2 An Insight into the Phytochemistry, Traditional Uses, and Pharmacology of *Ziziphus spina-christi* (L) Willd. *(Sidr)*: An Edible Wild Plant of Arabian Peninsula

U. M. Dhanalekshmi, Shah Alam Khan, Tanveer Alam, and Mubashir H. Masoodi

Abstract

Ziziphus spina-christi (L) Willd., belonging to the family Rhamnaceae, is a popular medicinal plant of Arabian peninsula. The plant being heat and drought resistant grows well in the extreme harsh environmental conditions of Middle East and North Africa (MENA) region. The ripe fruits are eaten as source of nourishment. The plant contains diverse classes of secondary plant metabolites such as cyclopeptide alkaloids, flavonoids, triterpenic acids, phenolic acids, tannins, volatile oils, fatty acids, saponins, etc.

Ziziphus spina-christi (*ZSC*) is used as a traditional medicine in Iran, India, Middle East, and several African countries. Almost all the parts of *ZSC* viz., the fruits, seeds, leaves, roots, and barks, are used by the herbalists and traditional medicinal practitioners for medicinal purpose to restore the good health. Many studies have shown the crude extracts of various parts of the *Ziziphus* plant to possess antimicrobial, anticancer, antidiabetic, antinociceptive, antihypertensive, antidiarrheal, and CNS effects. The outcomes of these scientific studies have by and large validated its folkloric uses. The plant owing to its high polyphenolic content has also been explored as an alternative source of biosynthesis of metal nanoparticles. Although *ZSC* fruits and leaves appear to be safe in experimental

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animals, there is a scarcity of the available scientific data on the toxicity associated with the consumption of the various parts of the *ZSC* plant.

This chapter aims to provide an updated comprehensive review of biologically active phytochemicals isolated from the various parts of the *ZSC*, traditional uses, patents granted, application in nanotechnology, and in vitro and in vivo pharmacological studies along with its toxicological profile.

Keywords

Ziziphus spina-christi · Christ's thorn · Cyclopeptide alkaloids · Traditional uses · *Sidr*

Abbreviations

5-HT	5-Hydroxyl tryptamine (serotonin)
ABTS	2,2-Azino-bis (3-ethylbenzothiazoline-6-sulphonic acid) assay
AcOH	Acetic acid
AgNPs	Silver nanoparticles
ALKP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BALP	Bone alkaline phosphatase
BHT	Butylated hydroxytoluene
BMD	Bone mineral density
cAMP	Cyclic adenosine monophosphate
CCl_4	Carbon tetrachloride
CNS	Central nervous system
COVID	Coronavirus disease
sCT	Serum calcitonin
CuNPs	Copper nanoparticles
CV	Crystal violet
DA	Dopamine
DENA	Diethyl nitrosamine
DNA	Deoxyribonucleic acid
DPPH	2,2-Diphenyl-1-picrylhydrazyl
EGFR	Epidermal growth factor receptor
FRAP	Ferric reducing/antioxidant power
GABA	Gamma-aminobutyric acid
GSH	Glutathione peroxidase
HbA1C	Hemoglobin A1c or glycated hemoglobin
HDL	High-density lipoproteins
HOMA	Homeostatic model assessment of β cell function
HOMA-IR	Homeostatic model assessment of insulin resistance

HORAC	Hydroxyl radical assay
HPLC-MS	High-performance liquid chromatography-mass spectrometry
HR	Heart rate
IGF-1	Insulin-like growth factor 1
IL-1β	Interleukin 1 beta
KATP	ATP-sensitive potassium channel
LD_{50}	Lethal dose in 50% of population
LDL	Low-density lipoproteins
LFT	Liver function tests
LPO	Lipid peroxidation
MCA	Metal chelation assay
MCH	Mean corpuscular hemoglobin
MDA	Malondialdehyde
MLZ	Mesalazine
MPP	1-methyl-4-phenylpyridinium
mRNA	Messenger ribonucleic acid
NE	Norepinephrine
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NO	Nitric oxide
OC	Osteocalcin
PC1	Procollagen type 1
PTH	Serum parathyroid hormone
PTZ	Pentylenetetrazol
qRT-PCR	Real-time quantitative reverse transcription Polymerase chain reaction
RFT	Renal function tests
RNA	Ribonucleic acid
ROS	Reactive oxygen species
SC	Subcutaneous
SGOT	Serum glutamate oxaloacetate transferase
SGPT	Serum glutamate pyruvate transaminase
SMA	Spontaneous motor activity
SOD	Superoxide dismutase
SRSA	Superoxide radical scavenging activity
STZ	Streptozotocin
TRAP	Tartrate-resistant acid phosphatase
TRPA	Total reducing power ability
VLDL	Very-low-density lipoproteins
WHO	World Health Organization
ZSC	*Ziziphus spina-christi*
*ZSC*F	*Ziziphus spina-christi* fruits

2.1 Introduction

Ziziphus spina-christi (L) Willd., (*ZSC*) commonly known as Sidr in Arabic and Christ's thorn or Jujube in English belongs to the family Rhamnaceae. It is geographically distributed in a vast area of Africa, Asia, and Middle East (Motamedi et al. 2014). The species is native to several countries including Chad, Djibouti, Eritrea, Ethiopia, Kenya, Libya, Mali, Mauritania, Nigeria, Pakistan, Senegal, Somalia, Tunisia, Turkey, and Zimbabwe. The species is exotically distributed in Algeria, Comoros, Egypt, India, Iran, Iraq, Israel, Jordan, Madagascar, Morocco, Holland, Saudi Arabia, Syria, United Arab Emirates, and Zanzibar (Orwa et al. 2009).

It is known to be as one of the most heat-tolerating and drought-resistant fruit crops adapted to the harsh environmental conditions of Arabian Peninsula (Sudhersan and Hussain 2003). There are about 100 species in the genus *Ziziphus*, but among all *ZSC* is widely cultivated in Arabian Peninsula along with few other *Ziziphus* species for their edible fruits and wood. The tropical evergreen Sidr tree is approximately 10–12 m in height and grows widely throughout Oman but more prominently in Dhofar region and in Northern Oman during monsoon season. Its characteristic leaves which are ovate to elliptical in shape and are thinly hairy, glabrous beneath along the veins, distinguish it from other *Ziziphus* species (Miller and Morris 1988). Leaves are alternate, 2–4 cm long, 1.5–3 cm across, and have rounded tip with crenate or serrate margin, and the base is round to subcordate (Fig. 2.1). Although the nutritional value of *ZSC* leaves is not very high for domestic animals, in Northern Oman leaves are used as a source of livestock forage and fodder under open grazing field (Ghazanfar 1994a, b; Ghazanfar and Sabahi 1993).

The *ZSC* fruit is called *nabaq* and is rich in vitamin C. Since ancient time *ZSC* fruits are consumed by a large population in Oman villages as a source of nourishment. The fruit ripens during hot and dry weather, and the pulp of the yellow ripe fruit (diameter 1–1.5 cm) with a single obovate seed (6–7 × 5–6 mm, brown) tastes like apple. The fruit, if stored in dry place for long time, becomes reddish brown, sweeter, and softer with age (Miller and Morris 1988). The kernels are also eaten raw or cooked in water, milk, or buttermilk to treat the pneumonia. The fruits are eaten by grazing sheep and goats and the foliage by camels. The powdered sun-dried fruits are mixed with water to prepare cakes similar to gingerbread (Ali et al. 2006).

In Oman, the fruits are traditionally used for cleansing the stomach, purification of blood, and occasionally as abortifacient. The fruit has also been reported to stimulate appetite if eaten before meal and believed to possess anti-hair-falling properties. The *ZSC* leaves either crushed or chewed were used as cleansing agent for the whole body, particularly for hair and scalp as shampoo. The paste of the boiled leaves is used to treat headache, to soothe skin ulcers and infected sores, to reduce inflammation and pain of joints or fractured limbs. The decoction of leaves is said to have oxytocic properties and thus used to prolong the labor (Miller and Morris 1988; Ghazanfar 1994a, b).

Flowers are in dense clusters in the axil of the leaves. The calyx is five lobed and cup-shaped at the base and the petals are yellowish. The *ZSC* flowers are very

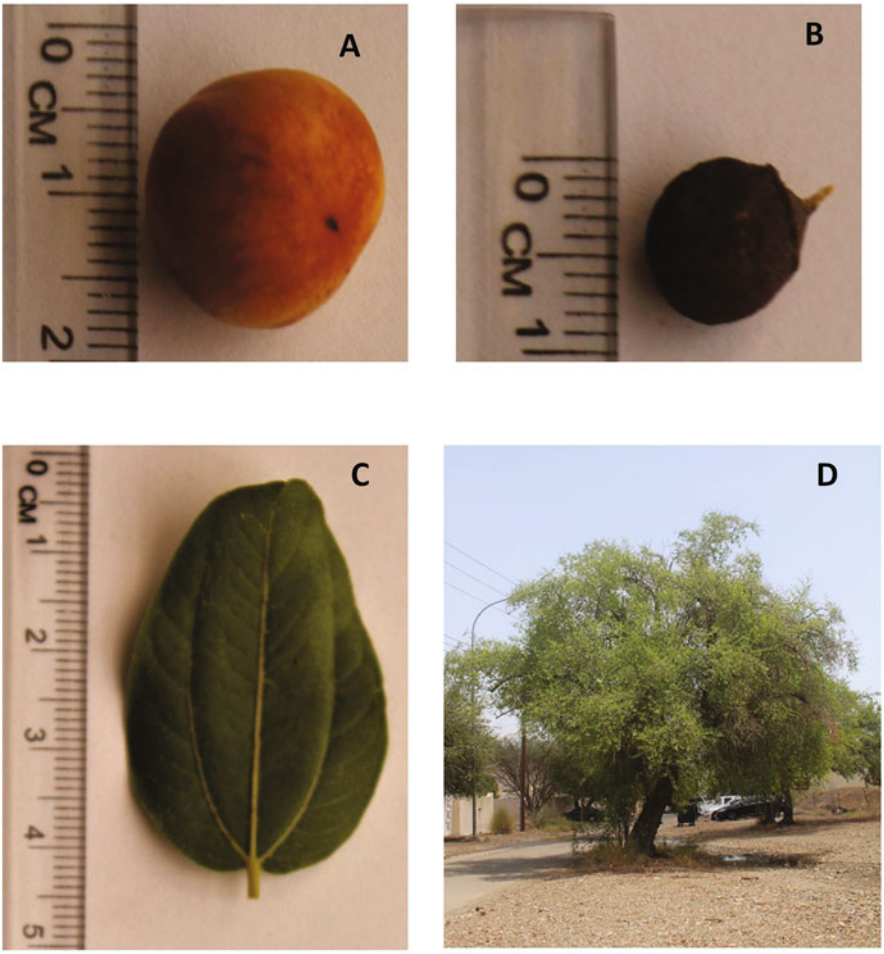


Fig. 2.1 Picture showing *ZSC* fruit (**a**), seed kernel (**b**), leaf (**c**), and full view of the tree (**d**). (Original pictures taken by Ms. Al Ghaliya Al Farsi, Oman)

important bee forage, and the honey produced there from is considered of excellent quality (Sudhersan et al. 2016).

2.2 Traditional/Folklore Medicinal Uses of *Ziziphus spina-christi*

ZSC has been traditionally utilized as a prominent medicine to uphold health (El Ghazali et al. 1994). Majority of the folklore claims of *ZSC* are scientifically validated and reported, but some traditional uses are prevalent in one or other cultural groups/regions. As per the WHO report, majority of the people from the

developing countries still rely on traditional cures prepared from natural sources for their primary healthcare needs. A large number of people especially in areas that have difficulty to access modern pharmaceuticals completely depend on traditional uses of natural medicine for acute and chronic ailments (Carmona and Pereira 2013). Various parts of the *Ziziphus* plant including crude extracts of root, stem, flower, fruit, and twigs have been extensively explored for the diverse pharmacological activities in order to validate its folklore claim. The results of several in vitro and in vivo pharmacological studies have validated and supported the ethnopharmacological uses of *ZSC* and are presented in Table 2.1.

ZSC is a very popular traditional medicine in Iran, India, Middle East, and several African countries. Almost all the parts of *ZSC*, viz., the fruits, seeds, leaves, roots, and bark, are used for medicinal purpose to maintain and restore good health (Asgarpanah and Haghighat 2012).

In India, a formulation prepared using *ZSC* bark is used for the cleansing of wounds and sores. The gum of the tree is used to treat eye diseases, while the leaves are chewed to mask the bitter or unpleasant taste of medicines (Miller and Morris 1988). A narcotic beverage made from the fruits is used as tranquilizer and sedative in Egypt and the southern Sahara (Younes et al. 1996). Egyptian use leaves along with the conventional medicines to treat abscesses, bubbles, and swollen eyes. The fiery wood debris is applied topically to treat snakebite (Abdel-Galil and El-Jissry 1991).

In Saudi Arabia, the fruits are eaten for their laxative property, and the leaves are used to heal wounds, to treat skin diseases, as diuretic, and also as a body wash. The stem bark is used in toothache and as an antipyretic (Tanira et al. 1988; Ali et al. 2006). In Morocco, the fruits are used for their emollient and astringent actions, while the leaves are used to reduce eye inflammation (Ali et al. 2006).

In Sudan, the sore throat is treated by eating fruits, the bark is used for chest pain, and a root infusion is taken orally to combat dysentery (El Ghazali et al. 1997). The roots are popularly used in the treatment of urinary and gynecological problems in Zimbabwe. Bark decoctions have been reported to be used for chest diseases in South Africa. In Mali and Niger, the roots and the leaves are utilized for gastric infections, chest pain, sexually transmitted diseases, diarrhea, wounds, constipation, and nervousness (El Ghazali et al. 1997; El Maaiden et al. 2020).

2.3 Phytochemistry of *ZSC*

The phytochemistry and related aspects of all the parts of *ZSC* plant have been extensively studied over the past five to six decades. The phytochemical analysis has resulted in the isolation, separation, and identification of hundreds of minor and major phytoconstituents of diverse chemical classes (Fig. 2.2). *ZSC* is reported to contain cyclopeptide alkaloids, flavonoids, triterpenic acids, phenolic acids, tannins, volatile oils, fatty acids, saponins, etc. However, maximum numbers of compounds have been isolated from the *ZSC* leaves (Fig. 2.3).

Table 2.1 Traditional pharmacological uses of various parts of *ZSC*

Plant parts	Traditional pharmacological uses	References
Leaf	Chest pains, asthma, headache, eye inflammations, diarrhea, stomach pain, constipation, hemorrhoids, anthelmintic, increase milk production, ease prolonged labor, blisters, skin diseases and disorders, abscesses and furuncles, lung-related problems, chest and pectoral problems, blood purifier and tonic, high blood pressure, fractures, emollient, cooling, tonic, stomachic, astringent, hair problems, infant's powder, nervousness, numb the taste buds, insomnia, antidiabetic, gonorrhea, sex diseases, inflammatory conditions, ulcers, wound healing, heartburn	Miller and Morris (1988), Dafni et al. (2005), Saied et al. (2008), Ads et al. (2017), Abdel-Zaher et al. (2005), Abdel-Galil and El-Jissry (1991), Kadioglu et al. (2016), Panche et al. (2016), Dkhil et al. (2018a, b), Dafni et al. (2005), Bown (1995), Neuwinger (1996), Iwu (1993), Asgarpanah and Haghighat (2012) and Deshpande et al. (2019)
Root	Toothache, gum problems, arthritis, general painkiller, eye inflammations, antipurgative	El Ghazali et al. (1994), Dafni et al. (2005), Saied et al. (2008), Abdel-Galil and El-Jissry (1991) and Neuwinger (1996)
Bark	Toothache, gum problems, anodyne, cooling, tonic stomachache, intestinal spasms, body rinse, to cure fresh wounds	El Ghazali et al. (1994), Dafni et al. (2005), Saied et al. (2008) and Abdel-Galil and El-Jissry (1991)
Stem	Nervousness, heart pains, muscle pains, scorpion sting, rheumatism, anti-inflammatory for eye wash, treat toothache and stomachache, antirheumatic, dysentery, bronchitis, coughs, and tuberculosis	El Kamali and El Khalifa (1999), Ali-Shtayeh et al. (1998), Dafni et al. (2005), Saied et al. (2008), Ads et al. (2017), Alzahrani et al. (2016), Panche et al. (2016) and Dkhil et al. (2018a, b)
Fruit	Anus problems, liver problems, swollen organs, weight reduction, colds, febrifuge, measles, stomachache, cooling, depurative, plood purifier and tonic, lung, chest, and pectoral problems, burns, blisters, wounds, promoting pregnancy, diarrhea, anthelmintic, stomach disorders, aches, constipation, heartburn, headache, chest pains, asthma, bruises, dysentery, bronchitis, coughs, tuberculosis	Jongbloed (2003), Dafni et al. (2005), Saied et al. (2008), Ads et al. (2017), Alzahrani et al. (2016), Abdel-Galil and El-Jissry (1991), Kadioglu et al. (2016), Panche et al. (2016), Neuwinger (1996), Guizani et al. (2013), Deshpande et al. (2019) and Asgarpanah and Haghighat (2012)
Seed	Hair problems, blisters, anthelmintic, eye inflammations, headache, chest pains, asthma, bruises	Dafni et al. (2005), Saied et al. (2008), Abdel-Galil and El-Jissry (1991), Dkhil et al. (2018a, b) and Asgarpanah and Haghighat (2012)
Wood	Toothache, gum problems	Dafni et al. (2005) and Saied et al. (2008)
Resin	Hair problems, febrifuge, skin diseases	Dafni et al. (2005) and Saied et al. (2008)

Fig. 2.2 Various chemical classes of phytochemicals identified in *ZSC*

2.3.1 Volatile Oils in the Leaves, Fruits, and Flowers of *ZSC*

The major volatile constituents of the leaves of *ZSC* grown in Iran were identified as geranyl acetone (14.1%) and farnesyl acetone C (9.9%). The minor volatile constituents of the *ZSC* leaves include β-eudesmol (3.8%), *E*-β-ionone (1.4%), spathulenol (1.2%), terpinolene (1.2%), germacrene D (1.1%), and nerolidol (1.1%). *Allo*-aromadendrene, β-pinene, β-caryophyllene, α-terpineol, α-pinene, 1,8-cineole, nerol, aromadendrene, δ-cadinene, *p*-cymene, and limonene were also detected in the oil, but their concentration was found to be less than 1% (Ghannadi et al. 2003). However, another study carried out by Fard et al. using the aerial parts of *aucheri* variety of *ZSC* grown in the same region of Iran could only identify 11 compounds representing 92.14% of the volatile oil. They identified carotol (42.20%) as the main constituent (Fard et al. 2020). On the other hand, the leaves

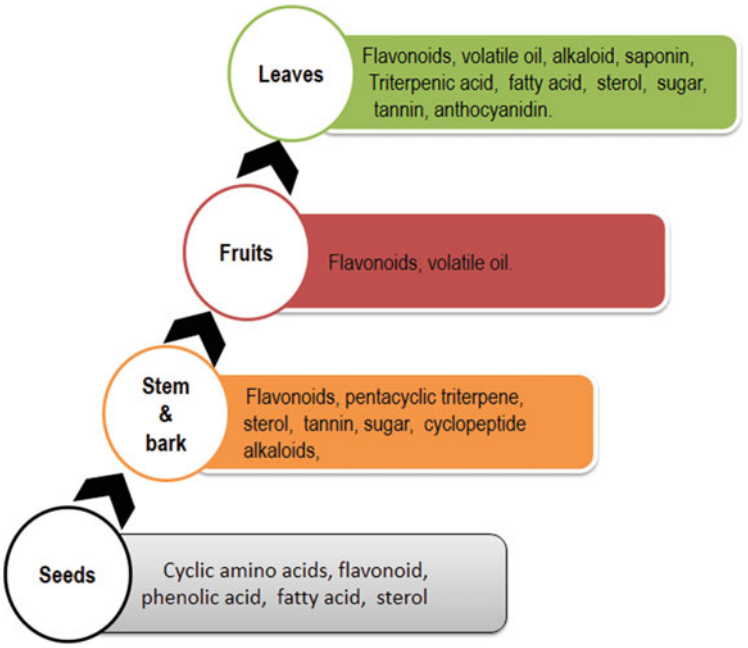


Fig. 2.3 Major chemical classes of phytochemicals present in different parts of *ZSC*

of the Egyptian variety have been reported to be rich in α-terpineol (16.4%) and linalool (11.5%) (Younes et al. 1996).

The chemical composition of volatile oil isolated from the fresh fruits of *ZSC* grown in Giza, Egypt, was reported by Said et al. (2010a, b). The GC-MS analysis revealed the presence of 21 chemical compounds in the fresh fruits constituting 99.3% of the oil. The major constituents of the oil were found to be dodecanoic acid (22.4%) and oleic acid methyl ester (17.1%) (Said et al. 2010a, b).

Flower volatile constituents of *ZSC* collected from Alexandria, Egypt, were isolated using closed-loop stripping analysis (CLSA) and solid-phase micro-extraction (SPME) techniques. The oil upon GC-MS analysis showed the presence of 22 volatile compounds belonging to different chemical classes, viz., aldehyde (19.69%), monoterpene-alcohol (22.78%), ketone (18.12%), ester (3.80%), and hydrocarbon (21.64%). Linalool (16.34%) was characterized as the major constituent, but nonanal (11.56%), D-limonene (6.43%), lavandulol (2.59%), and α-terpineol (0.96%) were also identified in the floral oil. The flowery, fruit, and sweet smell odors of the characterized volatile constituents were attributed to the characteristic unique odor of the flowers of *ZSC* (Shonouda et al. 2008). The chemical structures of some identified volatile constituents in the *ZSC* are presented in Fig. 2.4.

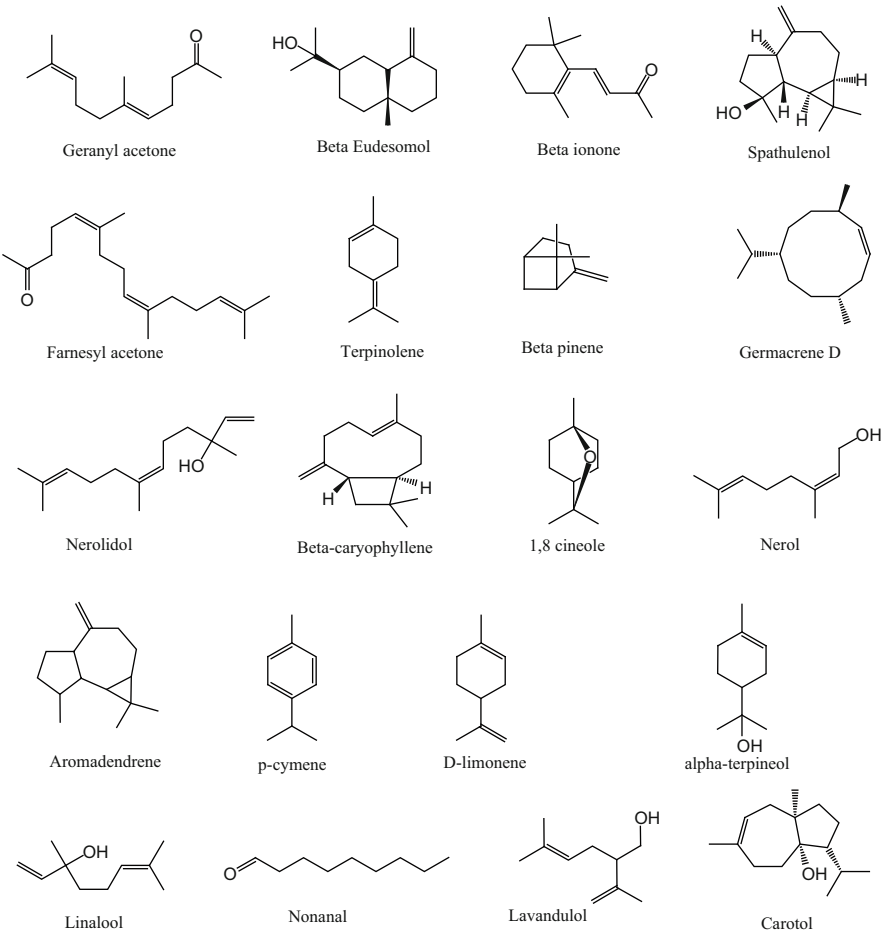


Fig. 2.4 Chemical structures of some important chemical constituents present in the *ZSC* volatile oil

2.3.2 Phytochemicals Isolated from the Leaves of *ZSC*

Phytochemical investigations of the leaves of *ZSC* have shown the presence of various chemical classes of secondary plant metabolites. However, the yield and extraction efficiency of biologically active secondary metabolites from the *ZSC* leaves depend upon the polarity of solvents. Leaves of *ZSC* are widely used by traditional medical practitioners/herbalists in the gulf region for the treatment of skin diseases and to heal wounds. The leaves are also used as anti-inflammatory, antipyretic, and diuretic and as a body wash. The chemical compounds characterized in the various organic extracts of *ZSC* leaves are presented in Table 2.2 which indicates that leaves predominantly contain flavonoid glycosides, cyclopeptide alkaloids, saponins, and triterpenic acid besides lipids, volatile oils, and carbohydrates. The

Table 2.2 Chemical compounds isolated from the *ZSC* leaves extract

S. no.	Chemical class	Name of chemical compound	Reference
1.	*C*-flavonoid glycoside	Naringenin-6,8-dihexoside	Okamura et al. (1981)
2.		(*Epi*)catechin-di-*C*-hexoside	Pawlowska et al. (2009)
3.		3′,5′-Di-*C*- β-D-glucosylphloretin	Nawwar et al. (1984)
4		Apigenin-6-*C*-glucoside	Nawwar et al. (1984)
5.	*O*-flavonoid glycoside	Myrecetin-3-*O*-(6-rhamnosyl) hexoside-*O*-glycoside	Sakna et al. (2019)
6.		Quercetin-3-*O*-(2,6-dirhamnosyl) hexoside	Bozicevic et al. (2017)
7.		Quercetin-3-*O*-(2,hexosyl)-6-rhamnosyl) hexoside	Sakna et al. (2019)
8.		Kaempferol-3-*O*-(2,6-dirhamnosyl) hexoside	Pawlowska et al. (2009)
9.		Quercetin-3-*O*-robinoside	Pawlowska et al. (2009)
10.		Quercetin-3-*O*-rutinoside	Pawlowska et al. (2009)
11.		Bayarin	Devkota et al. (2013)
12.		Quercetin-3-*O*-hexoside	Devkota et al. (2013)
13.		Kaempferol-3-*O*-rutinoside	Devkota et al. (2013)
14.		Quercetin-3-*O*-(2-pentosyl-rhamnoside)-4′-*O*-rhamnoside	Devkota et al. (2013)
15.		Taxifolin-3-*O*-glucoside	Ali et al. (1984)
16.		Apigenin-7-*O*-glucoside	Nawwar et al. (1984)
17.		Quercetin-3-*O*-glucoside-7-*O*-rhamnoside	Nawwar et al. (1984)
18.	*Acyl*-flavonoid glycoside	Quercetin-3-*O*-*p*-coumaroyl (2,6-dirhamnosyl)-hexoside	Sakna et al. (2019)
19.		6′″-Caffeoyl 3′,5′-di-C-glucopyranosylphloretin	Sakna et al. (2019)
20.		Quercetin-3-*O*-(4-*O*-*p*-coumaroyl)-2-rhamnosyl-[6-rhamnosyl]-galactoside (16)	Bozicevic et al. (2017)
21.		Kaempferol-3-*O*-(4-*O*-*p*-coumaroyl)-2-rhamnosyl-[6-rhamnosyl]-galactoside	Sakna et al. (2019)
22.		Quercetin-3-*O*-(4-*O*-*p*-coumaroyl)-2-rhamnosyl-[6-rhamnosyl]-glucoside	Sakna et al. (2019)
23.	Flavonoid Alkaloid	Taxifolin	Ali et al. 1984
24.		Dihydrokaempferol	Ali et al. (1984)
25.		Rutin	Nawwar et al. (1984)
26.		Hyperin	Nawwar et al. (1984)
27.		Quercetin	Nawwar et al. (1984)
28.		Mauritine F	Gournelis et al. (1998)
29.		Daechuine S5	Gournelis et al. (1998)
30.		4(13)-Nummularine-C	Sakna et al. (2019)
31.		Sanjoinine B	Gournelis et al. (1998)

(continued)

Table 2.2 (continued)

S. no.	Chemical class	Name of chemical compound	Reference
32.		Oxyphylline A	Tuenter et al. (2017a, b)
33.		Lotusanine A/Frangufoline	Gournelis et al. (1998)
34.		Jubanine C	Tripathi et al. (2001)
35.		Adouetine Z	Gournelis et al. (1998)
36.		Scutianine-A	Gournelis et al. (1998)
37.	Saponin	Jujubogenin-3-*O*-(di-deoxyhexosyl)-hexoside	Sakna et al. (2019)
38.		Jujuboside B1	Matsuda et al. (1999)
39.		Christinin A–D	Mahran et al. (1996)
40.		Christinin A1 and A2	Bozicevic et al. (2017)
41.		15-acetoxy lotoside IV	Bozicevic et al. (2017)
42.		Jujubasaponin II/III isomer	Yoshikawa et al. (1992)
43.		Jujubogenin	Kamil et al. (2000)
44.		Lotoside III	Bozicevic et al. (2017)
45.		Siconigenin-3-*O*-α-L-rhamnopyranosyl-(1 → 4)-α-L-rhamnopyranosyl-(1 → 2)-β-D-glucopyranoside	Bozicevic et al. (2017)
46.		Konarigenin-3-*O*-α-L-rhamnopyranosyl-(1 → 4)-α-L-rhamnopyranosyl-(1 → 2)-β-D-glucopyranoside	Bozicevic et al. (2017)
47.		Onigenin-3-*O*-α-L-rhamnopyranosyl-(1 → 4)-α-L-rhamnopyranosyl-(1 → 2)-β-D-glucopyranoside	Bozicevic et al. (2017)
48.	Triterpenic acid	Oleanonic acid	Guo et al. (2011)
49.		Ceanothic acid	Ikram and Tomlinson (1976)
50.		Alphitolic/maslinic acid	Bai et al. (2016)
51.		Zizyberanalic acid/pomonic acid	Guo et al. (2011)
52.		Ceanothic acid isomer	Guo et al. (2010) and Leal et al. (2010)
53.		3-*O*-*Z*-*p*-Coumaroylalphitolic acid/3-*O*-*Z*-*p*-coumaroylmaslinic acid	Guo et al. (2011)
54.		Betulinic acid	Ikram and Tomlinson (1976) and Ali et al. (1984)
55.		Ursolic acid	Ali et al. (1984)
56.	Fatty acid	Trihydroxy-octadecadienoic acid	Sakna et al. (2019)
57.		Dihydroxy dodecadienoic acid	Sakna et al. (2019)
58.		Trihydroxy-octadecenoic acid	Sakna et al. (2019)
59.		Amino-hexadecanediol	Sakna et al. (2019)
60.		Amino-methyl; heptadecanetriol	Sakna et al. (2019)
61.		2-Amino-1,3-octadecanediol	Sakna et al. (2019)
62.		Octadecatetraenoic acid	Sakna et al. (2019)

(continued)

Table 2.2 (continued)

S. no.	Chemical class	Name of chemical compound	Reference
63.		Myristic acid	Ali et al. (1984)
64.		Stearic acid	Ali et al. (1984)
65.		Oleic acid	Ali et al. (1984)
66.		Linoleic acid	Ali et al. (1984)
67.		Arachidic acid	Ali et al. (1984)
68.		Cetyl alcohol	Ali et al. (1984)
69.	Steroid/sterol	β-Sitosterol	Ali et al. (1984)
70.		Sitosterol β-D-glucoside	Weinges and Schick (1995)
71.	Sugar	Lactose, glucose, galactose, arabinose, sucrose, xylose, and rhamnose	Brantner and Males (1999) and Weinges and Schick (1995)
72.	Tannin	(+)-Gallocatechin (1.7%)	Weinges and Schick (1995)
73.		(−)-Epigallocatechin (0.9%)	Weinges and Schick (1995)
74.	Anthocyanidin	Dodecaacetylprodelphinidin B3	Weinges and Schick (1995)
75.		Polymers of prodelphinidins	Weinges and Schick (1995)

flavonoid content (145 mg/g) of dried extract of *ZSC* leaves is quite higher than the alkaloid (10.1 mg/g) or tannin contents (17.7 mg/g) (Khaleel 2018a). The traditional uses of leaves of *ZSC* could be attributed to the presence of large number of bioactive compounds. Several scientific studies have been conducted to validate the pharmacological properties of the characterized compounds in the leaves (Tanira et al. 1988; Glombitza et al. 1994). Christinin A, the principle saponin glycoside of leaves of *ZSC*, has been shown to exert hypoglycemic effect in diabetic rats (Glombitza et al. 1994). Presence of saponins in the leaves imparts good surface activity making it a good detergent even at low concentration. This justifies the folkloric use of aqueous extract of leaves as a natural shampoo in Oman and other gulf countries. A pure herbal shampoo formulated using aqueous *ZSC* leaves extract showed comparable results with the branded commercial shampoo available in the market in terms of cleansing, detergency, surface tension, bubble size, foam stability, % solid content, and conditioning performance (Al-Badi and Khan 2014).

Weinges and Schick detected dodecaacetylprodelphinidin B3, a proanthocyanidin from the dried leaves of *ZSC*. They also identified the presence of sugars [glucose (4.4%), sucrose (21%), oligomers and polymers of prodelphinidins (16%), betulinic acid (1.7%), sitosterol β-D-glucoside (2%), and tannins (+)-gallocatechin (1.7%) and (−)-epigallocatechin (0.9%)] in the butanol extract of the leaves (Weinges and Schick 1995). Bozicevic et al. (2017) characterized 10 dammarane-type saponins and 12 known phenolic compounds

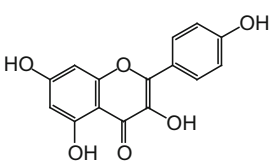
from the *ZSC* leaves. Eight saponins were isolated for the first time from *ZSC* leaves (Bozicevic et al. 2017). The list of chemical compounds isolated from the leaves of *ZSC* is presented in Table 2.2, and structures are given in Fig. 2.5.

2.3.3 Phytochemicals Isolated from the Stem, Root, and Barks of *ZSC*

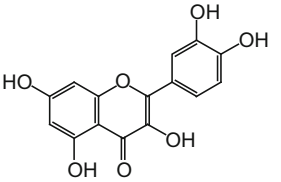
The phytochemical investigation of *ZSC* stem bark revealed the presence of a novel bioactive class of polyamidic compounds classified as cyclopeptide alkaloids (Tschesche et al. 1974; Shah et al. 1986; Abdel-Galil and El-Jissry 1991). Cyclopeptide alkaloids are made up of two parts, a 13-, 14-, or 15-membered macrocyclic ring and a side chain. Majority of these alkaloids contain a 14-membered ring, but few compounds with a 13-membered ring, e.g., amphibine-H, jubanine-A, and zizyphine-F belonging to zizyphine-A type, were also characterized. Cyclopeptide alkaloids with 14-membered rings are frangulanine-type compounds (with a β-hydroxyleucine moiety), amphibine-B/D/F-type compounds (with a β-hydroxyproline), and integerrine-type (with a β-hydroxyphenylalanine) moieties. Nummularine-D and Nummularine-E are examples of integerrine type of alkaloids. Occurrence of spinanine-A, B, and C, 14-membered cyclopeptide alkaloid of the amphibine-B type, has been reported in the bark (Tuenter et al. 2017a, b; Fathy et al. 1990). Some more cyclic peptide alkaloids such as franaganine, mauritine C, and sativanine A were also isolated from the stem bark of *ZSC* (Tschesche et al. 1974; Shah et al. 1986). Soliman et al. identified 13-dehydrobetulin [(EtOH) λ_{max} 210 nm)], a novel betulin derivative from *ZSC* stems (Soliman et al. 2019). Mohammed et al. demonstrated the anticholinergic properties of the ethanolic extracts of stem bark of *ZSC* and provided the scientific evidence that the plant's folkloric use as antispasmodic is partly or wholly due to the presence of bioactive cyclopeptide alkaloids (Mohammed et al. 2012).

A pentacyclic triterpene exhibiting antiplasmodial activity was isolated from the *ZSC* root bark. The bioactive compound was characterized as betulinic acid (also known as mairin) (Adzu et al. 2011).The organic extracts of various polarities of stem bark of *ZSC* have yielded betulin, hexadecanoic acid ethyl ester, and phytol in major amounts, while quercetin (0.46%), stigmasterol (0.65%), and α- sitosterol (0.68%) were detected in minor quantities (Ads et al. 2018). The bark contains condensed tannins (9.25%) as well as leucocyanidin (Singh et al. 1965). Free sugars such as fructose, glucose, raffinose, and sucrose have also been identified (Ghazanfar 1994a, b). Presence of epigallocatechin and gallocatechin in the *ZSC* stem extract is also documented (Kadioglu et al. 2016). Lupeol and betulinaldehyde, two lupane-type triterpenoids, and β-sitosterol, a sterol, were isolated for the first time from the root bark of *ZSC* grown in Sudan (Elnagar and Modawi 2016).

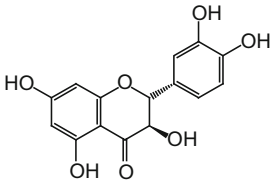
The ethanolic extract of *ZSC* roots furnished a flavonoid epicatechin which exhibited potent antioxidant and insecticidal activity (Elaoui et al. 2020). The chemical structures of some major phytochemicals isolated from the stem, root, and barks of *ZSC* are given in Fig. 2.6.



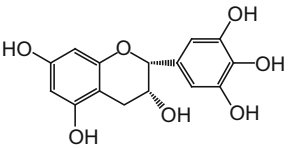
Kaempferol



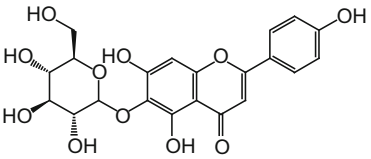
Quercetin



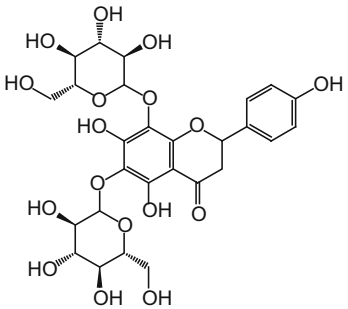
Taxifolin



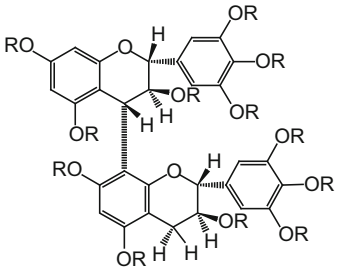
Epigallocatechin



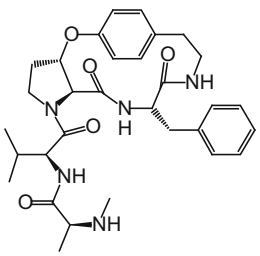
Apigenin-6- C-glucoside



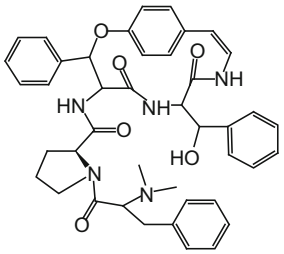
Naringenin 6,8 dihexoside



R=H=Procyanidine
R=$COCH_3$= decaacetylprocyanidine

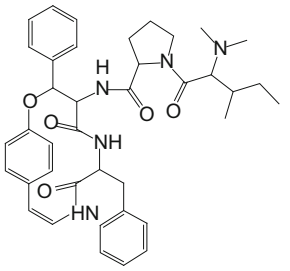


Mauritine F

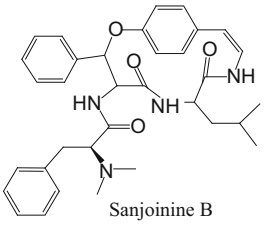


Oxyphylline A

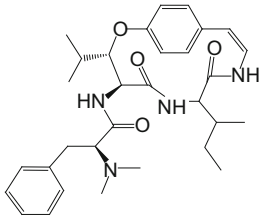
Fig. 2.5 Chemical structures of some important and major chemical constituents isolated from *ZSC* leaves



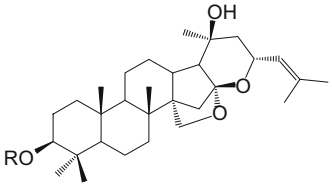
Jubanine C



Sanjoinine B

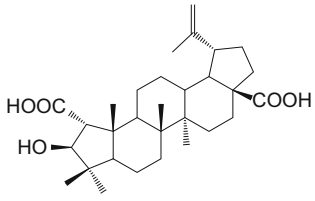


Lotusanine A

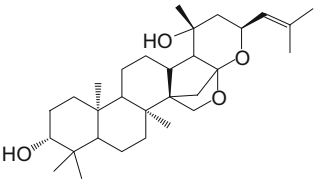


Christinin A R= [Fru-(1→2)]-[Glu-(13)]-Ara

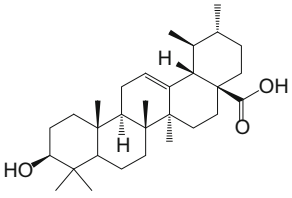
Christinin A R= [Glu-(1→2)]-[Rha-(13)]-Ara



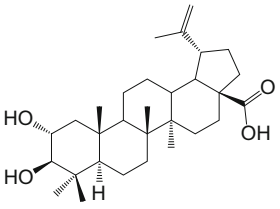
Ceanothic acid



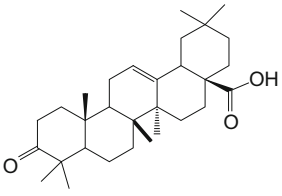
Jujubogenin



Ursolic acid



Alphitolic acid



Oleanonic acid

Fig. 2.5 (continued)

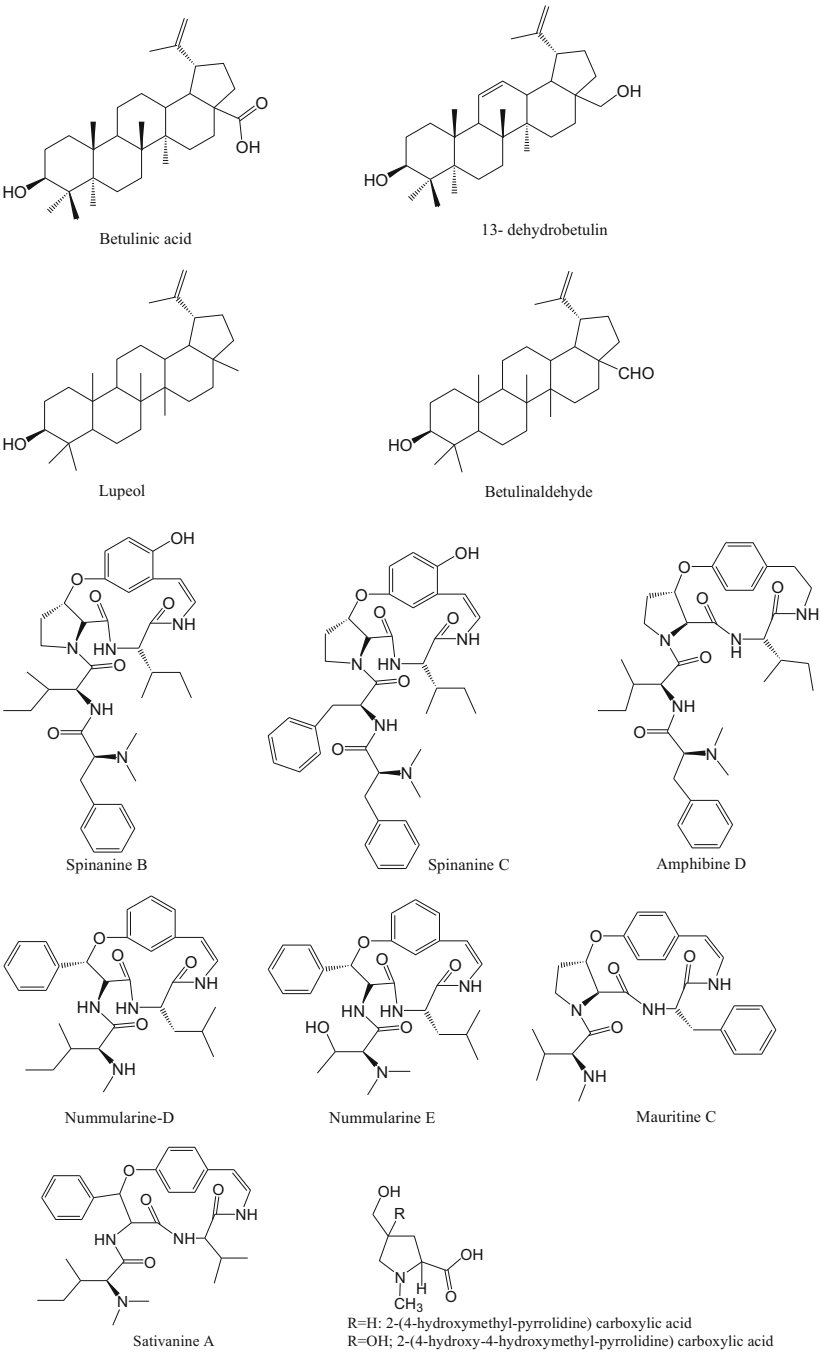


Fig. 2.6 Chemical structures of some important chemical constituents present in the *ZSC* stem, root, and bark

2.3.4 Phytochemicals Isolated from the Fruits of *ZSC*

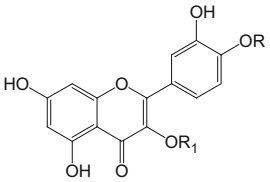
The edible part of *ZSC* fruits without seeds (pulp) is a good source of carbohydrates (85.69%). It contains free sugars [glucose (6.2%), rhamnose (2.6%), xylose (5.7%), and fructose (78%) of total sugars] and 7.5% of mucilage content making it a popular demulcent and emollient in the traditional medicine (Nazif 2002; Ads et al. 2017). Berry-Koch et al. reported that approximately 4.8 g protein, 0.9 g fat, 3.7 mg niacin, and 30 mg ascorbic are present in 100 g of the dried fruit pulp giving approximately 315 calories (Berry-Koch et al. 1990), while the content of protein and fat in Sudanese *ZSC* fruit pulp was found to be 4.56 and 1.17 g (Osman and Ahmed 2009).

Shahat et al. (2001) reported the isolation of the flavonoids quercetin, hyperoside, and rutin and a novel flavonol triglycoside quercetin-3-*O*-[β-xylosyl-(1 → 2)-α-rhamnoside] 4′-*O*-α- rhamnoside) from the ethylacetate fraction of the ethanolic extract of *ZSC* fruits (Shahat et al. 2001). The extract also exhibited significant antiviral activity against *Herpes simplex type 1* (HSV1). Pawlowska et al. (2009) isolated ten flavonoid glycosides of O and C types from the methanol extract of ripe edible fruits of *ZSC*. The glycosylated flavonoids were having quercetin and kaempferol aglycones connected to one, two, or three sugar moieties. One C-glycoside, 3′,5′-di-C-β-D-glucosylphloretin, was also detected by means of HPLC/ESI-MS analyses. The identified flavonoids include quercetin 3-*O*-robinobioside, quercetin 3-*O*-rutinoside, kaempferol 3-*O*-robinobioside, kaempferol 3-*O*-rutinoside, quercetin 3-*O*-α-L-arabinosyl-(1 → 2)-α-L-rhamnoside, quercetin 3-*O*-β-D-xylosyl-(1 → 2)-α-L-rhamnoside, quercetin 3-*O*-β-D-galactoside, quercetin 3-*O*-β-D-glucoside, and quercetin 3-*O*-β-D-xylosyl-(1 → 2)-α-L-rhamnoside-4′-*O*-α-L-rhamnoside (Pawlowska et al. 2009) (Fig. 2.7). Phenolic compounds such as *p*-hydroxybenzoic acid, tyrosol, vanillic acid, caffeic acid, gallic acid, *p*-coumaric acid, tannic acid, ferulic acid, etc. have been isolated from the fruits of *ZSC* (Amany et al. 2013).

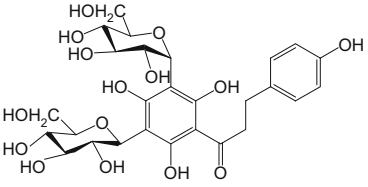
GC-MS analysis of nonpolar (n-hexane) extract of *ZSC* fruits led to the identification of 26 chemical compounds comprising of aromatic hydrocarbons and volatile compounds. The main aromatic hydrocarbons identified in the extracts were 6-phenyl-dodecane (14.90%); 6-phenyl-tridecane (11.38%); 2, 3, 4, and 5-phenyl-undecane (30.65%); and 2, 3, and 4-dodecane (15.67%). Some of the identified volatile constituents include m-cymene (1.95%), crypton (1.58%), α-pinene (1.20%), (+)-sabinene (1.11%), α-bergamotene (0.56%), and farnesan (0.47%) (El-Hefny et al. 2018).

2.3.5 Phytochemicals Isolated from the Seeds of *ZSC*

The total protein content and total lipid content of *ZSC* seeds were reported to be 15.9% and 2.3% of dry weight. Seeds showed the presence of 15 amino acids out of which 70% were non-essential and 17.1% semi-essential and essential amino acids made up only 12.8% of the total mixture (Hashem and Saleh 1999). Saponifiable fraction showed the presence of 13 fatty acids comprising of 83.5% unsaturated and



R	R_1	Chemical name
H	rha-(1→6)-gal	Quercetin 3-O-robinobioside
H	rha-(1→6)-glc	Quercetin 3-O-rutinoside
H	ara-(1→2)-rha	Quercetin 3-O-α-L-arabinosyl-(1→2)-α-L-rhamnoside
H	xyl-(1→2)-rha	Quercetin 3-O-β-D-xylosyl-(1→2)-α-L-rhamnoside
rha	xyl-(1→2)-rha	Quercetin 3-O-β-D-xylosyl-(1→2)-α-L-rhamnoside-4'-O-α-L-rhamnoside



3',5'-di-C-β-D-Glucosylphloretin

Fig. 2.7 Chemical structures of some major chemical constituents present in the *ZSC* fruits and seeds

16.5% saturated acids. Linoleic acid C18:2 (45%) and linolenic acid C18:3 (20.01%) were noted to be the major fatty acids. Hasham and Saleh suggested that the broad-spectrum antimicrobial activity of the plant extracts might be due to their high content of unsaturated fatty acids (Hashem and Saleh 1999). Unsaponifiable fraction contained a mixture of n-C12 to n-C30 hydrocarbons with hexacosane (n-C26) being the major component (12.9% of total unsaponifiable matter). Cholesterol and β-sitosterol were also detected in significant amounts of 21.7% and 27.1%, respectively (Nazif 2002).

Said et al. reported the isolation and characterization of two new cyclic amino acids, 4-hydroxymethyl-1-methyl pyrrolidine-2-carboxylic acid and 4-hydroxy-4-hydroxymethyl-1-methyl pyrrolidine-2-carboxylic acid (Said et al. 2010a, b), and three phenolic compounds (*p*-hydroxybenzoic acid, kaempferol, and rutin from the methanolic seeds extract of *ZSC* (Said et al. 2011). The HPLC-MS profiling of *ZSC* methanolic seed extract leads to the characterization of spinosin, 6‴ sinapoylspinosin, and 6‴ feruloylspinosin. These flavonoids have been known to act on the GABA and serotonin systems in CNS and produce anxiolytic, memory-ameliorating, and sleep-inducing effects. The flavonoids constituted 15.2%, 4.6%, and 9.7% of the total extract, respectively (Kadioglu et al. 2016; Wang et al. 2010; Liu et al. 2014). Proximate analysis of *ZSC* seed kernels (on dry weight basis) showed the presence of moisture (4.22%), crude protein (38.2%), crude fat

(30.19%), and carbohydrate (28.1%). The seed kernels were found to contain potassium (365.01 mg/100 g of dry sample), phosphorus (87.71 mg), sodium (24.96 mg), iron (4.21 mg), zinc (4.35 mg), copper (2.94 mg), and traces of manganese. The *ZSC* kernel oil contains 79.2% total unsaturated fatty acids and 20.8% total saturated fatty acids. Palmitic acid (C16:0) and stearic acid (C18:0) are two saturated fatty acids of the kernel oil, while oleic acid (C18:1) and linoleic acid (C18:2) are the unsaturated fatty acids which constitute 53.25 and 25.95% of the total fatty acids. The chemical composition of the seeds makes them a good source of edible oil with high nutritional value (Embaby and Mokhtar 2011).

2.4 In Vitro and In Vivo Pharmacological Uses

The dependence on nature to treat human diseases and disorders was established by observation as well as by trial and error method. Edible medicinal plants such as *ZSC* have an imperative role in retentive human health and longevity. *Ziziphus* species with enormous folklore claim are considered as a persuasive resource of therapeutic agents due the presence of a diverse range of pharmacologically active biomolecules. Scientific evidence reported on this plant divulge its valuable application in the field of pharmacy. The exploration of therapeutic potential of *ZSC* has revealed it to possess antimicrobial, anticancer, antidiabetic, antinociceptive, antihypertensive, antidiarrheal, and CNS effects (Fig. 2.8). It has been recommended that further investigations of their bioactive composition are essential to fully recognize the molecular mechanisms of their in vitro and in vivo therapeutic effect and to declare that the extracts are safe for human use. In this chapter, the experimental evidence of animal and human studies reported so far for the *ZSC* are described with the cynosure that the plant has been traditionally used to treat various diseases as mentioned in Table 2.3. In vitro and in vivo pharmacological activities of the *ZSC* studied for the treatment of different ailments and disorders are summarized as follows:

2.4.1 Antimicrobial Activity of *ZSC*

ZSC has been reported to contain a number of secondary plant metabolites that are primarily responsible for their broad spectrum of biological activity. *ZSC* has been shown to exhibit antimicrobial activity against bacteria, virus, and fungi in addition to its activity against other drug-resistant pathogenic species (Fig. 2.9) (Nazif 2002). Antibacterial effects of *ZSC* could be attributed to the presence of tannins (Elboosaty 2020). This is due to the fact that the tannins are associated with the protein, especially proline-rich proteins, and they bound to the iron, which contributes to the inhibition of the metabolism inside the microbe and helps to eliminate it (Michel et al. 2011). Saponin content of *ZSC* also plays a major role in manipulating the surface tension of the cell membranes, which leads to increasing the permeability of cells and hence could produce bactericidal effect (Arabski et al. 2012; Huang et al.

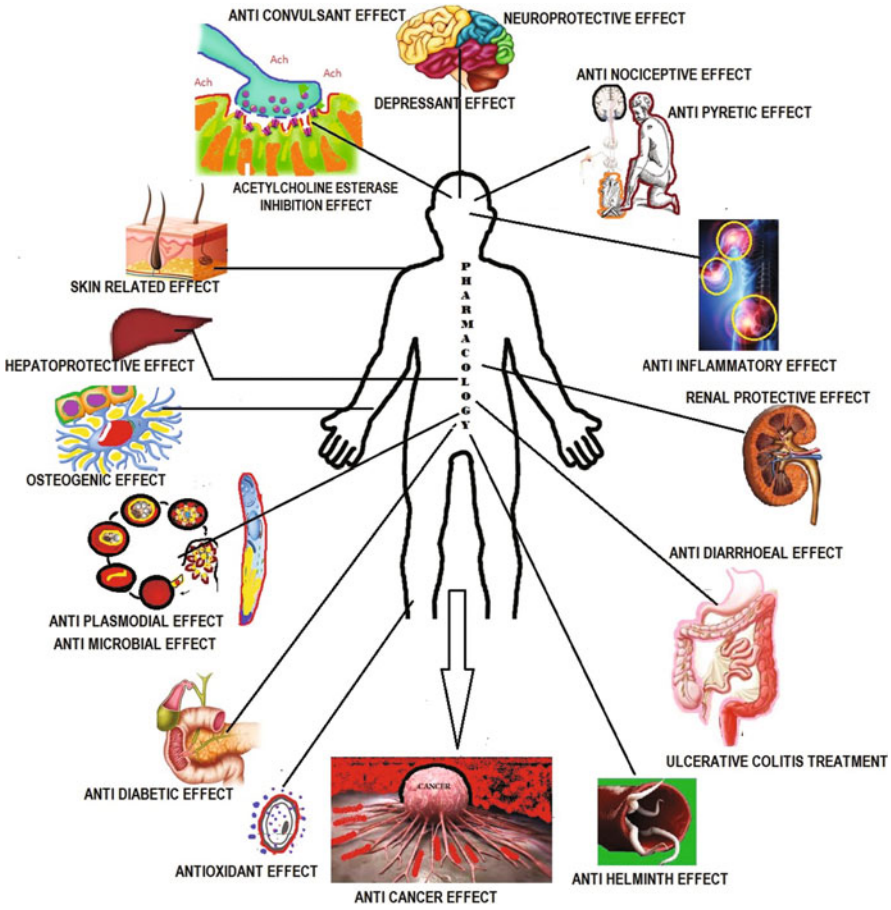


Fig. 2.8 In vitro and in vivo pharmacological effects of *Ziziphus spina-christi*

2018). The cyclopeptide alkaloids have the ability to inhibit the cell division/multiplication in microbes by binding to microbial DNA. Flavonoids could also be responsible for the antimicrobial activity as these can bind to DNA and RNA, thereby inhibiting protein and fat formation, causing energy metabolism to be impaired, thereby affecting the growth of the microbe (Panche et al. 2016). The details of the reported scientific evidences on the antibacterial, antifungal, and antiviral properties of various parts of *ZSC* are given in Table 2.3.

Table 2.3 Evaluation reports of antibacterial, antifungal, and antiviral activity of various parts of *ZSC*

Plant parts	Extract	Method	Organism tested	Standard	Notable results	Evidence reported
Antibacterial activity reports						
Stem bark	Ethanol, ethyl acetate, alkaline ethyl acetate	Agar well diffusion	*S. pneumoniae*, *B. subtilis*, *P. aeroginosa*, *E. coli*	Amphotericin B, ampicillin, gentamicin	Ethyl acetate extract is more effective	Ads et al. (2017)
Fresh fruit/ Fruit oil	n-hexane	Disc diffusion	Phytopathogenic bacteria: *P. carotovorum*, *D. solani*, *R. solanacearum*, *E. cloacae*, *B. pumilus*	Gentamicin 20 µg/disk	Different levels of activities	El-Hefny et al. (2018)
Leaf, Fruit	Aqueous, methanol	Agar well diffusion	*B. subtilis*, *B. aquimaris*, *C. michiganensis*, *E. coli*, *E. amylovora*, *P. syringae*	Ampicillin 50 mg/mL	Activity only against gram-positive bacteria	Mohamed et al. (2017)
Leaf, Stem bark, Leaf+ stem bark	Aqueous	Well diffusion	*K. pneumoniae*, *S. saprophyticus*, *S. pneumonia*, *Acinetobacter* spp., *E. coli*, *Serratia* spp., *S. typhi*, *P. aeroginosa*, *S. epiderdimis*, *S. pyogenes*, *S. aureus*, *Proteus mirabilis*, *Enterobacter* spp.	None reported	Organisms highly sensitive to combination of leaves and stem bark extract	Jebur et al. (2020)
Leaf	Aqueous, ethanol	Agar well diffusion	Hospital sample isolates: *B subtilis*, *E. coli*	None reported	Ethanol extract is more effective	Ebid (2015)
Fruit, leaf, seed, stem	Petroleum ether, chloroform, methanol, aqueous	Cup plate agar diffusion	*B. subtilis*, *S. aureus*, *E. coli*, *K. pneumoniae*,	Ampicillin, gentamicin, tetracyclin, 5–40 µg/mL	Methanol extracts of all parts are effective against the tested organism and	Ali et al. (2015)

			P. vulgaris, *P. aeruginosa*		aqueous extract was inactive	
Leaf, fruit, seed	Petroleum ether, chloroform, ethanol, water extracts and fractions	Microtitre plate dilution	*B. cereus*, *S. aureus*, *S. pyogenes*, *E. coli*, *E. cloacae*, *K. pneumoniae*, *P. vulgaris*, *P. aeruginosa*, *S. typhimurium*, *acid-fast bacilli M. fortuitum*	None reported	Chloroform extract of leaf and seed showed inhibitory and bactericidal activity against gram-positive microorganisms	Shahat et al. (2001)
Fruit-seed	Lipid content of seeds—its saponifiable and unsaponifiable fraction	Diffusion assay method	*B. subtilis*, *S. pyogenes*, *E. coli*, *S. cereviciae*	Ampicillin	Fatty acid fraction of lipids of seeds was active against *B. subtilis*, *E. coli*, *S. pyogenes*	Nazif (2002)
Leaf, Bark	Methanol	Cup plate agar diffusion	*E. coli*, *S. aureus*, *K. pneumonia*	None reported	Effective against *S. aureus* and *K. pneumoniae*	Mohamed et al. (2010)
Fruit-seed oil	Oil extract	Agar well diffusion	*Shigella* spp., *S. aureus*, *P. aeruginosa*, *E. coli*	Chloramphenicol 30 mg	Seed oil is active against *S. aureus* and *E. coli*	Bukar et al. (2015)
Bark, fruit, root, seed, leaf	Methanol, ethanol	Agar well diffusion	*P. aeruginosa*, *E. aerogenes*, *E. coli*, *K. pneumoniae*, *E. cloacae*, *E. faecalis*, *MRSA*	Erythromycin 50 mg/mL	*E. coli* and *MRSA* were moderately sensitive to extracts and resistant to erythromycin	Temerk et al. (2017)
Leaf	Aqueous, ethanol	Disk diffusion	*E. coli*, *S. aureus*, *K. pneumoniae*	Chloramphenicol 250 mg/mL	Highly effective against *E. coli*	Alhassan et al. (2019)
Stem bark	Petroleum ether, ethyl acetate, ethanol, methanol aqueous	Cup plate agar diffusion	*E. coli*, *P. aeruginosa*, *B. subtilis*, *S. aureus*	None reported	Methanol extract showed high activity at all concentrations	Makhawi et al. (2020)

(continued)

Table 2.3 (continued)

Plant parts	Extract	Method	Organism tested	Standard	Notable results	Evidence reported
Fruit	Ethanol, ethyl acetate	Modified agar diffusion	*S. aureus*, *E. coli*, *P. aeruginosa*, *S. aureus*, *E. faecalis*, *E. coli*, *E. faecalis*, *P. aeruginosa*	Ampicillin, gentamycin 10 μg/disk	Ethyl acetate extract was most active	Ali et al. (2001)
Leaf, seed	Aqueous, methanolic	Agar well diffusion	*Isolated from skin lesions: S. aureus*, *P. aeruginosa*, *E. coli*, *Acinetobacter* spp., *Enterococcus* spp.	Tetracyclin 30 mg	Aqueous leaves extract was effective against *S. aureus*	Al-Bayatti et al. (2011)
Leaf, fruit	Aqueous extracts	Agar diffusion	*S. aureus isolated from burn cases*	Penillin G, kanamycin, cephalexin, tetracyclin, neomycin, genetamicin, fusidic acid, tobramycin	Effective bacteriostatic action on *S. aureus* (750 and 1000 mg/mL)	Alsaimary (2009)
Leaf, flower, stem, young branch, fruit, root	Ethanol, aqueous	Disk diffusion	*S. aureus*, *K. pneumoniae*, *P. vulgaris*, *P. aeruginosa*, *E. coli*	Ampicillin, penicillin G, gentamicin	Ethanol extract has moderate effect on gram-negative bacilli	Ali-Shtayeh et al. (1998)
Leaf	Ethanol	Disk diffusion	Isolated from infected patient's urine, stool, blood and wounds: *S. aureus*, *Methicillin- and cefixime-resistant S. aureus strains*	None reported	Effective towards *MRSA* strains	Moghadam et al. (2010)
Leaf	Ethanol, methanol	Disk diffusion	*S. typhi*, *P. mirabilis*, *S. dysenteriae*, *E. coli*, *K. pneumoniae*,	Novobiocin Naficillin Colistin	Ethyl acetate extract was most active	Motamedi et al. (2014)

			B. melitensis, *B. bronshiseptica*, *P. aeruginosa*			
Stem bark Leaf	Ethanol, petroleum ether, ethyl acetate, aqueous, methanol	Agar well diffusion	*S. aureus*, *B. subtilis*, *E. coli*, *P. vulgaris*, *P. aeruginosa*, *S. paratyphi B*, *K. pneumoniae*	Gentamicin, tetracycline, ampicillin 40 mg/mL to 5 mg/mL	Ethanol extract was effective against all tested bacteria except *E. coli*	El-Kamali and Mahjoub (2009)
Leaf	Ethanol, methanol	Disk diffusion	*S. aureus*, *E. coli*, *K. pneumoniae*, *Salmonella* sp., *P. mirabilis*, *P. aeruginosa*, *Enterobacter* sp.	Amikacin, vancomycin, clarimazole, doxycycline, ceftazidime, neomycin, novobiocin	Extracts showed a stronger effect than standard antibiotic disks	Al-Mutairi et al. (2016)
Fruit	Methanol	Agar well diffusion	*S. aureus*, *S. epidermidis*, *E. faecalis*, *B. cereus*, *K. pneumonia*, *E. coli*	Chloramphenicol 5 mg/mL)	Moderate activity against the gram-positive bacteria	Abdallah (2017)
Pulp	Aqueous	Agar plate diffusion	*S. aureus*, *P. aeruginosa*, *S. pyogenes*, *E. coli* laboratory isolates	None reported	Effective against *E. coli* and *P. aeruginosa*	Tom et al. (2009)
Stem bark	Ethanol, chloroform, petroleum ether, ethyl acetate, butanol	Disk diffusion	*E. coli*, *P. aeruginosa*, *Bacillus* spp., *S. aureus*	None reported	Ethanol extract of bark showed bactericidal and bacteriostatic activity against all organisms	Alomari et al. (2017)
Leaf	Methanol, water	Agar diffusion	*B. subtilis*, *B. aquimaris*, *C. michiganensis*, *E. coli*, *E. amylovora*, *P. syringae*	Kanamycin for *B. subtilis* and *B. aquimaris*; ampicillin for *E. coli* and *E. amylovora*	Methanol extract was more effective against gram-negative bacteria when compared to the aqueous extract	Mohamed et al. (2017)

(continued)

Table 2.3 (continued)

Plant parts	Extract	Method	Organism tested	Standard	Notable results	Evidence reported
Leaf, bark	Dichloromethane, ethyl acetate, ethanol	Micro-dilution	*B. subtilis*, *S. aureus*, *E. coli*, *K. pneumoniae*	Neomycin	Weak antibacterial activity	Eldeen and Van Staden (2007)
Honey	Fresh samples	Well diffusion	*B. cereus*, *S. aureus*, *E. coli*, *S. enteritidis*	Tetracycline chloramphenicol	Effective bactericidal	Owayss et al. (2020)
Antifungal activity reports						
Unripe and ripe fruit	Ethanol	CLSI M27-A3 standard method	Isolated from the oral cavity of the liver transplant patients*:* *C. albicans*, *C. glabrata*	Nystatin, fluconazole	Unripe fruits was more effective than fluconazole	Mardani et al. (2018)
Leaf	Aqueous	Agar dilution	*Fusarium* sp., *Alternaria* spp., *Trichoderma* sp., *Colletotrichum* sp., *Drechslera* sp., *Fusariumoxysporum*, *Helminthosporium* sp., *Rhizoctonia solani*, *Macrophomina phaseolina*, *R. solani*	None reported	Significant activity against the growth of overall tested fungal genera	Alotibi et al. (2020)
Fruits, leaf, seed, stem	Petroleum ether, chloroform, methanol, aqueous	Cup plate agar diffusion	*A. niger*, *C. albicans*	Clotrimazole, nystatin	Not effective	Ali et al. (2015)
Leaf, flower, stem, young branch, fruit, root	Ethanol, aqueous	Disk diffusion	*C. albicans*	Nystatin	Not effective	Ali-Shtayeh et al. (1998)

Fruits	Aqueous extract	Agar disk diffusion method	*C. albicans*	Amphotericin B (5 mg/mL)	Extract showed promising anti-Candida activity	Pibalouti et al. (2009)
Leaf, fruit, seed	Petroleum ether, chloroform, ethanol, water	Microtitre agar plate	*C. albicans*, *A. niger*, *T. rubrum*	None reported	Chloroform leaves extract was moderately effective against the *T. rubrum*	Shahat et al. (2001)
Stem bark	Ethanol Ethyl acetate	Agar well diffusion assay	*A. fumigatus*, *S. racemosum*, *G. candidum*, *C. albicans*	Amphotericin B	AEA extract was effective against *A. fumigatus*, *S. racemosum*	Ads et al. (2017)
Pulp	Aqueous	Agar plate diffusion	*C. albicans*	None reported	Extract was effective	Tom et al. (2009)
Stem bark	Ethanol, petroleum ether, chloroform, ethyl acetate, butanol	Disk diffusion	*C. albicans*	None reported	Ethanol extract of bark was mildly effective	Alomari et al. (2017)
Fruit-seed	Lipid content of seeds—its saponifiable and unsaponifiable fraction	Diffusion assay method	*A. niger*, *A. flavus*	Canesten	Slight activity	Nazif (2002)
Antiviral activity reports						
Leaf, fruit, seed	Petroleum ether, chloroform, ethanol, aqueous	Host cell monolayer (Vero cells) infected with tested virus is used	*Herpes simplex type 1 (HSV1), measles Edmondston A (MEA), poliomyelitis virus type 1 (polio 1), vesicular stomatitis virus (VSV)*	None reported	Ethanol fraction of the fruits and the aqueous extract of the leaves were effective against *HSV1*	Shahat et al. (2001)
Leaf, bark	Methanol	Cup plate agar diffusion	*New castle disease, fowlpox viruses*	None reported	Extract showed mild antiviral activity	Mohamed et al. (2010)

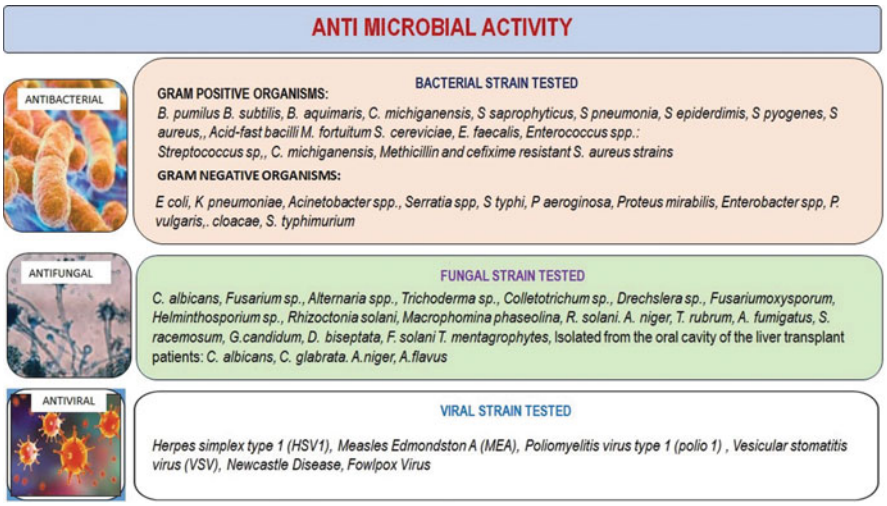


Fig. 2.9 Microbial strains used for the study of antimicrobial effects of *ZSC*

2.4.2 Antioxidant Activity of *ZSC*

In vitro antioxidant activity of *ZSC* fruits, leaf, bark, and seeds has been assessed using a variety of assay methods (Fig. 2.10), and the results indicate that *ZSC* exhibits robust free radical scavenging activity.

ZSC fruits (429 μg/mL) grown in Oman showed 91% inhibition in the ABTS method, 51% inhibition (at 140 mg/mL) of DPPH radical scavenging, and 47% of inhibition in the SRSA assay (at 20 μg/mL). The *ZSC*F extract could chelate ferrozine and form complexes with ferrous ions (Singh et al. 2012). The ethanolic extract of the dry seeds and fruit powder of *ZSC* grown in Oman showed DPPH scavenging activity in a dose-dependent manner, in which fruit extract exhibited (54.1%) inhibition at 200 μg/mL whereas seed extract showed only 42.6% inhibition at the same concentration. Contrary, *ZSC* seeds were found to contain the highest total phenolic content (Al Hakmani et al. 2014). Methanolic leaves extracts of five *ZSC* provenances (INRGREF, Tozeur, Degueche, Nafta, and Kebelli) showed that the Kebelli provenance *ZSC* has high antioxidant activity (0.086 μg/mL) in a DPPH assay (Elaloui et al. 2017). Methanolic extracts of *ZSC* leaves proved to have the highest phenolic content along with antioxidant activities (93.6%) with respect to standard ascorbic acid (87.4%) (Tawfik et al. 2015). Various concentrations of methanolic, aqueous, and ethanolic extracts of the *ZSC* leaves in the DPPH and reducing power assay methods revealed to possess concentration-dependent antioxidant activity with IC_{50} values of 21.4 and 24.2 μg/mL (Khaleel et al. 2016). Radical scavenging activity of ethanolic leaves extract is better than the hexane extracts (Abalaka et al. 2011). The ethyl acetate fraction of leaves extract exhibited higher inhibition of DPPH radical (96%) in comparison to the standard butylated hydroxyl anisole, n-butanol, and aqueous extracts. The total antioxidant activities of methanol,

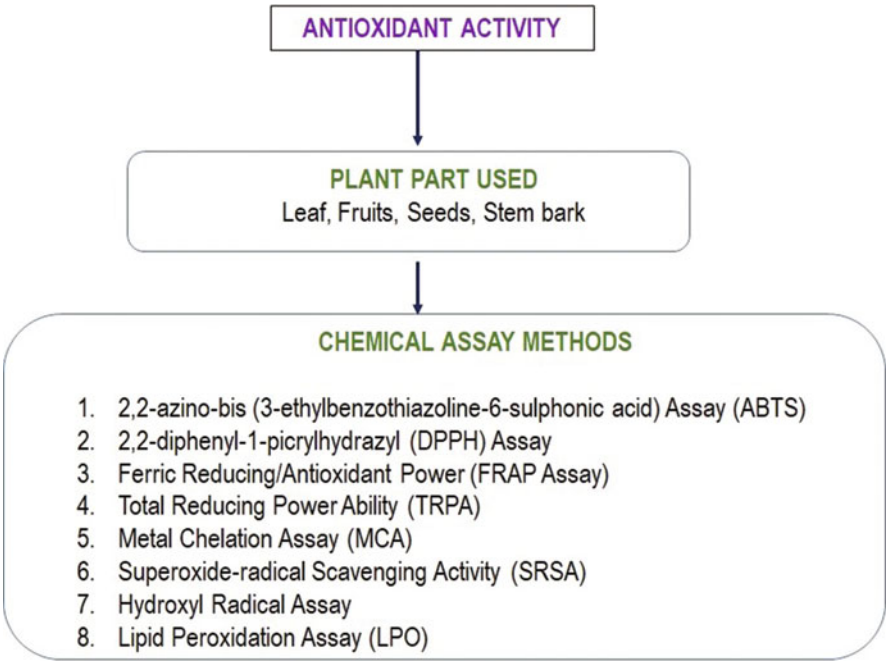


Fig. 2.10 Chemical assay methods and plant parts used for the determination of antioxidant activity of *ZSC*

ethanol, ethyl acetate, and aqueous extract range from 70.5 to 91.2% inhibition in the ABTS assay method (Al-Ghamdi and Shahat 2017). The total alcoholic extract of the plant leaves and stem bark has shown significant antioxidant effect (Adzu et al. 2003; Mohamed et al. 2017). Crude juices of Sidr (*ZSC*) leaves reported to exert effective antioxidant capacity by DPPH free radical scavenging method. It was reported that the administration of Sidr juice (leaves) did not cause any changes in liver and kidney functions proving their antioxidant ability in vivo (Al-Marzooq 2014). *n*-Butanol extracts of leaves of Omani *ZSC* have also been shown to exhibit antioxidant activity and radical scavenging activity (Al-Busafi et al. 2007). In general, the variation in the activity and chemical constituents like mineral level, polyphenolic content, and antioxidant capacity could be due to the difference in *Ziziphus* species, part of the plant analyzed, and its vegetation region (El-Maaiden et al. 2020).

2.4.3 Antipyretic Effect of *ZSC*

Traditional claim postulates that *ZSC* have antipyretic effect (Table 2.1), but the literature survey revealed only one study for evaluation of antipyretic activity has been carried out so far and the reason behind this is unknown. Tanira et al. (1988)

reported that the ethanolic extract of *ZSC* leaves exhibited a significant, though a moderate, antipyretic effect on hyperpyrexia-induced mice and are supporting the traditional claim (Tanira et al. 1988).

2.4.4 Antidiuretic Activity of *ZSC*

Diuretic activity of ethanolic extract of *ZSC* leaves in rats (500 mg/kg) was reported. Sodium and potassium content of the urine was determined using flame photometry to investigate the effect, but the extract failed to demonstrate any promising effect (Tanira et al. 1988). No other studies were undertaken to determine the antidiuretic activity of the *ZSC* plant extracts.

2.4.5 Anticancer Activity of *ZSC*

Therapeutic application of plant products in the management of cancer has gained a prominent role in medical field. The anticancer properties of *Ziziphus* plant has been believed by the people from different regions especially from China, Iran, and Arabia (Bown 1995; Vahedi et al. 2008; Deshpande et al. 2019). The honey of *ZSC* is considered as an alternative cytotoxic agent and was administered to patients suffering from different types of cancers including colon, breast, and liver cancers (El-Gendy 2010). The leaves extracts of *ZSC* have prominent cytotoxic activity against cancers of the cervix and the breast, and the aqueous fruit extract is effective against breast cancer (Jafarian et al. 2014; Farmani et al. 2016). Cytotoxic activity of *ZSC* leaves extract was explored scientifically, but it was not compared with any other plant parts of *ZSC*; however, variable cytotoxic activities may be attributed to different parts of the plant like fruits, seeds, and stem (Soliman et al. 2019). Pharmacological activity index and phytoconstituents of the same plant vary depending on the environmental climates and in turn may lead to genetic and chemical variations among individuals of the same species (Moustafa et al. 2016).

Fractions of different parts of the *ZSC* grown in the unique environmental conditions of UAE were tested against several cancer cell lines. The results indicated that the ethanolic extract of stem exhibited superior anticancer activity than that of the leaves and thorns. The stem extract showed potent and specific effect on HEPG2 cancer cells with a survival rate of 5% compared to 8%, 19.5%, and 21% survival rates for A549, MDA, and U87cells, respectively, and traditional claim of *Ziziphus* spp. as an alternative anticancer agent could be attributed to the presence of betulin derivatives (Soliman et al. 2019). The ethanolic fraction of leaves extract had the lowest IC_{50} value (0.02 mg/mL) and induced cell cycle arrest at the G1/S phase as well as apoptosis against MCF-7 (human breast adenocarcinoma) cell lines. The most active fraction of *ZSC* against breast cancer cell line was identified by fractionation strategy, and the results demonstrated that apoptosis induction mechanism is through a mitochondrial-independent pathway. Among all the fractions tested for cytotoxic effects in MCF-7 cells, ethanolic fraction was found to be highly active

with an IC_{50} of 0.02 mg/mL after 48 h of incubation at ½ IC_{50} concentration (Farmani et al. 2016). It has been established previously that induction of apoptosis is one of the mechanisms for the anticancer activities of *ZSC* extracts in different cancer cell lines (Huang et al. 2007). *ZSC* leaves extracts exhibit its cytotoxic effect through Bax-independent apoptotic pathway on MCF-7 cells (Ghaffari et al. 2020). The methanolic extract of the leaves of *ZSC* exhibited anticancer effect against diethylnitrosamine (DENA)-persuaded hepatocarcinoma in rats and is quantified through the expression of hepatocyte growth factor, insulin-like growth factor-1 receptor, B cell lymphoma-2, and matrix metalloproteinase-9 oncogenes (El-Din et al. 2019). It has also been reported that the dried *Ziziphus* plant has anticancer activity (Bown 1995; Vahedi et al. 2008). *ZSC* exhibits proapoptotic mechanism and is evident by the increased levels of cleaved caspase-3. An in vivo study concluded that *ZSC* extract could inhibit the early stage of colon carcinogenesis by preventing oxidative stress and inducing apoptosis (Guizani et al. 2013). The protective effects of *ZSC* fruit extract against 1-methyl-4-phenylpyridinium (MPP^+)-induced neurotoxicity in SH-SY5Y cell lines depict that protective effect of ZSC fruits might be mediated by its potent antioxidant properties (Singh et al. 2018). While discussing the reported anticancer activity, it has been observed that only tumor cell lines were used to evaluate the cytotoxic effects of *ZSC* extracts and the in vivo preclinical evaluations are very minimal. No clinical trials have been conducted in humans to examine the pharmacokinetics and therapeutic action of these compounds and extracts on cancer patients. Future research should emphasize on in vivo preclinical studies and clinical trials (Ghaffari et al. 2020).

2.4.6 Acetylcholinesterase Inhibitory Effect of *ZSC*

ZSC bark, leaves, and root showed inhibition effect on acetylcholinesterase enzyme by Ellman's method, and it sturdily supports further investigation into pharmacotherapeutics (Eldeen and Van Staden 2007). As per the traditional claim (Table 2.1), it has been apparent that *ZSC* possess pharmacological action related to nervous system, but till date the scientific evaluation regarding the cholinesterase inhibition effect is scarce. Dichloromethane, ethyl acetate, and ethanol extracts of *ZSC* plant parts were investigated for acetylcholinesterase inhibition effect. Moderate inhibitory activity is exhibited by dichloromethane and ethyl acetate (leaf and bark) extracts of *ZSC* (range of IC_{50} value was 1.0–0.3 mg/mL). The lowest IC_{50} value was detected with ethanolic extracts of the bark and root of *ZSC* (0.09 mg/mL) (Eldeen and Van Staden 2007).

2.4.7 Antidiabetic Activity of *ZSC*

ZSC is reported traditionally as a versatile hypoglycemic agent. Researches indicated that aqueous extract of plant decreases the level of blood glucose by two mechanisms by acting on glucose homeostasis in an extra-pancreatic way or by

improvement of liver action in diabetic rats. Saponin glycosides present in this plant are responsible for lowering level of glucagon (Elboosaty 2020; Deshpande et al. 2019). The hypoglycemic and antidiabetic activities of methanol extract (*ZSC*-1) as well as ethyl acetate (*ZSC*-2), n-butanol (*ZSC*-3), and aqueous (*ZSC*-4) fractions of *ZSC* leaves were evaluated in diabetic mice and compared with glibenclamide, and it was observed that fraction *ZSC*-3 displayed potential hypoglycemic activity (Al-Ghamdi and Shahat 2017). Effects of butanol extract of *ZSC* leaves and its principle saponin glycoside christinin A were evaluated in normal and streptozotocin diabetic rats. It has been reported that after 4 weeks of treatment, both the agents significantly reduced the level of serum glucose and activity of liver phosphorylase and glucose-6-phosphatase (G-6-Pase). Serum insulin and pancreatic cAMP levels also showed a significant increase with the butanol extract-treated diabetic rats (Glombitza et al. 1994). Avizeh et al. (2010) reported that the hydroalcoholic extract (500 mg/kg) of *ZSC* fruit had a mild, but significant, blood glucose-lowering effect after 10 days of oral administration to diabetic rats, and it also showed a simultaneous increase in the serum insulin level. Hence the long-term use of this agent may be advantageous over conventional drugs in relieving some of the complications caused by diabetes (Avizeh et al. 2010). Polysaccharides from *Ziziphus* spp. significantly lowered the levels of LDL cholesterol, triglycerides, total cholesterol, and very-low-density lipoprotein (VLDL) cholesterol and evidently increase the high-density lipoprotein (HDL) cholesterol levels in a fructose-induced animal model of diabetes (Zheng et al. 2019; Pandey et al. 2011). The antidiabetic effects of fruit extracts of *ZSC* in alloxan-induced diabetic rats showed a dose-dependent positive effect (Abubakar et al. 2018). In vitro α-glucosidase and α-amylase inhibitory activities for different concentrations of methanolic and ethanolic leaves extracts of *ZSC* were reported. Methanolic extract seems to be very potent in inhibiting both enzymes compared to ethanolic extract. The calculated IC_{50} was 8.9 and 305.6 μg/mL against α-glucosidase and 39.12 and 318.4 μg/mL against α-amylase for methanolic and ethanolic leaves extracts, respectively (Khaleel 2018b). Leaves of Christ's thorn are reported to possess antihyperglycemic activity, and triterpenoidal saponin glycosides, christinin A, B, C, and D, isolated from the butanol extract play a major role in the therapeutic activity of the plant (Mahran et al. 1996).

Butanol extract of *ZSC* leaves decreased the serum glucose level in control as well as in type-II diabetic rats. This antidiabetic response was arbitrated by releasing insulin, and this insulin tropic effect of *ZSC* leaves might be due to blockade of K-ATP channels of the pancreatic beta-cell membranes (Abdel-Zaher et al. 2005). Administration of 100 mg/kg *ZSC* leaves extract greatly ameliorated the diabetic disorders in rats (Parsaeyan and Rezwani 2014). Administration of *ZSC* ethanolic leaves extract (200 mg/kg b.w.) and plain and formulated soft gelatin capsules (450 mg) for 28 days in STZ diabetic rats revealed better glucose utilization by increasing insulin secretion and C-peptide levels with stabilization of percentage of glycated hemoglobin (HbA1C%) (Michel et al. 2011). It has been reported that pretreatment either with 100 mg/kg butanol extract or christinin A improved glucose-induced insulin release in non-diabetic control rats. Pretreatment with the

butanol extract or christinin A improved the oral glucose tolerance in type-II model; however there was no response in type-I diabetic rats (Abdel-Zaher et al. 2005).

2.4.8 Antidiarrheal Activity of *ZSC*

The fruits of *ZSC* administered in an adequate amount act as a laxative and decrease water maintenance, and the leaves have the ability to kill diarrhea-causing parasites and worms in the intestinal tract (Saied et al. 2008; Jongbloed 2003). In Sudan, *ZSC* root infusion is administered for the treatment of dysentery (El Ghazali et al. 1997). A preclinical study reported that methanol extract of *ZSC* of the stem bark possess antidiarrheal effect (Adzu et al. 2003). The accumulation of intraluminal fluid and gastrointestinal transit time were measured, and it was shown that the extract caused a dose-dependent protection of rats against castor oil-induced diarrhea and showed a prominent decrease in the intraluminal fluid accumulation and gastrointestinal transit time. Biologically active components like glycosides, resins, saponins, and tannins in *ZSC* extract may be useful against diarrhea, thereby vindicating its use in traditional practice as an antidiarrheal agent (Adzu et al. 2003, 2007a, b).

2.4.9 Anti-Inflammatory Activity of *ZSC*

ZSC is commonly used in traditional medicine across the gulf region for the management of pain and inflammatory-related problems (Asgarpanah and Haghighat 2012; Waggas and Al-Hasani 2009). The anti-inflammatory effects of fruits, seeds, and leaves of *ZSC* extracts were reported. The alcoholic extract of *ZSC* leaves reported a highly significant anti-inflammatory activity ($p < 0.05$), and the maximum effect (38%) was at 3 h, whereas the standard oxyphenbutazone showed much more significant reduction (65%) (Tanira et al. 1988). Anti-inflammatory activity of *ZSC* fruit/seed extracts was evaluated by an in vitro pilot study. The seed extract showed a significant difference in the inhibition of thermally induced protein denaturation when compared with fruit extract at concentrations of 100 and 500 μg/mL (Al Hakmani et al. 2014). Anti-inflammatory activity of methanolic extract against acetic acid (AcOH)-induced colitis in rats was reported. Administration of extract (400 mg/kg) resulted in a better reduction of inflammatory colonic injury than standard drug mesalazine (MLZ). Moreover, it effectively moderated the mRNA expression of redox-sensitive transcription factors like nuclear factor (erythroid-derived 2) and heme oxygenase-1 and also downregulated the expression of p38 mitogen-activated protein kinase and upregulated the vascular endothelial growth factor A and interleukin-1β in AcOH-induced colitis in rats. Hence, it could be considered as an alternative therapeutic option for the management of inflammatory bowel diseases (Almeer et al. 2018). Methanolic extract of *ZSC* leaves seems to be a strong potent in both enzymes inhibitory potential compared to ethanolic extract. At the concentration of 100 μg/mL, the anti-inflammatory effects were

95.3, 25.2, and 20.2% for methanolic extract, ethanolic extract, and standard diclofenac sodium, respectively (Khaleel 2018b).

New anti-inflammatory compounds from *ZSC* have been identified from ancient Egyptian prescriptions such as epigallocatechin, gallocatechin, spinosin, 6″' feruloylspinosin, and 6′" sinapoylspinosin which are crucial for pharmacological activity of crude extracts of seed, leaf, root, or stem playing a major role in the inhibition of NF-κB pathway (Kadioglu et al. 2016). *Ziziphus* species extract sharply increased the homeostasis model assessment of insulin resistance (HOMA-IR) and β-cell function (HOMA-β) and reduced the atherogenic index (AI) in mice exposed to high fructose water (Zheng et al. 2019). Sepsis induced by cecal ligation and puncture in mice was treated with *ZSC* leaves extract, and it exerted a myocardial and renal protective effect. Prophylactic treatment with *ZSC* leaves extract (100, 200, and 300 mg/kg) maintains the normal heart rate (HR); decreased the elevated levels of malondialdehyde; the activity of myeloperoxidase, nitric oxide (NO), and inducible NO synthase; and the expression of nuclear factor kappa B (NF-κB); but increased the content of glutathione and antioxidant enzyme activities in mice with sepsis. Lower levels of cytokines, including TNF-α and interleukin (IL)-1β, were evident from biochemical analyses, and qRT-PCR indicated that *ZSC* leaves extract treatment reduced myocardial and renal apoptosis. This effect may be attributed to the antioxidant, anti-inflammatory, and antiapoptotic activities of *ZSC* leaves extract (Dkhil et al. 2018a, b).

2.4.10 CNS-Related Activity of *ZSC*

ZSC possess anticonvulsant, neuroprotection, and CNS depression activity. The genus *Ziziphus* is proved to be effective on CNS (Kaleem et al. 2014). Anticonvulsant activity of *ZSC* extract is through the inhibition of the neurotransmitters at different brain regions. Intraperitoneal injection of *ZSC* leaves extract (50 mg/kg body weight) for 15 days and consequent withdrawal of extract administration produced a significant increase in the release of neurotransmitter in different parts of the brain of male albino rats. The inhibition of calcium-ATPase and phosphodiesterase leads to the increase in neurotransmitter content in CNS areas, and also at the same time, it inhibits Ca^{2+} calmodulin binding. It has been correlated that the ability of this plant extract to depress excitable tissue at all levels of the CNS directs to a decrease in the amount of transmitter released by the nerve impulse, as well as it leads to general depression of postsynaptic responsiveness and ion movement (Waggas 2006). The aqueous extract of roots of *ZSC* has pharmacological effect on exploratory behavior, spontaneous motor activity (SMA), pentobarbital-induced hypnosis, and motor coordination. It was found that this extract has a CNS depression activity (Adzu et al. 2002). *ZSC* leaves extract was examined for its anticonvulsant effect by using pentylenetetrazol (PTZ) model on male albino rats. It was concluded that the presence of peptide and cyclopeptide alkaloids in the *ZSC* leaves extract caused a decrease in NE, DA, and 5-HT contents in PTZ model (Waggas and Al-Hasani 2010). *ZSC* improved motor coordination in rats and shortened step-

through latency in Morris water maze test. Hydroalcoholic extract of *ZSC* leaves significantly ameliorated scopolamine-induced anxiety in rats (Setorki 2016).

ZSC ethanolic leaves extract showed neuroprotective activity against brain ischemia (induced), so it has the ability to decrease the brain damage caused by transient global cerebral ischemia and reperfusion (Setorki and Hooshmandi 2017). The protective effect on the cerebral oxidative stress and impairment induced by ischemia was mainly due to the increased activity of antioxidant defense system and inhibition of oxidative stress in the rat's brain. Other studies also reported the antioxidant activity of *ZSC* extract and its relation with neuroprotection (Abalaka et al. 2011; Michel et al. 2011). The phytoceutical from hexane extract of *ZSC* root bark (25, 50, and 100 mg/kg, p.o.) was tested against pentobarbital sleeping time, motor coordination test, and exploratory behavior in mice. Results showed that extract prolonged pentobarbital-induced hypnosis and decreased the head-dip responses in the exploratory behavior. However, it failed to give a positive result on the motor coordination test. These results demonstrated the potent central depressant effect of *ZSC* extract (Adzu et al. 2008). The pharmacological activity of *ZSC*F extract against 1-methyl-4-phenylpyridinium (MPP^+)-induced neurotoxicity in SH-SY5Y (neuronal) cell lines was evaluated. The effect of ZSCF on MPP^+-induced cell viability, membrane damage, and oxidative stress; mitochondrial membrane potential and activity of caspase-3, and protein expressions and apoptotic effect of cyto C, Bax, and Bcl-2 were measured. The results showed that *ZSC*F could be able to reduce the neurotoxicity of MPP^+ and offer neuroprotection in vitro and is reinforced by its potent antioxidant properties (Singh et al. 2012).

2.4.11 Antinociceptive Activity of *ZSC*

ZSC extract has the ability to suppress central and peripheral phases of nociception. The aqueous extract of *ZSC* root bark relieves pain via central and peripheral mechanisms and hence provides some justification for the folkloric use in the treatment of stomach pains (Adzu et al. 2001). Central analgesic activity of the extract is confirmed by the increase in the mean percentage effect on the hot plate test. *ZSC* aqueous extract of the leaves established a dose-dependent analgesic effect at different concentrations (250–1000 mg/kg), and it helps to reduce the number of writhes induced by a 0.6% aqueous solution of Ac-OH in Wistar rats. It has been reported that the aqueous extract of *ZSC* leaves (250 mg/kg) produced a similar effect to that of pethidine hydrochloride (10 mg/kg) (Effraim et al. 1998). Aqueous extracts of *ZSC* revealed a dose-dependent analgesic effect. With the aim of elucidating both central and peripherally mediated action in rats and mice, the chloroform and methanol fractions (70:30) of *ZSC* root (25, 50, and 100 mg/kg, i.p.) were tested on chemical (Ac-OH-induced writhing, formalin), mechanical (analgesiometer), and thermal (tail-flick) analgesic tests (Adzu and Haruna 2007). Contrary, alcoholic extract of *ZSC* leaves (500 mg/kg) failed to produce antinociceptive effect in tested rats (Tanira et al. 1988).

2.4.12 Anthelmintic Activity of *ZSC*

Antieimeria and anthelmintic activity of *ZSC* leaves extract at a dose of 100, 200, and 300 mg/kg was evaluated. For antieimeria activity, the mice infested with 1.2 × 103 *E. papillata*-sporulated oocysts were used. The anthelmintic potential of *ZSC* extract was investigated on adult earthworm, *Allolobophora caliginosa*. *ZSC* leaves extract significantly reduced the shedding of oocysts to about 10.7×10^3, 28.3×10^3, and 23.8×10^3 oocysts/g feces in 100, 200, and 300 mg/kg groups and was able to improve the induced jejunal injury by *E. papillata* infection by paralysis and death of worms (Alzahrani et al. 2016). The fact that *ZSC* holds anticoccidial activity has also been detailed in mice infected with *Cryptosporidium* spp. (Kadir et al. 2008). The mechanism of anticoccidial properties caused by *ZSC* was also similar to those occurring with most anticoccidial drugs (Wunderlich et al. 2014). Also, *ZSC* leaves extract has the ability to improve the histological damage done by *E. papillata*. In vitro and in vivo anthelmintic efficacy of aqueous and methanolic extracts of *ZSC* was proved using live *Haemonchus contortus* and experimentally induced *Haemonchus contortus* infection in Nubian goats. Crude aqueous extract and crude methanolic extract of *ZSC* leaves showed a significant anthelmintic effect ($p \leq 0.05$) by mortality and temporary paralysis of live *H. contortus*. *ZSC* leaves extract at the doses of 100 mg/kg and 400 mg/kg reported 61.5% and 78.7% reduction in percent of egg count in the feces (Intisar et al. 2015).

2.4.13 Hepatoprotective Activity of *ZSC*

Hepatoprotective effects against carbon tetrachloride (CCl_4)-induced liver injury is exhibited by the methanol and aqueous extract of leaves of *ZSC*. It also decreased the serum creatinine and uric acid level and enhanced protein depletion in kidney tissue with a significant reduction of MDA concentration. All the biochemical markers related with hepatic injury showed beneficial values after treatment with the extract (Al-Ghamdi et al. 2018). Aqueous extract of *ZSC* leaves showed effective results against CCl_4-induced hepatic fibrosis. The results of histopathological, biochemical, and histology texture analyses displayed that *ZSC* significantly hinder the progression of hepatic fibrosis with marked reduction in the activities of serum ALT and AST. *ZSC* aqueous leaves extract also reduced the expression of a-smooth muscle actin and the deposition of types I and III collagen in CCl_4-injured rats (Amin and Ghoneim 2009). The hepatoprotective effect of the *ZSC* fruits as an antioxidant against CCl_4-induced oxidative stress and hepatotoxicity in rats indicated that *ZSC*F restored normal levels of malondialdehyde and retained control activities of endogenous antioxidants such as superoxide dismutase (SOD) and glutathione peroxidase (GSH) (Yossef et al. 2011). The ameliorative role of *ZSC* leaves extracts against hepatic injury induced by *Plasmodium chabaudi*-infected erythrocytes has been related with its effect on oxidative marker in the infected liver tissues (Hafiz et al. 2019).

2.4.14 Antiplasmodial Activity of *ZSC*

ZSC is extensively used as traditional medicine in malaria endemic regions (Adzu et al. 2007a, b). *ZSC* leaves extract exerts its action against *Plasmodium* infection by significant restoration of hepatic oxidative markers, restoration of hemoglobin level and erythrocyte counts, as well as a reduction in the inflammatory cell count. Experimental mice infected with *P. chabaudi* showed infected erythrocytes, inflammatory cell infiltration, increased number of van Kupffer cells, and hepatocyte vacuolation. *ZSC* leaves extract treatment showed significant reduction in the level of mean corpuscular hemoglobin (MCH) and other pathological issues (Hafiz et al. 2019). *ZSC* showed significant beneficial effect on *P. berghei* parasite-induced hepatic and spleen tissue damage (Hafiz and Mubaraki 2016). *ZSC* leaves extract was able to significantly reduce the parasitemia level (Mishra and Bhatia 2014). *ZSC* leaves extract showed significant amelioration in the signs of inflammatory cell infiltration and hepatocyte vacuolation in the liver of infected mice with *P. berghei* (Hafiz and Mubaraki 2016). *ZSC* extracts have eloquent effects on hepatic tissues and have been evident from the histopathological pictures of the liver, kidney, and spleen affected by *Schistosoma* infection (Ali and Hamed 2006). Antitrypanosomal and antiplasmodial activity of *ZSC* leaves extract from Sudan was evaluated by in vitro assays. Methanolic extracts of leaves showed antiplasmodial activity against a chloroquine-sensitive strain of *P. falciparum* NF54, whereas the antitrypanosomal activity was evaluated against *Trypanosoma brucei rhodesiense* STI900 (African strain), and the results confirmed its traditional claim (Mohamed et al. 2017). *ZSC* chloroform fraction of root bark is a potential antiplasmodial agent against the *P. berghei*, justifying its folkloric usage as an antimalarial (Al-Said 1993). *ZSC* leaves extract has the ability to restore the normal levels of MDA in *Schistosoma mansoni*-infected mice (El-Rigal et al. 2006). From these scientific reports, it is evident that *ZSC* may be a source of potential chemotherapeutic antimalarial agent.

2.4.15 *ZSC* in Skin Diseases

The traditional claim of anti-inflammatory, soothing, and antibacterial activity of the *Ziziphus* tree represents a possible treatment option of the rash particularly in patients on EGFR blockers. A 50-year-old patient with a lung cancer developed a papulopustular rash after administering erlotinib. He treated himself with *ZSC* minced leaves, and he reported that his rash disappeared completely. Based on this clinical case report, a phase I trial of *Ziziphus* cream is undergoing which includes all patients on EGFR blockers. This study will help to discover a potential prevention and cure of the troublesome skin rash, and also it authorizes the clinical use of *ZSC* (Alzahrani et al. 2019).

2.4.16 Osteogenic Activity of *ZSC*

Administration of *ZSC* leaves extract to diabetic rats showed reduction of serum parathyroid hormone (PTH) with increased levels of CT which may have an association to enhanced bone mineralization and bone formation, probably due to presence of numerous types of flavonoids. Significant changes in PTH and bone tartrate-resistant acid phosphatase (TRAP) were observed along with decreases in serum calcitonin (sCT), procollagen type 1 (PC1), and osteocalcin (OC). In both serum and bone, there is a reduction in bone alkaline phosphatase (BALP), bone mineral density (BMD), and levels of Ca and P. Administration of *ZSC* leaves extract was helpful in reducing body weight loss and all diabetes-related bone changes followed by increasing IGF-1 bioavailability (El-Wakf et al. 2017).

2.4.17 Hypolipidemic Activity of *ZSC*

The antihyperlipidemic activity of *ZSC* could be attributed to inhibition of oxidative stress by phenolic compounds (El Rabey et al. 2014; Al-Sieni et al. 2020). *ZSC* leaves powder at the dose of 500 mg/kg body weight orally administered to hypercholesterolemic male rats showed improvement in the biochemical blood tests and the histology of the studied organs tissues. The concurrent treatment with *ZSC* seed aqueous extract in hypercholesterolemic rats showed reduction in the oxidative stress and restored the altered histological features to normal, and this could be related to the effect of phenolic compounds (Al-Sieni et al. 2020). *ZSC* leaves extract effectively reduced hyperlipidemia, lipid peroxidation, and activity of liver enzymes. The hypolipidemic effect of *ZSC* leaves extract is primarily due to its phenol constituents which inhibit oxidative stress (Parsaeyan and Rezwani 2014).

2.5 Patents Granted to *ZSC*

ZSC is considered as a good source of triterpenic acid, saponins, and flavonoid glycosides. It is quite popular for its folkloric use as a shampoo and in the treatment of skin diseases. Ghomi in 1998 obtained a patent for the *ZSC* formulation which was claimed to reverse the hair graying and was effective in treating psoriasis. It was claimed in the invention that the dried leaves extract of *ZSC* could be used to reduce skin inflammation and treat sunburn, nonspecific erythema, and itching. *ZSC* extract exerts cooling effect on skin and therefore is desirable to use as skin cleansers for sensitive skin. The extract is also effective as excortication agent (Ghomi 1998).

Mukherjee et al. (2006) developed an herbal-based formulation exhibiting broad-spectrum anticancer activity. The herbal preparation containing *Zizyphus* extract, rich in betulinic acid, was shown to inhibit protein kinase C activity of cancer cells and induce apoptosis (Mukherjee et al. 2006). Krasutsky et al. (2006) patented an azeotropic distillation method for the isolation of natural products such as betulin, lupeol, and/or betulinic acid in high yield (Krasutsky et al. 2006). A summary of few

Table 2.4 Patents granted to *ZSC*

S no	Patent no and year	Inventors	Invention title
1.	US5849302A 1998-12-15	MS Ghomi	Medicaments and cosmetics comprising *Zizyphus spina-christi* extracts
2.	US20060159783A1 United States 2006-07-20	R Mukherjee D Khattar M Jaggi A Singh M Kumar H Bala	Method for treating cancer using betulinic acid-rich herbal extract
3.	EP1687326A2 2006-08-09	PA Krasutsky O Kolomitsyna DA Krasutskyy OD Kacharov IV Kolomitsyn	Method for obtaining natural products from plant material

important patents granted to *ZSC* for its use in cosmetic and pharmaceutical industries is presented in Table 2.4.

2.6 *ZSC* in Nanotechnology

In the past decade, plant extracts and the natural products have been widely used for the synthesis of an array of metal nanoparticles (Haris et al. 2017). This shift in the paradigm from traditional chemical methods to green biosynthesis of nanoparticles is partly due to the cost-effective and environmental friendly method offered by the naturally occurring plant products. Medicinal plants contain diverse nature of secondary plant metabolites such as flavonoids, terpenoids, tannins, phenolic acids, and alkaloids, which act as reducing as well as capping agents for the synthesis of nanoparticles (AbuKhader and Khan 2017; Zayed et al. 2015). *ZSC* being rich in polyphenolic compounds have also been explored as an alternative source of biosynthesis of metal nanoparticles.

Zayed et al. (2015) used the *ZSC* leaves extract as a reducing and capping agent at the room temperature to synthesize Ag nanoparticles (AgNPs) via a single-step, rapid, cost-effective, and eco-friendly biosynthetic method. The nanoparticles were found to be spherical in shape with a uniform size distribution (average particle size diameter 19 nm). IR studies indicated the presence of hydroxyl, amino, carbonyl, and amide functionalities in the plant extract which could be responsible for the reduction and/or stabilizing the developed nanoparticles. The *ZSC*-stabilized AgNPs displayed an excellent catalytic activity and efficiently reduced 4-nitrophenol into 4-aminophenol (Zayed et al. 2015). AgNPs synthesized using aqueous leaves extract of *ZSC* have been shown to exhibit potent antibacterial activity against *S. aureus*, *Acinetobacter* sp., *P. aeruginosa*, and *E. coli*. These nanoparticles when loaded on band aids also showed excellent antibacterial effect against multidrug-resistant bacteria (Halawani 2017).

A study also reported the reliable antifungal activity of AgNPs synthesized using *ZSC* leaves extract against pathogenic fungal isolates *A. niger*, *A. flavus*, *P. digitatum*, and *F. oxysporum* (Abdelkader et al. 2019). Khani et al. (2018) used fruit extracts of *ZSC* for the green synthesis of copper nanoparticles (CuNPs). The CuNPs exhibited good antibacterial activity and were shown to act as an efficient adsorptive nanomaterial which was able to remove 95% of crystal violet (CV) dye from aqueous solution at optimized conditions (Khani et al. 2018).

2.7 *ZSC* as an Adsorbent to Remove Manganese from Aqueous Solution

Activated carbon from the *ZSC* seeds possesses good adsorption properties and has the ability to remove manganese metal from the water. The adsorption capacity of *ZSC* activated carbon is better than the natural zeolitic tuff, pecan nutshell biosorbent, *Pithecellobium dulce* carbon, and crab shell particles (Omri and Benzina 2012).

2.8 *ZSC* Toxicity

The scientific reports of *Ziziphus* species hold numerous gaps that need thorough exploration especially for biological activity and toxicity. Pharmacological activities of *ZSC* have been considered extensively, but there is a scarcity of the available scientific reports/data on the toxicity associated with the consumption of the various parts of the *ZSC* plant, although *ZSC* fruits and leaves appear to be safe as indicated by the relatively high LD_{50} values in experimental animals (Abdel-Zaher et al. 2005). Shah et al. (1989) reported that *ZSC* leaves extract did not produce acute toxicity in the animals but higher doses led to decreased locomotor activity. Swiss albino mice did not show any signs of toxicity, and also no mortality was observed even after the chronic treatment for 3 months (Shah et al. 1989). Similarly, Abdel-Zaher et al. (2005) did not observe any signs of hepatotoxicity and nephrotoxicity in rats upon chronic oral administration of the butanol extract of *ZSC* leaves (Abdel-Zaher et al. 2005). *ZSC* methanolic leaves extract had a markedly protective effect against aflatoxicosis, and it significantly improved all biochemical parameters and histological profiles of the liver, kidney, and testis of tested rats (Abdel-Wahhab et al. 2007). The acute toxicity/safety of the hexane root bark extract of *ZSC* in mice with the experimental doses of 25, 50, and 100 mg/kg reported LD_{50} of 871.78 mg/kg for intraperitoneal administration and clinched the safety limit of the *ZSC* (Adzu et al. 2008). In addition, the oral LD_{50} of the butanol extract of *ZSC* leaves in mice was 3820 mg/kg (Abdel-Zaher et al. 2005). Aliquots of the concentrated *ZSC* juice (fruits and leaves) were used to assess the safety limits of the phenolic compounds. LFT and RFT reports portrayed that the administration of *ZSC* juice did not cause any changes in liver and kidney functions. On the contrary, BHT at 200 ppm induced significant increases in the enzyme activities and the serum levels of total lipids, uric

acid, and creatinine (Amany et al. 2013). Abubakar et al. (2018) carried out first toxicity study by oral administration of 5000 mg/kg of *ZSC* hydro-methanolic fruit extract and recorded zero mortality rate proving its safety (Abubakar et al. 2018). The acute toxicity study of single dose of *ZSC* leaves methanolic extract (2000 mg/kg per oral) in adult male mice did not reveal any sign of toxicity or mortality during 2 weeks observation period. Furthermore, there were no significant changes in the mean body weight or absolute weight of the liver, kidney, spleen, or heart, indicating high safety of the extract (Dkhil et al. 2018a, b). *ZSC* leaves extract 300 mg/kg *ZSC* leaves extract depicted protective role in $HgCl_2$-induced nephrotoxicity and by acting on Kim-1 expression, lipid peroxidation, and nitric oxide production; suppression of the Nrf2-antioxidant response pathway; upregulation of IL1β, TNFα, and NOS2; and potentiation of proapoptotic activity. *ZSC* leaves extract has the ability to produce beneficial effects against mercury-induced renal toxicity (Almeer et al. 2019). These effects resulted from its chelation and antioxidant, anti-inflammatory, and antiapoptotic activities. *ZSC* minimized the pathological effect produced by mercury in the renal tissue, and also it enhanced Hg clearance and reduced its accumulation. *ZSC* leaves extract successfully inhibited the Kim-1expression induced by Hg exposure (Dkhil et al. 2018a, b). Upregulation of Nfe2l2, Hmox1 expression, and protection against Hg-induced oxidative stress in renal tissue were also supported by *ZSC*. *ZSC* leaves extract boosted Nfe2l2 and Hmox1 expression in an ulcerative colitis rat model. The antiapoptotic activity of *ZSC* leaves extract is mainly due to its ability to appease ROS, as mentioned by several studies (Almeer et al. 2018; Dkhil et al. 2018a, b; Singh et al. 2012).

Contrary to the above findings, a recent study conducted by Owolarafe et al. (2020) cautioned against the indiscriminate use of leaves. Owolarafe et al. (2020) investigated the hematological and hepatorenal toxicities of the aqueous methanol extracts of seeds of *ZSC* in Wistar albino rats. The seed extracts upon oral administration to rats at 200, 600, and 1000 mg/kg body weight for 2 weeks were found to cause hepatic vascular congestion and fibrosis at 600 and 1000 mg/kg body weight with no visible histoarchitectural effect on the kidney. Seed extract was noted to significantly ($P < 0.05$) reduce the levels of white blood cells, neutrophils, SGOT, chloride, urea, and creatinine and increase the levels of lymphocytes, platelets, direct and total bilirubin, albumin, SGPT, alkaline phosphatase (ALKP), SGOT, serum calcium, creatinine, urea, and organ-body weight ratios (Owolarafe et al. 2020).

2.9 Conclusion and Future Directives

It is perceptible that *ZSC* is a valuable medicinal resource encompassing phytoconstituents of diverse chemical classes with wide spectrum of pharmacological uses. The plant is traditionally considered as a safe herbal medicine. Its fruits are edible and widely consumed by the people in the gulf region. The contemporary congregate information shows that alkaloids, flavonoids, and saponin glycosides such as christinin A might be useful in the development of new drugs to treat various acute and chronic ailments. The limited preclinical and clinical reports available to

support the safety in different populations are still a question which severely limits the diversity of research and industrial application of *ZSC* in the medical field. Cyclopeptide alkaloids are the main phytoconstituents present in this plant species, and therefore the possible hepatorenal toxicity should not be ignored.

It is evident that *ZSC* possesses broad-spectrum antimicrobial property, and this might be helpful in the management of the new life-threatening diseases including COVID-19. Extensive pharmacological and chemical experiments integrating human clinical studies investigating inter- and intracellular metabolic pathways should be a focus in future. Isolation of bioactive molecules from *ZSC* might act as a good lead that can be employed in novel therapeutic formulation based on an increasing attention toward green chemistry and transitional medicinal plants in recent years. Utilization of medicinal plants for novel drug delivery applications has better stakes of being sustainable with potential medical and commercial impacts in the coming decades. *ZSC* has vast untapped therapeutic applications yet to be revealed and explored with a complementary blend of skills and expertise in the field of phytochemistry, pharmaceutics, and pharmacology.

References

Abalaka ME, Mann A, Adeyemo SO (2011) Studies on in-vitro antioxidant and free radical scavenging potential and phytochemical screening of leaves of *Ziziphus mauritiana* L. and *Ziziphus spina-christi* L. compared with ascorbic acid. J Med Genet Genomics 3(2):28–34

Abdallah EM (2017) Antibacterial activity of fruit methanol extract of *Ziziphus spina-christi* from Sudan. Int J Curr Microbiol App Sci 6(5):38–44

Abdel-Galil FM, El-Jissry MA (1991) Cyclopeptide alkaloids from *Zizyphus spina-christi*. Phytochemistry 30:1348–1349

Abdelkader H, Alzahrani H, Al-Ayafi A, Al-Mulah H, Al-Zubaidi S (2019) Green synthesis, characterization and antimicrobial activity of biosynthesized silver nanoparticles using *Ziziphus spina-christi* leaf extracts. Adv Microb Res 3:010

Abdel-Wahhab MA, Omara EA, Abdel-Galil MM, Hassan NS, Nada SA, Saeed A, El-Sayed MM (2007) *Zizyphus spina-christi* extract protects against aflatoxin B1-initiated hepatic carcinogenicity. Afr J Tradit Complement Altern Med 4:248–256

Abdel-Zaher AO, Salim SY, Assaf MH, Abdel-Hady RH (2005) Antidiabetic activity and toxicity of *Zizyphus spina-christi* leaves. J Ethnopharmacol 101(1–3):129–138

Abubakar S, Umar S, Alexander I, Abubakar N, Abdulazeez M, Sule M (2018) Evaluation of hypoglycaemic, hypolipidaemic and non toxic effect of hydro-methanolic extracts of *Ziziphus mauritiana*, *Ziziphus spina christi* fruit and glibenclamide on alloxan induced diabetic rats. J Drug Deliv Ther 8(3):82–92

AbuKhader MM, Khan SA (2017) Thymoquinone and nanoparticles: a promising approach for the clinical trials. J Bionanosci 11(4):258–265

Ads EN, Rajendrasozhan S, Hassan SI, Sharawy SMS, Humaidi JR (2017) Phytochemical, antimicrobial and cytotoxic evaluation of *Ziziphus spina-christi* (L.) stem bark. Biomed Res 28 (15):6646–6653

Ads EN, Rajendrasozhan S, Hassan SI, Sharawy SMS, Humaidi JR (2018) Phytochemical screening of different organic crude extracts from the stem bark of *Ziziphus spina-christi* (L.). Biomed Res 29(8):1645–1652

Adzu B, Haruna AK (2007) Studies on the use of *Zizyphus spina-christi* against pain in rats and mice. Afr J Biotechnol 6:1317–1324

Adzu B, Amos S, Wambebe C, Gamaniel K (2001) Anti-nociceptive activity of *Zizyphus spina-christi* root bark extract. Fitoterapia 72:344–350

Adzu B, Amos S, Dzma S, Wambebe C, Gamanile K (2002) Effect of *Zizyphus spina-christi* wild aqueous extract on the central nervous system in mice. J Ethnopharmacol 79(1):3–16

Adzu B, Amos S, Amizan MB, Gamaniel K (2003) Evaluation of the antidiarrhoeal effects of *Zizyphus spina-christi* stem bark in rats. Acta Trop 87:245–250

Adzu B, Abdul KH, Oluwakanyinsola AS, Umar AK, Anoka NJAN (2007a) *In vivo* antiplasmodial activity of ZS-2A: a fraction from chloroform extract of *Zizyphus spina-christi* root bark against *plasmodium berghei* in mice. Int J Biol Chem Sci 1(3):281–286

Adzu B, Haruna AK, Salawu OA, Sule A (2007b) Bioassay-guided evaluation of the antidiarrhoeal potentials of *Zizyphus spina-christi* root bark in rats. Int J Biol Chem Sci 1:15–20

Adzu B, Abdu KH, Mohammed I, Karniyus SG (2008) CNS activity of ZS-1A: a phytoceutical from *Zizyphus spina-christi* root bark. Int J Biol Chem Sci 2(4):456–461

Adzu B, Haruna AK, Ilyas M, Pateh UU, Tarfa FD, Chindo BA, Gamaniel KS (2011) Structural characterization of ZS—2A: an antiplasmodial compound isolated from *Zizyphus spina-christi* root bark. J Pharmacy Nutr Sci 1:48–53

Al-Badi K, Khan SA (2014) Formulation, evaluation and comparison of the herbal shampoo with the commercial shampoos. Beni Suef Uni J Basic Appl Sci 3(4):301–305

Al-Bayatti KK, Aziz FM, Abdalah ME (2011) A study of antibacterial activity of cidar (*Zizyphus spina christi* L.) on bacterial pathogens isolated from skin infections. Al-Mustansiriyah J Pharm Sci (AJPS) 9(1):13–20

Al-Busafi S, Al-Riyami M, Al-Ouwaisi K, Hisham A (2007) Screening of antioxidant and radical scavenging activities of some Omani medicinal plants. SQU J Sci 12(1):1–6

Al-Ghamdi AAM, Shahat AA (2017) Tropical antioxidant, hypoglycemic and anti-diabetic activities of *Ziziphus spina-christi* (L) Willd (Rhamnacae) leaf extract. Trop J Pharm Res 6 (11):2601–2610

Al-Ghamdi AAM, El-Zohri M, Shahat AA (2018) Hepatoprotective, nephroprotective, anti-amylase, and antiglucosidase effects of *Ziziphus spina-christi* (L.) against carbon tetrachloride-induced toxicity in rats. Trop J Pharm Res 18(4):781–790

Al Hakmani F, Khan SA, Ahmad A (2014) Determination of total phenol, in-vitro antioxidant and anti-inflammatory activity of seeds and fruits of *Zizyphus spina-christi* grown in Oman. Asian Pac J Trop Biomed 4:S656–S660

Alhassan KA, Indabawa AS, Shah MM (2019) Phytochemical analysis, proximate composition and antibacterial activities of Ziziphus species (*Z. jujube* and *Z. spina christi*). J Appl Adv Res 4 (1):42–46

Ali AA, El-Shanawani MA, Mesbah MK (1984) Phytochemical study of the leaves of *Ziziphus spina-christi* L. Willd. Bull Pharm Sci Assiut Univ 8:1–11

Ali NA, Julich WD, Kusnick C, Lindequist U (2001) Screening of Yemeni medicinal plants for antibacterial and cytotoxic activities. J Ethnopharmacol 74:173–179

Ali SA, Hamed MA (2006) Effect of *Ailanthus altissima* and *Zizyphus spina-christi* on bilharzial infestation in mice: Histological and histopathological studies. J App Sci 6:1437–1446

Ali SA, Bonkoungou E, Bowe C, de Kock C, Godara A, Williams JT (2006) Ber and other jujubes, *Ziziphus* species. In: Fruits for the future, vol 2, Revised edn. International Centre for Underutilised Crops, Southampton, p 289

Ali AB, Almagboul AZ, Mohammed OM (2015) Antimicrobial activity of fruits, leaves, seeds and stems extracts of *Ziziphus spina christi*. Arab J Med Aromat Plants (AJMAP) 1:94–107

Ali-Shtayeh MS, Yaghmour RMR, Faidi YR, Salem K (1998) Antimicrobial activity of 20 plants used in folkloric medicines in the Palestine area. J Ethnopharmacol 60:265–271

Al-Marzooq MA (2014) Phenolic compounds of Napek leave *(Zizyphus spina-christi L.)* as natural antioxidants. J Food Nutr Sci 2(5):207–214

Almeer RS, Mahmoud SM, Amin HK, Abdel Moneim AE (2018) *Ziziphus spina-christi* fruit extract suppresses oxidative stress and p38 MAPK expression in ulcerative colitis in rats via induction of Nrf2 and HO^{-1} expression. Food Chem Toxicol 115:49–62

Almeer RS, Albasher G, Alotibi F, Alarifi S, Ali D, Alkahtani S (2019) *Ziziphus spina-christi* leaf extract suppressed mercury chloride-induced nephrotoxicity via Nrf2 antioxidant pathway activation and inhibition of inflammatory and apoptotic signaling. Oxidative Med Cell Longev 13:5634685

Al-Mutairi MH, Ali S, Aly SM, Aldebasi Y (2016) Antibacterial activity of sider (*Ziziphus spina-christi*), leaves extract against selected pathogenic bacteria. Eur J Pharma Med Res 3 (5):138–144

Alomari AA, Fedelmula AA, Abdalla MOM (2017) Evaluation of the antibacterial and antifungal activities and phytochemical screening of bark extract of *Ziziphus spina Christi* L (*ZSC*) in AlBaha area. J Chem Biol Phys Sci (JCBPS) 7(1):077–086

Alotibi FO, Ashour EH, Al-Basher G (2020) Evaluation of the antifungal activity of *Rumex vesicarius* L. and *Ziziphus spina-christi* (L) Desf., aqueous extracts and assessment of the morphological changes induced to certain myco-phytopathogens. Saudi J Biol Sci 27 (10):2818–2828. https://doi.org/10.1016/j.sjbs.2020.06.051

Al-Said MS (1993) Traditional medicinal plants of Saudi Arabia. Am J Chin Med 21:291–298

Alsaimary IE (2009) Efficacy of some antibacterial agents on *Staphylococcus aureus* isolated from various burn cases. Int J Med Med Sci 1(4):110–114

Al-Sieni AI, El Rabey HA, Al-Seeni MN (2020) The aqueous extract of Christ's thorn (*Ziziphus spina-christi*) seed modulates hyperlipidemia in hypercholesterolemic male rat. Biomed Res 31 (3):71–78

Alzahrani F, Al-Shaebi EM, Dkhil MA, Al-Quraishy S (2016) *In vivo* anti-eimeria and *in vitro* anthelmintic activity of *Ziziphus spina-christi* leaf extracts. Pak J Zool 48(2):409–413

Alzahrani AM, Alzahrani AA, Alsharm AA (2019) The use of *Ziziphus spina-christi* extract in treating erlotinib (Tarceva®) associated rash: a case report. Case Rep Oncol 12:909–912

Amany MB, Shaker MA, Hoda AF (2013) Utilization from fruits and leaves of napek *(Zizyphus spina–christi l.)* as a source of bioactive components. Banat's J Biotechnol 4(7):16

Amin A, Ghoneim DM (2009) *Zizyphus spina-christi* protects against carbon tetrachloride-induced liver fibrosis in rats. Food Chem Toxicol 47:2111–2119

Arabski M, Michel A, Wegierek CA, Czerwonka G, Lankoff A, Kaca W (2012) Effects of saponins against clinical *E. coli* strains and eukaryotic cell line. J Biomed Biotechnol 2012:286216

Asgarpanah J, Haghighat E (2012) Phytochemistry and pharmacologic properties of *Ziziphus spina christi* (L.) Willd. Afr J Pharmacy Pharmacol 6(31):2332–2339

Avizeh RN, Hossein B, Mahdi MM (2010) Effect of glibenclamide and fruit extract of *Zizyphus spina-christi* on alloxan-induced diabetic dogs. Int J Appl Res Vet Med 8:109–113

Bai L, Zhang H, Liu Q, Zhao Y, Cui X, Guo S, Zhang L, Ho CT, Bai N (2016) Chemical characterization of the main bioactive constituents from fruits of *Ziziphus jujuba*. Food Funct 7(6):2870–2877

Berry-Koch A, Moench R, Hakewill P, Dualeh M (1990) Alleviation of nutritional deficiency diseases in refugees. Food Nutr Bull 12:106–112

Bown D (1995) Encyclopaedia of herbs and their uses. Dorling Kindersley, London

Bozicevic A, De Mieri M, Benedetto AD, Gafner F, Hamburger M (2017) Dammarane-type saponins from leaves of *Ziziphus spina-christi*. Phytochemistry 138:134–144

Brantner AH, Males Z (1999) Quality assessment of *Paliurus spina-christi* extracts. J Ethnopharmacol 66(2):175–179

Bukar AM, Kyari MZ, Gwaski PA, Gudusu M, Kuburi FS, Abadam YI (2015) Evaluation of phytochemical and potential antibacterial activity of *Ziziphus spina-christi* L. against some medically important pathogenic bacteria obtained from University of Maiduguri Teaching Hospital, Maiduguri, Borno state—Nigeria. J Pharmacog Phytochem 3(5):98–101

Carmona F, Pereira AMS (2013) Herbal medicines: old and new concepts, truths and misunderstandings. Rev Bras Farm 23(2):379–385

Dafni A, Levy S, Lev E (2005) The ethnobotany of Christ's thorn jujube (*Ziziphus spina-christi*) in Israel. J Ethnobiol Ethnomed 1:8. https://doi.org/10.1186/1746-4269-1-8

Deshpande PK, Shukla S, Gothalwal R (2019) Pharmacological updates on potential phytoconstituents of genus *Ziziphus*. Indian Res J Pharm Sci 6(2):1870–1878

Devkota HP, Watanabe T, Yahara S (2013) Flavonoids and saponins from *Ziziphus incurva*. Nat Prod Res 27(8):697–701

Dkhil MA, Kassab RB, Al-Quraishy S, Abdel-Daim MM, Zrieq R, Abdel Moneim AE (2018a) *Ziziphus spina-christi* (L.) leaf extract alleviates myocardial and renal dysfunction associated with sepsis in mice. Biomed Pharmacother 102:64–75

Dkhil MA, Al-Quraishy S, Moneim AEA (2018b) *Ziziphus spina-christi* leaf extract pretreatment inhibits liver and spleen injury in a mouse model of sepsis via anti-oxidant and antiinflammatory effects. Inflammopharmacology 26(3):779–791

Ebid AI (2015) Anti-bacterial activity of folk medicinal plant extracts of Saudi Arabia on isolated bacteria. J Appl Life Sci Int 3(1):49–54

Effraim KD, Osunkwo UA, Onyeyilli P, Ngulde A (1998) Preliminary investigation of the possible antinociceptive activity of aqueous leaf extract of *Ziziphus spina-christi* (LINN) Desf. Indian J Pharm 30(4):271–272

El Ghazali GEB, El Tohami MS, El Egami AAB (1994) Medicinal plants of the Sudan: medicinal plants of the White Nile provinces. Khartoum University Press, Khartoum

El Ghazali GEB, El Tohami MS, El Egami AAB, Abdalla WS, Mohammed MG (1997) Medicinal plants of the Sudan: medicinal plants of northern Kordofan. Omdurman Islamic University Printing and Publishing House, Omdurman

El Kamali HH, El Khalifa KF (1999) Folk medicinal plants of riverside forests of the southern Blue Nile district, Sudan. Fitoterapia 70:493–497

El Maaiden E, El Kharrassi Y, Qarah NAS, Essamadi AK, Moustaid K, Nasser B (2020) Genus *Ziziphus*: a comprehensive review on ethnopharmacological, phytochemical and pharmacological properties. J Ethnopharmacol 259:112950

El Rabey HA, Attia ES, Al-Seeni MN, Al-Sieni AI, Ibrahim IH, Meerasahib MF, Shaikh-Omer AM, Abuelgassim AO, Abuelgassim OA (2014) The hypolipidemic and antioxidant activity of Christ's thorn (*Ziziphus spina-christi*) leaves powder in hypercholesterolemic male rats. Life Sci J 11(10):1010–1021

Elaloui M, Ghazghazi H, Ennajah A, Manaa S, Guezmir W, Karray NB, Laamouri A (2017) Phenolic profile, antioxidant capacity of five *Ziziphus spina-christi* (L.) Willd provenances and their allelopathic effects on *Trigonella foenum-graecum* L. and *Lens culinaris* L. seeds. Nat Prod Res 31(10):1209–1213

Elaoui M, Hamdi SH, Nasr RB, Ghazghazi H, Bouslih E, Laamouri A, Ammari Y, Mediouni J (2020) Characterization of epicatechin contents in the *Ziziphus spina-christi* L. root extracts using LC-MS analyses and their insecticidal potential. Plant Biosyst 155:685–690. https://doi.org/10.1080/11263504.2020.1779837

Elboosaty WF (2020) Potent medicinal influences of *Ziziphus spina-christi*. Acta Sci Med Sci 4 (3):143–146

Eldeen IMS, Van Staden J (2007) *In vitro* pharmacological investigation of extracts from some trees used in Sudanese traditional medicine. South Afr J Bot 73:435–440

El-Din MS, Taha AM, Sayed AA, Salem AM (2019) *Ziziphus spina-christi* leaves methanolic extract alleviates diethylnitrosamine-induced hepatocellular carcinoma in rats. Biochem Cell Biol 97(4):437–445

El-Gendy MMA (2010) *In vitro*, evaluation of medicinal activity of Egyptian honey from different floral sources as anticancer and antimycotic infective agents. J Microbial Biochem Technol 5948:118–123

El-Hefny M, Mohamed AA, Salem MZM, Abd El-Kareem MSM, Ali HM (2018) Chemical composition, antioxidant capacity and antibacterial activity against some potato bacterial pathogens of fruit extracts from *Phytolacca dioica* and *Ziziphus spina-christi* grown in Egypt. Sci Hortic 233:225–232

El-Kamali HH, Mahjoub SA (2009) Antibacterial activity of *Francoeuria crispa*, *Pulicaria undulata*, *Ziziphus spina-christi* and *Cucurbita pepo* against seven standard pathogenic bacteria. Ethnobot Leaflets 6(6)

El-Maaiden E, El Kharrasi Y, Lamaoui M, Allai L, Essamadi AK, Nasser B, Moutaid K (2020) Variation in minerals, polyphenolics and antioxidant activity of pulp, seed and almond of different *Ziziphus species* grown in Morocco. Braz J Food Technol 23:e2019206

Elnagar NMI, Modawi BM (2016) Lupane-type triterpenoids and sterol from *Zizyphus spina christi* grown in Sudan. Orient J Chem 32(2):895–901

El-Rigal NS, Aly SA, Rizk M, Said A (2006) Use of *Ailanthus altissima* and *Ziziphus spina christi* extracts as folk medicine for treatment of some hepatic disorders in *Schistosoma mansoni* infected mice. Trends Med Res 1:100–112

El-Wakf AM, El-Komy MA, Mohammed EA (2017) Potent osteogenic action of *Ziziphus spina-christi* through up regulating IGF-1 and bone formation markers in diabetic male rats. Nat Sci 15 (11):133–141

Embaby HE, Mokhtar SM (2011) Chemical composition and nutritive value of Lantana and sweet pepper seeds and Nabak seed kernels. J Food Sci 76:C736–C741

Fard MPM, Ketabchi SR, Farjam MH (2020) Chemical composition, antimicrobial and antioxidant potential of essential oil of *Ziziphus spina-christi* var. Aucheri grown wild in Iran. J Med Plants By Prod 1:67–71

Farmani F, Moein M, Amanzadeh A, Kandelous HM, Ehsanpour Z, Salimi M (2016) Antiproliferative evaluation and apoptosis induction in MCF-7 cells by *Ziziphus spina christi* leaf extracts. Asian Pac J Cancer Prev 17(1):315–321

Fathy M, Galil A, Mervat A, El-Jissry (1990) Cyclopeptide alkaloids from *Zizyphus spina-christi*. Phytochemistry 30(4):1348–1349

Ghaffari K, Ahmadi R, Saberi B, Moulavi P (2020) Anti-proliferative effects of *Ziziphus spina-christi* and *Phlomis russeliana* leaf extracts on HEK293 and MCF-7 cell lines and evaluation of Bax and Bcl-2 genes expression level in MCF-7 cells. Asian Pac J Cancer Prev (APJCP) 22 (S1):81–87

Ghannadi A, Tavakoli N, Ardestani MM (2003) Volatile constituents of the leaves of *Ziziphus spina-christi* (L.) willd. From Bushehr, Iran. J Essent Oil Res 15(3):191–192

Ghazanfar SA (1994a) Handbook of Arabian medicinal plants. CRC, Boca Raton, p 182

Ghazanfar SA (1994b) Handbook of Arabian medicinal plants. CRC, Boca Raton, p 265

Ghazanfar SA, Sabahi AM (1993) Medicinal plants of northern and Central Oman. Econ Bot 47:89–98

Ghomi MS (1998) Medicaments and cosmetics comprising *Zizyphus spina-christi* extracts. US5849302A

Glombitza KW, Mahran GH, Mirhom YW, Michel KC, Motawi TK (1994) Hypoglycemic and antihyperglycemic effects of *Zizyphus spina-christi* in rats. Planta Med 60:244–247

Gournelis DC, Laskaris GG, Verpoorte R (1998) Cyclopeptide alkaloids. In: Herz W, Falk H, Kirby GW, Moore RE, Tamm C (eds) Progress in the chemistry of organic natural products, vol 75. Springer, New York, pp 1–175

Guizani N, Waly MI, Singh V, Rahman MS (2013) Nabag (*Zizyphus spina-christi*) extract prevents aberrant crypt foci development in colons of azoxymethane-treated rats by abrogating oxidative stress and inducing apoptosis. Asian Pac J Cancer Prev 14:5031–5035

Guo S, Duan JA, Tang YP, Yang NY, Qian DW, Su SL, Shang EX (2010) Characterization of triterpenic acids in fruits of *Ziziphus* species by HPLC-ELSD-MS. J Agric Food Chem 58:6285–6289

Guo S, Duan JA, Tang YP, Qian DW, Zhu Z, Qian Y, Su S (2011) UHPLC-TOF-MS coupled with chemometric method as a powerful technique for rapid exploring of differentiating components between two *Ziziphus* species. J Sep Sci 34:659–666

Hafiz TA, Mubaraki MA (2016) The potential role of *Ziziphus spina-christi* leaf extracts against *plasmodium berghei*-induced liver and spleen injury. Biomed Res Ind 27:1027–1032

Hafiz TA, Mubaraki MA, Diab MSM, Dkhil MA, Al-Quraishy S (2019) Ameliorative role of *Ziziphus spina-christi* leaf extracts against hepatic injury induced by *plasmodium chabaudi* infected erythrocytes. Saudi J Biol Sci 26:490–494

Halawani EM (2017) Rapid biosynthesis method and characterization of silver nanoparticles using *Zizyphus spina christi* leaf extract and their antibacterial efficacy in therapeutic application. J Biomater Nanobiotech 8:22–35

Haris M, Kumar A, Ahmad A, Abuzinadah MF, Basheikh M, Khan SA, Mujeeb M (2017) Microwave-assisted green synthesis and antimicrobial activity of silver nanoparticles derived from supercritical carbon dioxide extract of the fresh aerial parts of *Phyllanthus niruri* L. Trop J Pharm Res 16(12):2967–2976

Hashem FA, Saleh MM (1999) Antimicrobial components of some Cruciferae plants (*Diplotaxis harra* Foresk and *Erucaria microcarpa* Bioss). Phytother Res 13:329–332

Huang X, Kojima YA, Norikura T (2007) Mechanism of the anti-cancer activity of *Zizyphus jujuba* in HepG2 cells. Am J Chin Med 35:517–532

Huang Q, Liu X, Zhao G, Hu T, Wang Y (2018) Potential and challenges of tannins as an alternative to in-feed antibiotics for farm animal production. Anim Nutr 4(2):137–150

Ikram M, Tomlinson H (1976) Chemical constituents of *Ziziphus spina-christi*. Planta Med 29:289–291

Intisar AMO, Goreish I, Shaddad SA, Elamin TH, Eltayeb IB (2015) Anthelmintic activity of *Zizyphus spina-christi* leaves. J Forest Prod Indus 4(3):94–99

Iwu MM (1993) Handbook of African medicinal plants. CRC, Boca Raton

Jafarian A, Zolfaghari B, Shirani K (2014) Cytotoxicity of different extracts of arial parts of *Ziziphus spina-christi* on HeLa and MDA-MB-468 tumor cells. Adv Biomed Res 3:38

Jebur MH, Hind NKK, Hamza HJ, Alkaim AF (2020) The activity of aquatic extract of *Ziziphus spina-christi* against bacteria, an *in vitro* study. Int J Psychosoc Rehabil 24(5):1821–1827

Jongbloed M (2003) The comprehensive guide to the wildflowers of the United Arab Emirates. Environmental Research and Wildlife Development Agency (ERWDA), Abu Dhabi

Kadioglu O, Jacob S, Bohnert S et al (2016) Evaluating ancient Egyptian prescriptions today: anti-inflammatory activity of *Ziziphus spina-christi*. Phytomedicine 23:293–306

Kadir MAA, Al-Alousi TI, Al-Sawah DA (2008) Comparison between the efficacy of different medical herbs on Cryptosporidium spp. J Fac Med Baghdad 50:68–76

Kaleem WA, Muhammad N, Khan H, Rauf A (2014) Pharmacological and phytochemical studies of genus *Zizyphus*. Middle East J Sci Res 21(8):1243–1263

Kamil M, Jayaraj AF, Ahmad F, Gunasekhar C, Samuel S, Chan K, Habinullah M, Attas A (2000) Pharmacognostic and phytochemical standardization of *Calligonum comosum*. J Pharm Pharmacol 52:262–264

Khaleel SMJ (2018a) Studying the heavy metals composition and the impact of different common solvents on the extraction efficiency of phytochemical secondary metabolites from the leaves of *Ziziphus spina-christi* grown in Jordan. Pak J Nutr 17:392–398

Khaleel SMJ (2018b) Anti-α-glucosidase, anti-α-amylase and anti-inflammatory effects of leaf extracts of *Ziziphus Spina-christi* (Sedr) grown in Jordan. Res J Biol Sci 13:1–7

Khaleel SMJ, Jaran AS, Haddadin MSY (2016) Evaluation of total phenolic content and antioxidant activity of three leaf extracts of *Ziziphus spina-christi* (Sedr) grown in Jordan. Br J Med Med Res 14(6):1–8

Khani R, Roostaei B, Bagherzade G, Moudi M (2018) Green synthesis of copper nanoparticles by fruit extract of *Ziziphus spina-christi* (L.) Willd.: application for adsorption of triphenylmethane dye and antibacterial assay. J Mol Liq 255:541–549

Krasutsky PA, Kolomitsyna O, Krasutskyy DA, Kacharov OD, Kolomitsyn IV (2006) Method for obtaining natural products from plant material. EP1687326A2

Leal RIC, dos Santos KRN, Junior II, Antunes OAC, Porzel A, Wessjohann L, Kuster RM (2010) Ceanothane and Lupane type triterpenes from *Zizyphus joazeiro*—an anti-staphylococcal evaluation. Planta Med 76:47–52

Liu J, Zhai WM, Yang YX, Shi JL, Liu QT, Liu GL, Fang N, Li J, Guo JY (2014) GABA and 5-HT systems are implicated in the anxiolytic-like effect of spinosin in mice. Pharmacol Biochem Behav 128C:41–49

Mahran GH, Glombitza KW, Mirhom YW, Hartmann R, Michel CG (1996) Novel saponins from *Zizyphus spina-christi* growing in Egypt. Planta Med 62:163–165

Makhawi AM, Mustafa MI, Uagoub HA (2020) Phytochemical screening and antimicrobial activity of *Ziziphus spina-christi* stem barks. bioRxiv Preprint. https://doi.org/10.1101/2020.02.24.963157

Mardani M, Badiee P, Gharibnavaz M, Jassebi A, Jafarian H, Ghassemi F (2018) Comparison of anti-Candida activities of the ancient plants *Lawsonia inermis* and *Ziziphus spina christi* with antifungal drugs in Candida species isolated from oral cavity. J Conserv Dent 21:359–362

Matsuda H, Murakami T, Ikebata A, Yamahara J, Yoshikawa M (1999) Bioactive saponins and glycosides. XIV. Structure elucidation and immunological adjuvant activity of novel protojujubogenin type triterpene bisdesmosides, protojujubosides a, B, and B1, from the seeds of *Zizyphus jujuba* var. spinosa (*Zizyphi Spinosi* semen). Chem Pharm Bull(Tokyo) 47 (12):1744–1748

Michel CG, Nesseem DI, Ismail MF (2011) Anti-diabetic activity and stability study of the formulated leaf extract of *Zizyphus spina-christi* (L.) Willd with the influence of seasonal variation. J Ethnopharmacol 133(1):53–62

Miller AG, Morris M (1988) Plants of Dhofar, the southern region of Oman: traditional, economic and medicinal uses. The Office of the Adviser for Conservation of the Environment, Diwan of Royal Court, Sultanate of Oman

Mishra T, Bhatia A (2014) Antiplasmodial effects of the aqueous ethanolic seed extract of *Ziziphus mauritiana* against *Plasmodium berghei* in Swiss albino mice. Int J Pharmacol Res 4:111–116

Moghadam MS, Maleki S, Darabpour E, Motamedi H, Nejad SMS (2010) Antibacterial activity of eight Iranian plant extracts against methicillin and cefixime resistant *Staphylococcus aureus* strains. Asian Pac J Trop Med 3(4):262–265

Mohamed IE, El Nur EE, Abdelrahman ME (2010) The antibacterial, antiviral activities and phytochemical screening of some Sudanese medicinal plants. Eurasia J BioSci 4:8–16

Mohamed GEK, Ahmed R, Omnia TAA, Amna AYE, Matthias SU, Nikoli K (2017) Antimicrobial, antiparasitic and antioxidant activities of medicinal plants from Sudan. J Complement Med Alt Healthcare 2(5):555597

Mohammed GT, Yesufu HB, Khan IZ, Abdulrahman FI (2012) Effects of aqueous and ethanol extracts of the stem bark of *Zizyphus spina-christi* L. on isolated rabbit jejunum. J Pharm Biores 9:14–29

Motamedi M, Seyyednejad SM, Hasannejad Z, Dehghani F (2014) A comparative study on the effects of *Ziziphus spina-christi* alcoholic extracts on growth and structural integrity of bacterial pathogens. Iran J Pharm Sci 10(2):1–10

Moustafa MF, Hesham AE, Quraishi MS, Alrumman SA (2016) Variations in genetic and chemical constituents of *Ziziphus spina-christi* L. populations grown at various altitudinal zonation up to 2227 m height. J Genet Eng Biotechnol 14(2):349–362

Mukherjee R, Khattar D, Jaggi M, Singh A, Kumar M, Bala H (2006) Method for treating cancer using betulinic acidrich herbal extract. US20060159783A1

Nawwar MM, Ishak MS, Michael RN, Buddrus L (1984) Leaf flavonoids of *Zizyphus spina-christi*. Phytochemistry 23(9):2110–2111

Nazif NM (2002) Phytoconstituents of *Zizyphus spina-christi* L. fruits and their antimicrobial activity. Food Chem 76:77–81

Neuwinger H (1996) African ethnobotany poisons and drugs chemistry (Germany). Chapman and Hall GmbH, Weinheim (Bundes Republik Deutschland). ISBN 3-8261-0077-8

Okamura N, Yagi A, Nishioka I (1981) Studies on the constituents of *Zizyphi fructus*. V. Structures of glycosides of benzyl alcohol, vomifoliol and naringenin. Chem Pharm Bull 29 (12):3507–3514

Omri A, Benzina M (2012) Removal of manganese(II) ions from aqueous solutions by adsorption on activated carbon derived a new precursor: *Ziziphus spina-christi* seeds. Alex Eng J 51:343–350

Orwa C, Mutua A, Kindt R, Jamnadass R, Anthony S (2009) Agroforestree Database: a tree reference and selection guide version 4.0. http://www.worldagroforestry.org/sites/treedbs/treedatabases.asp

Osman MA, Ahmed MA (2009) Chemical and proximate composition of (*Zizyphus spina-christi*) nabag fruit. Nutr Food Sci 39(1):70–75

Owayss AA, Elbanna K, Iqbal J, Abulreesh HH, Organji SR, Raweh HSA, Alqarni AS (2020) In vitro antimicrobial activities of Saudi honeys originating from *Ziziphus spina-christi* L. and *Acacia gerrardii* Benth. Trees. Food Sci Nutr 8(1):390–401

Owolarafe TA, Salau AK, Salawu K (2020) Phytochemical screening and toxicity study of aqueous-methanol extract of *Ziziphus spina-christi* seeds in Wistar albino rats. Comp Clin Pathol 29:267–274

Panche AN, Diwan AD, Chandra SR (2016) Flavonoids: an overview. J Nutr Sci 5:e47

Pandey M, Debnath M, Gupta S, Chikara SK (2011) Phytomedicine: an ancient approach turning into future potential source of therapeutics. J Pharmacogn Phytother 3:113–117

Parsaeyan N, Rezwani ME (2014) The effect of Christ's Thorn (*Ziziphus spina-christi*) leaves extract on lipid profile, lipid peroxidation and liver enzymes of diabetic rats. Iran J Diab Obes 6 (4):163–167

Pawlowska AM, Camangi F, Bader A, Braca A (2009) Flavonoids of *Zizyphus jujuba* L. and *Zizyphus spina-christi* (L.) Willd (Rhamnaceae) fruits. Food Chem 112:858–862

Pibalouti AG, Bahmani M, Avijgan M (2009) Anti-candida activity of some of the Iranian medicinal plants. Electron J Biol 5(4):85–88

Said A, Fawzy G, Abu Tabl EA, Tzakou O (2010a) Volatile constituents of *Zizyphus jujuba* aerial parts and *Zizyphus spina-christi* fruits from Egypt. J Essent Oil Bearing Plants 13(2):170–174

Said A, Heufner A, Abu Tabl EA, Fawzy G (2010b) Isolation and identification of two new cyclic amino acids from the seeds of *Zizyphus spina-christi* L. (Wind) by means of ^{I}H-NMR-^{13}C-NMR-HSQC-HMBC and GC-MS. IUFS J Biol 69(2):77–85

Said A, Heufner A, Tabl EAA, Fawzy G (2011) Phenolic compounds from seeds of *Zizyphus spina-christi*. IUFS J Biol 70(1):39–43

Saied AS, Gebauer J, Hammer K, Buerkert A (2008) *Ziziphus spina-christi* (L.) Willd.: a multipurpose fruit tree. Genet Resour Crop Evol 55:929–937

Sakna ST, Mocan A, Sultani HN, El-fiky NM, Wessjohann LA, Farag MA (2019) Metabolites profiling of *Ziziphus* leaf taxa *via* UHPLC/PDA/ESI-MS in relation to their biological activities. Food Chem 293:233–246

Setorki M (2016) Effect of hydro-alcoholic extract of *Ziziphus spina-christi* against scopolamine-induced anxiety in rats. Bangladesh J Pharmacol 11:421–427

Setorki M, Hooshmandi Z (2017) Neuroprotective effect of *Ziziphus spina-christi* on brain injury induced by transient global cerebral ischemia and reperfusion in rat. Bangladesh J Pharmacol 12:69–76

Shah AH, Ageel AM, Tariq M, Mossa JS, Al-Yahya MA (1986) Chemical constituents of the stem bark of *Zizyphus spina-christi*. Fitoterapia 57:452–454

Shah AH, Qureshi S, Tariq M, Ageel AM (1989) Toxicity studies on six plants used in the traditional Arab system of medicine. Phytother Res 3(1):25–29

Shahat AA, Pieters L, Apers S, Nazeif NM, Abdel-Azim NS, Bergh DV, Vlienk AJ (2001) Chemical and biological investigations on *Zizyphus spina-christi* L. Phytother Res 15:593–597

Shonouda M, Angeli S, Schutz S, Vidal S (2008) Use of CLCA and SPME headspace techniques followed by GC-MS analysis to extract and identify the floral odorants. Pak J Biol Sci 11:1246–1251

Singh H, Seshadri TR, Subramanian GBV (1965) Chemical investigation of lac hosts. Curr Sci 34:344

Singh V, Guizani N, Essa MM, Rahman MS, Selvaraju S (2012) In vitro antioxidant activities of *Ziziphus spina-christi* fruits (Red Date) grown in Oman. Biotechnology 11(4):209–216

Singh V, Essa MM, Guizani N, Balakrishnan R, Hemalatha T, Manivasagam T, Justin-Thenmozhi-A, Elangovan N, Velusamy T (2018) Protective effect of *Zizyphus spina-christi* on MPP+-induced oxidative stress. Front Biosci 10:285–299

Soliman S, Hamoda AM, El-Shorbagi ANA, El-Keblawy AA (2019) Novel betulin derivative is responsible for the anticancer folk use of *Ziziphus spina-christi* from the hot environmental habitat of UAE. J Ethnopharmacol 231:403–408

Sudhersan C, Hussain J (2003) In vitro clonal propagation of a multipurpose tree, *Ziziphus spina-christi* (L.) Desf. Turk J Bot 27:167–171

Sudhersan C, Jibi S, Ashkanani J (2016) *Ziziphus*: a highly potential multipurpose woody perennial for desert environmental rehabilitation. Acta Hortic 1116:9–13

Tanira MOM, Ageel AM, Tariq M, Mohsin A, Shah AH (1988) Evaluation of some pharmacological, microbiological and physical properties of *Zizyphus spina-christi*. Int J Crude Drug Res 26:56–60

Tawfik K, Al-Barazi M, Bashir M, Al-Marzouq W, Al-Soufi R, Kharsa H (2015) A comparative study of antioxidant activities of *Ziziphus* and *colocynth* from Saudi Arabia deserts and proposed pharmaceutical products. Int Res J Pharm Appl Sci 5(3):08–13

Temerk HA, Salem WM, Sayed WF, Hassan FS (2017) Antibacterial effect of phytochemical extracts from *Ziziphus-spina christi* against some pathogenic bacteria. Egypt J Bot 57 (3):595–604

Tom GM, Yesufu HB, Abdulrahman FI (2009) Antimicrobial screening and effect of the pulp extracts of *Zizyphus spina-christi* (Linnaeus Desf) on some biochemical parameters in rats. J Pharm Bioresour 6(2):58–64

Tripathi M, Pandey MB, Jha RN, Pandey VB, Tripathi PN, Singh JP (2001) Cyclopeptide alkaloids from *Ziziphus jujuba*. Fitoterapia 72:507–510

Tschesche R, Wilhelm H, Kaussmann EU, Eckhardt G (1974) Alkaloids from Rhamnaceae. XVII. Mauritine-C, -D, −E and -F, new peptide alkaloids from *Ziziphus mauritiana*. Justus Lieb. Ann Chem 10:1694–1701

Tuenter E, Exarchou V, Apers S, Pieters L (2017a) Cyclopeptide alkaloids. Phytochem Rev 16:623–637

Tuenter E, Foubert K, Staerk D, Apers S, Pieters L (2017b) Isolation and structure elucidation of cyclopeptide alkaloids from *Ziziphus nummularia* and *Ziziphus spina-christi* by HPLC-DAD-MS and HPLC-PDA-(HRMS)-SPE-NMR. Phytochemistry 138:163–169

Vahedi F, Najafi MF, Bozari K (2008) Evaluation of inhibitory effect and apoptosis induction of *Ziziphus jujube* on tumor cell lines, an *in vitro* preliminary study. Cytotechnology 56:105–111

Waggas AM (2006) Effect of Sidr leaves extract on some neurotransmitter content in different brain areas of male albino rats. J Egypt Ger Soc Zool 51A:297–313

Waggas AM, Al-Hasani RH (2009) Effect of Sidr (*Zizyphus spina-christi*) fruit extract on the central nervous system in male albino rats. Am Eurasian J Sci Res 4(4):263–267

Waggas AM, Al-Hasani RH (2010) Neurophysiological study on possible protective and therapeutic effects of Sidr (*Zizyphus spina-christi* L.) leaf extract in male albino rats treated with pentylenetetrazol. Saudi J Biol Sci 17:269–274

Wang LE, Cui XY, Cui SY, Cao JX, Zhang J, Zhang YH, Zhang QY, Bai YJ, Zhao YY (2010) Potentiating effect of spinosin, a *C*-glycoside flavonoid of semen *Ziziphi spinosae*, on pentobarbital-induced sleep may be related to postsynaptic 5-HT(1A) receptors. Phytomedicine 17:404–409

Weinges K, Schick H (1995) Dodecaacetylprodelphinidin B3 from the dried leaves of *Ziziphus spina-christi*. Phytochemistry 38(2):505–507

Wunderlich F, Al-Quraishy S, Steinbrenner H, Sies H, Dkhil MA (2014) Towards identifying novel anti-Eimeria agents: trace elements, vitamins, and plant-based natural products. Parasitol Res 113:3547–3556

Yoshikawa K, Shimono N, Arihara S (1992) Antisweet natural products. VI Jujubasaponins IV, V and VI from *Zizyphus jujube* Mill. Chem Pharm Bull 40(9):2275–2278

Yossef HEE, Khdr AA, Mahran MZ (2011) Hepatoprotective activity and antioxidant effects of El Nabka (*Zizyphus spina-christi*) fruits on rats hepatotoxicity induced by carbon tetrachloride. Nat Sci 9(2):1–7

Younes ME, Amer MS, El-Messallami ADE (1996) Phytochemical examination of the leaves of the Egyptian *Zizyphus spina christi* "Nabc". Bull Natl Res Centre (Cairo) 21(1):35–40

Zayed MF, Eisa WH, Abdel-Moneam YK, El-kousy SM, Atia A (2015) *Ziziphus spina-christi* based bio-synthesis of Ag nanoparticles. J Ind Eng Chem 23:50–56

Zheng Y, Bai L, Zhou Y, Tong R, Zeng M, Li X, Shi J (2019) Polysaccharides from Chinese herbal medicine for antidiabetes recent advances. Int J Biol Macromol 121:1240–1253