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Review

Genus Ziziphus for the treatment of chronic inflammatory diseases

Abdulrhman Alsayari, Shadma Wahab *

Department of Pharmacognosy, College of Pharmacy, King Khalid University, Abha 61421, Saudi Arabia

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ABSTRACT

Natural products and traditional medicine are rich sources for developing therapeutics for chronic inflammatory diseases. However, the way from natural products/traditional medicines to Western pharmaceutical practices is not always straightforward. According to the World Health Organization (WHO), chronic diseases are the greatest threat to human health. 3 of 5 people die due to chronic inflammatory disorders worldwide like chronic respiratory diseases, stroke, cardiovascular diseases, cancer, diabetes, and obesity. Various nonsteroidal anti-inflammatory drugs (NSAIDs) are used to reduce inflammation and pain, but there are many side effects of these drugs' administration. Medicinal plants have therapeutic anti-inflammatory effects with low or no side effects. *Ziziphus* plant species are generally safe and not toxic to humans. Many studies on the *Ziziphus* species have shown that their therapeutic properties are attributed to the roots, leaves and fruits. Unfortunately, *Ziziphus* species from different regions worldwide with anti-inflammatory properties have not been documented in a single review paper. Therefore, it is crucial to establish ethnobotanical knowledge and applications of *Ziziphus* species against chronic inflammatory diseases. The current article exhaustively reviews phytochemical profile, pharmacological studies, toxicological effects, and ethnobotanical uses of Genus *Ziziphus* in chronic anti-inflammatory diseases. The present review article also highlights the most promising experimental data on *Ziziphus* extracts and pure compounds active in clinical trials and animal models of chronic inflammatory diseases. This review would be a valuable resource for contemporary researchers in the field to understand the promising role of the *Ziziphus* genus in chronic inflammatory disorders.

Contents

* Corresponding author.at: College of Pharmacy, King Khalid University, Abha, Kingdom of Saudi Arabia.
E-mail addresses: alsayari@kku.edu.sa (A. Alsayari), sabdulwahab@kku.edu.sa (S. Wahab).
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1. Introduction

Herbal medicine has been with us from primitive days to cure many diseases. These medicines have been used to prevent or treat many ailments, including chronic inflammatory diseases. Various nonsteroidal anti-inflammatory drugs (NSAIDs) are used to reduce inflammation and pain, but there are many side effects of these drugs' administration. Medicinal plants have therapeutic anti-inflammatory effects with low or no side effects (Alsayari et al., 2021). *Ziziphus* plant species are generally safe and non toxic to humans. Inflammation is one of the critical and root causes of various diseases. Therefore, there is an urgent need to understand the beneficial effects of herbal medicines in treating inflammatory conditions and extending our scientific understanding.

Ziziphus genus (Rhamnaceae) members, phytochemically, possess many saponins, tannins, flavonoids, cyclopeptide alkaloids, and a wider variety of phenolic compounds. For centuries, People have treated different disease conditions, including chronic inflammatory diseases using *Ziziphus* species. Most of these genus species are explored and validated for their ethnomedicinal uses, but still, many have to examine for their medicinal usefulness. *Ziziphus* is found mainly in warm temperatures and tropic regions in the world. It is extensively used by medicinal practitioners and local people in semi-arid and arid regions. *Ziziphus* genus is primarily used to heal numerous diseases and disorders in many countries and regions like Southern Africa, South America, India, China, and the Middle East. Approximately 135 plants species are comprised in genus *Ziziphus* (Ara et al., 2008; K.S. Mhaskar, E. Blatter, 2000). As per reported scientific literature, six species of the *Ziziphus* genus are mainly used, such as *Z. xylopyrus, Z. jujuba, Z. nummularia, Z.mauritiana, Zizyphus oxyphylla* and *Z. mauritiana* (El Maaiden et al., 2020). In traditional medicines, this genus has a pivotal role in treating or managing various diseases like antipyretic, analgesic, antibacterial, sedative, antioxidant, GIT protective, anti-diabetic, cardiovascular, antifungal and anti-inflammatory. Cyclopeptide alkaloids, polysaccharides, flavonoids, saponins and terpenoids have been isolated from this genus. The use of *Ziziphus* species therapeutics to treat chronic inflammatory diseases are widespread and on the rise. The chronic inflammatory responses are also the cause of atherosclerosis, obesity, diabetes, cancer, chronic constipation, obesity, and neurological disorder. However, genus *Ziziphus* effects in inflammatory diseases have not been thoroughly investigated.

Although, researchers have examined some of the *Ziziphus* species and documented their therapeutic and biological activities. Unfortunately, *Ziziphus* species worldwide from different regions with anti-inflammatory properties have not been documented in a single review paper. Therefore, it is crucial to establish ethnobotanical knowledge and applications of *Ziziphus* species against chronic inflammatory diseases. The current article exhaustively reviews phytochemical profile, pharmacological studies, toxicological effects, and ethnobotanical uses of genus *Ziziphus* in chronic anti-inflammatory diseases. Furthermore, genus *Ziziphus* bioactive compounds in inflammatory diseases ranging from fundamental research to human clinical trials have been thoroughly discussed. This review would be a valuable resource for contemporary researchers in the field to understand the promising role of the *Ziziphus* genus in chronic inflammatory disorders.

2. Methodology of literature review

In the current review article, the information was collected from a literature search using various computerises databases as PubMed, Google Scholar, Scopus, ScienceDirect, Saudi Digital Library. Keywords such as *Z. xylopyrus, Z. jujuba, Z. nummularia, Z. mauritiana, Zizyphus oxyphylla, Z. mauritiana,* ethno-medicinal uses, ethno-pharmacological aspects, antimicrobial activity, biological activity, pharmacological properties, anti-fungal, anti-inflammatory, phytochemistry, phytochemical components, anti-cancer, toxicology, cytotoxicity, anti-convulsant, antioxidant effect were used to search literature with respect to *Ziziphus* species. Phrases like "Genus *Ziziphus* in chronic diseases", "*Ziziphus* species in chronic disease", "*Ziziphus* in cardiovascular diseases", "*Ziziphus* role in cancer", *Ziziphus* role in diabetes" "*Ziziphus* in obesities", "*Ziziphus* role in inflammatory diseases" "*Ziziphus* role in chronic constipation", "*Ziziphus* role in neurological disorder" were used to search the literature related to chronic diseases. Further information was retrieved from various botanical books.

3. Ethnobotanical uses of Ziziphus species

A significant biosynthetic preference has been shown against *Ziziphus* species' inflammatory diseases, particularly *Z. jujuba, Z.-mauritiana, Z. nummularia, Z. xylopyrus, Zizyphus oxyphylla* and *Z. spina-christi.* Ethnopharmacology of these species has been discussed in this section. The geographical distribution of some commonly used *Ziziphus species* is shown in Fig. 1.

3.1. Ziziphus jujuba

Jujube is the common name of *Ziziphus jujube,* and it is also called red date, a Chinese date in the buckthorn family ("Ziziphus jujuba - Search results - Wikipedia," n.d.). It thought to be cultivated in northern India, southern Asia, southeastern Europe, Lebanon, southern and central China. In the Arab region, the

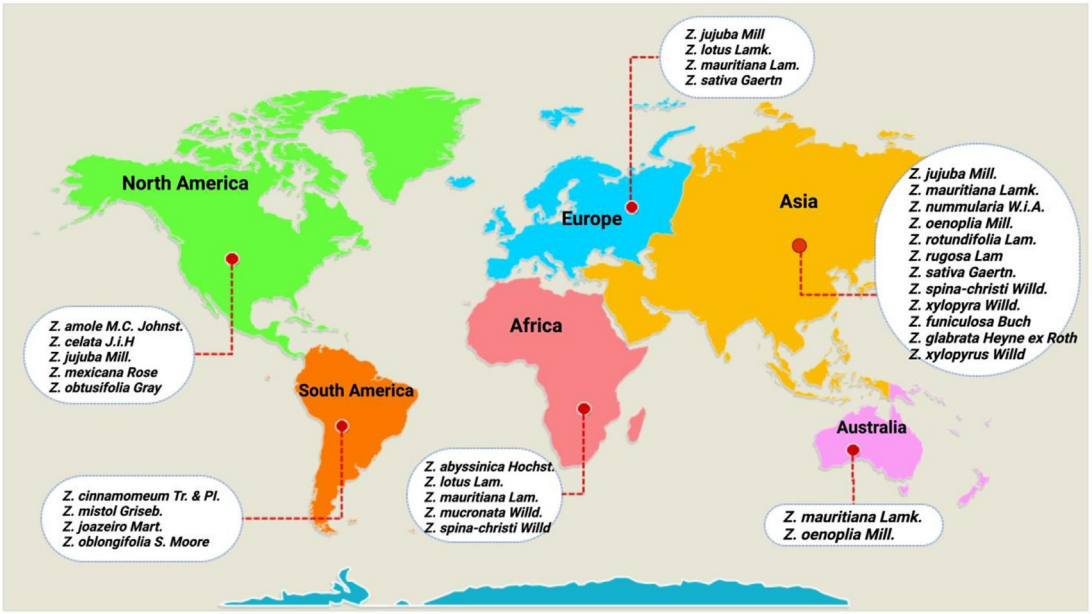


Fig. 1. The geographical distribution of some commonly used *Ziziphus species.*

Jujube is nearly related to the lote-trees (sing. "sidrah", pl. "sidr"). It is mentioned in the Quran four times, and this tree has a great status in Islam ("Sidra (name) - Wikipedia," n.d.). It is stated in the Chinese well known therapeutic book "Sheng Nong Ben Cao Jing" that *Z. jujuba* has diverse biological activities. *Ziziphus jujube* has shown antimicrobial and anti-inflammatory effects. Traditional Chinese medication supports its uses in styptic, tonic and anti-tumor (Mahajan and Chopda, 2009). *Z. jujuba* is also used in Japan to cure chronic hepatitis and chest and ribs pain. Iranian people are widely used as a folk medicine to reduce blood pressure, laxative agent, antitussive, cure wounds and oral wounds as Aphthous (Hamedi et al., 2016). *Z. jujuba* fruit, is aphrodisiac, laxative, tonic, digestible, used in vomiting, thirst, burning sensations, to cure blood sicknesses and to treat tuberculosis. Its seeds are helpful to cure leucorrhea and eye ailments (Mahajan and Chopda, 2009).

3.2. Ziziphus mauritiana

Ziziphus mauritiana is a beneficial fruit in India since ancient times. It was mentioned in Yajurveda (Macdonell, A. A., & Keith, 1958). In traditional medication, it is used to treat various diseases such as heartburn biliousness, biliousness, astringency, scabies, diuretic, and nausea. Fruit extract concentrates are used to improve healthy skin, moisturise and sunburn. The seed extract of *Ziziphus mauritiana in vitro* against various cell lines has shown anti-cancer potential (Mishra et al., 2011; Morton, 1987). During pregnancy, seeds are taken with buttermilk to stop nausea, vomiting and abdominal pains. *Z. mauritiana* seeds are crushed and used to manage sleeping disorders and anxiety in traditional Chinese medication. The seeds are blended with oil and employed to treat rheumatic arthritis (Kalaivani et al., 2012; Mishra et al., 2011). In Nigeria, dried root is used to treat diarrhoea, which is the leading cause of death, particularly in newborns (Mishra et al., 2011; Morton, 1987).

3.3. Ziziphus nummularia

Z. nummularia is a native of India's Thar desert, the southeastern part of Pakistan and south Iran. The fruit is used as eaten fresh or in confectionery, dried and pickled. Its juice is used as a refreshing drink. In India, dried fruit is used as astringent in bilious affliction. The leaves are antipyretic, reduce obesity, treat other skin diseases and scabies. The fruit of *Z. nummularia* is used to treat burning sensations, expels biliousness, thirst, vomiting and cooling (Upadhyay et al., 2011). Its seeds are helpful in leucorrhoea and also treat eye disorders (Aggarwal et al., 2018; Chopra, R.N., Nayar, S.L. and Chopra, 1986). It is used as a wound healer and to dress injuries (Kakrani et al., 1991). The brittle leaf juice of *Z. nummularia* is mixed with cow milk for smallpox since ancient times (Rauf et al., 2016).

3.4. Zizyphus xylopyrus

Zizyphus xylopyrus has tremendous medicinal importance, found in Pakistan, China, and the North-Western part of India. The different part of plants is used to treat various diseases such as diabetes, obesity, snake bite, diarrhoea, fever, digestive orders, and insomnia mentioned in Ayurvedic and folk medicines. In a study, ethanolic extract of *Zizyphus xylopyrus* has established a tribal claim of antiulcer activity. The mixture of fruit triturate of *Z. xyloyprus* is taken five days with milk to help in diabetes (Modi et al., 2014). A study reported that 15 ml of seed powder is taken with hot water or milk, two days in multiple times that assisted diabetes (Tetali et al., 2009). A mixture of fruit powder with a pinch of ginger is taken three times orally per day in stomach indigestion (Sudhakar Reddy et al., 2009). It is also reported that Eastern Ghats of Andra Pradesh in India used the leaf glue of this plant and latex of *Ipomea carnea* to treat pimples. Bark and leaf powder paste applied externally on the chest to treat chest pain of cough. As a treatment of indigestion and stomachache, thrice a day fruit powder (3–4 g) with a ginger pinch is advised (Yadav et al., 2011). Turkish people widely used *Z. xylopyrus* as sedative (Jagtap et al., 2006).

3.5. Z. Spina-Christi

Ziziphus spina-christi recognised as the Christ's throne jujube. It is a small tree or a spiny shrub that strongly resists drought and heat. It is a evergreen plant or tree in tropical Africa, Levant and

some tropical countries (National Academy of Sciences, 1980; Orwa et al., 2009). The morphological investigation has reported in Saudi Arabia two well-defined varieties, *Z. spina-christi* var. *spina-christi*, *Z. spina-christi* var. *mi-crophylla* and one plant affinities to *Z. spina-christi* var. *spina-christi* (Almalki and Alzahrani, 2018). Arabs have long used *Z. spina-christi* in folklore medicine to maintain health (El Ghazali et al., 1997). Extract of *Z. spina-christi* is vital in the development of drugs and showing various pharmacological activities. Natives of the Middle East, East and South of Asia are using it to cure many diseases like fever, dandruff, pain, inflammatory conditions, wounds and ulcers, asthma, and eye disorders. In the Middle East, this plant has been both food and medicine.

3.6. Zizyphus oxyphylla

Ziziphus oxyphylla (ZO) is mainly found in warm and tropic regions in the world. It is one of the species of genus Ziziphus that is widely used to treat different diseases like liver-related problems, jaundice, and diabetes. Phytochemical tests confirm alkaloids, flavonoids, phenolic compounds, and tannins. in ZO. Class of cyclopeptide alkaloids are the primary isolated compound of it. Various pharmacological activities for the crude extracts and their fraction confirmed antibacterial, acetylcholine esterase, antipyretic, antioxidant and anti-inflammatory *in vivo* and *in vitro*. Brine shrimp lethality and cytotoxicity insecticidal studies have shown no toxicity (Ahmad et al., 2017; Nisar et al., 2011).

4. Secondary metabolites found in *Ziziphus species.*

Phytochemistry is the branch involved in phytochemicals that are obtained from plants. This section strives to describe the structure of the large number of secondary metabolites found in *Ziziphus spp*. These phytochemicals are numbered 65 alkaloids, 151 flavonoids, 43 terpenoids, 31 saponins and 40 other compounds (El Maaiden et al., 2020). Leaves are the most common objectives for the isolation of compounds from the *Ziziphus genus*. *In vivo* and *in vitro* test models have shown the therapeutic application of the chemical constituents. Some of the secondary metabolites of the *Ziziphus genus* are described in Table 1.

5. Anti-inflammatory effect of genus *Ziziphus*

The inflammatory process helps protect the body from a destructive breakdown when it is under control. It is the cause of the unwanted deterioration of the body when it is unrestrained. Various ailments of humans' tendonitis, asthma, inflammatory bowel disease and arthritis happen due to the inflammation. There

Table 1
Some of the secondary metabolites of the Ziziphus genus.

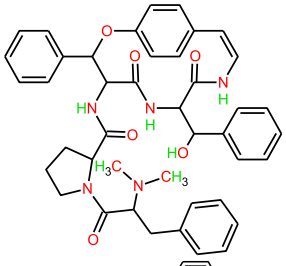
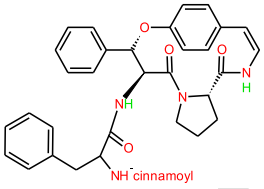
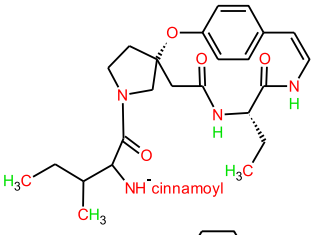
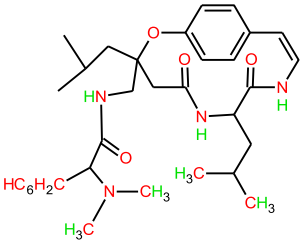
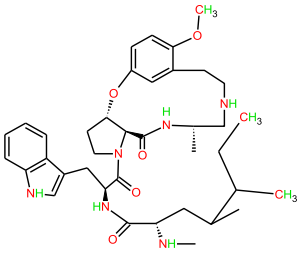
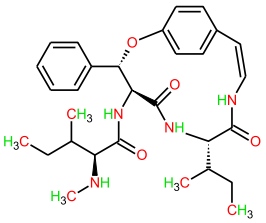
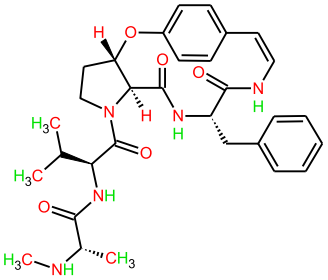
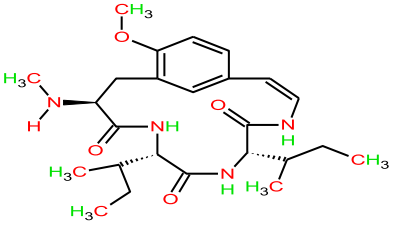
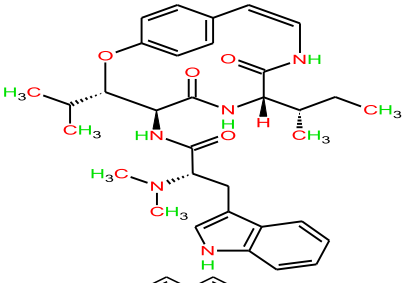
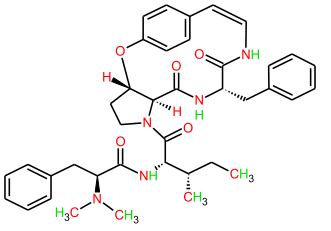
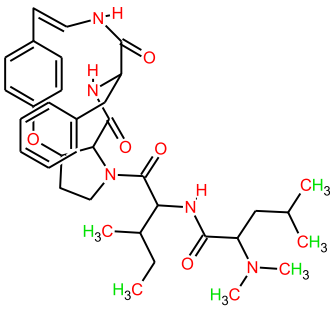
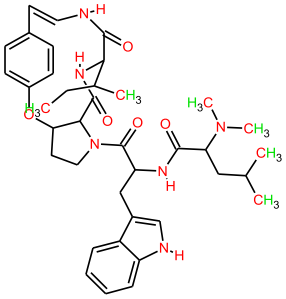
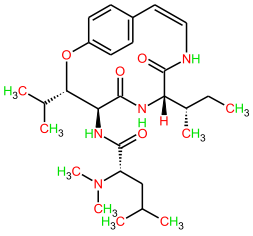
S.No	Compound	Structure	Molecular Formula	Molecular weight	References
1	Oxyphylline A		C42H45N5O6	715.847	(Inayat-Ur-Rahman et al., 2007)
2	Oxyphylline B		C31H30N3O4	508.5876	(El Maaiden et al., 2020)
3	Oxyphylline C		C24H32N3O4	426.52858	(El Maaiden et al., 2020)
4	Sanjoinine A		C31H36N4O4	528.6494	(El Maaiden et al., 2020)

Table 1 (*continued*)

S.No	Compound	Structure	Molecular Formula	Molecular weight	References
5	Mauritine M		C35H45N6O5	629.769	(El Maaiden et al., 2020)
6	Mauritine L		C30H40N4O4	520.663	(El Maaiden et al., 2020)
7	Mauritine F		C31H39N5O5	561.67186	(Cristau et al., 2005)
8	Abyssmine B		C25H38N4O4	458.59362	(Tschesche et al., 1974)
9	Amphibine A		C33H43N5O4	573.734	(Tschesche et al., 1972)
10	Amphibine B		C39H47N5O5	665.82098	(Tschesche et al., 1972)

(*continued on next page*)

Table 1 (*continued*)

S.No	Compound	Structure	Molecular Formula	Molecular weight	References
11	Amphibine C		C36H49N5O5	631.80476	(Tschesche et al., 1972)
12	Amphibine E		C38H50N6O5	670.8408	(Mongalo et al., 2020)
13	Adouetine X		C28H44N4O4	500.673	(Joullié and Richard, 2004)

are multiple disorders and conditions due to inflammation as autoimmune diseases, asthma, allergy, hepatitis, glomerulonephritis, coeliac disease, transplant rejection and inflammatory bowel disease. When the body identifies an invader, it begins a biological response to try to exclude it. This intruder could be a foreign body like a thorn, pathogens, or an irritant. Pathogens comprise viruses, bacteria, and other organisms are the cause of infections (Wahab et al., 2021). The body sometimes considers harmful its cells and tissues. These types of reactions could cause autoimmune diseases like type 1 diabetes. It believes that inflammation may contribute to chronic diseases and cause heart disease, obesity, cancer, chronic constipation, neurological disorder, and type 2 diabetes. People have higher levels of inflammatory markers in their bodies that are affected by these conditions. We can divide the inflammation into two categories acute and chronic. In the progression of inflammatory disorders, the key signalling molecules are reactive oxygen species (ROS). An increase of ROS generation by polymorphonuclear neutrophils at the inflammation site causes tissue injury and endothelial dysfunction. The vascular endothelium is vital in the passage of inflammatory and macromolecules from blood to the tissue [5]. Reactive oxygen species covalently binds with different cell organelles and the cause of various diseases [6,7].

Ziziphus jujuba Mill. (Rhamnaceae) leaves were examined to investigate the plant cell division's effects by a dried ethanolic extract of it. Two experimental inflammation models on rats were used to determine the anti-inflammatory and toxicity properties of *Ziziphus jujuba* Mill. There was no observation of mortality and toxic symptoms on animals. A statistically significant inhibitory effect was determined at 0.5% and 1% concentration on *Triticum radicles*' growth [54]. *Z. jujuba* fruit ethanolic extract was used to examine *in vivo* antibacterial, antidiarrheal, and anti-inflammatory activities. Anti-inflammatory results of the studies have shown that the ethanolic extract of *Z. jujuba* inhibited oedema in rats significantly, and the thickness of both right and left paw was affected (Mesaik et al., 2018). *Zizyphus lotus* was given intraperitoneally in different doses (50, 100 and 200 mg/kg body weight). These examinations have shown excellent anti-inflammatory response, but results depend upon the doses; therefore, *Zizyphus lotus* could be used to inhibit inflammation (Borgi et al., 2007). *Ziziphus mauritiana* has found 2.2% alkaloids,92.65% saponins and 5 μg/ml tannins in dried bark. The results of studies have exhibited that it is effective in anti-cancer and liver damage treatment (Bhatt and Dhyani, 2013). *Ziziphus spina-christi* was found in ancient Egyptian prescriptions to treat pain, swellings, and heat to have anti-inflammatory effects (Kadioglu et al., 2016). *Ziziphus Spina-christi* fruit extract against acetic acid-induced colitis in rats showed the protective and anti-inflammatory results in the teatment of inflammatory bowel disease (Almeer et al., 2018b). Summary of anti-inflammatory activities of some pharmacologically active *Ziziphus species* is detailed in Table 2. A significant cause of death worldwide is chronic inflammatory diseases. According to the World Health Organization (WHO), chronic diseases are the greatest threat to human health. 3 of 5 people die due to chronic inflammatory disorders worldwide like chronic respiratory diseases, stroke, cardiovascular diseases, cancer, diabetes, and obesity (de Barcelos et al., 2019; Deepak et al., 2019; Fleit, 2014; Tsai et al., 2019). The anti-inflammatory effect of the *Ziziphus genus* in some important chronic inflammatory disorders is discussed below.

Table 2
Anti-inflammatory activity of some pharmacologically active *Ziziphus species*.

Ziziphus Species	Part used	Model	Extract /Isolated compounds	Observations	Reference
Ziziphus spina-christi	Seed, leaf, root stem	*In vitro*	Epigallocatechin, gallocatechin, spinosin, 6′″ feruloylspinosin and 6′″ sinapoylspinosin and crude extracts	*Z. spina-christi* might possess anti-inflammatory activity as assumed by ancient Egyptian prescriptions.	(Kadioglu et al., 2016)
Ziziphus spina-christi	Leaf	*In vitro*	*Ziziphus spina-christi* leaf extract (ZSCLE)	This effect may be attributed to the antioxidant, anti-inflammatory, and anti-apoptotic activities of ZSCLE.	(Dkhil et al., 2018)
Ziziphus spina-christi	Leaf	*In vivo*	*Ziziphus spina-christi* leaf extract (ZLE)	*Ziziphus spina-christi* had anti-apoptotic, anti-fibrotic, antioxidant, and protective effects on *S. mansoni* induced liver wounds.	(Almeer et al., 2018a)
Ziziphus spina-christi	Fruit/ Seed	*In vitro*	Ethanolic extract of the leaves	It has significant anti-inflammatory and moderate antipyretic activities.	(Tanira et al., 1988)
Zizyphus spina-christ	Leaves and its major saponin glycoside	*In vitro*	Butanol extract	Safe alternative to lower blood glucose.	(Abdel-Zaher et al., 2005)
Zizyphus oxyphylla	Stem	*In vivo*	The crude extract of *Zizyphus oxyphylla*	The crude extract has shown significant results.	(Ali et al., 2015)
Zizyphus oxyphylla	Stem	*In vitro*	Crude methanolic extract	Crude extract and fractions showed significant phytotoxicity at higher doses.	(Kaleem et al., 2012)
Ziziphus jujuba	Leaves	*In vitro*	Ethanolic extract	Leaves extracts possess significant anti-inflammatory activity.	(Kumar et al., 2004)
Ziziphus jujuba	Fruit	*In vivo*	Ethanolic extract of *Z. jujuba*	It affected paw volume and thickness.	(Mesaik et al., 2018)
Ziziphus xylopyrus	Leaves	*In vitro*	Methanolic extract *Ziziphus xylopyrus*	Wound healing activity against Incision and excision wound.	(Jawaid T et al., 2017)
Ziziphus Xylopyrus	Stem	*In vitro*	Ethanolic extract	*Z. xylopyrus* has potential as an allergic anti-asthmatic agent.	(Gupta et al., 2016)
Z. mauritiana.	Bark	*In vitro*	Chloroform, ethanol, and aqueous extracts	The anti-inflammatory potential was shown by chloroform extract only.	(Deshpande et al., 2013)
Z. mauritiana	Fruit	*In vivo*	Ethanolic extract	Anti-inflammatory results demonstrated.	(Mesaik et al., 2018)
Z. mauritiana	Leaf	*In vitro*	Methanol extract	71.83% reduction in inflammation at a concentration of 400 mg/kg body weight of rats.	(Abdallah et al., 2016)
Z. mauritiana	Seed and stem bark	*In vitro and in vivo*	Methanol extract	Anti-inflammatory has shown.	(Akanda and Hasan, 2021)
Zizyphus nummularia	Root bark	*In vivo*	Crude ethanolic extract	Anti-inflammatory activity through inhibition of TNF-α and NO production.	(Ray et al., 2015)
Zizyphus nummularia	Leaves	*In vitro*	Alcoholic extract	Anti-inflammatory and wound repairing studies rationalize the traditional claim of *Z. nummalaria* leaves extracts.	(Yusufoglu, 2011)
Zizyphus nummularia	Root	*In vivo*	Methanolic extract	The anti-inflammatory and antipyretic activities have shown.	(Rauf et al., 2016)
Zizyphus nummularia	Crushed root, leaves	*In vitro*	Cyclopeptide alkaloids isolated from the leaves of *Z. nummularia*	Highly significant anti-nociceptive effects have shown.	(Goyal et al., 2013)
Zizyphus nummularia	Decoction of leaves	*In vitro*	Cyclopeptide alkaloids isolated from the leaves	Analgesic and anti-inflammatory.	(Goyal et al., 2013)
Ziziphus nummularia	Fruit	*In vitro*	Methanolic extracts of genotypes were screened for total phenolic compounds	It was concluded that the selected plant could be used as a remedy for oxidative stress and neurodegenerative diseases.	(Uddin et al., 2020)

5.1. Cardiovascular disease (CVD)

One of the most common causes of mortality in the world is acute myocardial infarction. Clinical scientists are examining the potential effect of administering cells to the ischemically injured heart. As a result of inflammation, the C-reactive proteins (CRP) form in the blood, and CRP concentration rises with the severity of inflammation. A pocket of fatty, soft plaque begins to build up and seeps into the arty channel, resulting in advanced coronary artery inflammation. Heart rehabilitation strategies are antioxidants, plants and exercises (Calvert, 2011; Leistner and Zeiher, 2012; Tschakert et al., 2016). According to the World Health Organization, middle-income countries are affected by CVD more than developed countries, and three fourth deaths occur due to CVD. People have risk factors such as diabetes, hyperlipidemia, and hypertension need more care and management using medicines and counselling (Chen, 2018).

Nitric oxide is involved in cardiovascular regulations, and *Ziziphus jujuba* stimulates the liberation of nitric oxide. Cardiovascular responses of hydroalcoholic extract of *Z. jujuba* in acute NG-nitro-L-arginine methyl ester (L-NAME) hypertensive rats were analysed. *Z. jujuba* extract's long-term consumption at low doses was attenuated cardiovascular responses induced by L-NAME. It shows that *Z. jujuba* effectively treats hypertension induced by a lack of NO (Mohebbati et al., 2018). *Z. jujuba* compounds like saponins, jujuboside have exhibited cardiovascular regulation (Steinkamp-Fenske et al., 2007). The effect of six weeks of interval training with or without the extract of *Ziziphus jujuba* on lipocalcin-2 and adiponectin levels in heart tissue in male Wistar rats with myocardial infarction was investigated. Due to the consumption of extract and six weeks of exercise, the LCN2 inflammatory factor decreased. Therefore, *Ziziphus jujuba* extract could be beneficial in cardiac rehabilitation after a heart attack (Hosseini et al., 2019). This study tries to find out the effect of traditional health practices in treating hypertension and diabetes. *Ziziphus* has found to be effective against both hypertension and diabetes (Sudhakar Reddy et al., 2009). Polyphenols from Chinese jujube peel (*Ziziphus jujube* Mill. cv. Dongzao) was evaluated the preventive effect against myocardial infarction provoked by biotoxicity of aluminum and isoproterenol in rats. The study results validated

that jujube phenolics are effective against ISO-induced myocardial injury and reduce aluminum toxicity (Frimpong and Nlooto, 2019). Hydroalcoholic extract of *Ziziphus jujuba* was investigated to evaluate cardiovascular parameters in normotensive rats. The current study revealed that *Ziziphus jujuba* hydroalcoholic extract showed inhibitory effect on the basal cardiovascular parameters, and its best result have shown at 200 mg/kg (Mohebbati et al., 2019). *Ziziphus jujuba* Mill reveals anti-hypertensive property. Various studies have shown that different parts of *Z. lotus* for scavenging free radicals like lipid peroxidation result in cell damage (Boulanouar et al., 2013; Ghalem et al., 2014; Ghazghazi et al., 2014; Hammi et al., 2015). Crude aqueous extract of *Ziziphus spina-christi* was tested in hypercholesterolemic male rats to evaluate the antioxidant and hypolipidemic activities. Phenolic constituents of *Ziziphus spina-christi* suppressed hypercholesterolemia, oxidative stress and revived the change histopathological and biochemical features (Al-Sieni et al., 2020). Schematized representation of inflammation in cardiovascular disease has been shown in Fig. 2 ("Inflammation's Role In Heart Disease | The Medical Group of South Florida," n.d.).

5.2. Diabetes

In the present time, the most prevalent endocrine disease that increases lipids and blood glucose is diabetes mellitus. Kidneys, cardiovascular system, eyes, and nervous system are affected by this disease. Inflammation results in the activation of several immune cells involved in the pancreatic beta-cell death through various inflammatory cytokines that produce insulin resistance. Several studies have shown that herbal extract of the medicinal plants has anti-diabetic effects that can be used to reduce blood glucose in diabetic patients. Schematized representation of inflammation in diabetes has been shown in Fig. 3.

In a study, experimental rats were induced by diabetes that was like human type 1 diabetes. Hydro-alcoholic extract of *Ziziphus Jujuba* leaves was evaluated to investigate the hypoglycemic effect, triglyceride, blood lipoproteins and total cholesterol. The results showed that *Z. Jujuba* leaves can be used in people with diabetes for lipid and glucose reduction (Shirdel Z et al., 2009). Metabolism of carbohydrates, protein and fat are affected by diabetes. It is a severe metabolic disorder. Diabetes mellitus is linked with oxidative stress that is the cause of an increase in reactive oxygen species production.

Currently, antioxidant properties have been found in the *Z. jujuba*-derived protein hydrolysates. The results of this study revealed that *Z. jujuba*-derived hydrolysates and the purified peptides could prevent oxidative reactions (Memarpoor-Yazdi et al., 2013). *In vitro* model of diabetic neuropathy was used to evaluate the effect of aqueous fruit extract of *Ziziphus jujuba* Lam on glucose-induced neurotoxicity in PC12 cells. Aqueous extract of *Z. jujuba* protected against hyperglycemia-induced cellular toxicity. The extract prevented reactive oxygen species (ROS) generation and neural apoptosis. *Z. jujuba* fruit can reduce diabetes complications such as neuropathy (Steinkamp-Fenske et al., 2007). An important role is played by postprandial hyperglycemia in developing type 2 diabetes. Starch and glycogen preventing a rapid rise in blood sugar are done by the inhibition of alpha-amylase. *Z. jujuba* can be proposed to treat diabetic patients due to its antioxidant properties and high polyphenolic content (Afrisham et al., 2015). Antioxidant and anti-diabetic effects of different parts of *Zizyphus lotus* aqueous extract in diabetic Wistar rats were examined. The root and leaf extracts reduced the level of glucose on the 21st day of post-administration. Diabetic animals' liver, erythrocytes and pancreas have improved by the antioxidant activity of root and leaf. The leaf and root modulated the concentrations of various vitamins like vitamin A, C and E in diabetic rats, but seed extract had not done this. Oral administration of *Zizyphus lotus L.* extracts from leaves and roots have exhibited antioxidant and anti-diabetic effects in diabetic rats. *Z. lotus L.* seems to be an excellent candidate to lower hyperglycaemia in diabetic patients in addition to conventional anti-diabetic drugs (Benammar and Baghdad, 2014). *Zizyphus mauritiana Lam* was administrated to Wistar rats made diabetics temporarily by oral

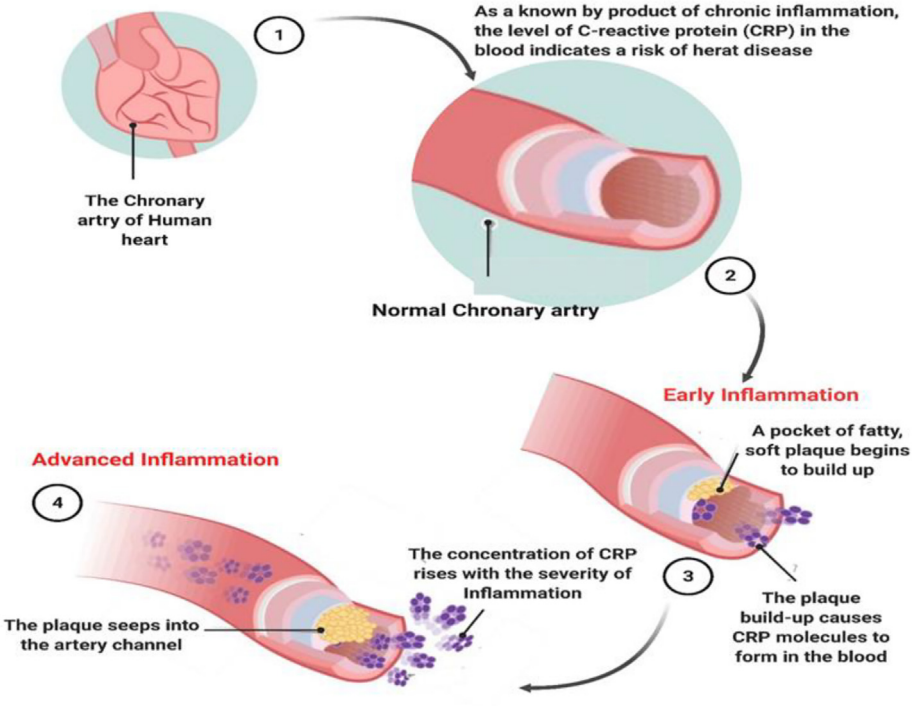


Fig. 2. Schematized representation of inflammation in cardiovascular disease.

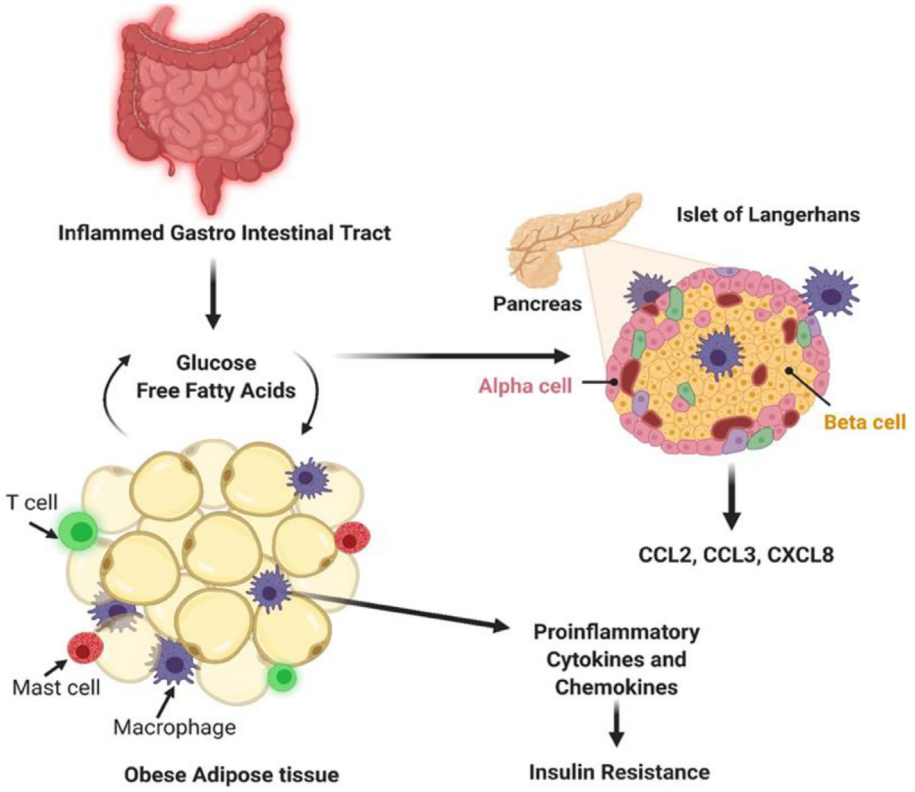


Fig. 3. Schematized representation of inflammation in diabetes.

glucose tolerance test. It has shown anti-diabetic status experimentally (Sy et al., 2005). Butanol extract of *Zizyphus spina-christi* leaves and its major saponin glycoside, christinin-A, were examined in diabetic rats, insulin levels and serum glucose in-diabetic control group, type-I (insulin-dependent) and type-II (non-insulin-dependent). Results of examination have revealed that *Ziziphus spina-christi* seems effective and safe to lower blood glucose (Abdel-Zaher et al., 2005). Furthermore, more comprehensive research is needed to explore the anti-diabetic abilities of *Ziziphus in vivo*.

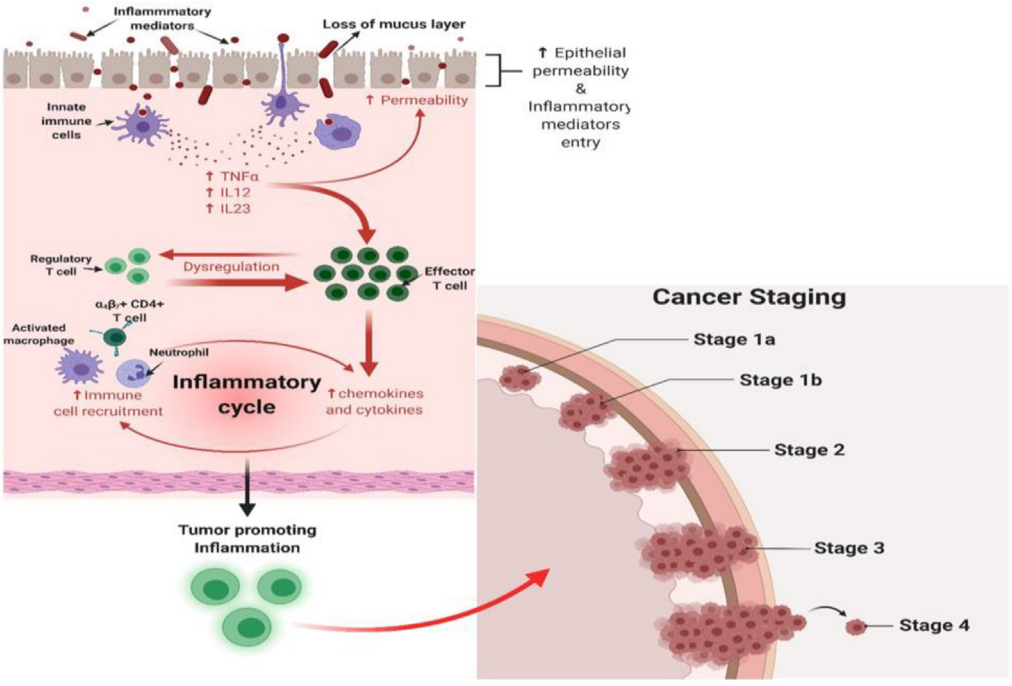


Fig. 4. Inflammatory mediators and cancer stages.

5.3. Cancer

Worldwide, cancer is the leading cause of death, and it is an increasing health problem. Abnormal cells that grow uncontrollably in almost any tissue and organ of the body are the cause of cancer. Cancer has been exerting tremendous emotional, physical, and financial burden on individuals, families, health systems and communities. Some of the important causes of cancer are ageing, lifestyle changes, population growth, and the adoption of cancer-causing behaviors. Injury or infection causes the production of inflammatory cytokines that activate innate and adaptive immunity to get rid of the pathogen. If initial disturbance of epithelial homeostasis occurred by an oncogenic event, the sterilizing immunity would not remove the initial insult (Greten and Grivennikov, 2019). This enhanced inflammation and cytokine-driven proliferation will facilitate tumor growth rather than restoring normal epithelial homeostasis. Inflammatory mediators and cancer stages have shown in Fig. 4.

Chemotherapy, radiation, surgery, immunotherapy, gene therapy and hormone therapy have been used as treatment forms, but there is a need to discover plant-based anti-cancer compounds. In recent years, various researches have demonstrated the significant roles of natural substances and bioactive compounds derived from plants discovering new anti-cancer drugs (Ho et al., 2002; Newman et al., 2003). Chemotherapy is a standard treatment for cancer patients, but it has side effects. Herbal medicine can be used to treat cancer compared to chemotherapy because they have low toxicity, low cost of treatment and fewer side effects (Ashton, 2004; Chun Cheng et al., 2012; Fan et al., 2013; Mans et al., 2000).

The triterpenic acids are found in glycones such as saponins or free acids that have shown various biological effects like hepatoprotective (Liu et al., 1998), antimicrobial (Gbaguidi et al., 2005), antioxidant and anti-inflammatory properties (Fan et al., 2004; Kalogeropoulos et al., 2010). Triterpenic acids have become attractive for researchers and health care products due to their antitumor and anticarcinogenic status (Romero et al., 2010). There are 10 triterpenic acids named ursonic, zizyberenalic, oleanolic (OA), betulinic (BA), ceanothenic, epiceanothic, zizyberanalic, zizyberanal, alphitolic, ceanothic acids and two triterpenes ursolic acid (UA), ziziberanalic acid are identified in dried jujube fruit (Guo et al., 2009). All the compounds have been isolated in the dried jujube fruit, and a few of them having toxicity UA, OA and BA. Fig. 5 have shown the chemical structures of these three toxic triterpenic acids isolated from dried jujube fruit (Pisha et al., 1995; Shyu et al., 2010).

The pathological and physiological process of cell death is defected by programmed and apoptosis. Thus, one of the most critical bioactive compounds' anti-cancer properties is the apoptotic process's modulation. The most promising natural compounds are betulinic acid (BA) with triterpenoids, and it is effective against a wide heterogeneity of cancer cells. *In-vivo* preclinically applied BA revealed some exceptional anti-cancer effects and comprehensive nonexistence of systemic toxicity in rodents. Betulinic acid (BA), supported with other therapeutics to induce tumor cell death, and various functional derivatives have been explored (Fulda, 2009). Mechanisms of BA action include the induction of apoptosis via the mitochondrial pathway and the loss of mitochondrial membrane potential without any effect on the caspase inhibitor. There are two major signaling pathways for apoptotic cell death: The extrinsic or receptor pathway and the intrinsic or mitochondrial pathway. Jujube bioactive compound through major signaling pathways induce apoptosis by several mechanisms of action. (Mullauer et al., 2010). In addition, there is another mechanism of action in which BA can trigger the generation of reactive oxygen species that activate the NF-κB (nuclear factor kappa-B) through the inflammatory signalling pathway of tumor cell lines. Inhibition of BA-induced NF-κB activation resultattenuated BA-induced apoptosis (Takada and Aggarwal, 2003).

Bioactive constituents of jujube fruit polysaccharides and triterpenic acids have shown anti-cancer and antiproliferative effects of various cancer cell lines. Jujube fruit's bioactive constituents are accountable for apoptosis. It is the primary mechanism of action of its active compound (Tahergorabi et al., 2015). A study has shown that *Z. jujube* ameliorates NMU carcinogenesis's adverse effects. *Z. jujube* could be useful to treat mammary tumor's (Hoshyar et al., 2015). Different concentrations of Jujube aqueous extract were investigated *in vitro* for anti-cancer and pro-apoptotic abilities of cervical and breast human cancer cells. Dose and time-dependent manner Jujube has significantly inhibited cancer cell viability. This study has shown that jujubes might be used as a natural potential and encouraging agent to protect or cure human cancers (Abedini et al., 2016). Anti-cancer potential of seed extract of *Ziziphus mauritiana* were evaluated *in vitro* against various cell lines and *in vivo* against Ehrich ascites carcinoma bearing Swiss albino mice. Extract of *Ziziphus mauritiana in vivo* has shown the potent anti-cancer potential, and 100–800 mg/kg body weight of plant extract significantly reduced tumor volume (Mishra et al., 2011). Biological activities of *Ziziphus species* unidentified and identified should be evaluated to find its anti-cancer effect.

5.4. Chronic constipation

Chronic constipation can be defined differently for different people. For some people, infrequent bowel movements for weeks at a time are called chronic constipation, and for others are straining or having difficulty passing stools. A stool cycle of less than

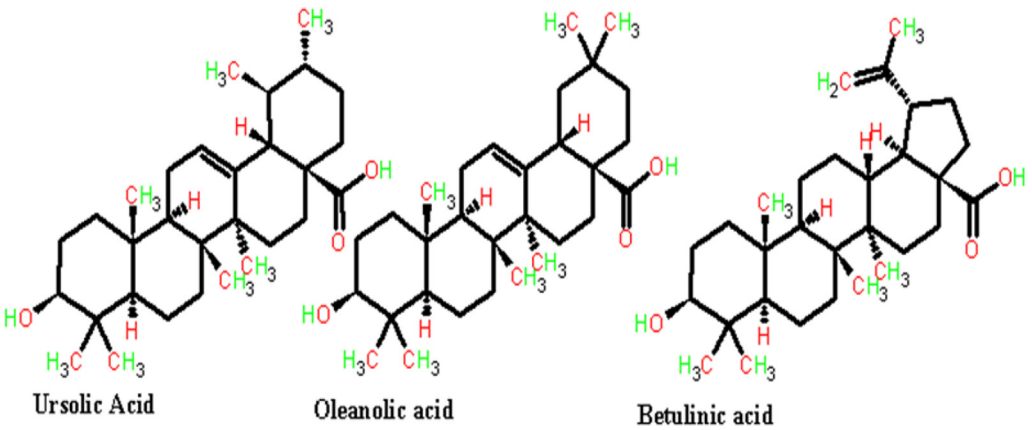


Fig. 5. Chemical structures of toxic triterpenic acid (oleanolic, betulinic and ursolic) isolated from dried jujube fruit.

three per week that lasts several months is generally called chronic constipation. Constipation is a state in which unsatisfactory defection with infrequent stool features and trouble in passing stools or both. Constipation is affecting all age groups and patient populations and varying patient to patient. It has a wide range of reported prevalence causes of different definitions. There are many factors for the pathogenesis of constipation such as genetic predisposition, type of diet, colonic motility, socioeconomic status, and biological and pharmaceutical factors. Chronic constipation and normal defecation have been illustrated in Fig. 6. Therapeutic and diagnostic options play a vital role in the therapy of chronic constipation (Forootan et al., 2018).

Ziziphus jujuba extract was investigated against its efficacy and safety for chronic constipation through questionnaire-based study. Patients suffering from constipation have taken fluid of *Z. jujuba* or placebo for 12 weeks. Before and after treatment, the sufferer filled questionnaires, transit time (TT) tests and a visual analogue scale. Results have shown that *Z. jujuba* extract is a safe and effective treatment for chronic constipation sufferers (Naftali et al., 2008). The bark of the *Z. nummularia* is used to treat chronic dysentery and diarrhea (Al-Saeedi et al., 2017; Kīrtikara and Basu, 2017). Unfortunately, there are not many studies found that have investigated the effect of *Ziziphus* species on chronic constipation.

5.5. Obesity

According to the World Health Organization, obesity has tripled since 1975 in the world. In 2016, more than 1.9 billion adults aged 18 years and older were overweight. Of these, over 650 million adults were obese. Obesity and overweight kill more people than underweight of the world's population. In 2019, 38 million children under the age of 5 were obese or overweight (Levesque, 2011). A study was conducted to investigate the *Ziziphus jujuba* leaves extract in cafeteria diet and atherogenic diet-induced obesity. Albino rats were fed by the cafeteria diet/atherogenic diet daily for 40 days with a regular diet. The body weight of the rats was measured every day for 40 days. Lipid levels and serum glucose and internal organs, and fat pad weight were examined on day 41 of 6 rats. The *Ziziphus jujuba* leaves extract therapy caused a significant reduction in body weight, daily food intake, lipid levels and serum glucose, fat pad weights and internal organs in the cafeteria and atherogenic diet-fed rats compared with the control group of rats. It is concluded that the alcoholic extract of *Z. jujuba* leaves has shown the anti-obese effect. Alcoholic extract of *Z. jujuba* has reduced the food intake, lipid levels, internal organs and fat pad weights, serum glucose and body weight in dietary obese rats (Ganachari et al., 2007). The objective of this research was to examine the anti-obesity activity of *Ziziphus mauritiana Lam* bark powder. *Ziziphus mauritiana Lam* bark powder had been fed to high fat diet-induced obesity rats. The study results have shown the anti-obesity and lipase inhibitory effect at 250 mg/kg and 500-mg/kg dose (Deshpande et al., 2012).

In another study, the anti-obesity effect of *Z. jujuba* on adipocyte differentiation of 3 T3-L1 preadipocytes was examined. Treatment with an extract of *Z. jujuba* suppressed lipid accumulation and glycerol-3-phosphate dehydrogenase (GPDH) activity without affecting cell viability. The study concluded that CHCl (3)-F may block adipogenesis, at least in part, by decreasing the expression of PPAR gamma, C/EBP alpha and beta (Kubota et al., 2009). A study investigated the hypolipidemic and anti-obesity activity of different doses (5, 15 and 30 g/day) of *Z. jujuba* powder and determined its liver function effect. It has shown that different doses of *Z. jujuba* powder hold anti-obesity and hypolipidemic potential and didn't shown any adverse effect on liver function as measured by AST and ALT (Mostafa and Labban, 2013).

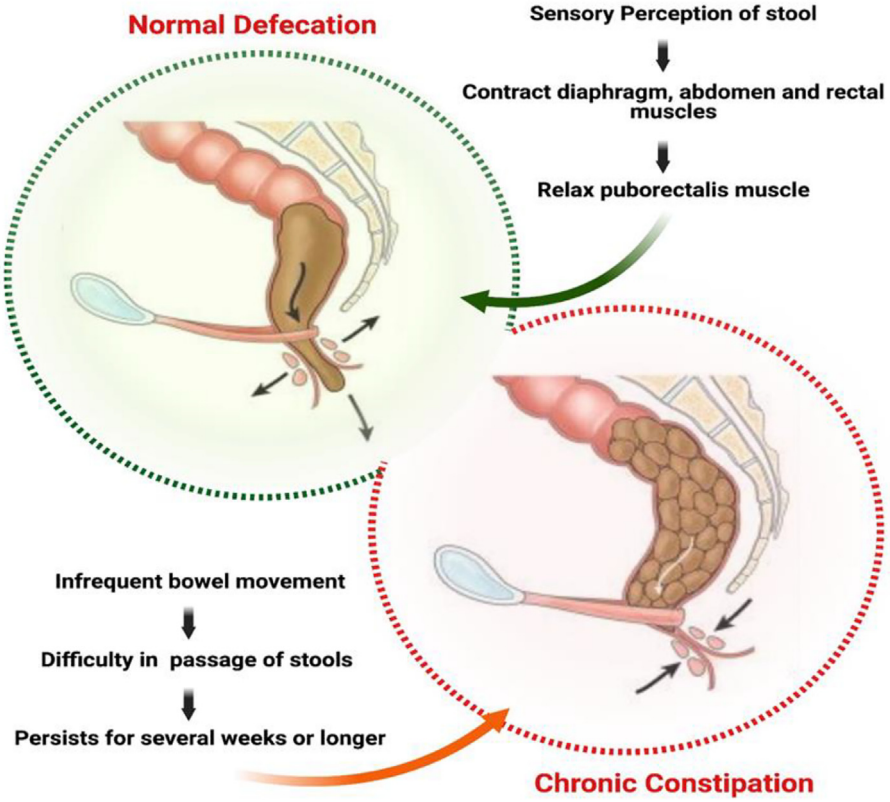


Fig. 6. Chronic constipation and normal defecation.

5.6. Neurological disorder

Neurobeneficial effects in modern science are benefiting the brain like neurotrophic action and neuroprotection effect. Neurodegenerative disease is a condition that affects the elderly. Neurological disorders are insomnia, depression, neurodegenerative diseases-several common pathological conditions are oxidative disorder stress, neurotrophic factor deficiency and neurogenesis impairment. Oxidative stress induces activation of microglia and astrocytes with a consequent increase of pro-inflammatory mediator production, and, in turn, glial activation leads to toxic radical release, exacerbating neuronal damage. In addition, the release of inflammatory cytokines leads to amyloid plaque and neurofibrillary tangle (NFT) formation, which triggers inflammatory molecule release and causes neuronal damage, with consequent neurodegeneration.

Jujube as herbal medicine have shown many functions, and it's one of the primary roles is calming down the mind with improving the quality of sleep. In addition, Jujube occupies neuroprotective activities like stimulating neuronal differentiation, including protecting neuronal cells against neurotoxin stress, increasing neurotrophic factors, and boosting learning and memory. The findings of various researches have shown that the jujube is a potential health supplement for preventing and treating neurological diseases (Chen et al., 2017). The signal of cAMP-PKA-CREB does neuronal differentiation of PC12 cells (Ravni et al., 2008). The engagement of the cAMP pathway revealed Jujube-induced neurite outgrowth and neurofilament expression. Results have shown that jujube-induced neurite outgrowth and neurofilament expressions, attenuated by the application of H89 (a cyclic AMP-dependent PKA inhibitor) (Chen et al., 2014a). Astrocytes are the amplest cell in the nervous system. Synthesise and release neurotrophic factors are its main functions. These functions are neurotrophin 3 (NT3) and NT4/5,brain-derived neurotrophic factor, NGF and glial cell line-derived neurotrophic factor (Ridet et al., 1997).

Jujube was investigated to find the effect on neurotrophic factor expression. Jujube water extract was used in a dose-dependent manner to stimulate neurotrophic factors, having the highest induction of ~ 100% for NGF, 100% for BDNF, 100% for GDNF, and 50% for NT3. For NT4 and NT5, no apparent morphological change was observed in jujube-treated astrocytes (Chen et al., 2017, 2014b). Choline acetyltransferase is activated by *Zizyphus jujube* and may positively affect Alzheimer's disease (AD). A study was conducted to investigate the effect of *Ziziphus jujuba* in a rat model of AD. Seven groups had been formed of 49 male Wistar, *Zizyphus jujube* extract at the doses 500 and 1,000 mg/kg b.w. per day for 15 days. The study concluded that *Zizyphus jujube* had shown the repairing effect on behavioural and memory disorders produced by nucleus basalis of Meynert lesion in rats; therefore, it could potentially affect AD patients (Rabiei et al., 2014). *Ziziphus jujuba Mill* var. Spinosa seeds were examined by behavioural tests like a tail-suspension test (TST), forced swimming test (FST) and open field test, and applied chronic unpredictable mild stress test to mice. The results revealed that extract could be used as an antidepressant (Oh et al., 2020). Flavonoids and saponins from the seed of *Z. jujuba* have exhibited hypnotic and sedative effects. There was a significant reduction in walking time and coordination movement of various organs of mice and prolonging the sleeping time (Jiang et al., 2007). The functions of a neuron are decreased in the process of neurodegeneration. The main factor of Alzheimer and Parkinson diseases is oxidative stress, which is also the cause of neuronal damage in diseases' progress (Lin and Beal, 2006). A study reported that jujube water extract protects neuronal cells against *tert*-butyl hydroperoxide-(tBHP-) induced oxidative injury in cultured cells. In cultured PC12 cells, tBHP-induced reactive oxygen species could be inhibited by jujube water extract. Jujube extracts protected PC12 cells against (tBHP-) induced cytotoxicity (Chen et al., 2013). After reviewing various articles, it is concluded that jujube flavonoid and nucleotide have shown beneficial brain

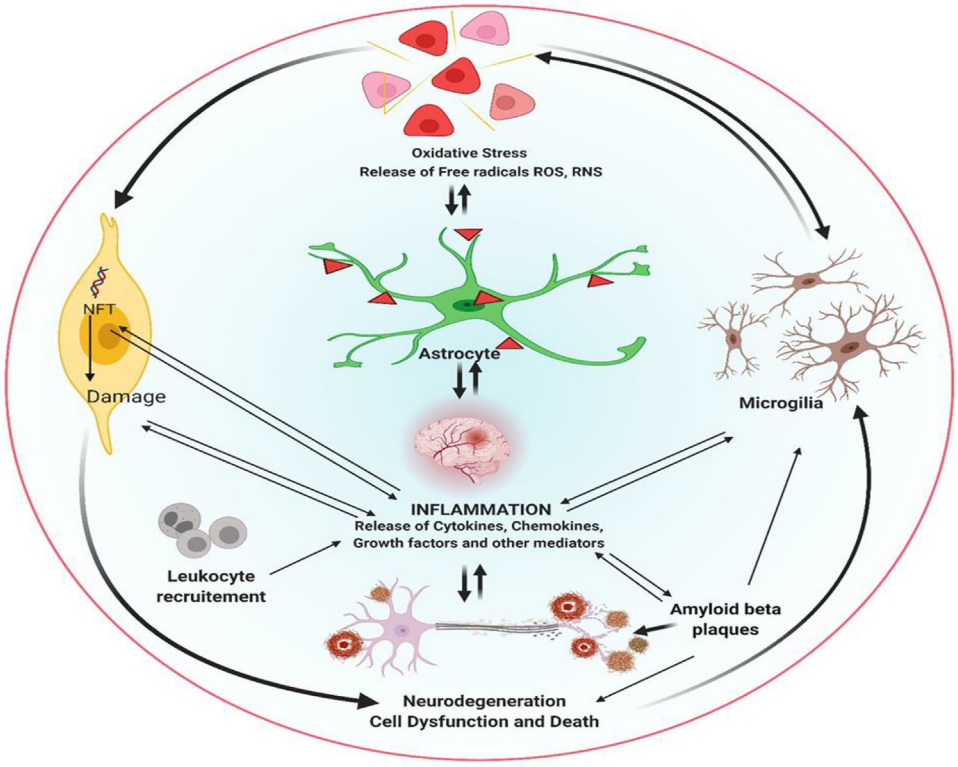


Fig. 7. Pathophysiology of the neurological disorder connecting oxidative stress, inflammation, and neurodegeneration.

functions. Pathophysiology of neurological disorder and the inflammatory factors have shown in Fig. 7.

6. Evaluations of *Ziziphus* genus impact on the chronic inflammatory disease by the human clinical trials

Ziziphus vulgaris dried powder was used to evaluate its effect on blood pressure, glycemic control, lipid concentrations, liver enzymes, and inflammation. A random human clinical trial of seventy-six diabetic participants of age between 20 and 65 years assigned to intervention (n = 38) and placebo (n = 38) groups. The intervention group was given 30 g/day dried *Z. vulgaris* for 12 weeks. The trials' results have shown a significant reduction in body mass index, weight, homeostasis model assessment-insulin resistance and insulin. Furthermore, dried fruit of *Z. vulgaris* could reduce cardiovascular risk factors in diabetic patients by improving glycemic control. It is concluded that type 2 diabetes patients taking off 30 g/day dried *Z. vulgaris* fruit for 12 weeks have anti-hyperglycemic, anti-hyperlipidemic and anti-inflammatory effects on type 2 diabetes mellitus (Irannejad niri et al., 2020). Antibiotics are the most prevalent treatment of acne in worldwide, but it has side effects. Persian people have used cedar (*Ziziphus spina-christi*) to cure diverse skin problems. A human clinical trial of eighty patients aged between 15 and 45 years was conducted to investigate the effect of *Ziziphus spina-christi* in the treatment of acne vulgaris. In a randomized, double-blind trial, participants received the topical cedar solution plus clindamycin 1% or topical placebo plus 1% clindamycin solution for six weeks. The results showed that clindamycin 1% plus cedar solution was more effective than 1% clindamycin plus placebo to cure acne vulgaris (Shakiba et al., 2019).

Gastroesophageal reflux disease (GERD) is the cause of acid regurgitation and heartburn. When stomach acid continually flows into the tube, which connects the stomach and mouth and irritates the esophagus' lining. Effective and safe treatment of GERD is considered proton-pump inhibitors (PPI). *Wu-chu-yu-tang* (WCYT) consists of *Evodia rutaecarpa* (Juss), Benth (Sichuan province, China), *Panax ginseng* C. A. Meyer (Jilin province, China), *Ziziphus jujube* Mill. A randomized, double-blind, placebo-controlled clinical trial was designed to judge the curative effect of WCYT on GERD using omeprazole as a PPI as a positive control. Ninety patients with GERD for 4 weeks randomly allocated to the control group and got an oral dose of omeprazole 20 mg once per day. The treatment group took oral administration of omeprazole 20 mg plus placebo once per day and WCYT (3.0 g) three times per day. The results have shown similar effects like omeprazole for GERD (Shih et al., 2019).

Asthma affects over 300 million people worldwide in which airways narrow and swell and may cause extra mucus. There is an extraordinary predominance of acceptance of complementary medicine for asthma. *Ziziphus* species have some active chemical constituents that have shown efficacy in the management of asthma. In a double-blind, randomized clinical trial, 46 children of 7 to 12 years having intermittent asthma participated. A mixture of the herbs *Ziziphus jujube*, *Glycyrrhiza glabra*, *Adiantum capillus-veneris*, *Matricaria chamomilla*, *Hyssopus officinalis*, *Malva sylvestris* was assigned randomly once daily or placebo for five days. Herbal mixture compared to placebo reduce the nighttime awakenings and severity of coughs. Still, in oral prednisolone, asthma exacerbation, outpatient visits, absence from school, hospitalization, PEF rate, respiratory distress, tachypnea, and in wheezing there were no significant reduction (Javid et al., 2019).

Several studies have proven that *Zizyphus Jujube* Fruits have anti-inflammatory and antimicrobial properties to heal wounds. One trial was conducted to find the effectiveness of jujube lotion to treat breast fissure. A double-blind clinical trial of randomly divided two groups was formed of 100 primiparous lactating women. The finding of this study revealed that the *Zizyphus jujube* fruits lotion heals nipple fissure faster and better than breast milk (Shahrahmani et al., 2018). In addition, a clinical trial on patients with type 2 diabetes mellitus (T2DM) was conducted to investigate *Ziziphus jujube* fruit (ZJF) infusion on the antioxidant status, glycemic control, and lipid profiles. 116, type 2 diabetes mellitus patients have participated in this randomized controlled clinical trial. They took ZJF infusion (10 g/100 ml boiling water) three times/day with a balanced diet before main meals for 12 weeks. ZJF infusion has shown significant improvement in glycosylated hemoglobin and a beneficial effect on the lipid profile compared to the control group (Yazdanpanah et al., 2017).

Traditional Chinese herbal medicine is a complex combination of two or more Chinese herbal formulations to get synergistic effects. Suan Zao Ren Tang (SZRT) is a combination of five herb *Radix glycyrrhizae*, *Rhizoma anemarrhena*, *Radix ligustici Chuanxiong*, *Sclerotium poriae cocos* and *Semen zizyphi spinosae.* In a double-blind, randomized, controlled trial, 90 participants were recruited with a sleep disorder and received methadone for at least one month. The objective of this research was to know the effectiveness of SZRT in the treatment of insomnia. SZRT has shown improvement in sleep disorder and sleeps quality compared to methadone-maintained patients with sleep complaints (Chan et al., 2015). PHY906 represents a decoction of a mixture of the four herbs *Ziziphus jujuba* Mill, *Paeonia lactiflora* Pall, *Glycyrrhiza uralensis fisch,* and *Scutellaria baicalensis georgi.* Preclinical and clinical studies were conducted to evaluate the effectiveness of PHY906 to enhance therapeutic indices of a broad spectrum of anticancer agents. Five clinical trials were conducted at five centres of Taiwan and the United States of America. Approximately 150 cancer patients had been treated with chemotherapy plus PHY906 in these clinical study centres. Preclinical trials have shown the effectiveness of PHY906 to enhance the therapeutic indices of a broad spectrum of anticancer agents. Advanced level clinical trials are going on to demonstrate the efficacy of PHY906 as an add-on therapy for cancer patients undergoing chemotherapy (Liu and Cheng, 2012). The summary of the human trial's findings to evaluate genus Ziziphus's effectiveness in inflammatory diseases is detailed in Table 3.

7. Toxicological effects

Everyone has the wish to use herbal medicine; currently, there are misconceptions toward herbal drugs' safety profile. Therefore, it is crucial to know its adverse effects. Genus *Ziziphus* is well known to all, and a lot of discussion is reported on its pharmacological properties. However, there are few side effects that have indicated the dilemma of the toxicity of *Ziziphus spp*. A study investigated the extract's acute and chronic oral toxicity from *Ziziphus attopensis* in male and female SD rats. *Ziziphus attopensis* was orally administered 5 g/kg body weight, body and organs weight were measured, necropsy and health were monitored. Behavior, organ, and body weights did not change compared to control rats; therefore, *Ziziphus attopensis* has not produced any acute toxicity. *Ziziphus attopensis* oral doses of 1, 2, 4, 8 g/kg body weight for 180 days were given to both male and female rats to determine the chronic toxicity. Biochemical parameters, body weight changes, organ weights, hematological parameters, histopathology examination and gross findings were monitored. The outcomes of the experiment did not show any difference with control groups. Interpretations of these results revealed that long term administration of *Ziziphus attopensis* does not cause chronic toxicity (Asgarpanah, 2012).

Table 3
Human trials findings to evaluate the effectiveness of genus Ziziphus in inflammatory diseases.

Participants	Interventions	Comparisons	Outcomes	Study design	References
Seventy-six diabetic participants	The intervention group received 30 g/day dried *Z. vulgaris* for 12 weeks.	Randomly assigned to intervention (n = 38) and placebo (n = 38) groups.	Consumption of dried *Z. vulgaris* fruit could have beneficial effects on improving glycemic control and reducing the cardiovascular risk factors in diabetic patients.	A randomised, double-blind, placebo-controlled trial.	(Irannejad niri et al., 2020)
Eighty patients aged between 15 and 45 years with mild to moderate acne vulgaris	The participants were allocated to receive the topical cedar (*Ziziphus spina-christi)* solution plus clindamycin 1% or topical placebo plus 1% clindamycin solution for six weeks.	Cedar solution plus clindamycin 1% or topical placebo plus 1% clindamycin solution for six weeks.	The topical cedar solution plus clindamycin 1% was more effective and safer than placebo plus 1% clindamycin to treat acne vulgaris.	A randomised, double-blind clinical trial.	(Shakiba et al., 2019)
Seventy-seven patients	An oral administration of omeprazole (20 mg) once per day and given WCYT placebo (3.0 g) three times per day for 4 weeks continuously, or the 2) treatment group (TG), who received oral administration of omeprazole (20 mg) placebo once per day and WCYT (3.0 g) three times per day for 4 weeks continuously.	Seventy-seven patients 37 in the control group and 40 target group.The therapeutic effect of WCYT on GERD using omeprazole as a PPI for positive control.	WCYT effects were like omeprazole for GERD treatment.	A randomised, double-blind, placebo-controlled clinical trial	(Shih et al., 2019)
Forty-six children (7–12 years old)	Daily receive either the herbal mixture (*Matricaria chamomilla*, *Althaea officinalis*, *Malva sylvestris*, *Hyssopus officinalis*, *Adiantum capillus-veneris*, *Glycyrrhiza glabra* and *Ziziphus jujube* or placebo for 5.	Herbal mixture with placebo	It reduced cough and nights awakening.	Double-blind, randomised clinical trial.	(Javid et al., 2019)
100 primiparous lactating women	In the *Jujube* group, mothers used 0.5 ml of Fruit Lotion, and in the control group, mothers applied 4–5 drops of their breast milk five times a day	*Jujube* group with the control group	The finding of this study revealed that the *Zizyphus jujube* fruits lotion heals nipple fissure faster and better than breast milk.	Double-blind clinical trial	(Shahrahmani et al., 2018)
116 participants with T2DM (older than 30 years)	Participants were assigned to consume a balanced diet or diet plus ZJF (*Ziziphus jujube fruit*) infusion (10 g/100 ml boiling water) three times/day before main meals for 12 weeks.	The consumption of ZJF infusion compared with the control group.	The consumption of ZJF infusion compared with the control group was associated with a significant improvement in glycosylated hemoglobin. ZJF had beneficial effects on glycosylated hemoglobin and lipid profile in T2DM patients.	Randomised controlled clinical trial	(Yazdanpanah et al., 2017)
90 participants were recruited.	Ninety patients were randomly assigned to the intervention group (Suan Zao Ren Tang) (n = 45) and placebo group (n = 45), and all participants were analysed. The participants were provided either SZRT or placebo, and the intervention period was four weeks.	SZRT (Suan Zao Ren Tang) with placebo	SZRT effectively improves sleep quality and sleep efficiency among methadone-maintained patients with sleep complaints.	Double-blind, randomised, controlled trial.	(Chan et al., 2015)
150 subjects	150 subjects have received PHY906 in combination with chemotherapy in these five clinical studies.	The PHY906 clinical program consists of five trials in three different types of cancers in both the United States and Taiwan	PHY906 could reduce chemotherapy-induced toxicities and increase chemotherapeutic efficacy	The PHY906 clinical program consists of five trials in three different types of cancers.	(Liu and Cheng, 2012)
Fifty consecutive patients with chronic	constipation.	Patients completed questionnaires and were given the consecutively numbered bottles in the order of their enrollment. All the patients adhered to the study drug, as reflected in the used vials brought back on each visit.	Constipated patients received liquid *Z. jujuba* or placebo for 12 weeks.	*Z. jujuba* extract is safe and effective for chronic idiopathic constipation and can be safely recommended for at least 12 weeks of treatment.	
	Questionnaires, a visual analog scale, and transit time (TT) tests.	(Naftali et al., 2008)			

Table 3 (*continued*)

Participants	Interventions	Comparisons	Outcomes	Study design	References
16 134 participants of insomnia in Taiwan during 2002.	Corresponding prescription files were analysed, and an association rule was applied to evaluate the co-prescription of CHM (Suan-zao-ren (*Ziziphus spinosa*) plus Long-dan-xie-gan-tang	Regular statistics were displayed for the use of frequency and patterns of CHM prescriptions for insomnia.	A better understanding of the use frequencies and patterns of CHM prescriptions for the treatment of insomnia in a Chinese population.	Patient management via TCM often includes a single prescription from a TCM physician containing an individual Chinese herb or multiple herbs of various dosages.	(Chen et al., 2007)

Abbreviations: WCYT: WCYT consists of *Evodia rutaecarpa* (Juss) Benth (Sichuan province, China), *Panax ginseng* C. A. Meyer (Jilin province, China), *Ziziphus jujube* Mill ; T2DM: Type 2 Diabetes Mellitus; SZRT: Suan Zao Ren Tang one of the most commonly prescribed traditional Chinese medications for the treatment of insomnia, improve subjective sleep among methadone-maintained persons with disturbed sleep quality; SZRT is composed of the following five herb ingredients: Semen *Zizyphi spinosae* (Suanzaoren), *Sclerotium poriae cocos* (Fuling), *Radix ligustici Chuanxiong* (Chuanxiong), *Rhizoma anemarrhena* (Zhimu), and *Radix glycyrrhizae* (Gancao); PHY906: PHY906 is a decoction of a mixture of the four herbs *Scutellaria baicalensis Georgi*, *Glycyrrhiza uralensis* Fisch, *Paeonia lactiflora* Pall, and *Ziziphus jujuba* Mill; CHM: Chinese herbal medicine; TCM: Traditional Chinese medicine.

Ethanolic extract of *Ziziphus jujuba* Mill leaves was tested to investigate anti-inflammatory and acute oral toxicity. Two experimental inflammation group of rats was treated by gavage for seven days with kaolin and carrageenan as inflammatory agents. No toxicity and mortality were observed on rats of two groups. The feeble anti-inflammatory effect was identified in both the inflammation models (Hovaneţ et al., 2016). *Ziziphus mauritiana* (Lam) leaf were examined for the genotoxic and cytotoxic effects using the *Allium cepa* model with different solvent extracts (20, 40, 60, 80, and 100 mg/l). The study revealed that *Ziziphus mauritiana* Lam extracts are genotoxic and cytotoxic; there were a decreasing percentage mitotic index and chromosomal aberration due to the presence of antimutagenic bioactive. Consequently, there is a need for care in its use (Owolarafe et al., 2020). Aqueous-methanol leaf extract of *Z.nummularia* was administered 3 and 5 g/ kg oral doses to mice for 24 h; the results did not show any mortality and behavioural changes (Hussain et al., 2017).

Aqueous extract of the roots of *Ziziphus mucronata* was examined for toxicity using the Brine Shrimp Lethality (BSL) assay; results revealed that 60 per cent mortality rate at 250, 500 and 1000 μg/ml at 24 h incubation period with concentrations ranging from 15.6 to 1000 (Bastos et al., 2008). Another examination of methanol extracts of roots and leaves showed an LD_{50} of 1180 and 4560 μg/ml respectively in a BSL assay. It is revealed that extract has no toxicity to the cell line (Mongalo et al., 2020; Y. et al., 2016). The aqueous root bark extract of *Z. spina christi* (25–100 ml/ kg) and the LD_{50} of the fraction was 871.78 mg/kg for intraperitoneal were administered to the Swiss mice. This study revealed that doses (25, 50 and 100 mg/kg) were within the safe limit (Adzu et al., 2009). A study was conducted to investigate the toxicity of six plants in the traditional Arab system of medicine. Acute toxicity tests were made for 24 h while the animals were treated for three months. Results have shown that *Z. spina-christi* reduced sperm abnormalities (Shah et al., 1989). All investigations have revealed that further potential chronic toxicity and acute toxicity are needed to establish the *Ziziphus* spp. as a therapeutic medicine.

8. Conclusion

Complementary medicines are the one of the essential aspects are herbal medicine. Many studies have been shown the role of *Ziziphus* species in inflammation remission. We introduce Genus *Ziziphus* anti-inflammatory effects evaluation in experimental and clinical studies; clinical studies data is more reliable than others among our research data. Six of the *Ziziphus* species had the most clinical evidence in different chronic inflammatory diseases. Studies have shown that *Ziziphus* species can modulate multiple molecular pathways involved in chronic inflammatory diseases. Investigations described here clearly highlight the use of *Ziziphus* species as novel anti-inflammatory agents for cardiovascular and diabetes. To date, clinical trials conducted with Genus *Ziziphus* are limited. Some conflicts could be resolved with more clinical studies with larger participants and *meta*-analysis. Most researchers have focused on the cyclopeptides alkaloid's role in curing various inflammatory diseases such as cardiovascular, diabetes, cancer, obesity, chronic constipation, and neurological disorders. Alkaloids and flavonoids are essential bio constituents indicating their potential use against chronic inflammatory diseases. The number of *Ziziphus* species that have been asserted to possess anti-inflammatory effects is so much that evaluating all of them is out of this paper's scope. However, an increasing rate of well-documented results has begun to provide a basis for considering the use of secondary metabolites in developing novel therapies for chronic inflammatory diseases. One of the clinical limitations of these substances in chronic inflammatory disease is low bioavailability. Thus, more evaluation is required to reveal herbal admixture and phytoconstituents of *Ziziphus* genus to reveal their full anti-inflammatory potential with improved bioavailability. To exhibit the efficacy and effectiveness of *Ziziphus* species in chronic inflammatory diseases, more stringent and methodologically research is needed to determine the dose and duration of treatment.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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