Journal of
Food Chemistry & Nanotechnology

https://doi.org/10.17756/jfcn.2023-s1-010

Review Article

Open Access

The Pharmacological Potential of Bioactive Components of *Zizypus jujuba* Seeds: A Review

Aman Jyoti[1], Jyoti Singh[1*] and Sezai Ercisli[2, 3]

[1]*Department of Food Technology and Nutrition, School of Agriculture, Lovely Professional University, Phagwara, Punjab, India*

[2]*Department of Horticulture, Faculty of Agriculture, Ataturk University, Erzurum, Turkey*

[3]*HGF Agro, ATA Teknokent, Erzurum, Turkey*

[*]Correspondence to:
Jyoti Singh
Department of Food Technology and Nutrition,
School of Agriculture,
Lovely Professional University,
Phagwara, Punjab, India.
E-mail: jyotisingh9377@gmail.com

Received: August 21, 2023
Accepted: October 20, 2023
Published: October 24, 2023

Citation: Jyoti A, Singh J, Ercisli S. 2023. The Pharmacological Potential of Bioactive Components of *Zizypus jujuba* Seeds: A Review. *J Food Chem Nanotechnol* 9(S1): S58-S71.

Copyright: © 2023 Jyoti et al. This is an Open Access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC-BY) (http://creativecommons.org/licenses/by/4.0/) which permits commercial use, including reproduction, adaptation, and distribution of the article provided the original author and source are credited.

Published by United Scientific Group

Abstract

Ziziphus jujuba or Jujube, belonging to the Rhamnaceae family, is used predominantly in China, India, and other Southeast Asian regions and has been used as a fruit and medicinal remedy since ancient times. Seeds of jujube have great pharmacological benefits like antioxidant, antimicrobial, anti-inflammatory, antipyretic, and diuretic activities. All these properties are owed to the various phytochemicals present like flavonoids, phenolic compounds, triterpenic acids, and polysaccharides. Seeds of *Z. jujuba* are used to treat a variety of conditions, including cardiovascular disease, gastrointestinal disorders like inflammatory bowel disease, sedative and hypnotic effects, anxiolytic properties that act as neuroprotectants in a variety of cognitive disorders, antibacterial and antiulcer properties that reduce inflammation, hypotensive and antinephritic properties, and antifertility/contraceptive activity. The seeds of *Z. jujuba* possess a lot of scope especially because of their high nutritive value moreover it is discarded as agricultural waste during its processing. Overall, the review emphasizes the potential of *Z. jujuba* seeds as a natural remedy for treating a variety of health conditions and encourages further research to fully understand its therapeutic properties and its action of mechanism. The various applications of *Z. jujuba* seeds in traditional medicine and to produce modern products make it a promising source of medicinal compounds and a nutritious superfood. Thus, jujube has a great possibility for future research to gain more knowledge of its health benefits.

Keywords

Ziziphus jujuba, Phytochemicals, Pharmacological, Triterpenic acids neuroprotectant, Antinephritic properties

Introduction

Z. jujuba, belonging to the Rhamnaceae family, is used predominantly in China, India, and other Southeast Asian regions. The fruits are among them and have a variety of health benefits, including antioxidant, antibacterial, and anti-inflammatory properties. They can also be used as a natural nutritional supplement to delay aging. In addition to being used to cure sleeplessness and as a functional meal to enhance learning and memory, the mature seed of wild jujube also has positive effects on illnesses of the central nervous system [1].

Z. jujuba seeds exhibit pharmacological benefits and have been used in traditional Chinese medicine anciently. With about 40 species under the genus *Ziziphus, Z. jujuba* has been highlighted as the most important one. It has been cultivated in China for about 4000 years [2]. It is used for treating a wide variety of health ailments like heart conditions, tonic spleen, cough, fever, fatigue, diarrhea, blood deficiency, wound healing, and stopping bleeding [3]. It is also used

for the treatment of various psychiatric disorders in ancient Chinese and Korean medicines [4].

Jujube extract consists of several bioactive compounds that are responsible for these pharmacological properties these are jujuphenoside and other 22 compounds. Jujube exhibits several other biological activities such as antimicrobial, antioxidant, anticancer, anti- inflammatory, anti-diabetic, hematopoietic, and diuretic properties [5]. Jujube has various constituents like phenolic acids, flavonoids, polysaccharides, triterpene acids, amino acids, and other minerals [6]. It has neuroprotective, sedative and hypnotic, hepatoprotective, wound-healing, anti-aging, and cognitive effects, as well as antioxidant, anti-inflammatory, anti-hypertensive, anti-bacterial, cytoprotective (antioxidant), anti-genotoxic, hematopoietic, anti-cancer, immunological and anti-complementary, synaptic transmission, and anti-anxiety activities [7]. Its extract can be used to develop a variety of other value-added products. It is used as food, a flavoring agent, and an additive moreover, it has been utilized in Chinese Traditional Medicine since long back [5].

Along with its use in the food sector, it is also used in non-food sectors like in animal feeds, the cosmetic industry, and as an adsorbent [8]. It is used in sunscreens as it contains sun protection factor and prevents damage that is caused due to harmful ultraviolet rays of the sun [9]. The essential oil extracted from the seed is a potent hair growth stimulator and increases the strength of the hair [10]. Jujube also prevents skin pigmentation and helps in the treatment of many skin-related issues like freckles, and hyperpigmentation and it helps in improving the texture of the skin [11].

Taxonomical classification

The jujube plant, scientifically known as *Z. jujuba*, belongs to the Plantae kingdom and the Spermatophyta phylum. It falls under the class of *Magnoliopsida* and the order Rosales, which is a part of the family Rhamnaceae. The jujube plant is a member of the genus *Ziziphus* and is classified under the species *Jujuba*. It is a eukaryotic plant that belongs to the subkingdom Viridiplantae and the super division Embryophyta. The jujube plant is a tracheophyte and a spermatophytina, which are subdivisions of the phylum Spermatophyta. Its taxonomic classification further includes the infra kingdom Streptophyta and the superorder Rosanae [12, 13].

Morphology

Jujube can grow in water-scarce and nutrient-poor areas [14]. The height of *Z. jujuba* can vary from about 8 to 12 meters [15]. It can range from a shrub to an erect semi-deciduous tree with much branching. The plant contains thorns [13]. The leaves are green with three parallel veins, rounded apex, and seriate margins [2]. They are arranged alternatively and are petiolate. The plant bears yellow or green-colored flowers arranged in small axillary clusters with an acrid smell [2]. The fruit is drupe type with varying size which is greenish when immature. The fruit is usually oval to elliptical [2]. Its color changes to red on reaching maturity [13]. The weight of the fruit ranges from about 0.14 g to 6.42 g [15]. The pulp of the fruit is usually sweet and acidic in taste and whitish in color



Figure 1: (A) Fruit of *Z. jujuba* **(B)** Transverse section of the fruit of *Z. jujuba* and **(C)** Seed of *Z. jujuba*.

[13]. The different part of fruit is shown in figure 1.

Chemical composition

The moisture content varies from 58.3% to 83% while the titrable acidity ranges from 0.20% to 3.12% as shown in table 1. With glucose ranging from 2.97% to 8.44%, sucrose from 1.6% to 25.8%, and fructose from 3.24% to 8.66%, the total sugar concentration ranges from 9.8% to 31.7% [16-19]. Protein concentrations range from 1.20 g to 5.67 g per 100 g, and ascorbic acid concentrations range from 77.2 mg to 244.57 mg per 100 g [17, 18, 20]. The ratio of sugar to acid varies from 1.5 to 14.75. The table 2 also lists the phenolic content, which includes catechin (38 - 632.39), epicatechin (29 - 285.07) and rutin (48 - 108.94 mg/g), as well as total phenolic content (275.6 - 600.4 mg gallic acid/100 g FW) and total flavonoids (62 - 284.9 mg rutin equivalent/100 g FW) [16-18, 21, 22].

Anti-nutritional compounds

Z. jujuba contains antinutritional factors like phytates, oxalates, tannins, and cyanide which can affect human health

Table 1: Chemical composition of *Z. jujuba*.

Constituents	Amount	References
Moisture content (%)	58.3 - 83	[16-18]
Titrable acidity (%)	0.20 - 3.12	[17, 18]
Total sugars (%)	9.8 - 31.7	[16-18]
Glucose (%)	2.97 - 8.44	[16, 18]
Sucrose (%)	1.6 - 25.8	[18, 19]
Fructose (%)	3.24 - 8.66	[16, 18]
Protein (g/100 g)	1.20 - 5.67	[17, 18, 20]
Ascorbic acid (mg/100 g)	77.2 - 244.57	[17, 18]
Sugar/Acid	1.5 - 14.75	[16, 18]
Catechin (mg/g)	38 - 632.39	[17, 21]
Epicatechin (mg/g)	29 - 285.07	[17, 21]
Rutin (mg/g)	48 - 108.94	[17, 21]
Total phenolic content (mg gallic acid/100 g FW)	275.6 - 600.4	[17, 22]
Total flavonoids (mg rutin equivalent/100 g FW)	62 - 284.9	[17, 22]

when consumed in high amounts as it forms complex important macro and micronutrients essential for various functions in the body, also it hinders absorption of various ions and minerals. Oxalate poisoning in diet may be challenging nutritional status as it may hinder in the absorption and utilization of calcium ions. Cyanides when in free form combine with sugar to form cyanogenic glycosides which is non-toxic but it is an effective inhibitor of cytochrome oxidase and interferes with the aerobic respiratory system. Excess tannins and saponin content in the body inhibit the activity and functioning of various enzymes like trypsin, amylase, and lipase and also hinder the absorption of vital minerals, specifically iron. Phytates are considered antinutritional factors and hinder the absorption of various macro and micronutrients such as carbohydrates and hurt mineral uptake [23]. Presence of tannin content of epicatechin and catechin was observed in the seeds of *Z. jujuba* [24]. About 4.38 to 8 mg EC/ dry weight tannin contents were analyzed in the seeds of *Z. jujuba* [25].

The modified vanillin-HCl method was used to measure the tannin content of control and fermented seeds. 5 ml of vanillin reagent was combined with approximately 1 ml of 1% HCl in methanol extract. At 30 °C, the reaction was kept going, and the absorbance was measured using an ultraviolet-visible spectrophotometer after 20 min at 500 nm. The catechin equivalents (mg catechin/g) are used to measure tannin content. Tannin content was reduced by 53.1%, 53.4%, 55.5%, and 62.8% after fermentation for 6, 12, 24, and 48 h, respectively. Many workers have noticed that natural fermentation significantly reduces tannin. Increased microbial enzyme activity, which causes the tannin components' breakdown and extractability, may be responsible for the fermented product's lower tannin concentration [26].

Extraction technique

The fruits were collected and washed to remove any dirt and debris then pulp was removed to separate the seeds. The

Table 2: Pharmacological properties of *Z. jujuba* seeds.

Pharmacological property	Mechanism of Action	References
Anti-inflammatory	Jujube extract reduces the levels of NO and histamine released as inflammatory response. Inhibiting the specialised leucocytes and neutrophils that are involved in causing the inflammatory response. ZY-2, ZY-3, and ZY-4 through its property of protecting intestinal epithelial barrier function anti-inflammatory properties.	[3, 39, 40]
Hepatoprotective	Damage by enhancing the activation of the Nrf2 pathway and inducing antioxidant defence mechanism for scavenging of the free radicals against CCL4 induced oxidative stress.	[41, 42]
Neuroprotective	Jujube stimulates neurite outgrowth and the expression of neurotrophic factors via cAMP-dependent PKA signalling. Jujube seeds provide neuroprotection by reducing the oxidative stress by increasing the expression of cellular Nrf2-dependent ARE-driven genes which inhibits the activity of choline acetyltransferase and increases acetylcholinesterase. Stimulates the transcription of gamma-aminobutyric acid (GABA) receptor subunits.	[40, 42]
Gastrointestinal tract	ZSS polysaccharides regulate TLR4 (Toll-like receptor 4) and NF-B (nuclear factor kappa-light-chain-enhancer of activated B cells) signalling pathways inhibiting the activation of TLR4 and subsequent downstream signalling pathways, such as NF-B and MAPK (mitogen-activated protein kinase).	[3, 43]
Antihypertensive	Attenuated blood pressure and mean arterial pressure and restored the cardiovascular condition. Jujuba seeds contains triterpenoids such as oleanonic acid , pomolic acid, pomonic acid which inhibit foam cell formation and also maintain the total cholesterol level in the body.	[42, 44, 45, 46]
Anti-cancer	Jujube extract blocks the ROS (Reactive oxygen species) regeneration through Fenton Reaction through conversion of hydroxyl peroxide which produces hydroxyl free radicals hence reducing the oxidative stress. Jujube extracts also have a dual regulation by MAPK kinase that regulates cell proliferation and cell death.	[29, 46]
Anemia	Activated hypoxia inducible factor-induces erythropoietin and increase the recycle heme iron erythrophagocytosis stimulates expression of HIF thus activating it and which further induces EPO ie. hormone stimulating blood production altering gene expression and increasing the EPO production thus increasing erythropoietin production.	[40, 47]
Hyperpigmentation	Reducing tyrosinase enzyme activity and the cAMP-CREB-mediated MITF axis, JUB, EPA, and FRS displayed strong anti-melanogenic actions. Spinosin suppresses the activity of melanocyte stimulating hormone.	[11, 46, 48]
Sleeping disorders	JuB had some sort of proliferative effect on the neurons. The sedative-hypnotic effect was primarily caused by GABA(A) 1, while GABA(A) 5 mediated muscular relaxation, which could hasten the emergence of the sedative-hypnotic effect.	[49, 50, 51, 52]
Anxiolytic	Protects the ischemic damage through antioxidant effects in the gerbil hippocampus. It increases the levels of the plasmin which causes the conversion of pro-Brain derived neurotrophic factors (BDNF) to mature-BDNF.	[7, 29, 42]

seeds were roasted or dried using a tray drier or oven drier at about 40 °C and then it was grounded into fine powder. The extracts were used for different extraction methods as shown in figure 2 [27]. It can be dried at 60 °C for 10 h Then after grinding it can be sieved by 40 mesh sieve to obtain a fine powder [28]. Jujuba seeds were then extracted with ethanol 60% v/v followed by homogenization and sonication then afterward it was fractionated with chloroform, n-hexane, ethyl acetate, n-butanol and water as a solvent and then the residues were examined for total phenolic content, total flavonoid content and antioxidant activity [29].

Methanolic extract

Methanolic extracts of jujube seed were obtained by extracting 5 g for 24 h with 100 ml of 80% methanol. After filtering the mixture dissolved in methanol (1:20 w/v). The filtrates from the two extraction phases were mixed and concentrated at 35 °C. Remove any leftover solvent at 35 °C at 60 mmHg in the oven [30]. It can be also extracted by using an 80:20 methanol/water solution in a percolator for around 7 days at room temperature [27].

Ethanolic extraction

The other study concentrated on the extraction using a combination of ethanol (70%) and chromatography techniques. It used extracts from jujube pulp and seed samples that had been extracted using various solvents and extraction methods. These extracts were further used for additional testing and analysis to find and describe the bioactive substances that were present in the samples [31].

Soxhlet extraction

The sample was extracted with petroleum ether in the Soxhlet apparatus which was followed filtration by applying pressure through Rota-`Vap. Then after drying extracts were again extracted in the Soxhlet apparatus with chloroform for 20 h Similarly, after drying extraction with methanol in the Soxhlet apparatus [32]. Similarly, extraction was carried out with methanol of 80% of the concentration using the Soxhlet apparatus for 4 h at 80 °C. The extracts were then evaporated in a vacuum and Buchi-type Rotavapor [27].

Hot water extraction method

It is combined solvent extraction, adsorption resin, anion exchange resin, dialysis, and freeze drying to extract polysaccharides from *Z. jujuba* seeds. The seeds were heated to a high temperature 60 °C for 3.5 h and then defatted before being removed. To get a pure polysaccharide extract, the resultant polysaccharide solution was purified using a variety of methods [33]. In a different investigation, jujube seeds were infused in boiling water for two hours before being filtered to create aqueous extracts. After drying the resultant extract, the percentage yield was determined [34].

Ultrasound-assisted extraction method

For the extraction of polysaccharide was carried out using ultrasonic bath extraction 80 - 200 W, filtration, concentration (30 - 70 °C), precipitation by 95% ethanol and 100% acetone (4:1), deproteinization, dialysis, and freeze-drying. This technique was further helpful for the analysis and testing of the bioactive substances in jujube seeds [33].

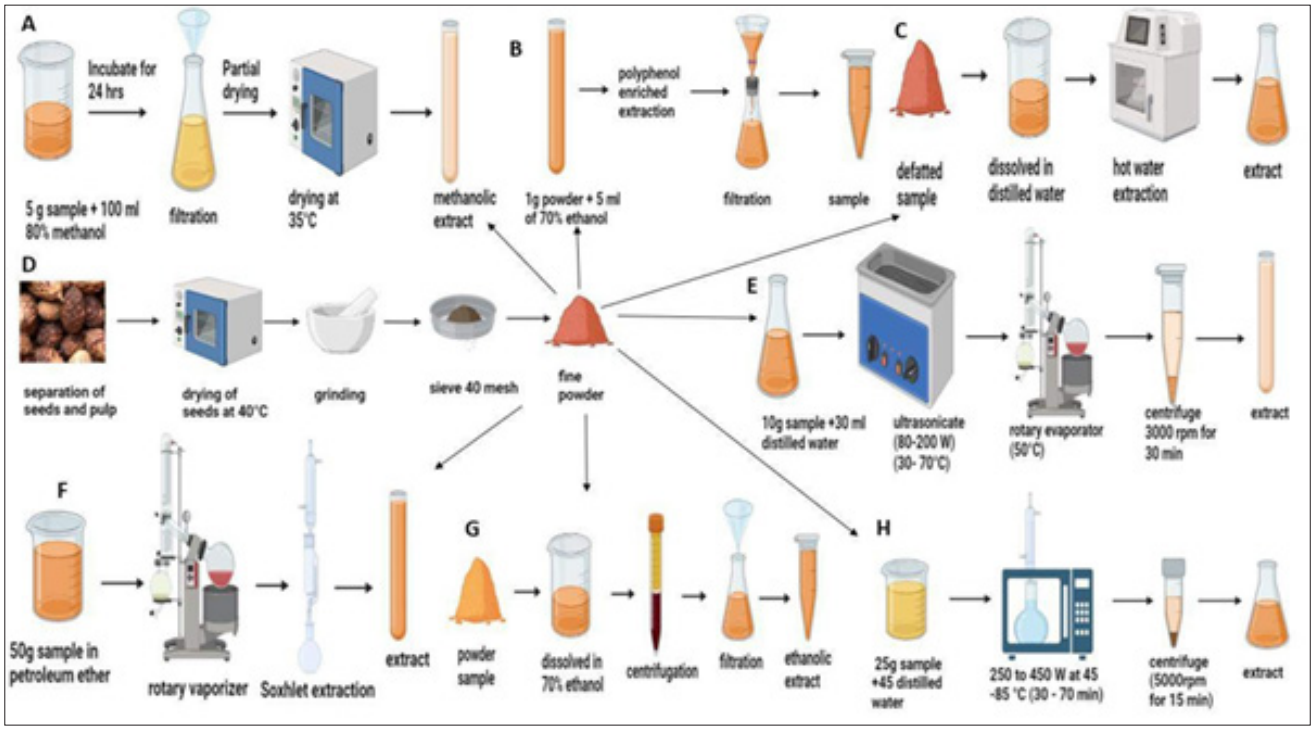


Figure 2: (A) Methanolic extract **(B)** Polyphenol enriched extract **(C)** Hot water extraction **(D)** Preparation of the powder **(E)** Ultrasound-assisted extraction **(F)** Soxhlet extraction **(G)** Ethanolic extract and **(H)** Microwave-assisted extraction.

Microwave-assisted extraction

A vessel system consisting microwave apparatus was used to extract jujube polysaccharides at 250 - 450 W at 45 - 85 ˚C for about 30 to 70 min and with a ratio of 25:45 w/w ratio of water to the jujuba seed powder. Followed by cooling and centrifugation at 5000 rpm for 15 min. Collect the precipitates in three cycles with 3 volumes of ethanol 95% v/v at 4 ˚C for 48 h. Dissolve the refined pellets in an adequate amount of the volume of the water and let it dialyze for about 4 days against water. Then deproteinize the retentate portion by the freeze- thaw process 10 times followed by filtration. Centrifuge the extracts to remove any insoluble particles collect the supernatant and lyophilize in the freeze-drying apparatus to get refined polysaccharide [34].

Polyphenol enriched extraction

Polyphenol enriched extraction was made from powdered *Ziziphus* seed. Three consecutive extractions were used to produce the extract (1 g powder in 5 ml 95 percent ethanol) at 25 ˚C until all phenolic components were used up. For thirty minutes, ultrasonography was used to help with each extraction. The samples were then combined, processed through filters, and dried in a Hoover stove [35].

Pharmacological effects

Ziziphus seeds have been studied to show sedative effects and hypnotic drugs in many Asian countries. Jujube seeds consist of a large amount of fatty acid, protein, sterols, terpenoid compounds like betulinic acid and botulin and also it is rich in vitamin C [36]. Extracts possess various properties and are used in the treatment of cardiovascular disease, reduce inflammation, gastrointestinal disorder like inflammatory bowel disease, sedative effects, anxiolytic properties which acts as neuroprotective in various cognitive disorders, antibacterial properties, antiulcer properties, antispastic properties, antiallergic, immunostimulant activity, hypotensive, antineuritic activity, antifertility/contraceptive activity, cancer (chemotherapy), wound healing capacity, sweetness inhibitor, permeability enhancement activity, purify blood help to cure anemia [17]. The fruits, seeds, and leaves of *Z. jujuba* are rich in bioactive secondary metabolites, which are fundamental molecules used to cure a variety of conditions and promote health. These conditions include allergies, urination issues, constipation, chronic bronchitis, liver illnesses, depression, and insomnia [37]. Studies have shown that *Ziziphi Spinosae Semen* has neuroprotective, sedative and hypnotic, hepatoprotective, wound-healing, anti-aging, and cognitive effects, as well as antioxidant, anti-inflammatory, anti-hypertensive, anti-bacterial, cytoprotective (antioxidant), anti-genotoxic, hematopoietic, anti-cancer, immunological and anti-complementary, synaptic transmission, and anti-anxiety activities as shown in table 2 [38, 39].

Erythropoiesis is thought to play a critical role in hematopoiesis, which is the process of red blood cell (RBC) production. In this process, EPO, an RBC-specific hormone, regulates erythropoiesis in the bone marrow. Jujube extract possesses hematopoietic function both *in vivo* and *in vitro*. Jujube contains certain components like flavonoids, saponin, polysaccharides, terpenoids, nucleotides, etc., which are responsible for erythropoiesis, erythropoiesis, erythrophagocytosis and other immune functions that help in treatment of anemia. Jujube promotes erythropoiesis by activating hypoxia-inducible factor-induced erythropoietin and has the potential to recycle heme iron during erythrophagocytosis, has a bidirectional role in regulating immune response under different conditions, and contains a variety of minerals, including iron. It stimulates expression of HIF thus activating it and which further induces EPO i.e., hormone stimulating blood production through its HRE sites present on the mRNA thus altering gene expression and increasing the EPO production thus increasing erythropoietin production and forming more RBC and increasing blood formation. Also, it causes the formation of lymphocytes T and B cells leading to an immune response [40]. Similar studies were conducted by [41] that it is also can be beneficial in preventing hematopoiesis and erythrophagocytosis.

Gastrointestinal health

The primary organ responsible for the movement and transformation that forms the basis and source of blood is the spleen. In terms of nutrition metabolism and immunological function, it performs duties that are comparable to those of the gut microbiota. Shwachaman diamond syndrome symptoms like numbness, abdominal distension, constipation, and weakness can arise when the structure and function of the gut microbiota are out of balance, and the imbalance of the gut microbiota may be a key biological mechanism of SDS according to traditional Chinese medicine. This study showed the impact of the seed extract from *Z. jujuba var. spinosa* on the variety of gut microbiota in rats with SDS, including *Lactobacillus* and *Bifidobacterium* which plays an important role in maintaining gastrointestinal health. The flavonoids present in *Ziziphi Spinosae Semen* can be easily metabolized by gut microbiota for instance, *Lactobacillus* is frequently employed in medicine as a probiotic to prevent the growth of tumors and to treat illnesses of the urinary and digestive tracts. Additionally, because it improves mouse immune function as part of its antitumor strategy, it may also contribute to better intestinal immune function [42-43]. *Ziziphus spina-christi* polysaccharides have been demonstrated to provide a protective role in mice with colitis brought on by 2,4,6-trinitrobenzene sulfonic acid. *ZSS* polysaccharides regulate TLR4 and NF-B (nuclear factor kappa-light- chain-enhancer of activated B cells) signaling pathways, due to which they have immunomodulatory effects. *ZSS* polysaccharides were found to reduce the production of pro- inflammatory cytokines like TNF-α, IL-1 (interleukin-1 beta), and IL-6, by inhibiting the activation of TLR4 and subsequent downstream signaling pathways, such as NF-B and MAPK (mitogen-activated protein kinase). The production of anti-inflammatory cytokines including IL-10 and TGF-β (transforming growth factor beta) was also found to be increased by *ZSS* polysaccharides, aiding in the reduction of inflammation. These results imply that *ZSS* polysaccharides could have the potential to be therapeutic in the treatment of inflammatory bowel disease [3].

Anti-hypertensive property

Elevated blood pressure known as hypertension is one of the major risk factors of premature morbidity and mortality worldwide. It often includes increased risk factors for cardiovascular diseases, such as type 2 diabetes, hypercholesterolemia, gout, or obesity [44, 45]. Hypertension is the most important threat to cardiovascular diseases. It is majorly controlled by Angiotensin-I-converting enzyme (ACE) and is generally inhibited by certain drugs to treat the hypertension issue but it may cause some of the side effects. Renin angiotensin pathway is majorly responsible to maintain the blood pressure of the body. ACE is a kind of protein that is involved in salt retention and maintaining the water balance and hence the blood pressure inside the blood vessels [46]. ACE involves the production of vasoconstrictive effects which also results in the release of the free radical hence increasing oxidative stress moreover it leads to the degradation of the bradykinins which are a potent vasodilator. The elevated levels of angiotensin increase the activity of nicotinamide adenine dinucleotide oxidase which increases the production of the free radicals. Drugs such as captopril and enalapril are used to prevent hypertension as these are potent inhibitors of the ACE but may include some side effects [47]. Jujuboside B noticeably tends to inhibit platelet aggregation and is considered to possess an active ingredient for the anti-platelet effect. During the acute hypertension induced intentionally in mice model, there was an elevation in systolic blood pressure and also the mean arterial pressure which also caused a decline in heart rate when treated with jujube extracts notably showed a protective effect and attenuated blood pressure and mean arterial pressure and restored the cardiovascular condition [48, 49]. Jujube seeds contain triterpenoids such as oleanonic acid, pomolic acid, and pomonic acid which inhibit foam cell formation and also maintain the total cholesterol level in the body [50-51].

Anti-diabetic property

Diabetes is the inability of the body to regulate the blood glucose level due to impairment in the release of insulin which is majorly responsible to maintain the blood glucose level, it also includes retinopathy, nephropathy, and neuropathy [52, 53]. *Z. jujuba* seeds are also effective in the maintenance of blood glucose and also lipid compositions when tested in the serum of dietary hyperlipidemic rats [54]. A study on mice was conducted on alloxan-induced mice of the ethanolic extracts of the seeds to study the hypoglycemic effects, it was observed that certain compounds present in the seeds which are polysaccharides, flavonoids, terpenoids. Tannins and some of the alkaloids are responsible for the hypoglycemic activity of the mice. It was observed that the administration of the extracts of the seeds for four weeks in the mice improved the blood glucose level and is effective in reducing hypoglycemic conditions in the mice these effects were due to the saponin and the triterpenoids in the seeds extracts [55]. Diabetic rats were treated with the doses of the *Z. jujuba* extracts 200 to 400 mg/kg bwt for six weeks which showed a lowering of the abnormally increased blood glucose level. It helped in the restoration of the hepatic and muscle glycogen levels and improved hexokinase activity that is involved in glycogenesis [56]. Additionally, the presence of bioactive substances may explain its protective effects against cardiovascular illnesses and type II diabetes as well as its anti-proliferative, anti-inflammatory, antioxidant, anti-obesity, anticancer, and pro-apoptotic action [37].

Hepatoprotective property

The liver is a vital organ in the human body and a primary location of xenobiotic metabolism. Toxic substances, medications, and virus infiltration by ingesting or any kind of infection of them can harm it affecting many metabolic pathways and other processes in the body [57]. Enzymatic indicators and markers for the estimation of hepatic injury like AST and ALT, which leak from hepatocytes into the bloodstream due to increased membrane permeability, can be used to measure the level of hepatic damage. The elevated levels of AST and ALT indicate the extent of the liver's structural integrity had been severely damaged. Therefore, the activity of the enzymes ALT and AST can be measured to assess hepatoprotective activity. However, some natural products have drawn a lot of interest to prevent liver injury to protect the liver from harm as hepatoprotective drugs may cause some side effects in the body. Polysaccharides extracted from the seeds of *Z. jujuba* can be useful to protect the liver from any damage due to its high antioxidant properties. The polysaccharide can be extracted from the sarcocarp of the seed which is a good source and has a bright red color used in many beverages and as functional food since ancient times. Cytochrome P4502E1 (CYP2E1) is an enzyme that is involved in the breakdown of CCl4 into the radical's trichloromethyl and proxy trichloromethyl, which can initiate the process of membrane lipid peroxidation and eventually lead to cell damage and finally cell necrosis. CCl4 can induce the mechanism for xenobiotic-induced oxidative hepatotoxicity that has been studied to increase oxidative stress. The intracellular antioxidant defense process involves scavenging free radicals and decreasing the generation of reactive metabolites by increasing endogenous antioxidant activity levels to prevent and treat oxidative stress [1].

Additionally, a regulatory mechanism to regulate the intracellular antioxidant involves-the NF-E2-related factor (Nrf2) pathway, a transcription factor with redox sensitivity-that modifies the intracellular antioxidant. In severe circumstances, Keap1 (Kelch-like ECH-associated protein 1) inactivates Nrf2 in the cytoplasm. Keap1 is oxidized due to increased oxidative stress, which leads to a lower affinity for Nrf2. This allows Nrf2 to go to the nucleus and regulate the transcription of antioxidants and the phase II bio transferase. Thus, activation of the Nrf2 pathway will reduce oxidative stress. In a study for the estimation of the hepatoprotective effects of *Z. jujuba* seeds in comparison to glutathione which is having high antioxidant properties, it was found that the polysaccharides from the sarcocarp of wild jujube (*Z. jujuba Mill. var. spinosa (Bunge) Hu ex H. F. Chou*) have excellent antioxidant properties in vitro and plays a major role in hepato-protective effects against CCl4-induced liver damage by enhancing the activation of the Nrf2 pathway and inducing antioxidant defenses mechanism for scavenging of the free radicals [39]. Notably, the polysaccharides consist

of uronic acid (15.3%) in relatively high concentrations. In addition, it was identified as an acidic heteropolysaccharide that constituted 89.83% of all the quantitative monosaccharides and was abundant in glucose (38.59%), arabinose (23.16%), galacturonic acid (17.64%), and galactose (10.44%). Therefore, it has a high potential for antioxidant supplementation to protect people from inflammation and aging brought on by ROS and has hepato- protective effects [41].

Neurodegenerative disorders

Jujube extracts have properties of calming the mind and also help in improving the quality of sleep as it possesses qualities like neuroprotective effects and neurotrophic action hence it is helpful in neurodegenerative disorders like depression, insomnia, neurons impairment and is also beneficial in reducing oxidative stress as shown in figure 3. Hence its extracts are traditionally considered to function as neuro-beneficial i.e., benefiting the brain functioning.

Neuron differentiation

Jujube stimulates neurite outgrowth and the expression of neurotrophic factors via cAMP- dependent PKA signal-

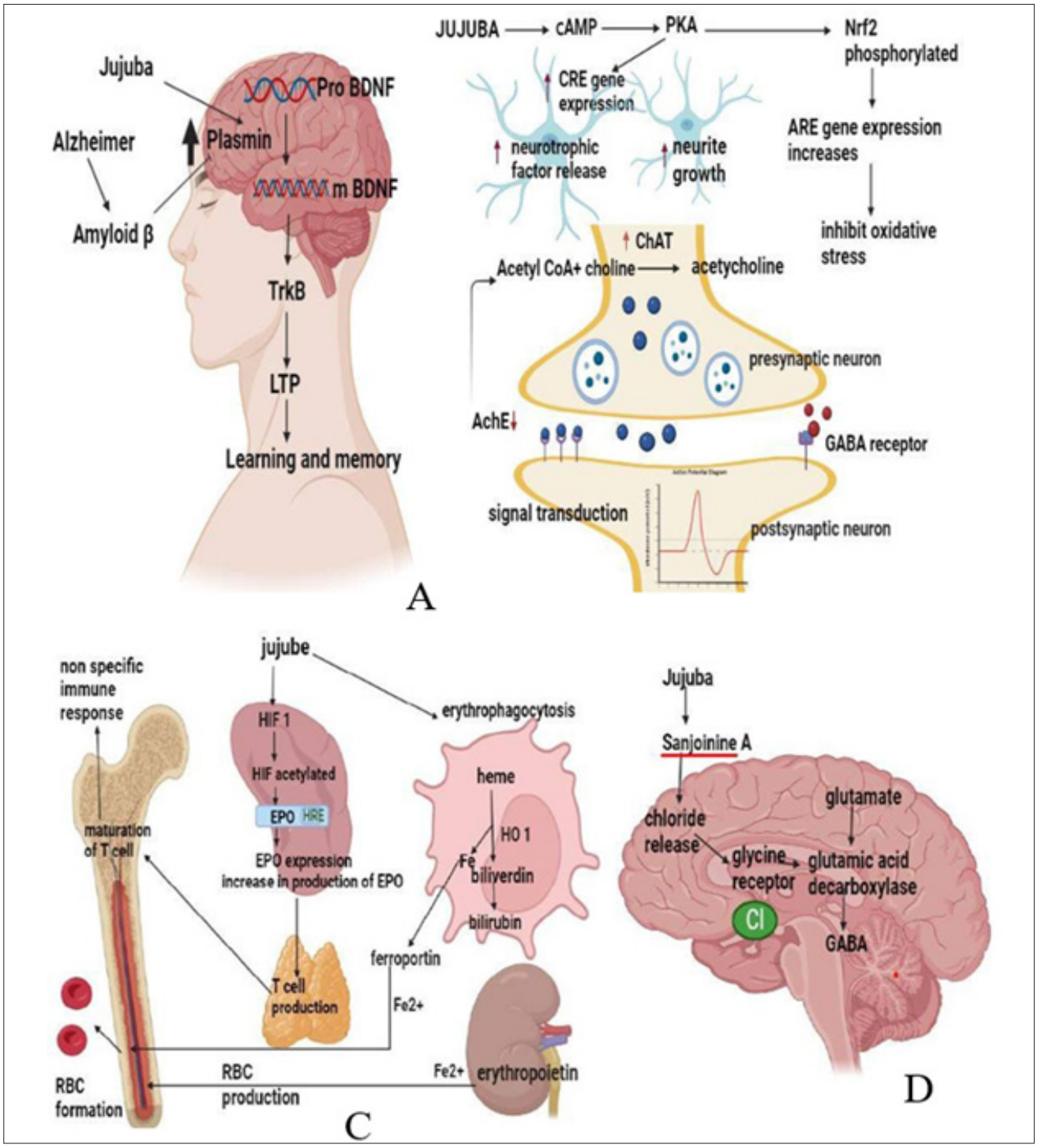


Figure 3: (A) mechanism of action of *Z. jujuba* on Alzheimer disease **(B)** mechanism of action of *Z. jujuba* on reducing the oxidative stress **(C)** mechanism of action of *Z. jujuba* showing effects of haematopoesis and **(D)** mechanism of action of *Z. jujuba* showing effects on Insomnia.

ing. Jujube inhibits the activity of choline acetyltransferase and increases AChE which causes the breakdown of Acetylcholine (Ach), an important neurotransmitter responsible for various cell signaling also it increases the expression for cellular Nrf2-dependent ARE-driven genes. The ACh levels in the brain are increased by jujube. In rat hippocampal neurons, it stimulates the transcriptional expression of GABA receptor subunits [42]. Similar results were obtained for the increases of the AChE in seizures for the uptake of the ACh released in the synaptic cleft [40].

Anxiolytic properties

In diseases like Parkinson's and Alzheimer diseases, there is neurodegeneration due to oxidative stress, and the function of the neuron is reduced. In cultured cells, it was observed that *Z. jujuba* extract noticeably decreases the oxidative stress caused due to tert-butyl hydroperoxide. This is caused due to activation of Nrf2 through phosphorylation by PKA which increases the transcriptional expression of the ARE gene which inhibits the tert-butyl hydroperoxide induced ROS which can cause the oxidative stress. Therefore, jujube extract protects the ischemic damage through antioxidant effects in the gerbil hippocampus [42]. Alzheimer's disease is a neurodegenerative disorder caused due to accumulation of amyloid plaque and neurofibrillary tangles in the hippocampus of the brain which affects memory and learning, through the modulation of serotonergic and neurotransmitters like GABA [29].

In Alzheimer's disease, the ameliorated induced dysfunction also affects the long-term potential through its impairment. Jujube extract increases the levels of the plasmin which causes the conversion of pro-BDNF to mature-BDNF which causes neurogenesis and is involved in synaptic plasticity in the hippocampus of the brain. BDNF further causes the activation of the TrkB which stimulates long-term potential which is essential in learning and memory [4]. Jujube extracts also inhibit AChE activity which is involved in the termination of the signals from one neuron to the other through synaptic cleft and through its uptake by converting it to acetyl CoA and choline by inhibiting AChE It maintains the level of the acetylcholine for proper nerve transmission [29]. The antidepressant activity was shown to increase the expression of BDNF, which is crucial for neurogenesis and antidepressant-like behavior.

The expression of BDNF in the mouse hippocampus has been reported to rise with long-term antidepressant use [7]. BDNF levels were higher in the dosed groups' hippocampal tissues than they were in the negative control group when the mice were introduced to the extract of seeds [7]. In Chinese herbal medicine jujube extracts are used to treat insomnia and markedly increase learning and memory. *Z. jujuba* consists of flavonoids that have sedative and hypnotic effects which help in increasing the quality of sleep hence treating insomnia as it stimulates the expression of GABA receptors in the hippocampus. It was observed that jujube extracts also increase neurotransmitter production like nitric oxide and ACh and hence increases estrogen production helping in disorders characterized by dementia improvising learning and memory [42].

Anti-cancer activity

A hepatocellular carcinoma is a form of cancer caused by hepatocytes (cells of the liver) which is responsible for death worldwide. *Z. jujuba Mill* seeds extract has anticancer activity as it causes apoptosis of cancer-causing cells due to an increase in the ROS level in human hepatoma cells (Hep G2) which can cause impairment of various intra and extra-mitochondrial membrane transport system and distribution of the ions in the mitochondrial membrane thus decreasing the potential of the mitochondrial membrane which causes apoptosis of the cells through arresting the cell cycles at different phase and thus scavenging the increased level of the ROS in the hepatocytes through apoptosis, necrosis and affecting the cell proliferation of these cells [1]. Jujube extract blocks the ROS regeneration through Fenton Reaction through conversion of hydroxyl peroxide which produces hydroxyl free radicals hence reducing the oxidative stress [29]. Jujube extracts also have a dual regulation by MAPK that regulates cell proliferation and cell death, activation of NF-kB can also induce the apoptosis of the cells that are affected through regulating the mitochondrial pathway [40]. In this investigation, we looked at the potential for five bioactive flavonoid glycosides from the dried mature seeds of *Z. jujuba var. inermis (Bunge)* Rehder to have anti-melanogenic effects. By reducing tyrosinase enzyme activity and the cAMP-CREB-mediated MITF axis, JUB, EPA, and FRS displayed strong anti-melanogenic actions [58]. The results demonstrated that the essential oil of *Z. jujuba* seeds exhibits antitumor and apoptotic properties through the expression of genes related to colorectal cancer carcinogenicity, p53, and KRAS, suggesting that these effects may be related to essential oil compounds, particularly eugenol [59]. Triterpenic acids were thought to be the main components responsible for the anti-inflammatory and anti-cancer effects [60].

Anti-inflammatory and anti-microbial

Inflammation is a physiological response of the body to stimuli such as infections and tissue injury. Excessive or persistent inflammation, on the other hand, causes a variety of pathological conditions such as bacterial sepsis, rheumatoid arthritis, and skin inflammation. The skin, as the primary interface between the body and the external environment, serves as the first line of defense against traumatic injury and microbial pathogen invasion. The skin has many active defense mechanisms in addition to its physical barrier properties, and regulation of these mechanisms is critical, as inappropriate or misdirected immune activity is implicated in the pathogenesis of a wide range of inflammatory skin disorders [61]. The essential oil of *Z. jujuba* may be useful as a therapeutic agent for the treatment of various inflammatory diseases. Seed essential oils are secondary metabolites with pharmacological properties due to phenolic compounds, oxygenated mono- and sesquiterpenes, and their respective hydrocarbons that are primarily anti-oxidative, antimicrobial, or immunomodulatory. Essential oil has been shown to have significant anti-inflammatory effects in a variety of inflammation models. It also reduces the release of prostaglandin which can initiate the inflammatory response, so jujube extracts reduce the levels of nitric oxide and histamine released as an inflammatory re-

sponse [40]. Jujube seeds consist of the components known as spinosyn that help in reducing inflammation it is done by inhibiting the specialized leukocytes and neutrophils that are involved in causing the inflammatory response in the body that is studied for the variety *ZSS* that are mature seeds of *Z. jujuba Mill. var. Spinosa* [31]. Infectious diseases like inflammatory bowel disease, obesity, etc. are only a few of the disorders that can be prevented in large part by maintaining a healthy intestinal epithelial barrier. In studies, the seeds of sour jujube (*Z. jujuba Mill. var. Spinosa*) were used to isolate three new acidic polysaccharides, ZY-2, ZY-3, and ZY-4 through its property of protecting intestinal epithelial barrier function anti-inflammatory properties, the acidic polysaccharides from sour jujube seeds showed anti-inflammatory properties [39]. Seeds extracts are also used to treat eye inflammation and leucorrhoea [13]. The bioactive substances that are found in the most potent extracts of the seeds were triterpenic acids that result in the anti-inflammatory property against the bacteria studied in research [62]. The mature seed has positive effects on disorders of the central nervous system, and it was frequently used to treat insomnia and as a functional food to enhance learning and memory while also improving sleep quality [1].

Hyperpigmentation

Melanin is synthesized by melanocytes that can cause pigmentation in the skin due to transferring of synthesized melanin to keratinocytes through dendrites of melanocytes. Melanin is synthesized through hydroxylation and oxidation of a copper-containing enzyme called tyrosinase. This reaction is catalyzed by the tyrosinase enzyme converting L- tyrosinase to 3,4-dihydroxy-L-phenylalanine and then it is oxidized to dopaquinone. Hyperpigmentation can be decreased by inhibition by suppression of melanin production. The seeds of *Z. jujuba* exhibit properties to inhibit the activity of tyrosinase hence suppressing the production of melanin showing anti-melanogenic effects. Thus, preventing melanogenesis which can be caused due to various reasons like melisma, freckles, and senile lentigines [11]. Spinosin is a flavonoid found in *Z. jujuba* due to which it shows anti-melanogenic and anti-tyrosinase activity. Spinosin suppresses the activity of melanocyte-stimulating hormone [48]. Studies have shown the potential for five bioactive flavonoid glycosides from the dried mature seeds of *Z. jujuba var. inermis (Bunge)* Rehder to have anti-melanogenic effects. The process of melanin synthesis in melanocytes, known as melanogenesis, involves the signaling system known as the cAMP-PKA-CREB axis. A second messenger called cAMP (cyclic adenosine monophosphate) stimulates protein kinase A, which phosphorylates CREB (cAMP response element-binding protein). Tyrosinase, the primary enzyme in melanogenesis, and other genes involved in melanin synthesis are activated by phosphorylated CREB binding to DNA and transcriptional activation. Hyperpigmentation can be treated and melanin production reduced by inhibiting this mechanism. By reducing tyrosinase enzyme activity and the cAMP-CREB-mediated MITF axis, JUB, EPA, and FRS displayed strong anti- melanogenic actions [58].

Sleeping disorder

Insomnia is a common and refractory sleep disorder characterized by frequent difficulty falling asleep and/or maintaining sleep, resulting in inadequate sleep. The most common symptoms are difficulty falling asleep, poor sleep quality, insufficient sleep time, and poor memory and attention. Insomnia is becoming more common as the pace of life quickens and work demands become more demanding. Insomnia can have adverse effects like chronic pain, sleep apnea, and cerebral infarction, can adversely affect the cardiovascular system and it also increases the risk of obesity, hypertension, and type 2 diabetes. Commonly used drugs such as benzodiazepines and nonbenzodiazepines can have a lot of side effects such as addiction and with-drawl symptoms. Jujube extracts regulate the neurotransmitter like serotonin, dopamine, glutamic acid, etc. maintaining the hypothalamic–pituitary–adrenal axis hormone levels thus, improving the central nervous system this process overall enhances the mood, behavior, and cognitive function thus improving the quality of the sleep [62]. Jujube extracts consist of a mixture of phytochemicals including alkaloids, saponins, and flavonoids.

Sanjonine A is a natural jujuboside present in the jujube seed which increases the synthesis of the GABA neurotransmitter which is inhibitory through the GABAergic pathway, involve the opening of the chloride channels and binding to the glycine receptors which complements the GABAergic pathway in the ventrolateral preoptic nucleus by activation of enzyme glutamic acid decarboxylase to synthesize GABA which is released at synaptic cleft and stops the transmission of the signals and leading to sleep [51]. Similar studies [52] showed that the seeds of jujube have sedative and hypnotic effects that can cure sleeping disorders. As a result of saponin hydrolysis, the primary byproducts were determined to be JuB and jujubogenin. According to our previous study, the rat intestinal flora could likewise break down the saponin into seven different metabolites, 23 with JuB and jujubogenin serving as the main hydrolysis byproducts.

This finding suggests that saponin may be the form that is absorbed and has the desired bioactivity. The sedative-hypnotic effects of JuB and jujubogenin were studied in highly purified and typical hippocampus neurons. According to a cell viability study, JuB had some sort of proliferative effect on the neurons. The sedative- hypnotic effect was primarily caused by GABA (A) 1, while GABA(A) 5 mediated muscular relaxation, which could hasten the emergence of the sedative-hypnotic effect [49]. A pharmacological investigation also showed that *ZSS* aqueous extract induced a sedative-hypnotic effect in insomnia model rat brains by increasing serotonin GABA, and dopamine levels while decreasing noradrenaline and glutamic acid levels [63].

Applications

Z. jujuba seeds often known as Chinese dates are used in both the food sector and non- food sectors in various ways jujube seeds are used medicinally in traditional Chinese medicine to treat a variety of illnesses, including digestive prob-

lems, sleeplessness, and anxiety. Additionally, it is thought that they have a relaxing impact on the nervous system [40, 42]. It is utilized in cooking particularly in some Asian cuisines that utilize jujube seeds to flavor foods. To add flavor and medicinal benefits to tea, they can be roasted, pounded into a powder, and used as a spice. Because of its moisturizing and anti-inflammatory effects, jujube seed oil is utilized in various cosmetic products. It is thought to help increase skin suppleness and lessen the visibility of wrinkles and fine lines [11, 49]. These are also used for the formation of the sodium or calcium alginates [64]. Cold pressing, which entails crushing the seeds and obtaining the oil without the use of heat, is the method used to extract the oil from the seeds [65].

Pharmaceuticals

Seeds extracts are used in the pharmaceutical as mucilage tables and also as essential oil and ingredients in many medicines due to property of anti-inflammatory, anti-microbial, and anti- hypotensive which make it highly potential to be used for treatment for many the disease especially, helping treat neurodegenerative disorders and sleeping disorders to its sedative and hypnotic properties. It is also used in the formation of mucilage tablets for proper delivery of drugs as shown in table 3 [66-68]. These are also used in preparation of the seeds essential oil due its anti-inflammatory properties.

Non-food sector

Jujube seeds have several uses outside of the food industry in addition to potential medical uses. A strong source of fatty acids, jujube seed oil has been utilized to make cosmetics and skincare items and hair care products [63, 65]. It is a common ingredient in anti-wrinkle creams and lotions since it is thought to offer moisturizing and anti-aging qualities. These are also used for the preparation of the animal feeds [66]. Jujube seeds can be used to make biofuels as well. Biodiesel, a renewable and sustainable substitute for conventional fossil fuels, can be made from the oil derived from jujube seeds [67]. This use of jujube seeds has the potential to lessen our reliance on fossil fuels and lessen the harmful effects of climate change [69].

Toxicity and recommendations

It was found through many studies that consumption of jujube in the long term does not have any side effects as such. Parameters like sleeping patterns, salivation, mucous membranes, fur, and skin remain normal in animals even after high doses of jujube are not much affected. This means that it is usually very less and acutely toxic, but it may be harmful to certain populations. When tried on the insomniac patients its extract was very safe and it helped to reduce the side effects of Alprazolam [70]. In a study utilizing brine prawn lethality and agar gel disc diffusion bioassay for the identification of the cytotoxic and antibacterial activities of different crude fractions of locally grown *Z. jujuba,* butanol extract showed the highest toxicity and chloroform extract showed the lowest toxicity whereas methanol extract showed moderate toxicity [71].

The studies suggest that jujube extracts may have potential as natural antioxidants and antimicrobial agents, without causing harm to healthy cells. Further studies are needed to explain the mechanisms of action and potential therapeutic applications of these extracts. Seed extracts including water, dichloromethane, ethyl acetate, and hexane had no significant cytotoxic effect against both Jurkat and Vero cell lines and have less cytotoxicity effects [30]. Subsequently, the ability of the ethyl acetate fraction and its identified phenolics to prevent oxidative stress was evaluated using the MTT assay. PC-12 cells were pre-treated with different concentrations of the ethyl acetate fraction or individual phenolic compounds for 2 h before exposure to H_2O_2-induced oxidative stress. The results showed that the ethyl acetate fraction and all seven identified phenolics significantly increased cell viability compared to the H_2O_2 group in a dose-dependent manner. The highest protective effect was observed with rutin, which increased cell viability by 64.3% at 50 μM.

Some findings suggest that the ethyl acetate fraction and its identified phenolics have the potential as neuroprotective agents against oxidative stress-induced damage. However, further studies are needed to elucidate the underlying mechanisms and evaluate their efficacy *in vivo*. Similar to these results, rutin has no significant cytotoxicity in macrophages [4]. The seed and stem bark plant extract of this plant was found safe up to 4000 mg/kg body weight dose [72]. Extracts are found to show hepatotoxicity and nephrotoxicity it was demonstrated through experiments on the mice to check for the elevation in the levels of lymphocyte, platelets, RBC, neutrophils, white blood cells, Na^+, K^+, Ca^{2+} when ethanolic extracts of the *Ziziphus* seeds were there into the body of the mice in different concentration 200 mg/kg body weight, 600 mg/kg per body weight and 1000 mg/kg body weight for two weeks. It was found that the ethanolic extract was showing toxic effects between 600 to 1000 mg/kg body weight [73]. A measure of toxicity through LD50 resulted in a range of 1200.24 mg/kg in rats of the ethanolic and ethyl acetate extracts of the endocarp [52]. However, anti-nutritional factors like tannins are responsible for the anti-diabetic property due to its antioxidants effects.

Conclusion

Traditional medicine has long used jujube seeds to treat a variety of medical conditions, such as anemia, cognitive disorders, and anxiety. A variety of ailments can be treated with the help of the bioactive substances that are found in jujube seeds. Fatigue body, weakness, and other symptoms are due to the body's insufficiency in the production of red blood cells, which causes anemia jujube seeds to be used to treat it as well. Additionally, carbohydrates and flavonoids found in jujube seeds have been demonstrated to increase erythropoiesis, the process to form new RBC. It also contains immune modulatory properties, due to which they can help in immune system regulation. Jujube seeds also help to boost the formation of white blood cells, which are essential for battling infections and other disorders. Moreover, jujube seeds are also used for the treatment of many inflammatory conditions including arthritis and asthma as they also contain saponins and triter-

Table 3: Applications of the *Z. jujuba* seeds.

Products	Procedure	Results	Ref.
Food sector			
Protein hydrosylate	Extraction by distilled water and ammonium sulphate salt, by 50 mM Tris-HCl buffer pH 7.5 and ammonium sulphate, by 0.6 M NaCl, 0.1% HCl and ammonium sulphate, by acetic acid and acetone.	Antioxidant activity was 9.411 µM of TE/g for the peptide and for encapsulated peptide was 6.78 µM of TE/g. DPPH radical scavenging assay of peptide and encapsulated peptide was 17.54% and 13.016%, respectively.	[20]
Traditional medicine	Grinding of the seed, soaking, boiling and then straining the decoction.	Anti-inflammatory, antimicrobial, for treatment of diarrhoea.	[40, 42]
Cookies	Combination of the jujube flour and wheat flour in different amount (25, 50, 75, and 100%) flour (200 g), fat (100 g), sugar (50 g) and Egg (54 g).	Moisture content 2.61 - 3.61%, crude protein 11.25 - 12.39%, fat 25.76 - 26.51%, ash 3.03 - 3.31%, carbohydrate 51.73 - 53.24% and the energy value was between 484.40 and 522.95 Kcal.	[62]
Seed oil	Grinding of the seed, soaking, boiling and then straining the decoction.	Eugenol (48.3%), isoeugenol (11.83%), caryophyllene (9.16%), eucalyptol (3.27%), caryophyllene oxide (3.14%), benzaldehyde.	[40]
Alginates	Modification of the sodium alginates with octenyl succinic anhydride.	Highest yield 35.21% having anti-microbial, anti-carcinogenic, and anti-oxidants.	[65]
Non- food products		**Functional properties**	
Hair products	Preparation of hair oil from the essential seeds oil.	Hair growth promoting , anti-dandruf.	[63, 65]
Facial cream	Analysis of the anti- tyrosinase activity.	Spinosin was -6.8 kcal/mol prevents hyperpigmentation, anti-tyrosinase.	[11, 49]
Animal feed	Produced by grinding of the seeds forming a powder.	Goat feed, poultry feed.	[66]
Biofuel/ biodiesel	Synthesized with magnesium oxide nanoparticles using *Ziziphus mauritiana* seeds extract.	Plant extracts as reducing agents for the synthesis of nanoparticles and as feedstock for biodiesel production.	[67]
Pharmaceutical products			
Mucilage tablets	Drying of the plant material, grinding, soaking for 6 h, boiling followed by formation of the mucilage. Then extraction with acetone followed by partial drying.	Granulating and binding properties in tablets.	[68-70]
		Binding property of mucilage of 10% w/v of *Z. jujuba* is equivalent to 10% w/v of guar gum mucilage.	
		Novel drug delivery systems and good replacement for synthetic polymers.	
Essential oil	Determination of toxicity and cell viability through Trypan Blue, MTT and clonogenic methods.	The major constituents of the oil were eugenol (49.37%), isoeugenol (9.60%) and eucalyptol (5.38%). Caryophyllene oxide (2.93%) and benzaldehyde (2.34%).	[59]

penoids that have anti- inflammatory properties. Also, it contains substances that have a soothing impact on the nervous system, jujube seeds had also been used as a natural sedative. Jujube seeds may also be anti-cancer because some research suggests they can prevent the development of cancer cells and provide a lot of health benefits due to the presence of bioactive components.

Acknowledgements

The authors extend their appreciation to the Lovely Professional University to provide services for the collection of secondary data.

Conflict of Interest

There is no conflict of interest among authors

References

1. Hua Y, Guo S, Xie H, Zhu Y, Yan H, et al. 2021. *Ziziphus jujuba* Mill. var. spinosa (Bunge) Hu ex H. F. chou seed ameliorates insomnia in rats by regulating metabolomics and intestinal flora composition. *Front Pharmacol* 12: 653767. https://doi.org/10.3389/fphar.2021.653767
2. Jin X. 2018. Jujuba—*Ziziphus jujuba*. In Rodrigues S, de Oliveira Silva E, de Brito ES (eds) Exotic Fruits. Academic Press, Cambridge, pp 263-269.
3. Li FT, Yang D, Song FY, Liu M, Dai YL, et al. 2020. *In vitro* effects of ginseng and the seed of *Zizyphus jujuba* var. spinosa on gut microbiota of rats with spleen deficiency. *Chem Biodivers* 17(9): e2000199. https://doi.org/10.1002/cbdv.202000199
4. Kwon H, Jung IH, Yi JH, Kim JH, Park JH, et al. 2017. The seed of *Zizyphus jujuba* var. spinosa attenuates alzheimer's disease-associated hippocampal synaptic deficits through BDNF/TrkB signaling *Biol Pharm Bull* 40(12): 2096-2104. https://doi.org/10.1248/bpb.b17-00378

5. Park HJ, Jung IH, Kwon H, Yu J, Jo E, et al. 2019. The ethanol extract of *Zizyphus jujuba* var. spinosa seeds ameliorates the memory deficits in Alzheimer's disease model mice. *J Ethnopharmacol* 233: 73-79. https://doi.org/10.1016/j.jep.2018.12.043
6. Akbar S. 2020. *Ziziphus jujuba* Mill. (Rhamnaceae). In Handbook of 200 Medicinal Plants. Springer, Cham, pp 2007-2016.
7. Oh JM, Ji M, Lee MJ, Jeong GS, Paik MJ, et al. 2020. Antidepressant-like effects of ethanol extract of *Ziziphus jujuba* mill seeds in mice. *Appl Sci* 10(20): 7374. https://doi.org/10.3390/app10207374
8. Fakhar N, Khan SA, Siddiqi WA, Khan TA. 2021. *Ziziphus jujube* waste-derived biomass as cost-effective adsorbent for the sequestration of Cd^{2+} from aqueous solution: isotherm and kinetics studies. *Environ Nanotechnol Monit Manag* 16: 100570. https://doi.org/10.1016/j.enmm.2021.100570
9. Asan-Ozusaglam M, Demır FH, Koc G, Tacer S. 2021. Investigation of the usage potential of olive and jujube extracts as natural alternatives to chemical containing sun cream. In proceedings of 3rd International Agricultural, Biological & Life Science Conference. AGBIOL, Turkey.
10. Katzer T, Leite Junior A, Beck R, da Silva C. 2019. Physiopathology and current treatments of androgenetic alopecia: going beyond androgens and anti-androgens. *Dermatol Ther* 32(5): e13059. https://doi.org/10.1111/dth.13059
11. Moon KM, Hwang YH, Yang JH, Ma JY, Lee B. 2019. Spinosin is a flavonoid in the seed of *Ziziphus jujuba* that prevents skin pigmentation in a human skin model. *J Funct Foods* 54: 449-456. https://doi.org/10.1016/j.jff.2019.01.044
12. Akhter C, Dar GH, Khuroo AA. 2013. *Ziziphus jujuba* Mill. subsp. spinosa (Bunge) Peng, Li & Li: a new plant record for the Indian subcontinent. *Taiwania* 58(2): 132-135. https://doi.org/10.6165/tai.2013.58.132
13. Hossain MH. 2019. A phytopharmacological review on the Omani medicinal plant: *Ziziphus jujube. J King Saud Univ* 31(4): 1352-1357. https://doi.org/10.1016/j.jksus.2018.12.003
14. Zhao G, Cui X, Sun J, Li T, Wang QI, et al. 2021. Analysis of the distribution pattern of Chinese *Ziziphus jujuba* under climate change based on optimized biomod2 and MaxEnt models. *Ecol Indic* 132: 108256. https://doi.org/10.1016/j.ecolind.2021.108256
15. Khadivi A, Beigi F. 2022. Morphological and chemical characterizations of jujube (*Ziziphus jujuba* Mill.) to select superior accessions. *Food Sci Nutr* 10(7): 2213-2223. https://doi.org/10.1002/fsn3.2831
16. Hernández F, Noguera-Artiaga L, Burló F, Wojdyło A, Carbonell-Barrachina ÁA, et al. 2016. Physico-chemical, nutritional, and volatile composition and sensory profile of Spanish jujube (*Ziziphus jujuba* Mill.) fruits. *J Sci Food Agric* 96(8): 2682-2691. https://doi.org/10.1002/jsfa.7386
17. Gao QH, Wu CS, Wang M. 2013. The jujube (*Ziziphus jujuba* Mill.) fruit: a review of current knowledge of fruit composition and health benefits. *J Agric Food Chem* 61(14): 3351-3363. https://doi.org/10.1021/jf4007032
18. Chen K, Fan D, FU B, Zhou J, Li H. 2019. Comparison of physical and chemical composition of three Chinese jujube (*Ziziphus jujuba* Mill.) cultivars cultivated in four districts of Xinjiang region in China. *Food Sci Technol* 39(4): 912-921. https://doi.org/10.1590/fst.11118
19. Almansa S, Hernández F, Legua P, Nicolás-Almansa M, Amorós A. 2016. Physico-chemical and physiological changes during fruit development and on-tree ripening of two Spanish jujube cultivars (*Ziziphus jujuba* Mill.). *J Sci Food Agric* 96(12): 4098-4105. https://doi.org/10.1002/jsfa.7610
20. Kanbargi KD, Sonawane SK, Arya SS. 2016. Functional and antioxidant activity of *Ziziphus jujube* seed protein hydrolysates. *Food Measure* 10: 226-235. https://doi.org/10.1007/s11694-015-9297-5
21. Xue X, Zhao A, Wang Y, Ren H, Du J, et al. 2021. Composition and content of phenolic acids and flavonoids among the different varieties, development stages, and tissues of Chinese Jujube (*Ziziphus jujuba* Mill.). *PLoS One* 16(10): e0254058. https://doi.org/10.1371/journal.pone.0254058
22. Zheng Q, Li Q, Yang T, Qi W, Zhang Y, et al. 2022. Flavonoid glucosides from *Ziziphus jujuba* seeds improve learning and memory in mice. *Rev Bras Farmacogn* 32: 99-110. https://doi.org/10.1007/s43450-021-00227-5
23. Nwakife NC, Iyaka YA, Musa M. 2021. Proximate, elemental and anti-nutritional compositions of the pulp and seeds of *Zizyphus lotus* L. from minna metropolis and its environs. *KASU J Chem Sci* 1(2): 57-67.
24. Abd-Alrahman SH, Salem-Bekhit MM, Elhalwagy ME, Abdel-Mageed WM, Radwan AA. 2013. Phytochemical screening and antimicrobial activity of EthOH/Water *Ziziphus jujuba* seeds extracts. *J Pure Appl Microbiol* 7: 813-818.
25. Elaloui M, Ennajah A, Ghazghazi H, Youssef IB, Othman NB, et al. 2017. Quantification of total phenols, flavonoides and tannins from *Ziziphus jujuba* (mill.) and *Ziziphus lotus* (l.) (Desf). Leaf extracts and their effects on antioxidant and antibacterial activities. *Int J Sec Metabolite* 4(1): 18-26. https://doi.org/10.21448/ijsm.275886
26. Hassan AB, Al Maiman SA, Mohammed MA, Alshammari GM, Alkhudhayri DA, et al. 2021. Effect of natural fermentation on the chemical composition, mineral content, phytochemical compounds, and antioxidant activity of *Ziziphus spina-christi* (L.) "Nabag" Seeds. *Processes* 9(7):1228. https://doi.org/10.3390/pr9071228
27. Salimi M, Sarkhail P, Sarkheil P, Kandelous HM, Baeeri M. 2016. Evaluation of anti-melanogenic activity of *Ziziphus jujuba* fruits obtained by two different extraction methods. *Res J Pharmacogn* 3(2): 1-7.
28. Wu Z, Li H, Wang Y, Yang D, Tan H, et al. 2019. Optimization extraction, structural features and antitumor activity of polysaccharides from *Z. jujuba cv. Ruoqiangzao* seeds. *Int J Biol Macromol* 135: 1151-1161. https://doi.org/10.1016/j.ijbiomac.2019.06.020
29. Choi J, An X, Lee BH, Lee JS, Heo HJ, et al. 2015. Protective effects of bioactive phenolics from jujube (*Ziziphus jujuba*) seeds against H_2O_2–induced oxidative stress in neuronal PC-12 cells. *Food Sci Biotechnol* 24: 2219-2227. https://doi.org/10.1007/s10068-015-0296-4
30. Rajaei A, Salarbashi D, Asrari N, Fazly Bazzaz BS, Aboutorabzade SM, et al. 2020. Antioxidant, antimicrobial, and cytotoxic activities of extracts from the seed and pulp of Jujube (*Ziziphus jujuba*) grown in Iran. *Food Sci Nutr* 9(2): 682-691. https://doi.org/10.1002/fsn3.2031
31. Liu SJ, Lv YP, Tang ZS, Zhang Y, Xu HB, et al. 2020. *Ziziphus jujuba* Mill., a plant used as medicinal food: a review of its phytochemistry, pharmacology, quality control and future research. *Phytochem Rev* 20: 507-541. https://doi.org/10.1007/s11101-020-09709-1
32. Ali AB, Almagboul AZ, Mohammed OM. 2015. Antimicrobial activity of fruits, leaves, seeds and stems extracts of *Ziziphus spina-christi. Arab J Med Aromatic Plants* 1(2): 94-107. https://doi.org/10.48347/IMIST.PRSM/ajmap-v1i2.4325
33. Lin T, Liu Y, Lai C, Yang T, Xie J, et al. 2018. The effect of ultrasound assisted extraction on structural composition, antioxidant activity and immunoregulation of polysaccharides from *Ziziphus jujuba* Mill var. *spinosa* seeds. *Ind Crops Prod* 125: 150-159. https://doi.org/10.1016/j.indcrop.2018.08.078
34. Rostami H, Gharibzahedi SMT. 2016. Microwave-assisted extraction of jujube polysaccharide: optimization purification and functional characterization. *Carbohydr Polym* 143: 100-107. https://doi.org/10.1016/j.carbpol.2016.01.075
35. Orqueda ME, Torres S, Zampini IC, Isla MI. 2022. *In vitro* hypoglycemic and anti-inflammatory potential and toxicity of powders from pulp and by-products of *Ziziphus mistol* from Argentina. *Foods* 11(14): 2125. https://doi.org/10.3390/foods11142125
36. San AM, Thongpraditchote S, Sithisarn P, Gritsanapan W. 2013. Total phenolics and total flavonoids contents and hypnotic effect in mice of *Ziziphus mauritiana* Lam. seed extract. *Evid Based Complement Alternat Med* 835854. https://doi.org/10.1155/2013/835854

37. Wojdyło A, Carbonell-Barrachina ÁA, Legua P, Hernández F. 2016. Phenolic composition, ascorbic acid content, and antioxidant capacity of Spanish jujube (*Ziziphus jujube* Mill.) fruits. *Food Chem* 201: 307-314. https://doi.org/10.1016/j.foodchem.2016.01.090

38. Gong L, Xie JB, Luo Y, Qiu ZD, Liu JR, et al. 2023. Research progress of quality control for the seed of *Ziziphus jujuba* var. spinosa (Bunge) Hu ex H.F. Chow (Suan-Zao-Ren) and its proprietary Chinese medicines. *J Ethnopharmacol* 307: 116204. https://doi.org/10.1016/j.jep.2023.116204

39. Liu SY, Gu B. 2023. Three new 8,4'-type oxyneolignans from the seeds of *Ziziphus jujuba* mill and their antitumor studies. *Nat Prod Res* 37(9): 1573-1576. https://doi.org/10.1080/14786419.2021.2023144

40. Rodriguez Villanueva J, Rodriguez Villanueva L. 2017. Experimental and clinical pharmacology of *Ziziphus jujuba* Mills. *Phytotherapy research* 31(3): 347-365. https://doi.org/10.1002/ptr.5759

41. Yue Y, Wu S, Zhang H, Zhang X, Niu Y, et al. 2014. Characterization and hepatoprotective effect of polysaccharides from *Ziziphus jujuba* Mill. var. spinosa (Bunge) Hu ex H. F. Chou sarcocarp. *Food Chem Toxicol* 74: 76-84. https://doi.org/10.1016/j.fct.2014.09.006

42. Chen J, Liu X, Li Z, Qi A, Yao P, et al. 2017. A review of dietary *Ziziphus jujuba* Fruit (Jujube): developing health food supplements for brain protection. *Evid Based Complement Alternat Med* 2017: 3019568. https://doi.org/10.1155/2017/3019568

43. Liu Y, Zhao X, Lin T, Wang Q, Zhang Y, et al. 2020. Molecular mechanisms of polysaccharides from *Ziziphus jujuba* Mill var. *spinosa* seeds regulating the bioavailability of spinosin and preventing colitis. *Int J Biol Macromol* 163: 1393-1402. https://doi.org/10.1016/j.ijbiomac.2020.07.229

44. Agunloye OM, Oboh G, Ademiluyi AO, Ademosun AO, Akindahunsi AA, et al. 2019. Cardio-protective and antioxidant properties of caffeic acid and chlorogenic acid: mechanistic role of angiotensin converting enzyme, cholinesterase and arginase activities in cyclosporine induced hypertensive rats. *Biomed Pharmacother* 109: 450-458. https://doi.org/10.1016/j.biopha.2018.10.044

45. Polaczyk M, Olszanecka A, Wojciechowska W, Rajzer M, Stolarz-Skrzypek K. 2022. The occurrence of drug-induced side effects in women and men with arterial hypertension and comorbidities. *Kardiol Pol* 80(11): 1094-1103. https://doi.org/10.33963/kp.a2022.0232

46. Mengesha HG, Petrucka P, Spence C, Tafesse TB. 2019. Effects of angiotensin converting enzyme gene polymorphism on hypertension in Africa: a meta-analysis and systematic review. *PLoS One* 14(2): e0211054. https://doi.org/10.1371/journal.pone.0211054

47. Chen J, Tsim KWK. 2020. A review of edible Jujube, the *Ziziphus jujuba* fruit: a heath food supplement for anemia prevalence. *Front Pharmacol* 11: 593655. https://doi.org/10.3389/fphar.2020.593655

48. Aafi E, Shams Ardakani MR, Ahmad Nasrollahi S, Mirabzadeh Ardakani M, Samadi A, et al. 2022. Brightening effect of *Ziziphus jujuba* (jujube) fruit extract on facial skin: a randomized, double-blind, clinical study. *Dermatol Ther* 35(7): e15535. https://doi.org/10.1111/dth.15535

49. Song P, Zhang Y, Ma G, Zhang Y, Zhou A, et al. 2017. Gastrointestinal absorption and metabolic dynamics of Jujuboside A, A Saponin derived from the seed of *Ziziphus jujuba*. *J Agric Food Chem* 65(38): 8331-8339. https://doi.org/10.1021/acs.jafc.7b02748

50. Du C, Yan Y, Shen C, Cui X, Pei X, et al. 2020. Comparative pharmacokinetics of six major compounds in normal and insomnia rats after oral administration of Ziziphi Spinosae *Semen* aqueous extract. *J Pharm Anal* 10(4): 385-395. https://doi.org/10.1016/j.jpha.2020.03.003

51. Shergis JL, Ni X, Sarris J, Zhang AL, Guo X, et al. 2017. *Ziziphus spinosa* seeds for insomnia: a review of chemistry and psychopharmacology. *Phytomedicine* 34: 38-43. https://doi.org/10.1016/j.phymed.2017.07.004

52. Soni H, Malik JK. 2021. Phyto-pharmacological potential of *Zizyphus jujube*: a review. *Sch Int J Biochem* 4(2): 1-5. https://doi.org/10.36348/sijb.2021.v04i01.001

53. Şensu E, Duran A, Özçelik B, Yücetepe A. 2023. Investigation of changes in some bioactive properties of phenolic extracts from pulp and seed tissues of *Ziziphus Jujuba* during *in vitro* digestion. *J Food* 48(3): 602-613. https://doi.org/10.15237/gida.GD23033

54. Mi W, Guo YJ, Hu P, Di X. 2022. Three new sesquineolignans from the seeds of *Ziziphus jujuba*. *Nat Prod Res* 36(14): 3638-3643. https://doi.org/10.1080/14786419.2021.1875465

55. Sakna ST, Maghraby YR, Abdelfattah MS, Farag MA. 2022. Phytochemical diversity and pharmacological effects of triterpenes from genus *Ziziphus*: a comprehensive review. *Phytochem Rev* 1-26. https://doi.org/10.1007/s11101-022-09835-y

56. Al-Awar MS. 2019. Anti-diabetic activities of *Zizyphus spina-christi* seeds embryos extract on general characteristics of diabetes, carbohydrate metabolism enzymes and lipids profile in rats. *Jordan J Pharm Sci* 12(2): 91-107.

57. Lavryshyn Y, Gutyj B. 2019. Protein synthesize function of bulls liver at experimental chronic cadmium toxicity. *Sci Messen LNU Vet Med Biotechnol Ser Vet Sci* 21(94): 92-96. https://doi.org/10.32718/nvlvet9417

58. Molagoda IMN, Lee KT, Athapaththu AMGK, Choi YH, Hwang J, et al. 2021. Flavonoid glycosides from *Ziziphus jujuba* var. *inermis* (Bunge) rehder seeds inhibit α-Melanocyte-stimulating hormone-mediated melanogenesis. *Int J Mol Sci* 22(14):7701. https://doi.org/10.3390/ijms22147701

59. Zamani Z, Ghodousi-Dehnavi E, Haji Hosseini R, Arjmand M, Nasri S. 2021. Apoptosis induced by *Zizyphus jujuba* seed essential oil in colorectal cancer cells line HT-29. *J Med Herbs* 12(3): 61-69.

60. Shahrajabian MH, Sun W, Cheng Q. 2020. Survey on some important functional foods from the Chinese and Eastern perspective. *Polish J Agron* 43: 47-56.

61. Jalil MIM, Mujassam M, Ahmad AA, Chinchulkar MG, Ibrahim NAS, et al. 2021. Investigations on *Ziziphus Jujuba* seed extract for antimicrobial activity -- a pilot study. *Int J Creative Res Thoughts* 9(12): 195-209.

62. Saadoudi M, Hambaba L, Abdeddaim M, Lekbir A, Bacha A, et al. 2017. Nutritional composition, physical properties and sensory evaluation of biscuit produced from jujubes (Fruits of *Zizyphus lotus* L.). *Ann Food Sci Technol* 18(3): 395-401.

63. Khoshdouni Farahani Z, Mousavi M, Seyedain Ardebili SM, Bakhoda H. 2021. Modification of sodium alginate by octenyl succinic anhydride to fabricate beads for encapsulating jujube extract. *Curr Res Food Sci* 5: 157-166. https://doi.org/10.1016/j.crfs.2021.11.014

64. Sekar M, Priya NV, Ramesh R, Kumar GS, Bharati AD, et al. 2016. Formulation and evaluation of hair tonic from *Ziziphus jujuba* leaf extract. *Int J Pharm Chem Biol Sci* 6(4): 447-454 .

65. Santhi R, Durairaj B, Manobharathi V. 2018. Enthralling the antidandruff potential of *Ziziphus jujuba* leaf and seed extracts and formulating a bioactive shampoo on *Malassezia* species. *Int J Pharm Pharm Res* 12(1): 348-357.

66. Xie B, Wang PJ, Yan ZW, Ren YS, Dong KH, et al. 2018. Growth performance, nutrient digestibility, carcass traits, body composition, and meat quality of goat fed Chinese jujube (*Ziziphus jujuba* Mill) fruit as a replacement for maize in diet. *Anim Feed Sci Technol* 246: 127-136. https://doi.org/10.1016/j.anifeedsci.2018.10.005

67. Saman S, Balouch A, Talpur FN, Memon AA, Mousavi BM, et al. 2021. Green synthesis of MgO nanocatalyst by using *Ziziphus mauritiana* leaves and seeds for biodiesel production. *Appl Organomet Chem* 35(5): e6199. https://doi.org/10.1002/aoc.6199

68. Chowdhury M, Sengupta A, Datta L, Chatterjee S. 2017. Role of mucilage as pharmaceutical additives and cytoprotective agent. *J Innov Pharm Biol Sci* 4(2): 46-52.

69. Gugulothu D, Suraj KC. 2018. Exploring *Ziziphus Sps* fruit mucilages as a pharmaceutical excipients in novel drug delivery systems. *J Pharm Innov* 2(2): 17-21.

70. Pereira GA, Silva EK, Peixoto Araujo NM, Arruda HS, Meireles MAA, et al. 2019. Obtaining a novel mucilage from mutamba seeds ex-

ploring different high-intensity ultrasound process conditions. *Ultrason Sonochem* 55: 332-340. https://doi.org/10.1016/j.ultsonch.2019.01.010

71. Al-Saeedi AH, Al-Ghafri MTH, Hossain MA. 2017. Brine shrimp toxicity of various polarities leaves and fruits crude fractions of *Ziziphus jujuba* native to Oman and their antimicrobial potency. *Sustain Chem Pharm* 5: 122-126. https://doi.org/10.1016/j.scp.2017.03.003

72. Akanda MKM, Hasan AHMN. 2021. Characterization of pharmacological properties of methanolic seed and stem bark extracts of *Ziziphus mauritiana* (BAU Kul) using *in-vitro* and *in-vivo* animal (Swiss albino male mice) model. *Clin Phytosci* 7: 8. https://doi.org/10.1186/s40816-020-00246-0

73. 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. https://doi.org/10.1007/s00580-019-03043-5