

# Review of the Nutritional Values and Biological Activities of *Ziziphus Spina-christi* (Sidr) Plant Extract

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**Abstract Background:** *Ziziphus spina-christi* of family Rhamnaceae is a terrestrial tree often recognized as Christ's thorn jujube. The plant of *Ziziphus spina-christi* grows in the South and East of Asia as well as in the Middle East zone. Nearly in most of the Arabic countries, Levant, and Saudi Arabia, *Ziziphus spina-christi* tree is called Sidr mentioned in the Holy Quran. It contains nutritional components that render the plant one of the principal food sources. The plant possesses diverse phytochemical active compounds mostly spinanine A,  $\beta$  sitosterol, rutin, quercetin, betulinic, and kinetic acid. In Saudi Arabia, the Sidr tree has an important therapeutic value as each part of the tree was used to maintain a healthy life. **Objective:** The present review aimed to collect the different nutritional values, pharmacologic, and biological activities that were linked with the utilization of different parts of *Ziziphus spina-christi* extracts, which have been reported in the literature. **Results:** Findings collected from the previously published studies showed that *Ziziphus spina-christi* extract possesses many pharmacological and biological activities such as hepato, cardio and nephroprotective, antidiabetic, antimicrobial, antiparasitic, anticancer, antiasthma, and antinociceptive activities. Many of these biological activities were attributed to the antioxidant action of *Ziziphus spina-christi* plant extract. **Conclusion:** It was experimentally proven that *Ziziphus spina-christi* extract from the Sidr tree mentioned in the Qur'an has many nutritional values and pharmacological effects that could qualify it to be the subject of other studies in humans until it is used as a supplement or alternative treatment in the future.

**Keywords:** *Ziziphus spina-christi*, Hepatoprotective, Nephroprotective, anticancer, antimicrobial

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## 1. Introduction

*Ziziphus spina-christi* (family Rhamnaceae, order of Rosales) is a wild tree commonly famous as Christ's thorn jujube. The family of Rhamnaceae involves 52 genus and 925 species spread around the world, especially across warm areas. The *Ziziphus* species of deciduous, evergreen trees and shrubs comprise of nearly 100-170 types that tolerate dryness and heat [1]. The plants usually grow in dry regions, deserts, semi-desert washes, savannahs as well as valleys [2]. The tree cultivated in the East and South areas of Asia and the Middle East region [3]. Generally, in Arabic, the fruits have been given the same tree name [4]. In most Arabic countries such as in Saudi Arabia, *Ziziphus spina-christi* tree was commonly named Sidr (related to the Lote-trees of the Quran) while the fruit was called Nabka [5,6]. This Sidr tree is one of the paradise trees. It is one of the most important types of native trees planted in the Arabian Peninsula, which has historical, medicinal and religious values [7]. The tree is referred to in the Holy Quran in four sites (Surat Saba [16], Surat al-Najm [14 and 16], and Surat Al-Waqi'ah

{28}). This demonstrated that this tree is of great importance [8].

*Ziziphus spina-christi* contains multiple nutritional components that render the plant one of the greatest food sources. The plant has been utilized in traditional medicine in Middle East, mainly the fruits, seeds, leaves, roots and bark [9]. The fruit of *Ziziphus spina-christi* is small, orange-yellow with spiked branches [10] that considers a rich source for important dietary components [11]. The dry fruits are wealthy in energy compounds (80.6% carbohydrates: starch, sucrose, glucose, and fructose) [4,12]. Furthermore, there are 0.9 g fat, 4.8 g protein, 140 mg calcium, 0.13 mg riboflavin, 0.04 mg thiamine, and 3.7 mg niacin per 100 gm dried fruit [13,14]. The fruit also contains high amount of vitamin C (98 mg) which is a considerably larger amount compared to those present in strawberry (59 mg), orange (50 mg), and grape (38 mg) [15]. It was reported that the fruits has rich amount of polyphenols (24.62 mg/g of gallic acid equivalent of dry extract) [16]. Phenolic compounds are important natural antioxidants that possess scavenging activity against free radicals [17,18,19,20].

The seeds of *Ziziphus spina-christi* hold 28.5% fats (mostly linoleic and linolenic acid), and 18.6% protein

(mostly sulphur-rich amino acids) [21]. The seeds have sedative effect and could be used to relieve pregnancy-related nausea, vomiting, and abdominal discomfort [22]. The *Ziziphus spina-christi* stem bark has been marked to have antifungal, antibacterial, and cytotoxic actions [23]. A study examining the antibacterial properties of *Ziziphus spina-christi* stem bark revealed the efficacy of stem bark to treat burns, wounds, stomach discomfort as well as urinary tract infection [24]. The leaves of the plant contain a substantial amount of calcium, iron, and magnesium [4]. They are traditionally utilized for the treatment of eye illness, atopic dermatitis, bronchitis, skin disease, ulcers, and wounds [22,25,26].

*Ziziphus spina-christi* owns a sundry of phytochemicals bioactive constituents mostly cyclopeptide, alkaloids (spinanine A), tannins, sterols ( $\beta$  sitosterol), peptide, flavonoids (rutin and quercetin), saponins (betulinic and kinetic acid), triterpenoids, saponin, quercetin, and triterpenic acids [27,28,29,30,31,32]. The extract of *Ziziphus spina-christi* leaf comprises four saponin glycosides known as (christanin A, B, C, and D) [21].

In Saudi Arabia, the Sidr tree possesses much curative importance as each division of the tree was utilized to support a healthy way of life [16,33]. *Ziziphus spina-christi* was observed to produce antibacterial, antifungal, antinociceptive, antioxidant, anti-inflammatory action, antiallergic, and anti-influenza [10,16,34,35,36,37,38,39]. Previous research on the beneficial activities of *Ziziphus spina-christi* related to the nervous system of being anxiolytic, analgesic, and anti-depressant have been also determined [5,40,41].

Due to the medical and curative significance of this blessed tree, the present review aimed to collect the different pharmacologic and therapeutic activities that were associated with the use of diverse parts of *Ziziphus spina-christi* extract that have been published in the literature.

## 2. Hepatoprotective Activity

Research study aimed to investigate the preventive action of *Ziziphus spina-christi* fruits on carbon tetrachloride associated liver damage in Wistar rats. The results revealed that feeding the rats with a diet containing 2.5, 5, 10, and 15% *Ziziphus spina-christi* fruits powder for 42 days produced a significant decrease in liver function markers of alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP). The addition of *Ziziphus spina-christi* fruits powder to the group of hepatotoxic rats diet produced significant decrease in Malondialdehyde (MDA) levels. *Ziziphus spina-christi* fruits powder was also able to maintain the actions of antioxidant enzymes (glutathione peroxidase (GSH-Px) and Superoxide dismutase (SOD)) [3].

The study also concluded that the protective effect resulted from the overwhelming mechanism of antioxidant enzymes and their scavenging effect on the free radicals [3]. The flavonoids antioxidant properties from different medical plants exert their stimulating actions on antioxidant enzymes [42]. *Ziziphus spina-christi* extract has been observed to contain high amounts of flavonoids and polyphenols [43]. Defensive effects of flavonoids and

polyphenols against oxidative stress-related diseases have been evident in previous research [44,45,46,47,48,49].

In a study performed to examine the probable protective action of *Ziziphus spina-christi* leaves extract versus *Plasmodium chabaudi* that caused hepatic illness, the authors concluded a marked decline in the blood parasite titre and a marked amelioration of the blood picture (RBCs and haemoglobin level), liver function markers (ALP, AST, and ALT), and liver histopathology. The discussed mechanism was related to the antioxidant catalase (CAT) effect of *Ziziphus spina-christi* [50].

A study reported hepatoprotective action of *Ziziphus spina-christi* aqueous extracts in rat model of hepatic fibrosis induced by carbon tetrachloride. The extract at 0.125, 0.250 and 0.350 g/kg was administered for eight weeks. *Ziziphus spina-christi* extract produced a marked decline in the hepatic function enzymes (AST, and ALT) impeding hepatic fibrosis progression. *Ziziphus spina-christi* aqueous extracts also helped to restore the normal levels of MDA and maintained endogenous antioxidants activities of CAT, GSH, and SOD. In addition, the extract diminished  $\alpha$ -smooth muscle actin expression and types I and III collagen deposition in the infected rats, showing improvement in the quantity and quality regarding to the distribution of type I collagen [51].

The protective impact of the methanolic extract of *Ziziphus spina-christi* leaves on hepatic and splenic injury was examined in male C57BL/6 mice model of cecal ligation and puncture induced sepsis. The study results indicated that daily oral administration of *Ziziphus spina-christi* leaf extract at doses of 100, 200, and 300 mg/kg for five days significantly inhibited liver and spleen injury induced by sepsis. The study findings suggest a therapeutic potential of *Ziziphus spina-christi* leaf extract for sepsis by enhancing antioxidant and anti-inflammatory effects [52].

## 3. Cardio and Nephroprotective Activity

A study reported that different doses at 100, 200, and 300 mg/kg of *Ziziphus spina-christi* leaves extract exerted a protective impact versus multiple-organ toxicities that accompanied sepsis on male mice. These findings could be relaying on the antioxidant, antiapoptotic, and anti-inflammatory actions of *Ziziphus spina-christi* leaf extract. Sepsis was produced by cecal ligation and puncture. This study discussed the protective impacts to be attributed to the antioxidant (decreased MDA, myeloperoxidase (MPO), and nitric oxide (NO)), anti-inflammatory (decreased, interleukin 1 beta (IL-1 $\beta$ ), tumour necrosis factor alpha (TNF- $\alpha$ ), and nuclear factor kappa B (NF- $\kappa$ B)), and antiapoptotic (decreased caspase-3 and Bax mRNA) activities [53].

## 4. Antidiabetic Activity

A study investigated the impact of hydroalcoholic extract of *Ziziphus spina-christi* fruit on the serum insulin level and blood glucose of diabetic dogs induced by alloxan compared to antidiabetic agent of glibenclamide. Oral administration for 10 days with 500 mg/kg *Ziziphus*

*spina-christi* fruit hydroalcoholic extract produced a marked decline in blood sugar concentration associated with a marked elevation in serum insulin concentration in alloxan model of diabetes in the dogs. The effect is better than that produced from the application of glibenclamide at a dose of 0.2 mg/kg [54].

One of the mechanisms by which the *Ziziphus* fruit regulate glucose homeostasis could be due to inhibition of glucose uptake in rats' small intestine [55]. This mechanism was reported in previous research of some medical plants [56,57]. Another mechanism of Improving the liver function and subsequently increasing the uptake of blood glucose was also proposed action of *Ziziphus vulgaris* [55].

Oral feeding with 200 mg/kg *Ziziphus spina-christi* leaves extract to Sprague Dawley male rats with diabetes induced by streptozotocin (50 mg/kg) for one month showed significant results. It lowered serum glucose; raised insulin and C-peptide; and ameliorated glycated haemoglobin (HbA1C%) levels. The saponin and polyphenols active constituents of *Ziziphus spina-christi* leaf extract were recognized to be responsible for the amended glucose utilization observed in this context. Besides, the extract significantly increased the total antioxidant capacity [6].

In another study, the hypoglycaemic, antidiabetic, antioxidant actions, in addition to the phenolic composition of different fractions of *Ziziphus spina-christi* were examined in Streptozotocin (60 mg/kg)-induced diabetes in male Swiss albino mice. The results revealed that the most significant antidiabetic effect was provoked next to the administration with 500 mg/kg n-butanol fraction. The total flavonoid in the n-butanol extract has been estimated as 28.2 mg/g while the total phenolic contents has been 68.3 mg/g [58].

## 5. Antihyperlipidemic Activity

Two months oral feeding of *Ziziphus spina-christi* leaves powder (500 mg/kg) to hypercholesterolemic rats exhibited a significant decline in lipid profile parameters. The antihyperlipidemic effect may be induced through inhibiting oxidative stress by its content of phenolic compounds [59].

Another study of the *Ziziphus spina-christi* leaf extract showed beneficial effects on lipid peroxidation, lipid profile, as well as liver function enzymes in rats with diabetes. The increasing doses of *Ziziphus spina-christi* leaf extracts at 50, 75, and 100 mg/kg for four weeks significantly lowered the mean of blood cholesterol, triglyceride, LDL-cholesterol, AST and ALT. On the other hand, the mean of HDL-cholesterol in diabetic rats was increased. The phenolic constituents of the extract suppressed the oxidative stress and reduced the hypercholesterolemia effect [60].

In addition, a study examining the impact of *Ziziphus spina-christi* and *Ziziphus mauritiana* fruits extract in diabetic rats induced by alloxan, revealed that both plants exerted dose-dependent hypolipidemic and hypoglycemic properties [61]. The fruit extract of *Ziziphus spina-christi* manifested more influence than *Ziziphus mauritiana*. This finding support the beneficial effect of plant fruits in the

management of hyperlipidemia associated with diabetes [61,62,63]. Saponins present in *Ziziphus spina-christi* have been reported to exert hypolipidemic effect to lower total cholesterol, LDL cholesterol, and triglycerides. This mechanism could be explained by the fact that saponins create an insoluble compound with cholesterol, which increases the excretion of lipid [64]. They also rise the activity of liver LDL receptor, and also reduces triglyceride synthesis [65].

## 6. Antimicrobial Activity

An early conducted study revealed that both alcoholic extract of *Ziziphus spina-christi* fruits and aqueous extract of *Ziziphus spina-christi* leaves induced a marked antiviral action versus *Herpes simplex* type 1. The chloroform extract of *Ziziphus spina-christi* leaves inhibits the Gram-positive pathogens *Streptococcus pyogenes* and *Bacillus cereus*. Furthermore, the petroleum ether extract of *Ziziphus spina-christi* leaves inhibits the growth of *Streptococcus pyogenes*. The chloroform extract of *Ziziphus spina-christi* seeds inhibits the growth of *Bacillus cereus*, *Streptococcus pyogenes* and *Staphylococcus aureus*. The chloroform extract of *Ziziphus spina-christi* leaf instigated a modest antifungal activity against *Trichophyton rubrum* [66].

Another previously published *in vitro* study showed that the chloroform, methanol, and petroleum ether extract of the fruits, leaves, stems, and seeds of *Ziziphus spina-christi* produced significant effects of antibacterial action against Gram positive of *Staphylococcus aureus* and *Bacillus subtilis*; and Gram negative of *Proteus vulgaris*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*. It was indicated that the methanolic extract was the most potent. The chloroform extract comes next whereas the petroleum ether extract exerted the least effect. All the extracts of the different herbal parts showed no fungicidal effects versus *Aspergillus niger* and *Candida albicans* [67].

Recently, the alcoholic extract of the aerial division of *Ziziphus spina-christi* has been found to exhibit an *in vitro* dose-dependent antimicrobial activity versus many Gram-positive bacteria (*Clostridium perfringens*, *Listeria monocytogenes*, *Bacillus cereus*, and *Staphylococcus aureus*) and against some Gram-negative bacteria (*Vibrio parahaemolyticus* and *Proteus vulgaris*) [68].

## 7. Antiparasitic Activity

The antischistosomal and hepatoprotective impact of the alcoholic roots extract of *Ziziphus spina-christi* was examined in male albino mice infected with *Schistosoma mansoni*. The study findings showed that application of *Ziziphus spina-christi* on the infected mice significantly decreased MDA concentration and increased antioxidant enzymes activity. Furthermore, the *Ziziphus spina-christi* extract significantly lowered the worm and egg counts and thus providing an evidence for antischistosomal efficacy [69].

Another study determined the antischistosomal activity of *Ziziphus spina-christi* leaf extract on CD-1 Swiss male

mice infected with *Schistosoma mansoni*. Treatment with the extract of *Ziziphus spina-christi* leaves showed significantly lowered hepatic fibrosis, apoptosis, and oxidative stress in the infected mice. The extract of *Ziziphus spina-christi* activated antifibrinogenic as well as Nrf2 pathways [70].

A study by Alzahrani et al., investigated the *Ziziphus spina-christi* leaves extract at different doses of 100, 200 and 300 mg/kg, to have anti-eimeria and anthelmintic activity. Experimental mice were infected with  $1.2 \times 10^3$  E. papillata-sporulated oocysts. The anthelmintic influence of *Ziziphus spina-christi* leaves extract was determined against adult earthworm, *Allolobophora caliginosa*. The treatment with *Ziziphus spina-christi* leaves extract significantly reduced the oocytes shed, and was able to recover the affected jejunum caused by E. papillata infection. A fewer number of parasitic stages was shown in the jejuna villi after the treatment. The number of goblet cells in the jejuna villi was significantly increased after treatment with 100 and 300 mg /Kg *Ziziphus spina-christi* leaves extract. Moreover, the in vivo experiment exhibited dose-dependent effect, with the increase of *Ziziphus spina-christi* leaves extract, there was a decreased in time taken to induce paralysis and death [71].

## 8. Anticancer Activity

In a study aimed to examine the antiproliferative impact of *Ziziphus spina-christi* on MCF-7 cells (human breast cancer). Ethanolic extract of *Ziziphus spina-christi* leaves possess the smallest IC<sub>50</sub> value, producing cell cycle arrest at the G1/S phase and apoptosis determined 48 h post treatment [28].

Another study performed also on MCF-7 cell line revealed a significant cytotoxic impact of various concentrations of *Ziziphus spina-christi* leaf hydroalcoholic extract (0.01, 0.1, 1, and 10 mg/ml). However, only the MCF-7 cell line exposed to 1 mg/ml *Ziziphus spina-christi* extract induced a marked increase in the apoptotic marker (Bax) expression and decreased the antiapoptotic marker (Bcl2) expression [72].

In a study of male Sprague-Dawley rats treated with Aflatoxin to induce hepatic carcinogenicity, the *Ziziphus* extract showed a protective role against aflatoxicosis. *Ziziphus* fruit extract of (5mg/kg b.w.) alone caused significant decline in AST, triglycerides, cholesterol, and uric acid. In addition, *Ziziphus* extract alleviated the activities of GPX and SOD caused by aflatoxin, promising as a rich-antioxidants plant [73].

Another study evaluated the antitumor effect of *Ziziphus spina-christi* leaf extract (100 and 300 mg/kg) against hepatic carcinoma in rats induced with diethylnitrosamine. The expressions of Bcl2, hepatocyte growth factor, matrix metalloproteinase-9 oncogenes, and insulin-like growth factor-1 receptor were quantified in liver samples. *Ziziphus spina-christi* leaf extract exerted a dose-dependent medicinal effect versus diethylnitrosamine-induced hepatic carcinoma by ameliorating oxidative stress and oncogenes [74]. Therefore, *Ziziphus spina-christi* is a promising candidate for developing anticancer medications [75].

## 9. Antiasthma Activity

A clinical trial aimed to investigate the therapeutic activity of the extract of *Ziziphus spina-christi* leaf in asthmatic subjects. The study was conducted on 50 asthmatic subjects where 25 served as control group (placebo) and 25 served as treatment group (*Ziziphus spina-christi* leaf extract). Both groups are treated with the conventional asthma medication plus either placebo or *Ziziphus spina-christi* extract. The extract was indicated to be inhaled two times daily every other day for a period of eight weeks. Patients treated with the extract showed better pulmonary function tests, ameliorated life quality, and decreased asthma frequency [76].

## 10. Anticonvulsant Activity

An early conducted study revealed that the *Ziziphus spina-christi* fruit extract (50 mg/kg) induced a significant reduction in neurotransmitter content (gamma-aminobutyric acid, serotonin, dopamine, and norepinephrine) in different areas of the brain in male rats. This finding could be due to the ascorbic acid content in fruit extract of *Ziziphus spina-christi* of which induced release of neurotransmitter from presynaptic by improved Ca<sup>2+</sup> influx [76].

In a study aimed to examine the neuroprotective impact of *Ziziphus spina-christi* leaf extract against pentylenetetrazol induced seizure in rats. Three weeks administration of *Ziziphus spina-christi* leaf extract in a dose of 50 mg/kg induced a significant improve in dopamine, norepinephrine and serotonin contents in different regions in the brain (cerebral cortex, hippocampus, brainstem, cerebellum, striatum, and hypothalamus). The neuroprotective activity of the *Ziziphus* extract could be related to the presence of cyclopeptide alkaloids, and peptide which inhibit neurotransmitter release [77].

In another study the neuroprotective effect of *Ziziphus spina-christi* leaves extract (50, 100, and 299 mg/kg) on cerebral ischemia/reperfusion-induced brain damage was examined in rats. The findings showed that the *Ziziphus* extract enhanced the motor balance and coordination as well as improved serum and brain antioxidant capacity in a dose-based manner. The mechanism involved may associated with inhibited oxidative stress and increased antioxidant defence system [41].

## 11. Antinociceptive and Anxiolytic Activity

The aqueous extract of *Ziziphus spina-christi* leaves (250 mg/kg) lowered the number of abdominal cramps induced with acetic acid in rats, and the effect was similar to pethidine (10 mg/kg) [78]. The analgesic activity of *Ziziphus spina-christi* root extract has been studied experimental animals utilizing both formalin and hot plate experiments. *Ziziphus spina-christi* root bark extract at doses of 50 and 100 mg/kg demonstrated a dose-dependent analgesic action [79].

The impact of *Ziziphus spina-christi* extract on anxiety related behaviour in rats induced with scopolamine was investigated. The hydroalcoholic extract of *Ziziphus spina-christi* doses of 50, 100 and 200 mg/kg showed anxiolytic activity linked to modulation of oxidative stress against DPPH free radicals. Previous research reported Scopolamine to induce oxidative stress in the brain of rats [80]. The progress of neurodegenerative diseases has been linked to oxidative stress that could result in accelerating aging process and anxiety-related behaviour [81]. The anxiolytic activity identified in this study may be associated with antioxidant effects of the extract.

## 12. Conclusion

From the collected studies, it could be concluded that *Ziziphus spina-christi* extract possesses many pharmacological and biological activities such as hepato, cardio and nephroprotective, antidiabetic, antihyperlipidemic, antimicrobial, antiparasitic, anticancer, antiasthma, anticonvulsant, and antinociceptive activities. It was experimentally proven that *Ziziphus spina-christi* extract from the Sidr tree mentioned in the Qur'an has many nutritional values and pharmacological effects that could qualify it to be the subject of other studies in humans until it is used as a supplement or alternative treatment in the future.

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