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Pharmacological review of *Ziziphus* plants and jujuboside A & B compounds

Abstract

Mucronata, spina-christi, muaritiani, oxphylla, xylopyrus, and *lotus* are few of the many medical plant species found in the genus *Ziziphus*. Most of the *Ziziphus's* species have established pharmacological effects. Phytopharmacological constituents such as jujuboside A and B have been isolated from the genus: *Ziziphus* and have been reported to possess potential health benefits. The literature for this review was conducted by searching various scientific electronic databases. Additional information was derived from other sources in the literature (books and journals). The review highlights the pharmacological studies of the *Ziziphus* genus and the jujuboside A and B compounds. The *Ziziphus* plant species as well as Jujuboside A and B compounds have being studied and reported to possess valuable pharmacological activities. Both the *Ziziphus* species and compounds possess vast potential health benefits that warrant further scientific exploration.

Keywords: *Ziziphus*, jujuboside, antimicrobial activity, pharmacological activity, *escherichia coli*

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Introduction

Nature supplies an infinite source of renewable products. Medicinal plants are one of nature's many treasures. Historically, medicinal plants have provided adequate efficacy and low-cost treatments compared to Western medicine.[1] Traditional remedies, on the other hand, are founded on ideas, theories, and individual experiences, which pose a problem to nonbelievers and people without experience.

A wide range of plant constituents are being researched for their potential therapeutic values,[2] with plants from the Genus *Ziziphus* providing part of the therapeutic benefit. The genus *Ziziphus*, which the ancient Greeks referred to as the tree zizyphon, derived from the Arabic Zizouf, is considered as a wild species genus. Currently, approximately 12 species are being medically cultivated.[3] *Ziziphus* has been found to have pharmacological properties such as anti-cancer, anti-diabetic, anti-inflammatory, anti-asthma, anti-depression, anti-diarrhoea, and the ability to improve hepatic illness, cardiovascular and renal disease.[4-7] While traditionally, plant parts used includes: the utilization glutinous roots as a painkiller and treatment of dysentery,[8] while the bark and leaves are used for respiratory ailments and skin swellings[9]. The roots are also used in steam baths to purify and improve complexion.[10] In East Africa, roots are used for snake bites.[7] The berries are edible and used in porridge and coffee substitutes.[11] A twig from the tree is still used in AmaZulu culture to attract and carry the spirit of the deceased from the place of death to the new resting place.[12] The mechanism of action could be due to its phytochemical composition, with the genus known to contain saponins, tannins, flavonoids, cyclopeptide alkaloids, and a larger range of phenolic compounds.

This article focusses on providing concrete scientific evidence of pharmacological effects and a synopsis of current research on the pharmacological benefits of Genus: *Ziziphus* plants and their isolated metabolites. This is also prompted by the 1:1660 doctor: patient ratio in traditional medicine in South Africa,[11] which validates the necessity to define the possible bioactive chemicals and their mechanisms, whether in synergy or individually.

Methodology

The review adopted the desk research method. The literature for this review was conducted by searching various scientific electronic databases including Google Scholar, PubMed, Web of Science, SciFinder, Science Direct, ACS Publications, Elsevier, and Wiley Online Library. Additional information was derived from other sources of literature (books and journals). The review reports on all aspects of the plant, including taxonomy, ethnobotanical and pharmacological activities.

Taxonomy and Botany

The taxonomy of ziziphus include: Domain: *Eukaryota*; Kingdom: *Plantae*; Subkingdom: *Viridiplantae*; Phylum: *Spermatophyta*; Subphylum: *Angiospermae*; Superdivision: Embryophyta; Division: Tracheophyta; Subdivision: Spermatophytina; Class: *Magnoliopsida*; Superorder: *Rosanae*; Order: *Rosales*; Family: *Rhamnaceae*; Genus: *Ziziphus*.[7]

The Ziziphus genus is home to approximateley 130-140 species of plants.[13] *Ziziphus* is a Latin word that means "thorny", just like many of its species.[11-14] Commonly known species of the *Ziziphus* genus are *mucronata; spina-christi; mauritiana; lotus; oxyphylla; mucronate; xylopyrus; glabrate; nummularia*. The species has thorny branches, grows to about 10 m in height, yellowish-green star-shaped blooms, lustrous and light green leaves, and fruits that are green when young and turn reddish-brown when ripe.[11]

Ziziphus pharmacological therapy uses

Ziziphus mucronata

Ziziphus mucronata (*Z. mucronata),* commonly known as Buffalo thorn, is a species of the Rhamnaceae family.[14] It is a small to medium tree with a wide canopy.[10] *Ziziphus mucronata* is a multipurpose plant that has long been used in African traditional medicine to cure a variety of serious human and animal diseases.[7] Angola, Botswana, Eritrea, Ethiopia, Ghana, Kenya, Lesotho, Mozambique, Zambia, Namibia, Niger, Senegal, Somalia, South Africa, Sudan, Swaziland, Tanzania, Uganda, and Zimbabwe are all home to the plant species.

In South Africa, Z. *mucronata* is found in all provinces of Limpopo, Mpumalanga, Kwazulu-Natal, Eastern Cape, Northern Cape, North West, Gauteng, and Free State, except for the Western Cape Province.[7,15]

Extracts of Z. mucronata have been shown to exhibit anticancer action against various cancer cell lines, including HeLa, Caco-2, A431, Chinese hamster ovary cells (CHO), HT29, and H4 cells.[16] In an *in vivo* wistar rat investigation, Idris[17] discovered that the methanol extracts of *Z. mucronata* leaves have non-lethal toxicity. Shawa[18] reached the same conclusion when testing the leave extracts on brine shrimp, although the root extract was significantly toxic. Moreover, an *in vivo* investigation on Wistar rats indicated that extracts of aqueous *Z. mucronata* leaves have pro-fertility effects.[15,19] According to Foyet[14] *Z. mucronata* leaves exhibited a neuroprotective effect in a scopolamine-induced Alzheimer's rat model. The findings of Shawa and Idris correlated with the most recent findings of Namadina[6] indicating insignificant toxicity of *Z. mucronata* with LD_{50} greater than 5000mg/kg. Meanwhile, an *in vitro* investigation of *Z. mucronata* was found to alleviate diabetic symptoms by suppressing the activity of the alpha amylase and glucosidase enzymes in a concentration-dependent manner.[20]

Z. mucronata has demonstrated to have antimicrobials activity against *E. coli, B. cereus and pumilus , P. vulgaris, S. marcescens, E. faecalis, S. aureus, E. cloacae, P. aeruginosa, K. pneumoniae, S. aureus, S. typhi, A. calcaoceuticus, C. krusei, C. albicans, C. neoformans, C. rugosa, P. notatum, A. niger, A. flavus and A. terreus.* [1,6,20-21] Aqueous and methanol stem bark extracts of Z. *mucronata* are reported to possess egg-hatch inhibition activity and induce larval mortality of *H. contortus*.[19]

Ziziphus xylopyrus

Ziziphus xylopyrus (Z. xylopyrus) is a large, spreading shrub with underdeveloped branches and rusty tomentose, commonly known as Kath ber.[20] Carbohydrates, steroids, alkaloids, glycosides, saponins, sterol, flavonoids, phenolic chemicals, and triterpenoids were discovered in the leaf extract after phytochemical screening with various solvents.[21,22] The cytopeptide alkaloid nummularie-K, amphibine-H, xylopyrine-A and B, sativanine-H, and nummularine-P have been isolated from the stem bark of Z. xylopyrus.[23-25] The isolation of the root bark indicated the presence of xylopyrine-F.[24]

Traditionally, the plant's roots decoction as well as the fruits' are believed to promote sterility in woman, seed paste is used to relieve chest pain in patients with cough and cold, the roots bark and fruit mixture is used for diarrhoea treatment, a pinch of ginger and the fruits powder mix is used to relieve stomach indigestion, and the leaves in the tropical forest of India's eastern Ghats are used to treat headache, hysteria, and fox bite.[21,26-28]

According to the study by Mansoori[2] *Z. xylopyrus* possess pharmacological activities such as: Anticataract, antimicrobial, antidiarrheal, antiulcer, and antidepressant activities. An *in vivo* investigation of Epsom salt-induced diarrhoea deduced that *Z. xylopyrus* has antidiarrheal activity.[29] Furthermore, Z. *oxlopyrus* showed considerable wound healing in both *in vitro* and in vivo rat studies.[30] *Z. xylopyrus* stem extract reduces immediate-type allergic responses and mast cell degranulation, as a result, *Z. xylopyrus* has the potential to be an allergic anti-asthmatic agent.[31]

In recent studies, *in vitro* investigation of *Z. oxylopyrus* fruit extracts showed efficacy in anti-diabetic activity through dose-dependent inhibition of alpha amylase and alpha glucosidase enzymes.[32] The extract of ethanol from the *Z. xylopyrus* stem bark and leaves extract has shown significant antioxidant activity.[33] Shaikh and Shaikh[34] summarised some of the pharmacological uses, including Antiulcer, analgesic, and anti-inflammatory, antimicrobial, and antifungal, antioxidant, wound healing, antidepressant, and antidiarrheal activity.

Ziziphus xylopyrus

Ziziphus oxyphylla (Z. oxyphylla) is found mainly in tropic and warm temperate parts of the world, particularly in India and Pakistan[35]. It is commonly known as pointed-leaf Jujube. Compounds found in Z. *oxyphylla* include p-coumaric acid, 3,4-dimethoxy benzoic acid, 4-heptyloxy benzoic acid, Oxyphylline-B, Oxyphylline-C, Oxyphylline-D, Nummularin-C, and Nummularin-R.[36,37] *Z. oxyphylla* is used in traditional medicine to treat inflammatory and painful disorders, particularly those of rheumatic origin, as an antipyretic, and to treat microbial infections, allergies, and diabetes.[38]

An *in vivo* study conducted by Abdullah[36] depicted that *Z. oxyphylla* has hepatoprotective activity on carbon tetrachloride-induced hepatotoxicity mice, which was mediated by the antioxidation defence system and membrane-stabilizing activity. The hepatoprotective effect of *Z. oxyphylla* has also been observed in a paracetamol-induced hepatotoxic rat model.[39] Three cyclopeptide alkaloids isolated from *Z. oxyphylla*, nummularine-R, nummularine-C, and hemsine-A, demonstrated substantial inhibition of -glucosidase and considerable anti-glycation activity but no inhibition of -chymotrypsin. As a result, it has a powerful anti-diabetic effect.[40]

P-coumaric acid, extracted from the *Z. oxyphylla* roots extract, showed high free radical scavenging and anticholinesterase activity, indicating that it might be utilized to treat oxidative stress and dementia in humans.[36] While, Oxyphylline-B and Nummularin-R, both isolated from the *Z. ozphylla,* showed a promising improvement in pain relief[36]. The antimicrobial activity of *Z. oxyphylla* roots and leaves against *E. coli, S. aureus, T. cruzi, P. falciparum, L. infentum, T. Brucei, T. rubrum, A. fumigatus and C. albicans* has been assessed and reported.[41]

Ziziphus lotus

Ziziphus lotus (*Z. lotus*) is a member of the Rhamnaceae family and is found in tropical and subtropical regions of North America, South America, Asia, Africa, Oceania, and Europe.[41-43] Since its extract has antibacterial, antioxidant, anti-inflammatory, analgesic, and antifungal qualities, the fruit, and leaves of *Z. lotus* are commonly used in traditional medicine for the treatment of numerous ailments such as diabetes, diarrhoea, bronchitis, and abscess.[44-46]

Z. lotus has demonstrated anti-microbial activity against *E. coli, S. aureus,* and *epidermis,*[47] which supports the findings of Merium, (2017), that *Z. lotus* has anti-microbial activities against *E. coli, F. Solani* as well as *B. Cinerea.*[48] Abderrahim[52] further supports the anti- microbial activity against *S. aereus, E. coli and P aeruginosa* however, no significant activity was recorded against *C. albicans*. Moreover, Elaloui[53] depicted that *Z. lotus* has anti-bacterial and anti-fungal activity with zone of inhibition ranging from 22-23.5mm against *E. coli, S. aureus, K pneumoniea, B. cimerea, F. solani and F. ulmorum.*

Z. lotus possesses antioxidant properties.[49-51] *Z. lotus'* antioxidation activity may be attributable to the positive association between antioxidation and phenolic content.[53,54] According to Benammar[55] *Z. lotus* roots, stem, leaves, seed, and pulp possess antioxidation activity as well as modulate the T-cell proliferation and IL-2 mRNA expression.

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Ziziphus spina-christi

Ziziphus spina-christi (*Z. spina-christi*) is a shrub, sometimes a tall tree, reaching a height of 20 m and a diameter of 60 cm; its bark is light grey, very cracked, and scaly; the trunk is twisted; the crown is thick; the shoots are whitish, flexible, and drooping; and the thorns are in pairs, one straight and the other curved[55,56]. Its native range includes North Africa, South Europe, the Mediterranean, Australia, tropical America, South and East Asia, and the Middle East[57]. *The extract of Z. spinachristi* was found to contain beutic acid and ceanothic acid, cyclopeptides, saponin glycosides and flavonoids, lipids, protein, free sugar and mucilage.[58]

Ziziphus. Spina-christi plant parts have traditionally been used to cure a variety of ailments throughout the world: Flowers, leaves, and roots have been used to relieve stomach discomfort, a condition that has been documented in Malawi, Iran, and Sudan.[59,60] The leaves are used to cure skin ailments in Palestine.[61] People in Turkey use the fruit's fibre content to treat constipation.[62] In Nigeria, cough medication is often produced from the roots.[63] Fruits are used to cure diarrhoea, rheumatism, scorpion stings, malaria, and antispasmodics in Sudan.[64]

Pretreatment with *Z. spina-christi* leaf extract reduces liver and spleen injury in a mouse model through antioxidant and anti-inflammatory effects.[65] Furthermore, Dkhil[65] reported that anti-inflammatory activity may be due to inhibition of MAPK-mediated inflammatory responses, with the antioxidant effect possibly linked to the mediation of free radical quenching and the improvement of the endogenous antioxidant defence system. Almeer,[66] discovered that mercury chloride ($HgCl_2$) intoxication promotes testicular dysfunction by increasing its accumulation, loss of the testis index, hormonal alterations, induction of oxidative reactions, enhancement of inflammatory and immune responses, and activation of the apoptotic pathway in rats, which treatment with *Z. spina-christi* leaves extracts (ZSCLE) considerably reduced the changes caused by $HgCl_2$ intoxication in testicular tissue, implying that ZSCLE could be used to reduce Hg-induced testicular dysfunction.[67]

The leaves of *Z. spina-christi* have anticancer properties, which have been demonstrated against human breast carcinoma cells.[68,69] While Ads,[68] demonstrated that stem bark extract had anticancer effects against colon and breast cancers cells. Jafarian, Zolfaghari, and Shirani[69] observed antitumor activity of *Z. spina-christi* leaves extracts in Hela and colon carcinoma cells, with methanol-chloroform being the most potent. Adzu[58] discovered that the *Z. spina-christi* extract protected rats against castor oil-induced diarrhoea, reduced intraluminal fluid buildup, and improved gastrointestinal transit.

Ads,[68] showed that *Z. spina-christi* leaves extract have antimicrobial activity against *A. fumigatus, S. raemosum, G. candidum, C., S. pneumoniae, B. subtilis and E. coli* and no activity against *C. albicans and P. aeruginosa.* While Ali, Almagboul, and Mohammed,[70] recorded antimicrobial activity of methanol leaves, stem, and fruit extracts of Z. spina-christi against *B. subtilis, S. aureus, E. coli, P aureginosa* and no activity was recorded against *C. albicans* and *A. niger.* The fruits and leaves of *Z. spina-christi* demonstrated antifungal activity against A. *altermata, citri, and radicina.*[69-72]

Ziziphus muaritiana

Ziziphus mauritiana (Indian jujube) (*Z. muaritiana*) is a small evergreen shrub with short spines and numerous dangling branches with pointy stipules.[73] It grows in tropical and sub-tropical regions of the world[74]. The leaves are generally 2.5-4.0 cm long and 1.8-3.8 cm broad, alternating, oval, or oblong elliptic, whole, with three conspicuous basal veins and a rounded apex.[75] *Z. mauritiana* contains several chemicals, including pectin A, jujubosides A, B, A1, B1, C, acetyljujuboside B, protojujubosides A, B, B1, and ziziphin[76]. Ripe fruits have a high nutritional value as they are high in ascorbic acid, retinol, and B complex, as well as minerals such as Ca, K, Br, Rb, and La.[77,78] Various parts of this plant have been used in traditional medicine to treat a variety of diseases including asthma, allergies, depression, and ulcers.[79]

The leaves of *Z. muaritiana* have been reported to possess anti-ageing, skin whitening, and moisturizing characteristics.[80] The leaves extract also showed considerable antibacterial activity against *B. aureus* and *P. vulgaris*. Furthermore, Ashraf[73] reported that the leaves have antimicrobial activity against *E. coli, B. substillis, P. ultocida, S. aureus, A. ger, and F. lani.* Abalaka[80] reported that the leaves have antimicrobial activity against *E. coli, S aureus, and S. pyogenes.* Although stem bark has potential wound healing properties and ameliorates gastrointestinal distress and urinary tract infection.[81] The seed and fruit could be utilized to produce cooking oil[82]. *Z. mauritiana* seed extract contains compounds that may have numerous activities involving different mechanisms in exerting hypoglycemic and antihyperglycemic effects.[83]

The hepatoprotective effect of an ethanol extract of *Z. mauritiana* leaf against CCl4-induced liver damage in rats, as well as the antidiarrheal activity of a methanol root extract, have both been documented.[84,85] Ashraf[73] reported that the extract of *Z. muaritiana* leaves has anti-tumour activity against leukemic monocyte lymphoma (U937) and colon carcinoma (HCT-116). *Z. muaritiana* seed was reported to have antiproliferative effect against Human promyelocytic leukemia cells (HL-60), acute lymphoblastic leukemia cells (Molt-4) and human cervical cancer cells (HeLa).[86] While Goyal,[75] *et al.* reported that the leaves have cytotoxic effects against Vero cell line. On the contrary to Goyat, the seed extract is reported to exhibit insignificant antiproliferative effects against normal human gingival fibroblast cells.[86]

Pharmacological activities of jujuboside A and B

Jujuboside A

Jujuboside A (JuA) is triperpenoid saponins isolated semen *Ziziphus spinose.*[87] They are the primary active component ofthe mature seed of wild *Ziziphus jujube.*[88] The mature seed of *Ziziphus jujuba*, *Ziziphus spinosae*, is widely used in China, Japan, Korea, and other oriental countries for medicinal purposes.[89] Jujuboside A isolated from suanzaoren is considered one of the most important pharmacological molecules responsible for insomnia therapy.[90] The Suanzaoren decoction is made up of five herbs*: Semen ziziphus spinosae, Rhizoma chuanxiong, Poria, Rhizoma anemarrhenae, and Radixglycyrrhizae*, with the dried seed of *Ziziphus jujuba* being the main ingredient.[91]

Endogenous adenosine and uridine are central nervous system active substances that have been linked to promote sleep, JuA promotes adenosine and uridine release in the prefrontal cortex of mice via acting on the ENT transporter in the central nervous system, suggesting that JuA may induce/promote sleep.[90] The administration of JuA to mice has shown the inhibition of spontaneous activity.[92] Inhibition might contribute to the promotion of sleep. JuA has the potential to improve sleep quality, lengthen sleep duration, and considerably increase non-rapid eye movement sleep (NREMS).

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Alpha 1, 5, 2 subunit gene expression could be part of the molecular mechanism underlying its therapeutic sedative-hypnotic effects.[93] By activating tonic GABAergic inhibition, JuA protects sleep loss-induced dysregulation in the excitatory signalling pathway and mEPSC in APP/PS1 mice.[94]

The anti-inflammatory action of JuA was attributed to the downregulation of pro-inflammatory factors (TNF-, IL-1, and IL-6) in the study investigating the induction of coronary heart disease in rats. Furthermore, in rats with induced coronary heart disease, JuA has an anti-apoptotic effect on cardiomyocytes.[95] JuA has been shown to prevent norepinephrine-induced apoptosis in rat cardiomyocytes (H9c2) through regulation of mitogen-activated protein kinase and AKT ssignalling pathways by enhancing ERK activation and increasing P-AKT expression.[96] Han[96] investigated the protective effect and potential mechanism of JuA on ISO-induced cardiomyocyte injury, discovering that JuA pre-treatment may increase cell viability and improve the injury of H9C2 cells caused by ISO.

JuA boosted HSP90 expression and PPAR stability in an ERK-dependent manner, as well as improved clearance in microglia, in the Alzheimer's study. JuA was also shown to prevent A or DL-homocysteine-induced tau protein phosphorylation and that JuA administration significantly improved learning and memory deficits in APP/PS1 transgenic mice.[97] Sleep loss impairs spatial memory in Alzheimer's disease and JuA is a viable target for the therapy of sleep loss-induced changes in Alzheimer's disease and other neurological disorders characterized by brain excitotoxicity.[93] Liu,[98] investigated the pharmacological activity of JuA in mice induced by cognitive impairment, reporting that JuA has mitigative effects on learning and memory impairment, therefore potentially have therapeutic effects on Alzheimer's disease.

Jujubosibe B

Jujuboside B (JuB) is a natural saponin triterpenoid found in the fruit plant *Ziziphus jujuba* Mill.[100] This plant's fruit is reported to have physiological effects ranging from anticancer to anti-inflammatory to antioxidant.[94,98,99] Ninave and Patil's,[99] study on JuB demonstrated its significant anti-asthmatic effect in mice, inhibiting clonidine-induced catalepsy, milk-induced leucocytosis, eosinophilia, mast cell degranulation, passive paw anaphylaxis, and lower inflammatory cells in bronchoalveolar lavage fluid. Furthermore, JuB also alleviated the severity of pulmonary inflammation, reducing T-helper type 2 T-helper cytokines in serum and lung homogenates. In an investigation of fine matter (PM2.5) lung toxicity in an animal model, JuB was reported to be used as potential therapeutic agent for PM2.5-induced lung damage.[100-101]

JuB has been reported to promote death of acute leukaemia cells and inhibit the growth of transplanted tumour of HCT 116 cells in nude mice.[102,103] An *in vitro* study showed that JuB can induce apoptosis in colon cancer cells through ROS-induced mitochondrial-dependent apoptosis and mediated by the P13K/Akt pathways. Moreover, it was demonstrated that JuB has a significant cytotoxic effect on human normal epithelial cells in a dose-dependent manner. While the *in vivo* part of the study, JuB demonstrated significant anti-proliferative effect on colorectal cancer on mouse model and the use of NAC (ROS inhibitor) and LY 294002 (P13K inhibitor) plus JuB respectively, which further confirms that the pro-apoptotic effect of JuB is mediated by P13K/Akt pathways induced by mitochondria dysfunction through ROS accumulation.[104] Guo,[105,106] reported that JuB possess anti-cancer effect against breast cancer cells through apoptosis mediated by NOXA and AMPK signalling pathway induced autophagy.

Yang's,[107] study reveals that JuB treatment inhibits tumour progression in mice by modulating the inflammatory response, dephosphorylating CREB, and blocking the PI3K / Akt and MAPK/ERK pathways. While the in vitro part of the study showed that JuB suppresses tumour development in breast cancer cell lines with an IC_{50} of approximately 60 mol/L. The JuB IC_{50} in A546 cells with the non-cytotoxic range (0-200μM) of the normal cell reported by Li.[105] Jujuboside B promoted autophagy and apoptosis in cancer cells (AGS and HCT116) and substantially reduced tumour growth in a nude mouse xenograft model. The activation of p38/JNK to promote extrinsic pathway-mediated apoptosis through FasL regulation in AGS Cells was confirmed by administration of JuB treated cells with SB202190 (p38/ inhibitor) and SP600125 (a JNK inhibitor).[106]

JuB has been shown to improve depression-like phenotypes in both tumour and non-tumour groups of mice.[107] JuB has been shown to be protective against liver injury by inhibiting TLR4 overexpression, which when activated by LPS activates inflammatory signalling pathways, it also inhibits MyD88 and TRIF-dependent signaling pathways of the TLR system, and lower serum levels of ALT and AST, which were activated and elevated during LPS-induced liver failure.[108] Jujuboside B effectively decreased collagen-induced platelet aggregation as well as thrombin, AA, and ADP-induced platelet aggregation by decreasing collagen-induced TXB2 production, which is generated from TXA2, a key mediator of collagen-induced platelet action and aggregation.[109]

JuB reduces, in dose dependant manner, tension of a rat thoracic aorta ring measured using wise myograph system, with the suspected mechanism of action involving the increase in extracellulary Ca^{2+} influx increase through TRPC channel, phosphorylated eNOS and promoted NO generation in the endothelial cells.[110] JuB was reported by Kim[111] to have hepatoprotective effect on rats with cecal ligation and puncture (CLP)-induced sepsis, the effect suspected to be mediated by anti-inflammatory response regulation, antioxidation downregulation, and upregulation of GR expression relieves febrile seizures by subduing of excitability of hippocampal neurones mediated by hampering of AMPAR activity and reduction of intracellular free calcium.[112]

Conclusion

The genus: *Ziziphus* has the potential to be used in pharmaceutics, as it has shown good potency for many pharmacological activities. Jujubosides A and B show the need to investigate and isolate individual secondary metabolites and further use them individually and/or in synergy with other secondary metabolites or known therapies, medications, or compounds. However, both the *Ziziphus* species and compounds Jujuboside A and B compounds need to be further explored scientifically.

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Declaration of conflict of interest

The authors declare that there is no conflict of interest.

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