Anticancer activity of "Ziziphus jujuba" - A Review

Abstract

Ziziphus jujuba Mill. (Z. jujube) is a conventional plant that has a long history of usage in nutrients and the therapeutic interventions of a wide range of ailments. It grows mainly in South and East Asia, and also in Australia and Europe. Mounting data supports the health advantages of Z. jujuba, including anticancer, anti-inflammation, anti-obesity, antioxidant, and hepato- and gastrointestinal protective characteristics. Chemotherapy, particularly with cis-diamminedichloroplatinium (CDDP, cisplatin) and its derivatives, is commonly used to treat cancer. Although it is an effective therapy for human tumors, drug resistance impedes successful treatment. A better knowledge of the processes and develop strategies to address chemoresistance can improve patient outcomes dramatically. Numerous researchers have recently focused their attention on the increasing occurrence of numerous types of malignancies worldwide. The anticancer efficacy of Z. jujuba was discussed in this review study.

Keywords: Medicinal plant, Anticancer activity, , *Ziziphus jujuba*

Introduction

Plants have long served as the foundation for traditional medicinal systems, providing humans with ongoing cures for ancient times. Medicinal herb has been critical in the production of numerous medications [Atanasov et al., 2015]. Medicinal plants are regarded as a rich source of a diverse array of compounds that can be utilized in the production of pharmaceutical products. Cancer is among the most lethal diseases, associated with abnormal cell proliferation. In both developing and developed countries, it is the most important public health problem. The most widely known cause of cancer is a changing lifestyle, and as a result, it has become a worldwide problem. As a result, it is critical to provide the most effective treatment for this disease as soon as possible. Due to the fact that chemotherapy and radiation therapy have a variety of adverse effects, it is necessary to develop novel medications for the management of this disease; this could be achieved by utilizing naturally occurring substances. [Dias et al.,2012].

According to the World Health Organization (WHO), over 14 million people have been diagnosed with cancer in 2012, and 8 million died as a result of the disease (www.who.int). Due to the high mortality and incidence, it is a significant public health and economic issue that necessitates comprehensive prevention. Although radiotherapy, immunotherapy, and chemotherapy are the most often utilized methods for cancer treatment, these procedures have a detrimental effect on healthy cells. Thus, the prevention of carcinogenic behavior in healthy tissues through the use of routinely used medicines pushes researchers to develop new, safe techniques of cancer treatment. Natural medications, on the other hand, provide an alternate strategy for preventing the emergence and spread of cancer [Saini et al., 2012]. The unfathomable diversity of the plant world provides an unparalleled opportunity for the development of novel anti-cancer agents. The isolation and identification of chemicals derived from plants continue to advance, most notably in the development of cancer chemotherapeutic medicines. In this regard, innovative anti-cancer agents derived from natural resources have the potential to improve the efficacy of current chemotherapeutic agents. Sevelal natual compounds originating from plant sources inhibit carcinogenesis at various stages [Wang et al., 2012]. Natural compounds have a benefit over manmade synthetic chemicals in that they are abundant in nature. Furthermore, because these substances are natural, the risk of building resistance to them is much reduced. Natural compounds with cytotoxic qualities and the ability to kill cancer cells have been the subject of numerous studies. As a result, the purpose of this review is to shed light on the anti-cancer capabilities of the medicinal herb Ziziphus jujube.

Ziziphus jujube

Ziziphus jujuba Mill. (Z. jujube), sometimes known as jujube, it is a herbaceous plant that is used in traditional medicine. It is a member of the Rhamnaceae family and is among the most crucial Ziziphus species. 2008 [Huang et al.] Z. jujuba is found throughout Asia and America's tropical and subtropical climates, as well as the Mediterranean region. [Plastina and colleagues, 2012]. It is locally referred to as chhotiber and is a tiny, thorny shrub that grows primarily in dry and arid regions of North-Western India [Chopra et al., 1956]. The plant grows to a height of 1-2 metres and is greatly valued because of its nutrient dense edible fruits and herbal remedies. It's a prickly shrub with velvety-textured pale violet stems and branches.

Z. jujuba mature fruit are crimson to purplish-black in color, like little dates, and are referred to in China as the date or red date. In Persian cuisine, the dried fruit of Z. jujuba is referred to as "annab." Jujube trees are found throughout Iran's dry and semiarid regions, most notably in Birjand, South Khorasan province [Vahedi et al., 2008]. Production has expanded dramatically over the last decade as a result of the plant's widespread use in the culinary and pharmaceutical industries. China accounts for 90% of global Z. jujuba output, as the plant is indigenous to the country and has a history dating back over 4,000 years..[Li et al., 2007]

Ethnomedicine

Various portions of Z. jujuba can be used to treat a variety of ailments, including diabetes, diarrhea, skin infections, liver complaints, urinary disorders, obesity, fever, pharyngitis, bronchitis, anemia, sleeplessness, and cancer, as well as blood purification and gastrointestinal tract tonification. [Pawlowska et al., 2009].

It has a strong astringent effect and is used to cure bilious sickness, scabies, and boils. Fruit is cooling, astringent, tonic, digestible, laxative, aphrodisiac, and anti-emetic and helps to eliminate biliousness, thirst, and burning sensation. The fruit is used to relieve stomach pain during pregnancy, as an antidote for aconite toxicity, and to treat wounds externally.

Inhalation of smoke made from dried leaves is used to treat colds and coughs. The bark decoction has been used as a hip bath to alleviate joint stiffness and as a gargle to treat sore throats and bleeding gums. The root is supposed to be cooling and bitter and is said to alleviate biliousness, coughing, and headaches.

The bark and root extracts are beneficial in the treatment of asthma, bronchitis, and fever. Additionally, the leaves are used to treat sexually transmitted diseases[6]. The bark is beneficial for diarrhea, dysentery, and colic. Inner bark infusion is used to treat constipation as a purgative

Nutrients

Numerous studies published in recent years have revealed the crucial role of bioactive compounds and natural products obtained from natural in the development of innovative drugs, particularly anticancer treatments. [Newman et al., 2003]

Vitamin C, phenolics, flavonoids, triterpenic acids, and polysaccharides are the active elements in jujube fruit, which would be regarded a healthy dietary choice[Gao et al., 2013]. This fruit contains 68.0% moisture, and its pulp contains acids (3.92%), total sugars (8.68%), reducing sugars (1.85%), non-reducing sugars (1.85%) pectin (1.72%), and tannins (1.32 percent). Additionally, it contains 2.56 mg of vitamin C per 100 grams of pulp, and the pulp's total mineral content is 1.38 percent in the form of ash. Proteins account for up 2.56 percent of the jujube pulp, while minerals such as phosphate, potassium, calcium, magnesium, and iron account for the remainder. Jujube fruit is also a source of vitamins such as thiamin, riboflavin, niacin, vitamin B-6, and vitamin A on a secondary basis. [Gao et al.,2011]. [Table 1].

Contents	Unit	Value per 100 g
Water	G	20.19
Energy	kcal	281
Protein	G	4.72
Total lipid (fat)	G	0.5
Carbohydrate by difference	g	72.52
Fiber, total dietary	G	6
Minerals		
Calcium, Ca	mg	63
Iron, Fe	mg	5.09
Phosphorus, P	mg	68
Potassium, K	mg	217
Sodium, Na	mg	5
Zinc, Zn	mg	0.39
Vitamins		
Vitamin C, total ascorbic acid	mg	217.6
Thiamin	mg	0.047
Ribolavin	mg	0.053
Vitamin B-12	mg	0
Lipids		

Cholesterol	mg	0

Table 1: Nutritional Value of Jujube

(Source: USDA Food Composition Databases, 2017)

The dried pulp of Z. jujuba is a rich in essential unsaturated fatty acids. Oleic, linoleic (omega-6), palmitic, and palmitoleic acids are the primary fatty acids found in jujube. [San and colleagues, 2010] Jujube fruits consist of a variety of amino acids and proteins; throughout the development phase of the fruit, when it is picked, the protein and free asparagine content is significantly altered. Free amino acids combined exhibit a 3.3-fold rise from S1 to S5 stages of ripeness and a reduction from S6 to S8 stages of ripeness (S1-S8 are the eight stages of maturation of jujube extracts). Furthermore, during the final three stages of maturation, the concentration of free asparagines decreases, culminating at S5. [Choi et al., 2012]

By slowing digestion, the jujube fruit's dietary fiber and fructose content contribute to blood sugar management.[Gusakova and colleagues, 1999] The jujube fruit covers a range of sugars, including glucose, fructose, sucrose, rhamnose, and sorbitol. The jujube fruit also contains a lot of vitamin C, which is a water-soluble antioxidant[Li and colleagues, 2007]. The post - harvest grading process is crucial for maximising the jujube fruit's economic and nutritional benefits, especially the preservation of vitamin C content throughout storage and marketing. [Barrett and colleagues, 2012] Additionally, the jujube is packed with additional vitamins, though to a lesser amount, including thiamin, riboflavin, niacin, vitamin B6, and vitamin A. Additionally, jujube fruit is a good source of nutrients like magnesium, phosphorus, potassium, sodium, and zinc.

Bioactive compounds

Numerous research has revealed that jujube contains a variety of bioactive components, such as triterpenic acids, flavonoids, cerebrosides, phenolic acids, -tocopherol, -carotene, and polysaccharides. Each of the jujube's components provides a variety of health benefits, making it a nutritious food option. [Gao et al., 2013]

Jujube fruit contains a higher concentration of total phenolic compounds than other commonly consumed fruits with antioxidant properties, such as cherry, apple, persimmon, or red grape[Carlsen and colleagues, 2010]. The derivatives of phenolic substances include flavonoids, phenolic acids, tannins, stilbenes, and lignans. [Archivio et al.,2017]

Anticancer activity of *Z. Jujuba*

Cancer is among the most common diseases in the world, taking millions of lives and causing a significant public health burden. Despite the fact that chemotherapy has a slew of side effects, it remains the gold standard for cancer treatment. Due to the anticipated low cost, fewer complications, and low toxicity of drug candidates like herbal remedies with anticancer effects, the invention of novel agents such as herbal remedies with anticancer properties may promote a bright future in cancer treatment[Mans et al.2007]

Triterpenic acids are found as free acids or glycones, like saponins, and have a wide range of biological effects, include anti-inflammatory, antibacterial, hepatoprotective, and antioxidant properties. The anticarcinogenic and anticancer capabilities of triterpenic acids have make these increasingly popular in the fields of scientific research and health-care products in recent years. [Romero and colleagues, 2010]

Guo et al. found ten triterpenic acids in the dried jujube fruit in 2009, including ceanothic, alphitolic, zizyberanal, zizyberanalic, epiceanothic, ceanothenic, betulinic (BA), oleanolic (OA), ursonic, and zizyberenalic acids, as well as two triterpenes, ziziberanalic acid and ursolic [Guo et al., 2009].

Among the many chemicals present in dried jujube fruit, only three are cytotoxic: BA, OA, and UA. Apoptosis or programmed cell death defects perform a function in a variety of physiological and pathological processes that have been frequently associated with the multi - stage process of tumour development. Thus, among the most essential processes underpinning the anticancer actions of bioactive substances is their modulation of the apoptotic process[Fulda et al.,2009].

Anticancer activity of Ziziphus jujube in invitro

Numerous research have been conducted to determine the anticancer properties of Ziziphus jujube extract or its active constituents in various malignant cell lines. This inhibitory action could be a result of inducing apoptosis and cell cycle arrest by altering the level of expression of the associated genes. On the other hand, the cytotoxicity of various Ziziphus jujube components varies significantly. Thus, additional research is required to elucidate the precise molecular pathways behind these effects. [Gao et al.,2013].

Anticancer activity of Ziziphus jujube in invivo

Apart from in vitro studies, numerous in vivo studies have demonstrated Ziziphus jujube's anticancer potential. CKBM is a traditional Chinese medication composed of yeast and herbs, as well as Ziziphus jujube. In 2004, Chan et al. and Shin et al. found that CKBM showed antitumorogenic and pro-apoptotic effects in nude mice on human hepatocellular carcinoma and gastric cancer, respectively. [Chan et al.,2004, 8]. Furthermore, numerous studies studies have found PHY906, a mixture of four herbs (Scutellar-iabaicalensis Geori, Glycyrrhizauralensis Fisch, Paeo-nialactiflora Pall, and Ziziphus jujube Mill), seems to have a considerable anticancer effect and improves the cytotoxicity of chemotherapeutic agents such as CPT-11, Irinotcan, and Capecitabin in female BDF. Furthermore, bioactive compounds produced from Ziziphus jujube, such as betulinic acid and ursolic acid, have been shown to exhibit antitumorigenic and pro-apoptotic activities in vivo [Damle et al., 2013]. Another study published in 2014 examined the anticancer mechanism of Jujuboside B in vivo and invitro. Jujuboside B was found to decrease tumour growth in a tumour xerograph model using HCT 116 cells.

Additionally, molecular studies have demonstrated that this therapy inhibits the proliferation biomarker Ki-67 expression in tumour tissues [Xu et al., 2014]. The same year, Hoshyar et al. discovered that Ziziphus jujube possesses anti-cancer properties in breast tumours. This effect might be attributed to Z. jujube's anti-oxidant properties. Furthermore, the results showed that Ziziphus ju-jube treatment significantly affected serum lactate dehydrogenase (LDH) and alkaline phosphatase (ALP) levels, total protein, and albumin levels [Hoshyar et al., 2015]. In 2015, Liu et al. studied the preventive benefits of dietary Ziziphus jujube on colon carcinogenesis associated with colitis in mice treated with zoxymethane (AOM)-dextran sodium sulphate (DSS). The results indicated that this treatment resulted in the creation of aberrant crypt foci (ACF) and slowed the progression of hyperplasia to dysplasia. [Periasamy et al.,2015].

Cancer and Chemoresistance

While chemotherapy is a successful therapy for certain forms of human cancer, chemoresistance remains a substantial barrier to therapeutic success. Chemoresistance is a complex issue that has traditionally been linked to altered drug transport, modified drug targets, altered gene expression (e.g., multidrug resistance gene), and lower drug-induced macromolecular damage or improved DNA repair efficiency. [Reed et al., 1996] According to recent studies, the failure of cells to undergo apoptosis is a significant predictor of chemoresistance[Cheng et al.2002]. Dysregulation of antiapoptotic [e.g., Akt, X-linked IAP (Xiap), and FLICE-like inhibitory protein (FLIP)] and proapoptotic [e.g., Fas, caspases, and p53] pathways has been seen in chemoresistant cancer cells [Abedini et al., 2004]. and proapoptotic [for example, Fas, caspases, and p53]

In these circumstances, FLIP has been shown to be a predictor of ovarian cancer (OVCA) chemoresistance, and cis-diamminedichloroplatinium (CDDP, cisplatin) decreases FLIPL and FLIPS (two FLIP isoforms) levels in chemosensitive OVCA cells though not in resistant counterparts[Abedini and colleagues, 2004].

Furthermore, we investigated the possibility that CDDP's inability to suppress FLIP is a factor in human OVCA chemo resistance. CDDP reduces FLIP content and induces apoptosis in cisplatin-sensitive cells but not in cisplatin-resistant cells; FLIP overexpression via cDNA transfection effectively inhibits CDDP-induced apoptosis in chemosensitive cells; and FLIP siRNA expression facilitates CDDP-induced apoptosis in the chemoresistant counterpart. These data suggest that suppressing FLIP may boost chemoresistant cells' susceptibility to CDDP and may constitute a potential therapeutic approach for CDDP-resistant OVCA associated with FLIP overexpression.

The tumour suppressor protein p53 is a transcription factor that regulates the cell cycle, DNA repair, and apoptosis. DNA-damaging chemicals such as CDDP quickly upregulate p53 [Buttitta and colleagues, 1997]. It is kept at a low level by its negative regulator, mouse double minute 2 homolog (MDM2), which ubiquitinates p53 and directs it to the proteasome for destruction. In human OVCA cells, TP53 mutations are frequently detected and are related with lower chemoresponsiveness. Additionally, we studied the role of Itch, an E3-ligase protein, and p53 in the CDDP-induced downregulation of FLIP. We demonstrated that CDDP improves the connection between FLIP, p53, and Itch and causes FLIP ubiquitination and degradation in a p53- and Itch-dependent manner. These results indicate that altering the FLIP content of OVCA may be a viable approach for overcoming chemoresistance [Abedini and co-authors] .2008]

In several malignancies, Akt/PKB (protein kinase B) promotes survival and malignant transformation.[Sun et al., 2001] [Sun et al., 2001] It is a factor in CDDP resistance, and stimulation of the PI-3K/Akt pathway results in increased FLIP mRNA and/or protein expression in human cancer cells. [Suhara et al., 2001]

Additionally, we have shown that p53 promotes FLIP-Itch interactions as well as FLIP ubiquitination and destruction in chemosensitive cells. However, Akt reduces FLIP-p53 interaction, FLIP ubiquitination, and death in chemoresistant cells, implying that Akt modulation may be a viable strategy for overcoming chemoresistance in human OVCA. [Abedini and colleagues, 2009]

Angiogenesis, or the development of new capillaries from old ones, is a closely regulated process impacted by a range of angiogenic and antiangiogenic stimuli. Tumor angiogenesis is important in the progression of cancer because cancer cells require blood artery supply for growth and spread. Currently, despite advances in therapy modalities, cancer patients continue to have poor results; hence, the identification of antiangiogenic molecules, such as bioactive chemicals found in medicinal herbs like z. jujuba, can be used as an adjuvant technique to current cancer treatment methods [Khazaei and colleagues, 2015]

Additionally, it has been demonstrated that gelsolin (GSN) plays a critical role in the regulation of chemoresistance in gynaecological and head–neck malignancies, suggesting that it may be a viable therapeutic target in chemoresistant tumours[Wang and colleagues, 2014]. Although Z. jujuba has been shown to be toxic, it is unknown if it impacts CDDP-induced apoptosis and chemosensitivity. Identifying the method by which Z. jujuba kills cancer cells could lead to better cancer treatment options in the future.

CONCLUSION

Phytochemical analysis in conjunction with biological activity data confirms that jujube is a source of bioactive chemicals that may enhance human health. Among the bioactive components found in jujube fruit, this review paper demonstrates that triterpenic acids and polysaccharides have antiproliferative and anticancer effects on a variety of cancer cell lines. The stimulation of apoptosis appears to be one of the primary mechanisms underlying the jujube fruit's anticancer activity, owing to the presence of bioactive chemicals. However, the biological impacts of other documented and unknown substances found in these fruits should be explored in places with adequate climatic conditions for their growth.

Future Possibilities

Herbal diet is a means of achieving therapeutic effects by using natural herbs as ingredients in cooking procedures, particularly medicinal and culinary a double herbs. Because of its health benefits, jujube has been a popular fruit in daily life for thousands of years. Jujube is a common element in herbal cuisine and is said to be a stimulating or nutritious meal. It can be drunk as a decoction on its own or combined with other foods to make a wonderful soup. According to the cellular and animal studies stated above, jujube has the potential to be exploited to create medical foods and supplements for the prevention of anaemia, cancer, inflammation, and iron/vitamin deficiency.

Consumption of jujube is thought to increase blood flow to the spleen meridian, which improves nutrient absorption and boosts the immune system. Despite the fact that numerous controlled trials have demonstrated that jujube is a safe and effective plant for human consumption [Sabzghabaee et al., 2013], there is currently no human study assessing the effects of jujube on blood insufficiency. Furthermore, there are no documented toxicity or drug interaction problems with jujube use.

Apart from their medicinal virtues, fresh immature jujubes are widely consumed as fruits, and dried jujubes are indeed consumed as a snack or with tea. In China, jujube has been used to manufacture a number of products, including juice, vinegar, and wine. Jujube is mashed into cakes in southern India with tamarind, jaggery, salt, and chilies. In Lebanon and Persia, jujube is consumed with desserts as a digestive aid. In Morocco, honey prepared from jujube extract is thought to be beneficial for sore throats[Lim, 2013].

Because of their health benefits, natural herbal extracts have become increasingly popular in dairy products. [Feng et al. 2019] demonstrated a novel technique for producing a unique goat dairy product with good nutritional qualities by using jujube pulp as an ingredient. Immature jujube water extract was found to be more effective at stimulating HRE transcriptional activity than mature jujube water extract [Chen et al., 2015; Guo et al., 2015]. These data suggest that when jujube is processed for health food supplements, its maturity should be considered.

The study highlights the efficacy of "Herbal" which is an ancient tradition, used in some parts of India. This ancient concept should be carefully evaluated in the light of modern medical science and can be utilized partially if found suitable.

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