

# Chemical Constituents, Medicinal, and Pharmacological Applications, and Toxicology of Fructus Zizyphi

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**Abstract:** Fructus Zizyphi refers to the fruits of *Zizyphus jujuba* plant, and this plant is geographically distributed in East Asia and South Europe. This plant belongs to the family Rhamnaceae, and this plant is a shrub of 10 m in height. This review aimed to focus on chemical constituents, medicinal and pharmacological applications, and the toxicology of Fructus Zizyphi. The major chemical constituents of Fructus Zizyphi are triterpenes and triterpene saponins. Fructus Zizyphi treats insomnia, increases body weight, strengthens body muscle, decreases body temperature, increases urine volume, accelerates women's period, calms and reinforces agents, chases phlegm, treats vision, skin inflammation, hepatitis, respiratory diseases, diabetes, gastric ulcer, and different skin wounds. The pharmacology of Fructus Zizyphi includes experimental pharmacology and clinical pharmacology. Experimental pharmacology includes antiallergenic, anti-inflammatory, analgesic, anti-hyperglycemic, anti-hypercholesterolemic, central nervous system depressant, immune stimulation, and platelet aggregation activities. Fructus Zizyphi ethanol extracts to mice in drinking water daily for 3 months without any effect on animal death, hematology, organ weight, or sperm secretion. Fructus Zizyphi was not mutagenic. Fructus Zizyphi declined gastric adenocarcinoma progress. Fructus Zizyphi without general precautions, drug connections; drug and laboratory test relations; teratogenic or non-teratogenic effects in pregnancy; nursing mothers; or pediatric use. In conclusion, Fructus Zizyphi had antiallergenic, anti-inflammatory, analgesic, anti-hyperglycemic, anti-hypercholesterolemic, central nervous system depressant, immune stimulation, platelet aggregation activities, and without any effect on animals death, hematology, organ weight or sperm secretion.

**Keywords:** Fructus Zizyphi; *Zizyphus jujuba*; Rhamnaceae; medicine; pharmacology; dose.

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## 1. Introduction

Fructus Zizyphi means the fruits of *Zizyphus jujuba* Mill. (Family Rhamnaceae) [1-5]. Many famous names of Fructus Zizyphi occurred, such as badari, bor, black date, borehannu, common jujube, hei zao, lantakkura, onnab, regi, vadai, vagari, and zao [1-3,5-12]. *Zizyphus jujuba* Mill. plant is spreading through many countries such as East Asia, South Europe, India, China, Korea, Japan, and South East Asia countries [5,9-11]. *Zizyphus jujube* plant is a shrub that reaches to 10 m in height with many spines arranged in groups of 2 spines (1 straight and 1 rounded). The plant leaves are petiolate in shape, 2 to 7 cm in length, 2.5 to 3 cm in width, and the leaves' top are obtuse in shape. The propyl gallate enriched the post-harvest value of *Zizyphus jujuba* fruits by variable antioxidant rate and preserving peel structure [13]. The exposure of *Zizyphus jujuba* plant to ultrasound, chlorine, or both, did not affect plant weight,

freshness, color, flavor, and total soluble ingredients compared with the control plant [14]. Hu et al. [15] detected 26 chloroplasts in *Zizyphus jujuba* plant and the genome = 161, 367-161, 849 base pairs, while Zhang et al. [16] identified 986 metabolites in *Zizyphus jujuba* plant (15 triterpenes and seven 2,3-oxidosqualene cyclases metabolites). Panzade et al. [17] detected 12 nuclear factors-Y, which caused the increase of the nuclear factor-Y gene family in *Zizyphus jujuba* plant. The plant flowers are 7 to 8 in each group, the flower calyx has a cup-shaped tube and 5 slices, the flower petals are 5 in numbers, yellow in color, and the flower stamens are 5 in numbers and arranged condensed at the bottom. The plant fruits are drupes, square in shape, 1.5 to 5 cm long, and become reddish brown in a mature state [7,9,10]. Fructus Zizyphi is wide ovoid in shape, 2 to 3 cm long, equal to 1 to 2 cm in diameter. Fructus Zizyphi is reddish brown in color with rough crinkles in the mature state, while in the younger Fructus Zizyphi state is dark greyish red with small crinkles. Fructus Zizyphi has 2 sides (one side is scratched while the other side is a mark of peduncle). Fructus Zizyphi epicarp is tinny, Fructus Zizyphi mesocarp is density, Fructus Zizyphi endocarp is rigid with 2 loculi, and Fructus Zizyphi seeds are flat and ovoid [1,3,4]. Fructus Zizyphi's odor is perfumed, while Fructus Zizyphi taste is sweet [1,3,4]. *Zizyphus jujuba* plant regulates the human appetite due to the main components of *Zizyphus jujuba* have a strong binding effect on the major human tissues/organs [18].

The green *Zizyphus jujuba* plant has many antioxidant constituents, such as catechin, epicatechin, and proanthocyanidin, while the ripening *Zizyphus jujuba* plant is a source for fresh fruit and commercial processing [19]. *Zizyphus jujuba* plant represents more than 4% of the diet people live in in the dry savanna of Africa who eats this plant which has more nutritious value throughout the year [20]. *Zizyphus jujuba* polysaccharides protect gastric barrier function and the survival of poisoned mice by preventive inflammation and apoptosis [21]. *Zizyphus jujuba* fruit of low location rate was caused by resource limitation or fruit consumption [22]. *Zizyphus jujuba* leaf contains 778 metabolites, and flavonoids are the main metabolites that cause the leaf color. The light controls the flavonoid accumulation in the plant leaf [23]. The triterpenic acids of *Zizyphus jujuba* have good antioxidant activity [24]. Lactic acid bacteria fermentation increased the total phenolic content while decreasing the total flavonoid content of *Zizyphus Jujuba* juices [25].

This review aimed to focus on chemical constituents, medicinal and pharmacological applications, and the toxicology of Fructus Zizyphi.

## 2. Chemical Constituents of Fructus Zizyphi

The presence of 3-*O-trans*- and 3-*O-cis-p*-coumaroylalphitolic acid, as well as jujubosides A and B ingredients in Fructus Zizyphi [26]. A new and proficient ingredient named 2"-*O*-glycosyltransferase ZjOGT38 was isolated from *Zizyphus jujuba* plant [27]. Liu and Gu [28] detected 3 new oxyneolignans ingredients from *Zizyphus jujuba* seeds. The catechin, magnoflorine, and procyanidin B4 were detected from Fructus Zizyphi [29]. Mi et al. [30] detected 3 sesqueneolignans *Zizyphus*mps A-C from the seeds of *Zizyphus jujuba*. Furthermore, *Zizyphus jujube* fruit contains many constituents, such as polysaccharides, polyphenols, amino acids, nucleotides, fatty acids, dietary fiber, and alkaloids [31].

## 3. Major Chemical Constituents of Fructus Zizyphi

The triterpenes and triterpene saponins, such as maslinic, alphitolic, ursolic, betulinic, oleanolic, and coumaroylalphitolic acids, are the main chemical constituents of Fructus

Zizyphi. Fructus Zizyphi also contains spinosin, zizyphus saponins I, II, III, jujuboside B, and swertisin as the main ingredients of Fructus Zizyphi [12,32-36]. Fructus Zizyphi seeds contain 3 triterpene oligoglycosides [37,38]. Fructus Zizyphi contains cyclic adenine monophosphate (= 100 to 500 nmol/g) and cyclic guanine monophosphate (= 30 to 50 nmol/g) [39,40]. Fructus Zizyphi also contains zizyphus-arabinan (a polysaccharide compound) [41]. The flavonoids constituents are rich in *Zizyphus jujuba* plant [42]. There are 7 phenolic acids and flavonoids such as catechin, rutin, quercetin, luteolin, spinosin, gallic acid, and chlorogenic acid were detected in all *Zizyphus jujuba* tissues where quercetin and rutin occur in the leaves; catechin and rutin occur in the stems; and catechin, epicatechin, and rutin occur in the fruits [43]. There are 29 triterpenes found in the fruits of *Zizyphus jujuba* by chromatography analysis and established by spectroscopic procedures [44].

#### 4. Medicinal Uses of Fructus Zizyphi

Fructus Zizyphi is used for the treatment of insomnia [1,45]. Fructus Zizyphi increases body weight and strengthens the body muscle. Fructus Zizyphi is also applied as an immune stimulant [1]. Fructus Zizyphi decreases body temperature, increases urine volume, accelerates women's period, calming and reinforcing agents, and chases the phlegm. Fructus Zizyphi is used to treat vision, skin inflammation, hepatitis, respiratory diseases, diabetes, skin itches, gastric ulcer, and different skin wounds [12,46]. *Zizyphus jujuba* polysaccharides are used to protect and cure oral infectious diseases [47]. Fructus Zizyphi is used to treat anorexia, fatigue, and loose stools caused by spleen deficiency which alters metabolic outlines, and the intestinal flora is cured successfully by Fructus Zizyphi [48]. *Zizyphus jujuba* is used as an effective treatment for insomnia [49]. *Zizyphus jujuba* plant fruit constituents possess anticancer, antioxidant, anti-inflammatory, anti-hyperlipidemic, anti-hyperglycemic, immunoregulatory, neuroprotective, sedative, and antiviral effects [31]. *Zizyphus jujuba* is used in skin whitening products globally [50]. One hundred fifty-one xenobiotics (58 prototypes and 93 metabolites) were detected in rats after eating Zizyphi Spinosae Semen, where these 151 xenobiotics were distributed as follows; 16 substances in plasma, 114 in urine, 51 in bile, and 120 in feces, respectively [51].

#### 5. Pharmacology of Fructus Zizyphi

##### 5.1. Experimental pharmacology.

##### 5.1.1. Antiallergenic activity.

Injection of 100 mg/kg of ethanol extract of Fructus Zizyphi daily for 5 days stopped the hemagglutination-caused anaphylaxis and prohibited hypotonic and hemolysis of the red blood cell membrane [52]. The triterpene ingredients of Fructus declined the histamine secretion caused by antigen-antibody response [37].

##### 5.1.2. Anti-inflammatory activity.

In an *in-vitro* study, the methanol extract of Fructus Zizyphi (0.1 mg/ml) did not quash interleukin-8 from rat macrophages [53]. In another *in-vitro* study, the Zizyphusarabinan ingredient (500 µg/ml) of Fructus Zizyphi had anti-complementary activity in human serum [42]. The *n*-butanol and diethyl ether extracts of *Zizyphus jujuba* seeds exhibited anti-inflammatory activity *in vitro* [54]. Injection of 500 mg/kg of ethanol extract of Fructus Zizyphi

daily for 4 days inhibited carrageenan-caused edema by 50% and cotton pellet-caused granulomas by 25% [46]. Fructus Zizyphi has an anti-inflammatory effect in Japanese Kampo medicine [55]. The ingredients of *Ziziphus jujuba* inhibit inflammation and oxidative stress [56].

#### 5.1.3. Analgesic activity.

The water extract (2%) of Fructus Zizyphi did not stop conduction in the frog sciatic nerve [57]. Injection of ethanol extract (500 mg/kg) of Fructus Zizyphi declined the sensitivity of animals in the hotplate and tail-flick tests; therefore, Fructus Zizyphi had an analgesic effect [46]. *Ziziphus jujuba* seed is used to treat insomnia as a result of its sedative and hypnotic activities. This effect is due to *Ziziphus jujuba* modifying the metabolic outlines and the intestinal flora [43].

#### 5.1.4. Anti-hyperglycemic activity.

Injection of 1 g/kg of ethanol extract of *Ziziphus jujuba* seeds declined the mean blood glucose levels in diabetic animals [58]. The decoction of *Ziziphus jujuba* plant is used to treat diabetes in Morocco [59].

#### 5.1.5. Anti-hypercholesterolemic activity.

*Ziziphus jujuba* leaf extract is used in folklore medicine as an anti-obesity agent due to the control of adipogenesis process [60]. The anti-hypercholesterolemic activity of Fructus Zizyphi protects from cardiac disease and COVID-19 [61-63].

#### 5.1.6. Central nervous system depressant activity.

Injection of water extract of *Ziziphus jujuba* seeds (500 mg/kg) daily to animals decreased the central nervous system activity and counteracted the caffeine-caused higher central nervous system activity [64]. Injection of methanol extract of *Ziziphus jujuba* seeds (500 mg/kg) did not have any effect on barbiturate-caused sleeping time [65]. *Ziziphus jujuba* seeds extract saponin ingredient increased barbiturate-caused sleeping time [66]. Injection of 1 g/kg of butanol, methanol, and alkaloid-ingredient of Fructus Zizyphi extract had a tranquilizing effect in animals [64,67]. Injection of spinosin and swertisin (500 mg/kg) ingredients of *Ziziphus jujuba* seeds petroleum ether extract had a central nervous system-depressant effect and increased hexobarbital-caused sleeping time by 50% [66]. *Ziziphi Spinosa Semen* plant has a main role in protecting against Alzheimer's disease [68]. *Ziziphus jujuba* fermented by yeast has a protective role in mental injury and memory damage. Therefore, the plant offers protection against Alzheimer's disease [69]. *Ziziphus jujuba* extract has anti-amnesic and neuroprotective effects [70]. *Ziziphus jujube* water extract amends cholinergic and anti-inflammatory variations. This plant is used in the treatment of dementia because this plant improves acetylcholinesterase and neuroinflammation [71].

#### 5.1.7. Immune stimulation activity.

In an *in-vitro* study, the polysaccharide (0.5 mg/ml) ingredient of Fructus Zizyphi water extract had anti-complement activity in human serum [41]. Injection of 1 g/kg of this polysaccharide ingredient of Fructus Zizyphi increased the activity of natural killer cells [72].

#### 5.1.8. Platelet aggregation inhibition.

In an *in-vitro* study, the hexane and methanol extracts of *Zizyphus jujuba* seeds (5 mg/ml) declined collagen-caused platelet aggregation [73]. *Zizyphus jujube* seeds decrease the body's lipid content and metabolism [74]. Jujuboside B constituent of *Zizyphus jujuba* seeds have protection and a cure in vascular-related diseases [75]. *Zizyphus jujuba* treats chest pain, asymmetrical heartbeat, and coronary heart disease [76].

#### 5.2. Clinical pharmacology.

Fructus Zizyphi is used in Kampo and folklore Chinese medicine. Many clinical studies evaluated Fructus Zizyphi as an anticonvulsant, with memory-increasing, and anti-inflammatory activities. The oral intake of *Zizyphus jujuba* seeds (0.8 g/day) in humans caused a central nervous system depressant effect, which is used for the treatment of insomnia [45]. The medicinal uses of Fructus Zizyphi are similar to that of Anisi etheroleum [77]. A clinical study contained 46 participants (23 control without *Zizyphus jujube* and 23 oral administrated *Zizyphus jujube*/ 2 times daily for 8 weeks), and the results revealed that *Zizyphus jujuba* juice is effective and nontoxic for treating hyperpigmentation of the human face [78].

### 6. Toxicity of Fructus Zizyphi

The dose (100 mg/kg) of Fructus Zizyphi ethanol extract to mice in drinking water daily for 3 months without any effect on animals' death, hematology, organ weight, or sperm secretion [46]. Injection of Fructus Zizyphi water extracts (3 doses of 0.5 mg/kg, 1 mg/kg, or 3 mg/kg) for 1 day to mice without any acute toxic effect [46]. Injection of Fructus Zizyphi ethanol extracts (3 doses of 1 g/kg, for 1 day) without any acute toxic effect, only animal sedation was observed with 3 doses of 3 g/kg [46]. *Zizyphus jujuba* extract protects against the liver, heart, and brain toxicity caused by Adriamycin [79]. *Zizyphus jujuba* plant improved liver injury and oxidative damage in experimental animals [80].

In an *in-vitro* study, methanol extract of zizyphi spinosi semen prevents neuronal cell damage. The methanol extract of zizyphi spinosi semen stopped the higher cytosolic calcium level and prevented the synthesis of reactive oxygen species in cultured rat cerebellar granule cells [81]. Oral intake with *Zizyphus jujuba* plant diminishes inflammation; therefore, this plant inhibits colon cancer in experimental animals [82]. *Zizyphus jujuba* water extract increased the antioxidant activity and topped the secretion of harmful radicals. Also, *Zizyphus jujuba* improved the intracellular antioxidant level in human fibroblast cells. Consequently, *Zizyphus jujuba* water extract prevented cellular toxicity by increasing the antioxidant level in the cells, and therefore this plant was used to treat many oxidative stress-related diseases [83].

### 7. Adverse Reactions of Fructus Zizyphi

There were not any publications regarding the adverse reactions of Fructus Zizyphi.

### 8. Contraindications of Fructus Zizyphi

There were not any publications regarding the contraindications of Fructus Zizyphi

### 9. Warnings of Fructus Zizyphi

There were not any publications regarding the warnings of Fructus Zizyphi.



## 10. Precautions of Fructus Zizyphi

### 10.1. Carcinogenesis, mutagenesis, impairment of fertility.

The water and methanol extracts of Fructus Zizyphi were not mutagenic in *Salmonella typhimurium* strains or the *Bacillus subtilis* test at 100 mg/ml of the extracts [84]. *Ziziphus jujuba* plant protects against cancer development, especially colon cancer [85]. *Ziziphus jujuba* plant has an antimicrobial effect, and the plant has antioxidant activity [86]. *Ziziphus jujuba* constituents (polysaccharides and ginger 6-gingerol) are important for keeping healthy and stopping cancer [87]. The Fructus Zizyphi ethanol extract (4 mg/ml) was not mutagenic also in the *Escherichia coli* test or *Salmonella typhimurium* test [85]. *Ziziphus jujuba* has antibacterial activity (7.81-31.25 µg/mL) [88]. The glycosides constituents (jujuboside B, epiceanothic acid, and 6"-feruloylspinosin) of *Ziziphus jujuba* seeds have strong anti-melanogenic activities [89]. Injection of 1 g/day for 15 months of Fructus Zizyphi declined gastric adenocarcinoma progress [90]. The Fructus Zizyphi ethanol extract in drinking water (100 mg/kg) in animals for 3 months without any toxic effect on the sperm [46]. *Ziziphus jujuba* extract prevents the testis toxicity caused by Adriamycin. The plant extract recovers oxidative stress, sperm motility and normality, hormonal change, and pathological changes in testicular tissue; therefore, it is an active treatment in fixing testicular tissue injury [91].

### 10.2. Other precautions.

There were no publications regarding the general precautions, drug connections; drug and laboratory test relations; teratogenic or non-teratogenic effects in pregnancy; nursing mothers; or pediatric use for Fructus Zizyphi. *Ziziphus jujuba* plant possesses estrogenic and antiprogesterogenic effects; therefore, it is used to improve menopause-like symptoms in women [92].

## 11. Dosage Forms of Fructus Zizyphi

Fructus Zizyphi is found in many forms, such as dried fruits, water extract, and hydroalcoholic extract. Fructus Zizyphi must store in a black sealed bottle to avoid heat and light. The daily dose of Fructus Zizyphi = 6 to 15 g of dried fruits [1].

## 12. Conclusion

Fructus Zizyphi is the fruit of *Ziziphus jujuba* plant, which occurred in East Asia and South Europe. The triterpenes and triterpene saponins are the major constituents of Fructus Zizyphi. Fructus Zizyphi treats vision, hepatitis, respiratory diseases, diabetes, gastric ulcer, and skin wounds. The pharmacology of Fructus Zizyphi includes experimental pharmacology and clinical pharmacology. There are no adverse reactions, contraindications, or warnings of Fructus Zizyphi. There are many forms of Fructus Zizyphi, such as dried fruits, water extract, and hydroalcoholic extract. The daily dose of Fructus Zizyphi = 6 to 15 g of dried fruits.

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## Conflict of interest

The author declares no conflict of interest.

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