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Review

Phytochemistry and pharmacologic properties of *Ziziphus spina christi* (L.) Willd.

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Ziziphus spina-christi **known as Christ's Thorn Jujube, is a native plant that grows in tropical and subtropical regions especially in Middle East. Its extracts are important in drug development with pharmacological activities in the Middle East and South and East of Asia including Iran. For a long time,** ***Z. spina-christi*** **has been used in alternative medicine for the treatment of fever, pain, dandruff, wounds and ulcers, inflammatory conditions, asthma and to cure eye diseases.** ***Z. spina-christi*** **has recently been shown to have antibacterial, antifungal, antioxidant, anti-hyperglycemic, and antinociceptive activities. Flavonoids, alkaloids and saponins are the main phytochemicals that are reported from this plant. Geranyl acetone, methyl hexadecanoate, methyl octadecanoate, farnesyl acetone C, hexadecanol and ethyl octadecanoate are characterized as the major components of the leaves' volatile oil. Due to the easy collection of the plant materials, its being cheap and widespread in many countries and also remarkable biological activities, this plant has become both medicine and food in some parts of the world, especially throughout the Middle East including Iran. This paper presents comprehensive analyzed information on the botanical, chemical and pharmacological aspects of** ***Z. spina-christi.***

Key words: *Ziziphus spina-christi*, rhamnaceae, pharmacology, phytochemistry.

INTRODUCTION

Ziziphus spina-christi commonly known as Christ's Thorn Jujube, is a deciduous tree and native to the warm-temperate and subtropical regions, including North Africa, South Europe, Mediterranean, Australia, tropical America, South and East of Asia and Middle East (Yossef et al., 2011). It belongs to the Rhamnaceae family in the order of Rosales that contains about 60 genera and more than 850 species. The genus *Ziziphus* consists of about 100 species of deciduous or evergreen trees and shrubs throughout the world (Abalaka et al., 2010). *Z. spina-christi* has been among the key plants of the Iranian traditional medicine since ancient times and is indigenous and naturalized throughout Iran (Solati and Soleimani, 2010). It has been known as "Sedr" in Iran and wildly distributed in East, South, North-East and central parts of Iran (Salehi, 2010).

Z. spina-christi is a shrub, sometimes a tall tree, reaching a height of 20 m and a diameter of 60 cm; its bark is light-grey, very cracked, scaly; trunk twisted; very branched, crown thick; shoots whitish, flexible, drooping; thorns in pairs, one straight, the other curved (Figure 1). Its leaves are glabrous on upper surface, finely pubescent below, ovate-lanceolate or ellipsoid, apex acute or obtuse, margins almost entire, lateral veins conspicuous (Figure 2). Flowers in cymes, subsessile, peduncle 1 to 3 mm (Figure 3). Fruit about 1 cm in diameter (Figure 4) (Zargari, 1988). *Z. spina-christi* has very nutritious fruits that are usually eaten fresh. The flowers are important source for honey in Yemen and Eritrea (Adzu and Haruna, 2007). The fruits are applied on cuts and ulcers. They are also used to treat pulmonary ailments and fevers and to promote the healing of fresh wounds, for dysentery (Abalaka et al., 2010).

For a long time, in folklore medicine, *Z. vulgaris* has been used for the treatment of some diseases, such as

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Figure 1. *Ziziphus spina-christi* L.

Figure 2. The leaves of *Z. spina-christi*.

digestive disorders, weakness, liver complaints, obesity, urinary troubles, diabetes, skin infections, loss of appetite, fever, pharyngitis, bronchitis, anemia, diarrhea, and insomnia (Han and Park, 1986; Kirtikar and Basu, 1984). The leaves are applied locally to sores, and the roots are used to cure and prevent skin diseases (Adzu et al., 2001). The seeds are sedative and are taken sometime with buttermilk to halt nausea, vomiting and abdominal pains associated with pregnancy (Kaaria, 1998). The leaves are applied as poultices and are

Figure 3. *Z. spina-christi* flower.

Figure 4. The fruits of *Z. spina-christi*.

helpful in liver troubles, asthma and fever (Michel, 2002). *Z. spina-christi* extract has also been reported to possess protective effect against aflatoxicosis (Abdel-Wahhab et al., 2007) and anti-conceptive properties in the rat and have a calming effect on the central nervous system. Flavonoids, alkaloids, triterpenoids, saponins, lipids,

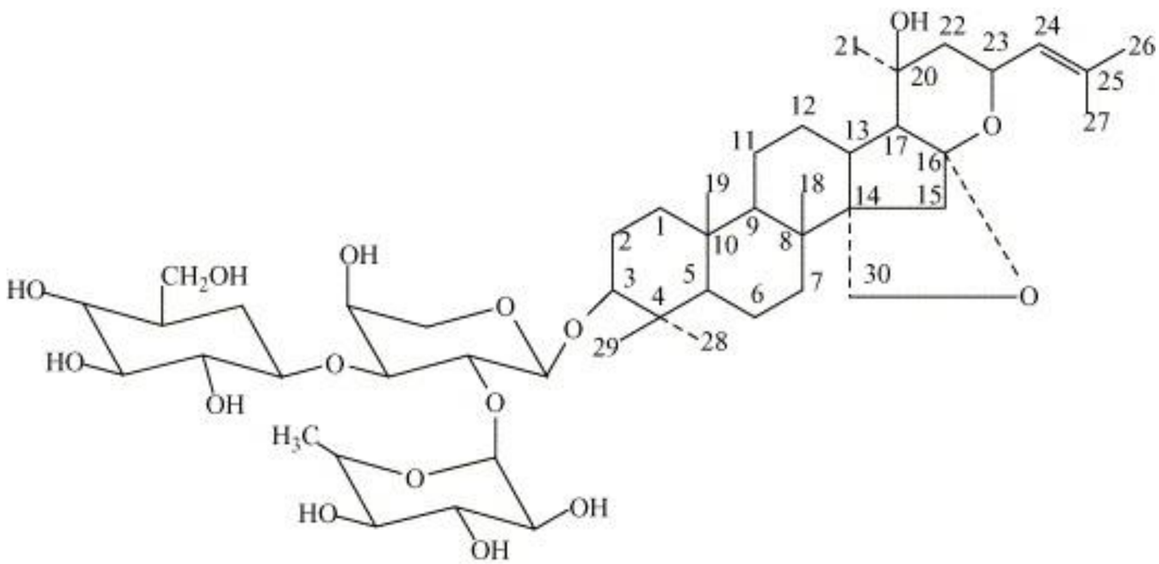

Figure 5. Molecular structure of christinin-A, the major components of *Z. spina-christi* leaves.

proteins, free sugar and mucilage are the main important compounds characterized in this plant (Adzu et al., 2003). Plant materials are cheap and significantly contribute to the improvement of human health in terms of cure and prevention of diseases (Okoko and Oruambo, 2008). Plants have been useful as food and medicine and a few have been studied especially African medicinal plants (Abalaka et al., 2010). They contain vitamins needed by human body for healthy living (Szeto et al., 2002; Jimoh et al., 2008). From current pharmaceutical studies, additional pharmaceutical applications of *Z. spina-christi* have revealed antifungal, antibacterial, antinociceptive, antioxidant, antidiabetic, antiplasmodial, anti-schistosomiasis, analgesic and anticonvulsant activities among others (Adamu et al., 2006; El-Kamali and Mahjoub, 2009; Adzu et al., 2001, 2011; Abalaka et al., 2011; Abdel-Zaher et al., 2005; El-Rigal et al., 2006; Adzu and Haruna, 2007; Waggas and Al-Hasani 2010).

Since a review and systemic analysis of chemistry, pharmacology and clinical properties of *Z. spina-christi* have not been reported, we prompted to provide the currently available information on traditional and local knowledge, ethnobiological and ethnomedicinal issues, identification of pharmacologically important molecules and pharmacological studies on this useful plant. The aim of this paper is to introduce *Z. spina-christi* as a potent medicinal plant by highlighting its traditional applications, as well as the recent findings for novel pharmacological and clinical applications.

CHEMICAL COMPOSITION

A survey of the literature revealed that a number of cyclopeptide and isoquinoline alkaloids, flavonoids, terpenoids and their glycosides have been found to occur in various amounts in most *Ziziphus* species. The leaves of these plants contain betulinic and ceanothic acids, various flavonoids, saponins, erols, tannins and triterpenes (Ali and Hamed, 2006; Glombitza et al., 1994). The extract of *Z. spina-christi* was shown to contain butic acid and ceanothic acid (a ring-A homologue of betulinic acid), cyclopeptides, as well as saponin glycoside and flavonoids, lipids, protein, free sugar and mucilage (Adzu et al., 2003). Cardiac glycosides and polyphenols (such as tannins) are also reported from the leaves (Abalaka et al., 2010).

Geranyl acetate (14.0%), methyl hexadecanoate (10.0%), methyl octadecanoate (9.9%), farnesyl acetone C (9.9%), hexadecanol (9.7%) and ethyl octadecanoate (8.0%) were characterized as the main components of *Z. spina-christi* leaves essential oil (Ghannadi et al., 2002). Zizyphine-F, jubanine-A and amphibine-H and a new peptide alkaloid spinanine-A have been isolated from the stem bark of *Z. spina-christi*. Spinanine-A is a 14-membered cyclopeptide alkaloid of the amphibine-B type (Fathy et al., 1990). Christinin-A is the major saponin of the leaves (Patel et al., 2012) (Figure 5). Dodecaacetylprodelphinidin B3 has been also isolated from the leaves (Weinges and Schick, 1995). New flavonoid, quercetin 3-xylosyl(1→2)rhamnoside-4′-rhamnoside (Pawlowska et al., 2008) accompanying with rutin, hyperin, quercetin, apigenin-7-O-glucoide, isovitexin and quercetin-3-O lucoside-7-O-rhamnoside were characterized from *Z. spina-christi* fruits. A flavonoid, C-glycoside, 3′,5′-di-C-β-d-glucosylphloretin, was also identified in *Z. spina-christi* leaves (Nawwar et al., 1983). In addition, 4-hydroxymethyl-1-methyl pyrrolidine-2-carboxylic acid and 4-hydroxy-4-hydroxymethyl-1-methyl pyrrolidine-2-carboxylic acid were characterized as two new cyclic amino acids from *Z. spina-christi* seeds (Said et al., 2010).

POTENTIALS OF *Z. SPINA-CHRISTI*

A tropical evergreen tree of many parts of Iran, it is cultivated mainly as a dry crop for its mucilage nutritious fruits, honey production and landscaping purposes. It serves the ecosystem by controlling erosion, acting as wind break and it improves soil quality by increasing available phosphorus. Traditionally, it is used in Iran as a medicinal plant; the fruits are used for the treatment of fever, pain, dandruff, wounds and ulcers, in inflammatory conditions, asthma and to cure eye diseases, while the seeds are used as a tonic (Shah et al., 1989; Adzu and Haruna, 2007). Extracts from the plant could be useful in the treatment of nosocomial infections, opportunistic infection of the unary tract, infantile gastroenteritis, traveler’s diarrhea, wound infection, meningitis, and wounds infection which are diseases caused by some of these organisms (Adzu and Haruna, 2007). Additionally, *Z. spina-christi* fruit extract causes neurotransmitters release, which is probably related to presence of ascorbic acid and the leaves may potentially be safe for use as sedative drug (Waggas and Al-Hasani 2010). A variable activity of the plant extract is against *Staphylococcus aureus* which highly infects various burns (Alsaimary, 2009).

Moreover, the methanol extract of Sidir could be used not only as a safe potential natural functional food ingredient or as therapeutic drug in the treatment of diabetes, but also it is effective in reducing both hyperlipidemia and oxidative stress accompanying diabetes (Hussein et al., 2006; Sudhersan and Hussain, 2003). It easily domesticated and can be grown commercially for the benefit of pharmaceutical industry and vegetation purposes.

Antibacterial and antifungal properties

The aqueous extract of *Z. spina-christi* stem bark has shown significant antibacterial activity against *S. aureus, Bacillus subtilis, Escherichia coli, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella para typhi B* and *Klebsiella pneumonia* (El-Kamali and Mahjoub, 2009). *Z. spina-christi* stem bark aqueous extract has shown highly significant antibacterial effect activity on some Gram negative bacterial growth including *Brucella abortus, Brucella melitensis, Proteus spp., Klebsiella spp., P. aeruginosa, E. coli and Enterobacter spp.* in comparison with eight antibiotics (Korji, 2012). Alcoholic extract of the leaves has also shown good antibacterial activity against *S. aureus* isolated from eye infections (conjunctivitis). An inhibition zone of 20 mm was recorded for 1 mg/ml of the extract (Alsaimary, 2012). Additionally, the leaves were active against *Salmonella typhi, Proteus mirabilis, Shigella dysenteriae, E. coli, K. pneumonia, B. melitensis, Bordetella bronchiseptica* and *P. aeruginosa*. The highest activity (20 mm) was against *B. bronchiseptica* byconcentration of 100 mg/ml (Motamedi et al., 2009)The pulp aqueous extract of *Z. spina-christi* also showed inhibitory activity on *E. coli, P. aeruginosa and Candida albicans in vivo*. The extract showed MIC of 6.25 mg/ml against *E. coli* and *C. albicans*. The minimum bactericidal concentration of the pulp aqueous extract was 12.5mg/ml for *Streptococcus pyogenes* (Tom et al., 2009). Methanol extract of *Z. spina-christi* roots showed antifungal activity against dermatophytes, including *Trichophyton rubrum, T. mentagaphytes, Microsporum canis* and *Aspergillus fumigatus* (Adamu et al., 2006). The fruits were also active against *C. albicans* (Ghasemi Pirbalouti et al., 2009).

As shown by these results, the extracts from *Z. spina-christi* could be useful in the treatment of nosocomial infections, opportunistic infection of the unary tract (UTI), infantile gastroenteritis, travelers’ diarrhea, wound infection, meningitis and wounds infection which are diseases caused by some of these organisms.

Antinociceptive effects

The antinociceptive effect of the aqueous extract of *Z. spina-christi* root bark was shown in mice and rats by acetic acid-induced writhing, formalin and thermal (hot plate) tests. The extract (50 and 100 mg/kg, i.p.) demonstrated a dose-dependent analgesic effect in all the tests used. Its i.p. LD_{50} in mice was 2236.07 mg/kg (Adzu et al., 2001). The aqueous extract of the leaves were also active. The extract (250-1000 mg kg^{-1}) in a dose-dependent fashion significantly reduced the number of writhes induced by 0.6% aqueous solution of acetic acid in Wistar rats. At a dose of 250 mg/kg, the extract produced comparable effect to that of 10 mg/kg of pethidine hydrochloride in suppressing the number of writhing induced by acetic acid (Effraim et al., 1998).

Antioxidant activity

An antioxidant is defined as ‘any substance that, when present at low concentrations compared to those of an oxidizable substrate, significantly delays or prevents oxidation of that substrate’ (Rhee et al., 2009; Wiseman et al., 1997; Mates et al., 1999). Antioxidants are of interest to biologists and clinicians because they help to protect the human body against damages induced by reactive free radicals generated in atherosclerosis, ischemic heart disease, cancer, Alzheimer's disease, Parkinson's disease and even in aging process (Aruoma, 2003; Hemati et al., 2010). There are many evidences that natural products and their derivatives have efficient anti-oxidative characteristics, consequently linked to anti-cancer, hypolipidemic, anti-aging and anti-inflammatory activities (Rhee et al., 2009; Wiseman et al., 1997; Hogg, 1998; Mates et al., 1999; Aruoma, 2003; Cho et al., 2006).

The anti-oxidative capacities of ethanol and petroleum ether extracts of *Z. spina-christi* leaves were evaluated by hydroxyl radical, 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical, lipid peroxidation and superoxide radical standardization methods (Abalaka et al., 2011). The EC_{50} values for hydroxyl radical with ethanol and hexane extract of *Z. spina-christi* were found to be 198.34 and 234.11 µg, while that of ascorbic acid was found to be 219.31 µg. The EC_{50} values for the two plant extracts were ethanol 101.02 µg and hexane 124.21 µg. These results compare favorably with that of standard ascorbic acid which had the EC_{50} value of 78.12. Moreover, the EC_{50} values for lipid peroxidation with ethanol extract and hexane extract of *Z. spina-christi* were 298.65 and 376.35 µg, while that of ascorbic acid was 191.42 µg. The EC_{50} value for superoxide radical scavenging with ethanol and hexane extract of *Z. spina-christi* were 156.45 and 265.22 µg, while that of ascorbic acid was 138.26 µg (Abalaka et al., 2011). These activities indicate that the extracts from *Z. spina-christi* are good antioxidants.

It was also indicated that the fruits contained high level of total phenolic compounds (7.55mg /g as gallic acid) (Yossef et al., 2011). The fruit administration inhibited lipid peroxidation at higher level after CCL4 treatment. Interestingly, the methanolic extract of these fruits with dose of 200 mg/kg was able to increase the activities of endogenous antioxidant enzymes (superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px)) and levels of GSH in hepatic tissue. The fruits extract pretreatment demonstrated to inhibit malondialdehyde (MDA) of the reactive oxygen radical production (Xiangchun et al., 2009).

Antidiabetic properties

Pretreatment either with 100 mg/kg butanol extracts of the leaves or christinin-A, the major saponin glycoside of the leaves, potentiated glucose-induced insulin release in non-diabetic control rats. In type-II but not in type-I diabetic rats, pretreatment with the butanol extract or christinin-A improved the oral glucose tolerance and potentiated glucose-induced insulin release. Treatment either with 100 mg/kg butanol extract or christinin-A reduced the serum glucose level and increased the serum insulin level of non-diabetic control and type-II diabetic rats but not of type-I diabetic rats. Pretreatment of non-diabetic control and type-II diabetic rats either with 100 mg/kg butanol extract or christinin-A also enhanced the glucose lowering and insulinotropic effect of 5 g/kg glibenclamide. The hyperglycemic and hypoinsulinemic effects of 30 mg/kg diazoxide in non-diabetic control and type-II diabetic rats were inhibited and antagonized, respectively by pretreatment with the butanol extract or christinin-A. Treatment of rats with 100 mg/kg butanol extract for 3 months produced no functional or structural disturbances in liver and kidney and no haematological changes. In addition, the oral LD50 of the butanol extract in mice was 3820 mg/kg, while that of glibenclamide was 3160 mg/kg. Thus, *Z. spina-christi* leaves appear to be a safe alternative to lower blood glucose. The safe insulinotropic and subsequent hypoglycemic effects of *Z. spina-christi* leaves may be due to a sulfonylurea-like activity (Abdel-Zaher et al., 2005).

Oral administration of *Z. spina-christi* leaf extract, plain and formulated for 28 days, reduced blood glucose level with significant increase in serum insulin and C-peptide levels. Marked elevation in total antioxidant capacity with normalization of percentage of glycated hemoglobin (HbA1C%) was reported. Moreover, they succeeded in reducing the elevated blood lactate level and to elevate the reduced blood pyruvate content of diabetic rats. In line with amelioration of the diabetic state, the extract, plain and formulated, restored liver and muscle glycogen content together with significant decrease of hepatic glucose-6-phosphatase and increase in glucose-6-phosphate dehydrogenase activities. *In vitro* experiments showed a dose-dependent inhibitory activity of the extract against α-amylase enzyme with IC_{50} at 0.3 mg/ml. Such finding has been supported by the *in vivo* suppression of starch digestion and absorption by the extract in normal rats. The results revealed that *Z. spina-christi* leaf extract improved glucose utilization in diabetic rats by increasing insulin secretion, which may be due to both saponin and polyphenols content, and controlling hyperglycemia through attenuation of meal-derived glucose absorption that might be attributed to the total polyphenols (Michel et al., 2011).

CONCLUSION

The objective of this paper has been to show the recent advances in the exploration of *Z. spina-christi* as phytotherapy and to illustrate its potential as a therapeutic agent. With the current information, it is evident that *Z. spina-christi* has pharmacological functions, including antihyperglycemic, antibacterial, antifungal, antioxidant and antinociceptive activities, among others. As the current information shows, it is also possible that various flavonoids and saponin glycosides such as christinin-A might be useful in the development of new drugs to treat various diseases. It must be kept in mind that clinicians should remain cautious until more definitive studies demonstrate the safety, quality and efficacy of *Z. spina-christi*. For these reasons, extensive pharmacological and chemical experiments, together with human metabolism will be a focus for future studies. Last but not the least, this article emphasizes the potential of

Z. spina-christi to be employed in new therapeutic drugs and provide the basis for future research on the application of transitional medicinal plants.

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