the induction of glutathione peroxidase, besides its direct antioxidant properties; therefore, *in vivo* artichoke extract administration may be useful for preventing oxidative stress-induced hepatotoxicity.

Saffa et al. [85] investigated the efficacy of total methanolic extract of artichoke and its fraction in rats and noticed a decline in serum ALT and AST levels. Huber et al. [86] used the artichoke leaf extract (3200 mg/day) doses. They found neither restoration of ALT and AST level nor alteration in viral load even after 12 weeks of treatment. However, fatigue and joint problems significantly improved after 4 weeks of treatment and were suggested to be due to the severity of damage to hepatocytes. Kaymaz et al. [87] induced hepatotoxicity in rats with alpha-amanitine. They observed the restoration of various oxidative stress parameters (MDA, SOD, CAT, & GPX) when treated by the aqueous extract of artichoke 1500 mg/kg. These beneficial effects were due to the presence of a hepatoprotective and regenerative phenolic compound, called cynarine. Furthermore, cynarine was recorded for its antiatherosclerotic, antioxidative, and hypocholesterolemic effects. Ben-Hod et al. [88] reported that cynarine has cholagogue and chlorotic effects; it provided hepatic detoxification by bile secretion. Adzet et al. [31] studied the impact of cynarine on the carbon tetrachloride mediated hepatotoxicity model and asserted for its antioxidant mediated hepatoprotective properties.

Tang et al. [89] evaluated the influence of the ethanolic extract of artichoke in alcohol-induced liver damage mice models. The damage of the liver was reflected concerning raised AST, ALT, TC, TG, and oxidative stress markers. These parameters declined and were restored

when treated with artichoke leaf extract 1.6 gm/kg body weight. Similarly, the photomicrograph of the liver treated with artichoke extract exerted reduction in necrotized and inflamed areas and regenerated and restored the hepatic micro-architecture. The expression level of pro-inflammatory markers, i.e., Toll-Like Receptor (TLR) 4 and Nuclear Factor-Kappa B (NF-κB) were also elevated in alcohol-exposed mice. Besides, it was attenuated by artichoke extract in a dose-dependent manner, i.e., associated with TLR4 down-regulation, and ultimately activation inhibition of NF-κB thereof.

Sharma et al. [90] explored the hepatoprotective potential of *C. scolymus* in cisplatin-induced hepatotoxicity. They observed that pre and post-treatment with artichoke extract of 150 mg/kg and 300 mg/kg body weight attenuated the altered levels of various enzymatic and oxidative parameters in blood and hepatic tissues. This reduced hepatic oxidative biomarkers and histopathological alterations indicated the good hepatoprotective potential of *C. scolymus* in cisplatin-induced hepatotoxicity.

Bundy et al. [91] investigated the effects of 1280mg of aqueous artichoke leaf extract administered daily for 12 weeks on lipid levels in otherwise healthy adults with mild to moderate hypercholesterolemia. Bundy et al. found the artichoke extract helpful in the control of fatty liver and hyperlipidemia in rats as well as humans. Zapolska-Downar et al. [92] assessed the status of oxidative stress and inflammation in atherogenesis, and the influence of aqueous and ethanolic artichoke extracts on ROS production stimulated by inflammatory mediators and ox-LDL. They claimed that the aqueous and ethanolic extracts of artichoke leaves inhibited oxidative stress in a dose- and time-dependent manner in cultured endothelial cells and monocytes. Ethanolic artichoke extract was in most cases effective in neutralizing the stimulatory effects on ROS production and inhibited TNFα, LPS, or ox-LDL stimulated ROS production. It can be elucidated partially owing to the antioxidant activity of flavonoids and hydroxycinnamic acids, i.e., effective hydrogen donors [93-97]. Kucukgergin et al. [57] investigated the impact of artichoke leaf extract (1.5 g/kg/day) on serum and hepatic lipid levels and pro-oxidant-antioxidant balance in the liver and heart of hypercholesterolemic rats; they instituted a decline in the liver and heart MDA and diene Conjugate levels and upsurges in liver vitamin E and GPx activities in artichoke leaf extract treated hypercholesterolemic rats. Thus, artichoke leaf extract reduced serum lipids and hypercholesterolemia mediated pro-oxidant status in the heart and liver tissues.

Nephroprotective activity: Various experimental studies indicated that oral administrations of artichoke protect the renal damage induced by the diverse type of chemicals viz. gentamicin, cisplatin, diclofenac, 5-fluorouracil, and high-fat-fed diet. A high-fat diet fed to rats led to severe renal injury, evidenced by elevating the levels of markers, such as urea, uric acid, and creatinine. Studies suggested that a high-fat diet leads to obesity, generating the elevation of kidney functions, which causes further damage, characterized by the rise of creatinine in the blood. Consequently, it increases uric acid levels. Other complications of high-fat diet mediated obesity include diabetes, and hypertension, verified by histopathological findings viz. greater Bowman's capsule space, and distal convoluted tubules.

Ben Salem et al. [49] reported that the ethanolic extract of artichoke reversed the renal damage markers and renal oxidative stress markers to a greater degree towards normal in high-fat diet-fed rats. According to Ben Salem et al., [98] artichoke has the potential to be a novel drug for renal ailment secondary to abnormal lipid metabolism. According to Jaleel et al., [99] ethylene glycol-induced nephrolith rats, when subjected to artichoke leaf extract restored the biomarkers of renal function respecting creatinine, urea, and uric acid, as well as its oxidative stress markers. Additionally, the micro-architecture of kidneys exhibited neither any alterations nor any crystal in the tubular lumen. The restoration of ethylene glycol-induced renal micro-architecture alterations was accredited to multiple bioactive antioxidant vizcynarin, luteolin, and chlorogenic acids in the artichoke leaf extract [100]. Caffeoylquinic acids and flavonoids in artichoke leaf extract yielded efficient antioxidant activity [101]. Morsy and Kamel [102] also found reduced oxidative damage by artichoke leaf extract, evidenced by declined MDA level and SOD activity in tissue. These components improved the glutathione level and negated lipid peroxidation. Renal damage induced due to lipid accumulation facilitated gain in organ weight and pro-inflammatory cytokines, which further lead to lipid and protein oxidation and kidney damage [103] in consequence. Domitrovic et al. [104] reported that chlorogenic acid attenuated the cisplatin-induced renal damage via the suppression of oxidative stress, inflammation, apoptosis, and autophagy, which facilitated kidney rejuvenation and improvement in the activities involving renal cell membrane transportations in mice. Alkushi [105] induced a cholesterol-fed renal damage model and investigated the effects of *C. cardunculus* over hypercholesterolemic rats with elevated levels of creatinine, urea, or uric acid in the blood. Alkushi stated that the leaf extract of *C. cardunculus* improved the kidney indices, compared to the pulp extract,

Table 4. The pharmacological potential of the different parts of the *Cynara scolymus* extracts in different experimental models

Plant Extract		Experimental Model	Reference
Antihypercholesterolemic effects	Artichoke leaf extract	Patients with non-alcoholic steatohepatitis	[47]
	Artichoke leaf extract	High-fat diet rats	[49-50]
	Artichoke leaf extract	Streptozotocin-induced diabetic rats	[51]
	Artichoke leaf extract	Rats fed on hypercholesterolemic ration	[52]
	Artichoke	Hypercholesterolemic subjects	[53]
	Fibre free extract	Type 2 diabetic human controlled trial	[55]
	Leaf and stem decoctions	High fat fed male rats	[56]
	Artichoke leaf extract	Rats fed on high cholesterol diet	[57-59]
Anti-obesity effects	Artichoke extract	Chocolate flavored beverage in rats	[61-63]
	C. scolymus extract	A double-blind placebo-controlled clinical trial	[65]
	Artichoke extract	High fat-induced obesity in rats	[49]
Antidiabetic effects	Artichoke extract	Patients with metabolic syndrome	[66]
	Artichoke extract	Wistar rats and obese Zucker rats	[67]
	Artichoke leaf extract	Streptozotocin-induced diabetic rats	[51]
	Ethanolic extract	Alloxan-diabetic rats	[30]
	Aqueous extract	Streptozotocin-induced hyperglycemic rats	[70]
Hepatoprotective effects	Stem extract of artichoke	H4IIE Hepatocytes culture	[68]
	Artichoke leaf extract	High fat-induced hepatotoxicity in rats	[75]
	Artichoke leaf extract	Diazinon-induced liver injury in rats	[76]
	Artichoke leaf extract	Carbon tetrachloride-induced hepatotoxicity in rats	[77-78, 82]
	Methanolic extract	Steatohepatitis induced in rat	[85]
	Artichoke leaf extract	Chronic hepatitis C-a pilot study	[86]
	Aqueous artichoke extract	Alpha-amanitine induced hepatotoxicity in rats	[87]
	Artichoke extract	Carbon tetrachloride-induced hepatotoxicity	[31]
	Artichoke floral extract	Cisplatin-induced hepatotoxicity in rats	[90]
	Artichoke leaf extract	Paracetamol induced hepatotoxicity	[102]
	Artichoke leaf extract	Hypercholesterolemic rats	[57]
Nephroprotective effects	Ethanolic leaf extract	High-fat diet rats	[49]
	Ethanolic leaf extract	Rats	[98]
	Artichoke leaf extract	Ethylene induced nephrolith rats	[99-103]
	Chlorogenic acid	Cisplatin-induced renal damage in mice	[104]
	C.cardunculus extract	Hypercholesterolemic rats	[105]
	Artichoke leaf extract	Gentamicin induced nephrotoxicity in rats	[106]
	Artichoke extract	5-fluorouracil induced nephrotoxicity in rats	[107]
	Artichoke floral extract	Cisplatin-induced nephrotoxicity in rats	[108]
	Artichoke leaf extract	Diclofenac induced nephrotoxicity	[109]
Gastrointestinal effects	Methanolic extract	Ethanol-induced gastric ulcer	[110]
	Artichoke extract	*In vitro* and *in vivo*	[111]

Plant Extract		Experimental Model	Reference
Antimicrobial effects	Artichoke leaf extract	Against Staphylococcus aureus and others	[113]
	Ethanolic extract	Against Listeria innocua	[114]
	Artichoke rhizome extract	Phenolic toxicity against microorganisms	[115]
	Ethanolic leaf extract	Against bacterial species of food interest	[116]
Reproductive effects	Artichoke extract	Male gonads of rats	[121]
	Artichoke extract	Cadmium-induced testicular toxicity	[122]
	Artichoke leaves meal	Mandarah hens	[123]
	Artichoke leaf extract	Nandrolone decanoate induced alterations in testes	[126]
	Dry artichoke leaf extract	On fetal development in Wistar rats	[127]
Anticancer effects	Artichoke leaf extract	Human liver cancer cell line	[74]
	Cynarine	Cancerous human cells	[130]
	Leaf polyphenolic extract	Human breast cancer line	[129]
	Artichoke	Mesothelioma cell lines	[131]
	Artichoke extract	Oral squamous carcinoma cell line	[132]

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reflected by a decline in creatinine and uric acid levels in hypercholesterolemic rats in a dose-dependent manner.

Khattab et al. [106] orally administered artichoke leaf extract in rats after inducing nephrotoxicity by gentamicin. The simultaneous administration of artichoke leaf extract during gentamicin therapy prevented the increase in the level of MDA and reduced the total kidney function parameters, albumen, and potassium with a significant increase in the serum levels of total proteins and sodium (Na^+). It also changed the micro-architecture of the kidney towards the restoration of gentamicin-induced severe alterations near normal; thus, could be beneficial for kidney patients. Najim et al. [107] explored the nephroprotective effects of artichoke against fluorouracil-induced nephrotoxicity in Wistar rats. They concluded that the methanol extract of artichoke and may be useful to mitigate 5-fluorouracil-induced nephrotoxicity. Sharma et al. [108] studied the nephroprotective potential of *C. scolymus* floral extract in cisplatin-induced nephrotoxicity in rats; they detected that pre and post-treatment of plant extract at the dose rate of 150mg/kg and 300mg/kg body weight attenuated the alterations in the levels of various enzymatic and oxidative parameters in blood and renal tissue in a dose-dependent manner. These findings were also reflected by attenuation in cisplatin-induced degenerative and necrotic changes of proximal convoluted tubules.

Elshamy et al. [109] argued that the nephroprotective activity of artichoke extracts. Furthermore, they documented that the extract at the dose of 100 mg/kg reduced urea and creatinine levels in non-steroidal anti-inflammatory drugs (diclophenac) induced acute kidney injury in rats. The diclofenac-induced surge in MDA and the corresponding decline in GSH contents in the kidney tissue was effectively reversed in the presence of extracts; it was reflected concerning significant MDA decrease and GSH increase, compared to diclofenac alone. The diclofenac-induced decline in PGE2 content in kidney tissue was effectively restored when treated with aqueous and alcoholic artichoke extracts. The treatment with alcoholic artichoke extracts extended the dose-dependent preservation of kidney PGE2 content. The nephroprotective activities of alcoholic artichoke extract were evidenced by the relative recovery of diclofenac-induced kidney tissues damage reflected by declined glomerular and tubular damage, in a dose-dependent manner. The alcoholic extract provided a better dose-dependent response, which may be due to the enriched flavonoids and glycosidic derivatives, along with phenolic acids.

Gastrointestinal effect: From a nutritional point of view, globe artichoke heads approximately contain 7.0% carbohydrates, 3.0% proteins, and <0.3% of lipids. Moreover, 75% of the total sugar content in edible parts is attributed to the water-soluble polysaccharide inulin. The content of inulin increases with the plant development and reaching 30% of the edible portion in the artichoke heads of marketable quality [5]. Nassar et al. [110] evaluated the role of the methanolic extract on *C. scolymus* as an anti-ulcer agent on ethanol-induced gastric

ulcer in rats; they found the high anti-ulcerogenic potential of scales of *C. scolymus* heads. Similarly, Valerio et al. [111], in an *in vitro* study, found that inulin extracted from globe artichoke is a potent probiotic stimulator of beneficial *Bifidobacterium bifidum*. They investigated the ability of artichoke to serve as a vehicle for the delivery of probiotic bacterial strains. Furthermore, cynarin, one of the main caffeoylquinic acid, but not the most abundant one, reveals choleretic activity [34]. Inulin is a non-digestible oligosaccharide belonging to family fructans. It is considered a dietary fiber. This is because, as reaching the colon as an intact molecule, insulin serves as the substrate for bifidobacteria growth and makes them the predominant species [112]. The special linkages of inulin cannot degrade by the human digestive system. Therefore, the assumed dose does not increase the level of glucose blood. This is because the molecule is not absorbed in the gastrointestinal tract where it acts by increasing water flow (osmotic process); consequently, it is fermented by microflora. For this reason, artichoke can be considered a functional food composed of inulin, a critical dietary fiber [112].

Antimicrobial activity: The flavonoids and other phytochemical ingredients present in plant extract possess antimicrobial properties. The antibacterial activities of the leaves extracts of *C. scolymus* reported on *Staphylococcus aureus*, *S. epidermidis*, *Micrococcus luteus*, and *Escherichia coli*, and no activity on *Salmonella thyphymurium* [113]. Vamanu et al. [114] studied the antimicrobial and antioxidant effects of the ethanolic extract of *C. scolymus*. They reported that extracts possess inhibitory activity against *Listeria innocua*; they also possess an effective antioxidant activity. The researchers concluded that the freeze-dried extract of *C. scolymus* is capable of yielding nutritional supplements with antimicrobial and antioxidant activities. Similarly, Alghazeer et al. [115] observed that the rhizomes extracts of *C. scolymus* can be used for treating infectious diseases and can be a promising source of some compounds that could be used to formulate new antimicrobial drugs of natural origin. The mechanism of phenolic toxicity on microorganisms might concern their reaction with sulfhydryl groups or through more non-specific interactions with the proteins. Recently, Scavo et al. [116] studied the antimicrobial activity of cultivated cardoon (*C. cardunculus*) leaf extracts on the bacterial species of agricultural and food interest. They found that ethanolic extract was more active, followed by hydro-alcoholic and aqueous extracts, and all extracts effectively inhibited the growth of gram-positive species. The antimicrobial activity of the artichoke extract may be due to the presence of caffeoylquinic acids, apigenin, luteolin, and the sesquiterpene lactone cynaropicrin.

Reproductive effects: Infertility in mammals is a global problem and affects 15% of couples, particularly in industrialized countries. Of which, approximately 50% of the cases are attributed to the male partner [117]. Environmental toxicants (particularly, metals, & agrochemicals, etc.) contribute to 23% of all male infertility cases due to toxicant-induced oxidative damage in testes [118-120]. Ilieva et al. [121] studied the effects of artichoke (*C. scolymus*) on the male gonads of rats. An electron microscopic study indicated no significant changes in the structure of rat semen at cellular and sub-cellular levels. The supplementation of *C. scolymus* extract provided protective effects on Cadmium-induced testicular toxicity in experimentally-induced testicular toxicity (seminiferous tubules & Leydig cells) model [122]. Similarly, Radwan et al. [123] studied the effects of feeding Artichoke Leaves Meal (ALM) on the productive and reproductive performance of Mandarah hens. They observed that ALM up to 8% may present beneficial effects on semen quality. Improving fertility, hatchability, and semen quality in ALM interventions may be due to the contents of cynarin (1.19%) and flavonoids (1.06%), i.e., classified as antioxidants [16]. The role of antioxidants is well explained by Keslo et al. [124] and Aitken [125], who reported that the presence of high concentrations of polyunsaturated fatty acids in spermatozoa, requires an efficient antioxidant system to protect sperm from peroxidative damage. Mohammed et al. [126] also studied the effects of *C. scolymus* leaves extract on the nandrolone decanoate-induced alterations in testicular function and sperm quality in albino rats. The results of the experiment concluded that the co-treatment of nandrolone-intoxicated rats with *C. scolymus* leaves extract ameliorated the toxic effects of nandrolone decanoate on the testicular structure and function, probably due to its antioxidant capacity. However, Gotardo et al. [127] reported the negative impact of dry extracts of *C. scolymus* leaves on maternal reproductive outcomes of fetal developments in Wister rats. He suggested that consuming *C. scolymus* during pregnancy adversely impacts fetuses depicted by reduced fetal length and body weight also in pregnant dams it causes hypocholesterolemia which might attribute to low fetal body weight.

Anticancer effects: Numerous epidemiological studies suggested that diets particularly rich in fruits and vegetables have cancer-preventive properties. The beneficial effects of diets are attributable, at least in part, to polyphenols which have antitumor activities in animal models and humans. Chemoprevention is a promising strategy that uses natural dietary compounds and synthetic substances to block, inhibit, reverse, or delay the process of carcinogenesis. Essential preventive mechanisms include the suppression of cell proliferation and apoptosis and the modulation of epigenetic processes [128, 129].

Miccadei et al. [74] reported that the artichoke leaf extract from the edible part of artichoke reduced the cell viability and induced apoptosis on the human liver cancer cell line. A similar study by Gezer et al. [130] on cancerous human cells using cynarine gave an affirmative answer, increased survival rates and decreased oxidative stress. Mileo et al. [129] demonstrated that prolonged low doses of artichoke leaf polyphenolic extract at sublethal concentration inhibited breast cancer cell growth; thus, they were suggested to be potential chemo-preventive and anticancer dietary compounds. High doses of polyphenolic extracts induce apoptosis and decrease the invasive potential of the human breast cancer cell line, MDA-MB231 [129]. Pulito et al. [131] investigated anti-carcinogenic effects; they found that treating *C. scolymus* strongly affects cell growth, migration, and tumor engraftment of mesothelioma cell lines. Hassabou and Farag [132] studied the anti-carcinogenic activities of artichoke extract. They found that it has potent cytotoxic activity along with cell cycle arrest, and apoptotic effects, on oral squamous carcinoma cell lines. Tanaka et al. [133] reported that the presence of cynaropicrin in *C. scolymus* overpowers photo-aging of the skin by inhibiting the transcription activity of nuclear factor-kappa B. The pharmacological potential of the different parts of the Cynara scolymus extracts in different experimental models are shown in Table 4.

Conclusion

Increasing attention is being paid to developing herbal medicines as a newly emerging treatment for the welfare of patients in the last few decades. The present review detailed the versatile therapeutic efficiency and diverse application of *C. scolymus*. This medicinal herb has been rightly used in traditional medicine for a long and is helpful in the cure of various ailments. There is an urge to highlight such medicinal plants which can be promising and beneficial for human welfare.

Ethical Considerations

Compliance with ethical guidelines

The authors followed all ethics committee codes during the processing.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

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