"*Ziziphus jujuba*": A red fruit with promising anticancer activities

Zoya Tahergorabi, Mohammad Reza Abedini, Moodi Mitra[1], Mohammad Hassanpour Fard, Hossein Beydokhti[2]

Departments of Pharmacology and Physiology, Berberis and Jujube Research Center, [1]Social Determinants of Health Research Center, Departments of Public Health, [2]Medical Library and Information Sciences, Birjand University of Medical Sciences, South Khorasan, Birjand, Iran

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ABSTRACT

Ziziphus jujuba Mill. (*Z. jujuba*) is a traditional herb with a long history of use for nutrition and the treatment of a broad spectrum of diseases. It grows mostly in South and East Asia, as well as in Australia and Europe. Mounting evidence shows the health benefits of *Z. jujuba*, including anticancer, anti-inflammation, antiobesity, antioxidant, and hepato- and gastrointestinal protective properties, which are due to its bioactive compounds. Chemotherapy, such as with *cis*-diamminedichloroplatinium (CDDP, cisplatin) and its derivatives, is widely used in cancer treatment. It is an effective treatment for human cancers, including ovarian cancer; however, drug resistance is a major obstacle to successful treatment. A better understanding of the mechanisms and strategies for overcoming chemoresistance can greatly improve therapeutic outcomes for patients. In this review article, the bioactive compounds present in *Z. jujuba* are explained. The high prevalence of many different cancers worldwide has recently attracted the attention of many researchers. This is why our research group focused on studying the anticancer activity of *Z. jujuba* as well as its impact on chemoresistance both *in vivo* and *in vitro*. We hope that these studies can lead to a promising future for cancer patients.

Key words: Anticancer activity, bioactive compounds, chemoresistance, *Ziziphus jujuba* Mill

INTRODUCTION

The practice of application of medicinal plants for relief from many illnesses dates back to ancient times.[1] *Ziziphus jujuba* Mill., (*Z. jujuba*) or the jujube, a herbal plant used in traditional medicine, belongs to the Rhamnaceae family and is one of the most important *Ziziphus* species.[2]

In terms of geographical distribution, *Z. jujuba* is widely located in the tropical and subtropical regions of Asia and America as well as in the Mediterranean regions.[3]

Address for correspondence:
Dr. Mohammad Hassanpour Fard, Department of Pharmacology, Birjand University of Medical Sciences, Khorasan, Birjand, Iran.
E-mail: mhassanpour61@yahoo.com

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The mature fruit of *Z. jujuba* are red to purplish black in color, resembling small dates, and in China are known as the date or red date. The dried fruit of *Z. jujuba* is known in Persian cuisine as "annab." Jujube trees grow in the arid and semiarid zones of Iran, especially in Birjand, South Khorasan province [Figure 1].[4] Because of the plant's extensive utilization in food and pharmaceutical industries, production has increased sharply over the past decade. China has been the site of 90% of *Z. jujuba* production in the world, as it is indigenous to China with a history of over 4,000 years.[2,5,6]

Different parts of *Z. jujuba* can be used for the curing of many kinds of illness including diabetes, diarrhea, skin infections, liver complaints, urinary disorders, obesity, fever, pharyngitis, bronchitis, anemia, insomnia, cancer, and also for blood purification and tonification of the gastrointestinal tract.[7-9]

Cancer continues to be and is increasingly a serious health problem, and one of the leading causes of death in the world. Aging and the growth of the world population, changes in lifestyle, and the adoption of cancer-causing behaviors are some of the reasons for this prevalence. According to cancer statistics in 2013, stomach and liver cancers are the most common in Asia and both of them are associated with high mortality rates, while bladder cancer is the most common in the USA. Colorectal

Figure 1: *Z. jujuba* in South Khorasan province, Birjand

and breast cancers have high incidence rates in all countries. Pancreatic cancer is also listed among the top five cancers in all countries except for China and Brazil.[10]

Some fruits and vegetables have protective effects on organs that are damaged by anticancer drugs. For example, whole fruit extract of pomegranate can reduce the myocardial toxicity induced by doxorubicin, which is an anthracycline antibiotic with broad antitumor spectrum and has been used against a wide variety of hematopoietic malignancies and solid tumors.[11,12] Also, Hassanpour *et al.* showed that the juice of *Lagenaria siceraria* (Molina) Standley (bottle gourd) had the same cardioprotective effect, which was less than that of the whole fruit extract of pomegranate.[13,14]

The same researchers attributed the cardioprotective effect of pomegranate and bottle gourd to the preservation of endogenous antioxidants and reduction of lipid peroxidation. The high antioxidant contents of these fruits can neutralize the free radicals generated by doxorubicin, causing an unusual and often irreversible cardiomyopathy.

NUTRIENTS

Several studies in recent years have shown the important roles of bioactive compounds and natural substances derived from plants in the discovery of new drugs, particularly anticancer drugs.[15]

Dried pulp of *Z. jujuba* is a source of essential unsaturated fatty acids. The main fatty acids in the jujube are oleic, linoleic (omega-6), palmitic, and palmitoleic acids.[16] Jujube fruits contain various types of amino acids and proteins; in the maturity stage when the Jujube fruits are harvested; the protein and free asparagines content are influenced potently. Combined free amino acids show a 3.3-fold increase from S1 to S5 stages of ripeness and a decrease from S6 to S8 (S1-S8 are the eight stages of maturation of jujube extracts). Additionally, free asparagines decrease during the last three stages of maturity, while their peak level is at S5.[17]

Dietary fiber and fructose contents of the jujube fruit play a role in the regulation of blood sugar levels by slowing digestion.[18] The major sugars found in the jujube fruit are glucose, fructose, sucrose, rhamnose, and sorbitol. The jujube fruit is also abundant in vitamin C, which is one of the watersoluble antioxidants.[19] The postharvest sorting process is important for increasing the economic benefits and dietary values of the jujube fruit, especially vitamin C content protection during storage and marketing.[20] Moreover, the jujube is enriched, though to a lesser extent, with other vitamins including thiamin, riboflavin, niacin, vitamin B_6, and vitamin A. Jujube fruit is also considered a good source of minerals such as magnesium, phosphorus, potassium, sodium, and zinc.[19]

BIOACTIVE COMPOUNDS

Various studies have shown that the jujube fruit contains many bioactive compounds, including triterpenic acids, flavonoids, cerebrosides, phenolic acids, α-tocopherol, β-carotene, and polysaccharides. Each constituent of the jujube presents some health benefits, thus making it a healthy food choice.[21]

Jujube fruit has more total phenolic compounds compared to other common fruits that exhibit antioxidant activities, such as cherry, apple, persimmon, or red grape.[22] Flavonoids, phenolic acids, tannins, stilbenes, and lignans are derivatives of phenolic compounds.[23]

ANTICANCER ACTIVITY OF *Z. JUJUBA*

Cancer is considered to be one of the most common diseases, causing death worldwide, and is a serious public health problem. According to the World Health Organization, 10 million new cases of cancer are diagnosed by physicians each year and based on statistical trends, this figure is estimated to double by 2020.[24] Although chemotherapy has many side effects, it remains a standard method for the treatment of cancer patients. Due to their projected low costs, fewer side effects, and low toxicity compared to the standard treatment, the development of new agents such as medicinal herbs with anticancer effects can herald a promising future in cancer treatment.[25,26]

Triterpenic acids are in the form of free acids or glycones such as saponins, which have multiple biological effects including anti-inflammatory,[27] antimicrobial,[28] hepatoprotective,[29] and antioxidant[30] effects. In recent years, the anticarcinogenic and antitumor activities of triterpenic acids have made them attractive in the fields of scientific research and health-care products.[31]

Guo *et al.* in 2009 identified 10 triterpenic acids, that is, ceanothic, alphitolic, zizyberanal, zizyberanalic, epiceanothic, ceanothenic, betulinic (BA), oleanolic (OA), ursonic, and zizyberenalic acids, and two triterpenes, that is, ziziberanalic acid and ursolic acid (UA), in the dried jujube fruit.[32] Among all the compounds found in the dried jujube fruit, a few have cytotoxic effects: BA,

OA, and UA. Their chemical structures have been shown in Figure 2.[33,34] Defects in apoptosis or programmed cell death play a role in various physiological and pathological processes, which are characteristically linked to the multistep process of tumor genesis. Thus, one of the most important mechanisms of the anticancer properties of bioactive compounds is the modulation of the apoptotic process.[35]

UA

In a study carried out by Kim in 2000, it has been shown that UA exerts proapoptotic activity and decreases cell viability in a concentration- and time-dependent fashion on HepG2 human hepatoblastoma cells. UA at the dose of 30 μm induced DNA fragmentation and the activation of caspase-3.[36]

In another study in 2010, UA effects were investigated on mammary tumor cells both *in vivo* and *in vitro*. Female ovariectomized C57BL/6 mice as a model of the postmenopausal state received for 8 weeks either control diet [following the American Institute of Nutrition (AIN) formula, AIN-93G] or diet supplemented with UA at three different concentrations: 0.05%, 0.10%, and 0.25%. After 3 weeks on the diet, the mice were injected with syngeneic MMTV-Wnt-1 mammary tumor cells. In addition, the growth-inhibitory effects of UA on WA4 mammary tumor cells *in vitro* were studied. UA was effective in inhibiting WA4 cell proliferation at 25 μm and 50 μm, which supported the antitumor activity in the mouse model of postmenopausal breast cancer. All doses of UA in Ki-67 immunohistochemical staining showed inhibition of proliferation *in vivo*, while at the concentration of 0.10%, it had the greatest effect in decreasing the final tumor size. It seems that the modulation of phosphatidylinositol 3 kinase (PI3K/AKt) and mitogen-activated protein kinase (MAPK) cellular signaling pathways involved in UA affects cell survival and apoptosis.[37]

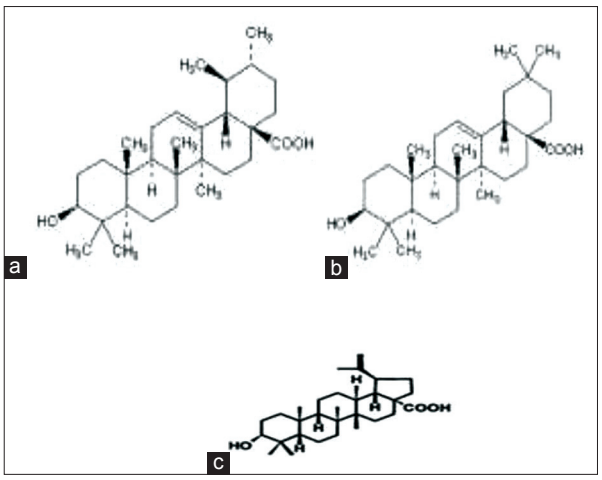

Figure 2: The chemical structure of Ursolic acid (UA) (a) Oleanolic acid (OA), (b) Betulinic acid (BA), (c) Bioactive compounds present in *Z. jujuba* with cytotoxic effects

UA and OA are the two triterpene acids that have similar chemical structures but different positions on a methyl group in the E loop.[38] UA and OA were studied by Li *et al.* in 2002 and they demonstrated marked antitumor effects on the human colon carcinoma cell line HC-T15.[39] Colorectal cancer, with its high incidence in Australia, New Zealand, and East Asia, is recognized to be the fourth-most common cancer in the world.[40]

The study revealed that the concentration of 60 μmol/L of UA or OA as treatment for the duration of 24-72 h could increase the number of dead cells and cell fragmentations more than the 30 μmol/L concentration. Cell cycle analysis by flow cytometry showed that UA 30 μmol/L and OA 60 μmol/L for the duration of 36 h and 72 h, respectively, caused the accumulation of HCT-15 cells in the G0/G1 phases and concomitant cell decrease in the S phase.[39]

Additionally, Shyu *et al.* in 2010 demonstrated the inhibitory effects of OA and UA on human hepatocellular carcinoma (HCC) HuH-7 cell population growth with (IC_{50}) 100 μm and 75 μm, respectively.[33] HCC is a form of cancer that involves the predominant cell type of the liver, hepatocytes; it is the fifth-most common cancer and the third-most frequent cancer causing death worldwide.[41] OA and UA increased the permeability of the transition pore in the mitochondria that in turn cause the rapid release of caspase activators such as cytochrome c into the cytoplasm and the subsequent activation of caspase-9 and caspase-3, followed by the cleavage of poly (ADP-ribose) polymerase (PARP) and the induction of apoptosis in HuH-7 cells.[33] Several other studies also showed that UA and OA induce apoptosis in HL-60 leukemia cells, B16F10 melanoma cells, MCF-7 breast cancer cells, and DU-145 prostate cancer cells.[42-45]

BA

BA, a pentacyclic triterpene and lipophilic compound, has selectively demonstrated cytotoxic effects in both *in vitro* and xenograft mouse models of human melanoma and neuroectodermal tumors (neuroblastoma, glioblastoma, medulloblastoma), both of which arise from the neural crest. BA acts through caspase activation in neuroectodermal cells. Melanoma, a malignant neoplasm of melanocytes, according to surveillance in epidemiology, is the sixth-most common fatal malignancy in the USA.[34,46]

In the study carried out by Selzer *et al.*, BA induced apoptosis in human melanoma cells, and the effects of BA in combination with irradiation were clearly additive, thus possibly differing in their mode of action. The growth-inhibitory effect of BA has been reported to be more pronounced on human melanoma cell lines than on normal human melanocytes. Interestingly, in spite of the induction of apoptosis, BA induced the expression of MC1-1 (a member of BCL-2 protein family showing antiapoptotic activity).

Additionally, in another study, BA showed synergistic cytotoxic effects on melanoma cells in combination with vincristine.[47]

Furthermore, the antitumor activity of BA has been reported in the broad spectrum of cancer cell lines, including leukemia, colon, lung, prostate, head and neck, and cervical.[45,48-50]

In the study carried out by Damle *et al.* in 2013, BA showed cytotoxic activity on MCF-7 breast adenocarcinoma xenografts in athymic nude mice. Also, BA in MCF-7 cells *in vitro* after injections in the concentrations of 50 mg/kg and 100 mg/kg body weight in mice decreased tumor size by 52% and 77%, respectively. This antitumor activity possibly resulted from the decreased angiogenesis, proliferation, and invasion in the BA-treated animals.[51] Breast cancer is a major public health problem and is considered to be the most common cancer in women worldwide, accounting for 23% of all cancers in women.[52]

Cytotoxic effects of the water extract of the jujube *in vitro* were shown to occur on the Jurkat leukemia cell line. Furthermore, HeLa and HEP-2 cells from the epithelioid cervix and human larynx carcinomas were affected by the dialyzed extract of jujube. However, it seems that the lack of DNA fragmentation by the induction of apoptosis in these two latter cell lines indicate that other mechanisms may contribute to cell death.[4]

In an *in vivo* model of metastatic melanoma, the concomitant use of BA and vincristine augmented suppression of the experimental lung metastasis of melanoma cells in mice, compared to the animals treated with vincristine alone. Of course, there were no systemic toxicities or weight loss in BA-treated mice even at a high systemic dose.

One of the most striking features of BA and its derivatives is their different effects on cancer cells and healthy cells; they are less toxic to cells of healthy tissues.[47]

Mechanisms of BA action include the induction of apoptosis via mitochondrial pathway and the loss of mitochondrial membrane potential without any effect on the caspase inhibitor.[35] There are two major signaling pathways for apoptotic cell death: The extrinsic or receptor pathway and the intrinsic or mitochondrial pathway.[53] A schematic presentation of the major signaling pathways for apoptotic cell death and bioactive compounds present in the jujube, inducing apoptosis through several mechanisms for the anticancer activities, is presented in Figure 3.[54] In another mechanism, BA can trigger the production of reactive oxygen species (ROS), which in turn can activate nuclear factor kappa-B (NF-κB), an inflammatory signaling pathway in a variety of tumor cell lines, and the inhibition of BA-induced NF-κB activation can attenuate BA-induced apoptosis.[55]

With regard to yet another mechanism, the Bcl-2 family of proteins include both antiapoptotic members, such as Bcl-2, Bcl-X_L, and Mcl-1, and proapoptotic ones, such as Bax, Bak, Bad,

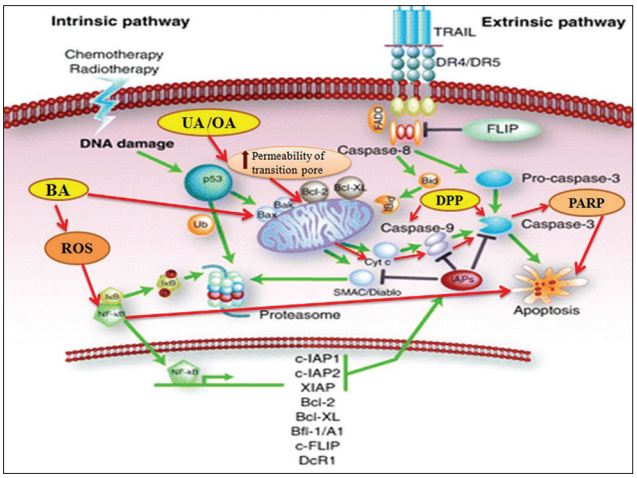

Figure 3: Schematic presentation of major signaling pathways for apoptotic cell deathand bioactive compounds available in *Z. jujuba*, which induce apoptosis through several mechanisms for anticancer activities. UA = Ursolic acid, OA = Oleanolic acid, BA = Betulinic acid, DPP = deproteinized polysaccharide

and BH3 domain.[56] BA has been reported in neuroblastoma, glioblastoma, and melanoma cells, upregulating the proapoptotic Bcl-2 family protein Bax. The expression levels of antiapoptotic Bcl-2 remained unchanged in neuroblastoma and squamous cell carcinoma cells but increase in glioblastoma cells.[47,48,57] BA can also inhibit aminopeptidase N, an enzyme involved in the regulation of angiogenesis that is overexpressed in several cancers.[58]

Jujube extract is used in the treatment of breast cancer in traditional Chinese medicine; the bioactive compounds of triterpenic acids, such as ZE2 and ZE4, are present in the extract. These compounds are effective in inhibiting cell growth and inducing cell apoptosis, as has been shown in *in vitro* studies on the MCF-7 (estrogen receptor alpha-positive) and SKBR3 (estrogen receptor alpha-negative) breast cancer cell lines, by DNA fragmentation and terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end-labeling (TUNEL) staining.[59]

In another study, deproteinized polysaccharide (DPP) obtained from the water extract of jujube revealed an antiproliferative effect *in vitro* on melanoma cells in a dose- and time-dependent fashion. Also, the cell cycle assay showed melanoma cells to be arrested in the G2/M phases. Additionally, there was a generation of apoptotic bodies accompanied by an increase in caspase-3 and caspase-9 activities.[59]

Finally, in a study in 2012, normal liver (Chang) and lung (Hel 299) cells and HeLa cervical cancer cells, A549 lung cancer cells, and U937 lymphoma cancer cells were treated with jujube extracts in different (eight; S1-S8) stages of maturation, at four concentrations (1 μg/ml, 10 μg/ml, 50 μg/ml, and 100 μg/ml). HeLa cervical cancer cells were inhibited by the extract derived at all growth stages dose-dependently, whereas

the inhibition of Hel 299 normal lung and A549 lung cancer cells decreased with fruit maturation in correlation with the flavonoid content.[17] Therefore, fruit maturity may have an influence on both the nutritional and bioactive components of the jujube and, consequently, on anticancer activity.

CANCER AND CHEMORESISTANCE

Although chemotherapy is an effective treatment for some human cancers, chemoresistance remains a major hurdle for successful clinical treatment. Chemoresistance is a multifactorial difficulty and has been traditionally thought to arise from altered drug transportation, modified drug targets, gene expression (e.g. multidrug resistance gene), and reduced drug-induced macromolecular damage or increased DNA repair efficiency.[60] Recent evidence has suggested that the inability of the cells to undergo apoptosis is one of the key determinants for chemoresistance.[61] Dysregulation of antiapoptotic [e.g. Akt, X-linked IAP (Xiap), and FLICE-like inhibitory protein (FLIP)][62-65] and proapoptotic (e.g. Fas, caspases, and p53)[66,67] pathways have been found in chemoresistant cancer cells.

In these contexts, it has been shown that FLIP is a determinant of OVCA (ovarian cancer) chemoresistance and *cis*-diamminedichloroplatinium (CDDP, cisplatin) decreases FLIPL and FLIPS (two FLIP isoforms) contents in chemosensitive OVCA cells but not in their resistant counterparts.[64] We have also tested the hypothesis that the inability of CDDP to downregulate FLIP may in part be a contributing factor for chemoresistance in human OVCA. We hereby report that: CDDP decreases FLIP content and induces apoptosis in the cisplatin-sensitive cells but not in the -resistant counterpart; the overexpression of FLIP by cDNA transfection is effective in attenuating CDDP-induced apoptosis in chemosensitive cells; and FLIP siRNA expression facilitates apoptotic cell death in the chemoresistant counterpart induced by CDDP. These findings suggest that the downregulation of FLIP may increase the sensitivity of chemoresistant cells to CDDP and may be a potential therapeutic strategy for CDDP-resistant OVCA associated with FLIP overexpression.[64]

The tumor suppressor protein p53 is a transcription factor regulating the cell cycle, DNA repair, and apoptosis, and is rapidly upregulated by DNA-damaging agents including CDDP.[68] It is maintained at low levels by its negative regulator, mouse double minute 2 homolog (MDM2), which ubiquitinates p53, targeting it for proteasomal degradation.[69] TP53 mutations are frequently observed in human OVCA cells[70] and are associated with decreased chemoresponsiveness.[65] In this regard, we also investigated the involvement of Itch, an E3-ligase protein, and p53 in CDDP-induced FLIP downregulation. We showed that CDDP enhances FLIP-p53-Itch interaction and induces FLIP ubiquitination and degradation in a p53- and Itch-dependent fashion. These results suggest that the modulation of FLIP content may be an effective strategy to overcome chemoresistance in OVCA.[71]

Akt/PKB (protein kinase B) promotes survival and malignant transformation in different cancers.[65,72,73] It is a determinant of CDDP resistance, and activation of the PI-3K/Akt pathway increases FLIP mRNA and/or protein expression in human cancer cells.[74-77]

We have also demonstrated that p53 facilitates FLIP-Itch interactions and FLIP ubiquitination and degradation in chemosensitive cells. However, in chemoresistant cells, Akt inhibits FLIP-p53 interaction, FLIP ubiquitination, and apoptosis, suggesting that Akt modulation may be an effective means to overcome chemoresistance in human OVCA.[78]

Angiogenesis, the growth of new capillaries from preexisting ones, is a regulated process which is modulated by numerous angiogenic and antiangiogenic factors. Since cancer cells require to blood vessel supply for growth and metastasis therefore, tumor angiogenesis is an important factor in the progression of cancer. Nowadays, despite advances in the therapeutic modalities treatment, results are disappointing in cancer patients hence; identification of antiangiogenic molecules including bioactive compounds present in medicinal herbs such as z. jujuba can be considered as an adjuvant strategy beside standard methods for cancer treatment.[79-81]

It has also been shown that gelsolin (GSN) plays a key role in the regulation of gynecological and Head–Neck cancer chemoresistance, it may be an appropriate therapeutic target in chemoresistant cancers.[82,83]

It has been shown that *Z. jujuba* shows cytotoxic activity;[4] however, if and how it regulates CDDP-induced apoptosis and chemosensitivity is still unclear. Understanding the mechanism by which *Z. jujuba* shows its cytotoxic activity can improve therapeutic strategies for future cancer treatment.

CONCLUSION

Phytochemical data combined with information about biological activity confirm that jujube fruits are rich in bioactive compounds that can benefit human health. This review article shows that among the bioactive compounds present in jujube fruit, triterpenic acids and polysaccharides have antiproliferative and anticancer effects on various cancer cell lines. It seems that the induction of apoptosis is one of the main mechanisms for the anticancer activities of the jujube fruit, due to the presence of the bioactive compounds. However, the biological effects of other identified and unidentified compounds in these fruits should be also investigated in areas where there are suitable climatic conditions for the cultivation of these plants.

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