Nutritional Compounds in *Ziziphus Jujuba*: Effects on Enzymatic Oxidant Systems and GABA Receptor Activities

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Abstract

Jujube is known for its relaxing and sleep inducing effects. In the Compendium of Materia Medica, Jujube dates are described as a treatment for the deficiency of sweat and thirst, and sleeplessness. Traditional Chinese Medicine utilizes complex, multi-ingredient formulations derived from natural herbs that demonstrate high efficacy and low toxicity. Multi-ingredient formulations may address the multifactorial nature of mood disorders more effectively through synergistic biochemical effects. Pharmacological studies have shown that jujube contains flavonoids, saponin, vitamins, and polysaccharides among other chemical components (Shen et al. 2022). These nutrients and bioactive compounds contribute to jujube's therapeutic effects through actions within the enzymatic oxidant systems and neurotransmission which could be beneficial in the treatment of insomnia. Jujube proves to have cascading neurological benefits through reduced inflammatory responses and increased actions at the GABA receptors, which could in turn upregulate BDNF and promote neuroplasticity.

Introduction to Jujube

Jujube (*Ziziphus jujuba* Mill.) is a tree species in China with a long medicinal history. It is a plant in the *Rhamnacease* family and is native to China. It's also known as Chinese date or red dates. Jujube has an ancient history of cultivation, and there are extensive planting areas and diverse varieties. In Traditional Chinese Medicine, the jujube was considered a vital food and medicinal herb. According to Chinese medicinal theory, jujube has effects that calm the mind and relieve mental tension, and benefits sleep, learning, and memory consolidation. It is prescribed as a single herb or as an ingredient in tranquilizing herbal formula. Additionally it is considered to have numerous neuroprotective activities including neuron differentiation, protection against oxidation insult, and in an ancient Chinese book on herbal medicine *Huangdi Neijing* (475-221 BC), jujube is marked as one of the 5 most valuable fruits in China. In an even earlier medical book, *Shennong Bencao Jing* (300 BC-200 AD) described jujube as a superior herbal medicine that can improve our life-span by nourishing blood, improving sleep quality, and regulating the digestive system (Chen et al., 2017). Today, there are large quantities of jujube-related products in the world and the annual output of exported jujube fruits is more than 10,000 tons (Cai et al., 2024, Chen et al., 2017).

Traditional Chinese Medicine Approach

Mood disorders are chronic conditions with marked disruptions in emotions (severe lows called depression or highs called hypomania or mania). The pathogenesis of these disorders are often unclear,

but they are related to the function of the hypothalamic-pituitary-adrenal axis (HPA axis), neurotransmitter dysregulation, and inflammatory responses (Shen et al., 2022). Clinical treatments are mostly treated with combinations of drugs but treatment still remains ineffective as these drugs often have late onset of action, poor side effects, and low efficacy (Shen et al., 2022; Ip et al.,2008). Alternatively, Traditional Chinese medicine (TCM) is a source of diverse and complex chemicals that possess a wide variety of biological activities and has a proven record of high efficacy and low toxicity (Ip et al., 2008). The multi-ingredient TCM formulae, often a mixture of several different herbs, is hypothesized to more effectively combat multifactorial disorders, such as mood disorders, through a combination of biochemical effects. Jujube is a common ingredient in these herbal concoctions. For example, *Chaihu-Jia-Longgu Decoction* is a formula used for depression treatment in Japan and was reported to remarkably suppress the excessive increase of glutamate in the hippocampal extracellular fluid of zinc deficient rats (Ip et al., 2008). *Jiawei-Xiaoyao-San* has been used to treat patients with neuropsychiatric disorders and was found effective in the treatment of tremor in antipsychotic-induced parkinsonism and panic disorders. Additionally, *Ganmaidazao-tang* and *Chaihu-guizhi-tang* both contain jujube, but further studies are required to specify mechanisms of their antidepressant effects (Ip et al., 2008).

Nutrient Composition of the Jujube

Jujube (Ziziphus jujuba Mill.) is a food and medicine with high nutritional value due to its high content of nutrients and non-volatile compounds. It is rich in vitamins and bioactive compounds (Cai et al., 2024). Fresh jujube contains 200-800 mg/ 100 g of vitamin C and it has been coined the “Natural Vitamin C pill.” Bioactive compounds have unique physiological processes in living organisms and can affect growth and metabolism. Jujube contains polysaccharides, triterpenoids, flavonoids, polyphenolic compounds (Cai et al., 2024).

Cai and colleagues classified Jujube nutrient content into three main categories: macronutrients, micronutrients, and bioactive compounds. Macronutrients are nutrients that the human body needs to consume in large quantities. Fresh jujube carbohydrate content ranges from 23-32% while protein is 1.2%. When Fresh jujube is instead processed and dried, carbohydrate and protein content change to 63-76.3% and 2.9-6.3%. Fiber is also included in the carbohydrate makeup and can control excessive calorie intake. Cai and colleagues report that the fiber content of Chinese jujubes ranges from 6.03% to 8.90%. On the other hand, micronutrients refer to the vitamins and minerals which are vital to normal functioning of the body. Studies show that jujube is rich in vitamins A, C, and B complex. In addition, jujube contains major elements such as potassium (K), magnesium (Mg), calcium (Ca), phosphate (P), and trace elements such as iron (Fe), manganese (Mn), copper (Cu), zinc (Zn). It was found that K, P, Ca, and Mn were the primary mineral components. Besides mineral content, jujube also has a large amount of vitamin C (192-359 mg/100 g) (Cai et al., 2024). Finally, bioactive compounds affect specific physiological functions in living organisms that relate to growth and metabolism processes. The bioactive compounds include polysaccharides, triterpenoids, flavonoids, and polyphenolic compounds. Across 15 species Chinese jujubes, Cai reported that the total polyphenolic compound content was 0.0558-2.520

mg GAE/ g FW, total flavonoid content was 0.47-2.0 mg RE/g FW, polysaccharide content was 3.103-21.815 mg/g FW, and cAMP content was 17.38-193.93 ug/g FW (Cai et al., 2024).

Jujube's bioactive compounds and high nutrient density contribute to its therapeutic properties. It was found that the main active ingredients in jujube are its flavonoids, polysaccharide, and triterpenic acids. Overall, both flavonoid and polysaccharide content was responsible for its antioxidant effects. The polysaccharide content in particular could account for its immune-modulating and hematopoietic functions. In addition, triterpenic acids showed evidence of anti-inflammatory and anticancer activities. Lastly, betulinic acid and jujuboside B could account for beneficial effects on the cardiovascular system (Chen, Lie, et al., 2017).

Jujube antioxidant properties

Oxidative stress refers to an imbalance of the levels of oxidants and antioxidants within a system, favoring oxidants. Often, oxidative stress is a contributor in pathology and disease progression. The kynurenine pathway is a model of depression in which peripheral inflammation due to oxidation can lead to excess quinolinic acid and a buildup of kynurenine in the system. This malfunction in the metabolic pathway is associated with a range of neuropsychiatric disorders such as major depressive disorder, bipolar disorder, and schizophrenia. More specifically, inflammation in this pathway in the body is characterized by a buildup of reactive oxygen species (ROS). The build up of ROS can affect many signaling pathways and biological processes. Therefore, oxidative stress can aggravate symptoms of diseases by modifying proteins, fostering inflammation, triggering apoptosis, and deregulating autophagy (Zhu et al., 2024).

In the human body, oxidation is regulated by two antioxidant systems: enzymatic and nonenzymatic. The enzymatic antioxidants include superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase GSH-Px, while the non-enzymatic antioxidants include vitamins C and E. Both systems work in tandem to reduce oxidative stress. Enzymatic oxidants work together to reduce ROS and limit toxicity. To start, SOD is the first line of defense against ROS radical oxygen species, and it catalyzes the conversion of superoxide radicals into oxygen and hydrogen peroxide. Moreover, CAT is the core antioxidant enzyme in most organisms that catalyzes the decomposition of hydrogen peroxide into water and oxygen. Lastly, GSH-Px reduces hydrogen peroxide or organic hydroperoxides to water or a corresponding alcohol. On the other hand, Malondialdehyde (MDA) is a highly reactive metabolite that results from lipid peroxidation of polyunsaturated fatty acid. As lipids are very susceptible to oxidative stress, changes in MDA can reflect the degree of oxidative stress and is considered a trustworthy biomarker of lipid peroxidation.

Zhu and colleagues reviewed studies that found jujube fruit extracts (*jujube polysaccharides*) were useful in decreasing levels of malondialdehyde (MDA), as well as increasing levels of SOD and GSH-Px which indirectly evidence that jujube can reduce lipid peroxidation and balance oxidative stress levels in mice. Jujube did not have a significant impact on CAT levels. Furthermore, research results from

Haung and colleagues indicated that *jujube flavonoids* displayed a protective antioxidant effect on APAP-induced liver injury in mice. Pretreatment with jujube could preserve the structural integrity of hepatocytes and alleviate the APAP-induced liver damage and inhibit inflammatory responses initiated by APAP. Its antioxidant activity might result from activation of Nrf2 and reduction of inflammation via inhibition of NF-kB (Haung et al., 2017). Overall, jujube flavonoids and polysaccharides have an enhancing effect on biological metabolism processes and show potential as an adjunct treatment to slow down the progression of many diseases where oxidative stress is relevant (Zhu et al. 2024).

Jujube Flavonoids

One of the main active components of jujube are its flavonoids, which are mostly flavonoid carbohydrates (Ip et al., 2008). Flavonoids possess a number of medicinal benefits, including anticancer, antioxidant, anti-inflammatory, and antiviral properties depending on the type of flavonoid and its bioavailability (Ullah et al., 2020). Ip and colleagues reported that jujube flavonoids could have effects on the GABA/Glutamate ratio. GABA is an inhibitory neurotransmitter, and glutamate (GLU) is an excitatory neurotransmitter. An imbalance in the ratio of the two can lead to neuronal degeneration and necrosis and is thought to be a contributing mechanism in various neurological disorders. Serum levels of GABA and brain-derived neurotrophic factor (BDNF), a molecule important in synaptic plasticity, are positively correlated, and impairment of synaptic plasticity can be caused by a decrease in central BDNF levels. Sour date brassica had significant sedative-hypnotic effects and increased the duration of sodium barbiturate-mediated sleep. Ip reported that sour date palm soup could increase BDNF protein expression and could help improve sleep-induced anxiety-like behavior in rats (Ip et al., 2008). Additionally, spinosin and swertish, two flavonoids isolated from jujube seeds were reported to possess significant sedative activity (Chen et al., 2017). Further, in a study on Tianwang Tonic Heart Dan, total saponin of sour date palm could alter the content of Glu and GABA neurotransmitters and have receptors in the cortex and hippocampus of aged insomniac rats, and led to an increase in slow-wave sleep (Ip et al. 2008).

Jujube Saponins

Jujube date contains saponin compounds which are thought to partially regulate jujube's hypnotic effect through wide reaching actions at the GABA receptors. Saponins are secondary plant metabolites that are naturally found in many plant parts (leaves, flowers, and fruits) and are widely used in the pharmaceutical industry. Cao and colleagues reported that Jujuboside A, one of the saponins from the seed of *Z. jujuba*, had hypnotic effects in pentobarbital treated mice. Specifically, they found an influential relationship between jujubosides on GABA and the serotonergic system. To investigate this effect, the researchers extracted jujuboside saponin from the seed of jujube and separated it from any flavonoids present in the solution. Then, pentobarbital treated mice were administered low doses of jujubosides, 5-hydroxytryptophan (5-HTP), and P-chlorophenylalanine (PCPA). PCPA is an inhibitor of tryptophan hydroxylase activity and therefore inhibits serotonin synthesis. 5-HTP is a chemical that the body makes from the amino acid tryptophan, which is the precursor to serotonin. Pentobarbital is a CNS

depressant that acts by binding to GABA subtype A receptors. The hypnotic properties of the candidate drugs and their given properties were measured using an EEG. In pentobarbital-treated mice, jujubosides significantly increased the effect of pentobarbital (45mg/kg). This augmented effect was further increased by 5-HTP (2 mg/kg). The combined effect of jujuboside effect on 5-HTP and pentobarbital treated mice suggested that the potentiation of jujubosides was related to serotonergic systems. Overall, jujube saponin was found to have hypnotic effects in normal rats and also elevate sleep in pentobarbital treated mice pointing further to its effects at the GABA receptor (Cao et al., 2010). Additionally, Chen and colleagues reported that Jujuboside A, another saponin, stimulated the expression of GABA receptor subunits in rat hippocampal neurons. Moreover, it was found that Jujuboside ameliorated behavioral disorders in dementia mouse models that were induced by Abeta1-42, a major component of cerebrovascular amyloid deposits (Chen et al., 2017). Overall, these studies point out evidence for jujube's hypnotic effects because Jujube saponins have enhancing effects at the GABA receptor which relaxes the system, and there is also evidence that Jujube saponin could even have potential benefits for memory and cognition.

Discussion

In the Compendium of Materia Medica, Jujube dates are described as a treatment for the deficiency of sweat and thirst, and sleeplessness. Traditional Chinese Medicine utilizes complex, multi-ingredient formulations derived from natural herbs that demonstrate high efficacy and low toxicity. Multi-ingredient formulations may address the multifactorial nature of mood disorders more effectively through synergistic biochemical effects. Pharmacological studies have shown that jujube contains flavonoids, saponin, vitamins, and polysaccharides among other chemical components (Shen et al. 2022). These nutrients and bioactive compounds contribute to jujube's therapeutic effects through actions within the enzymatic oxidant systems and neurotransmission. It's important to note that there is variability in the quality of jujube extracts used in these studies, and that further research is needed to determine potential side effects or interactions that could occur when jujube is combined with other treatments.

In a broader context, jujube has potential as a long term treatment for insomnia, a common sleep disorder that has a complex bidirectional relationship with anxiety and depression. It is listed as a sleep-wake disorder that involves challenges falling asleep and frequent waking during the night or early in the morning. The mechanisms of the pathogenesis of insomnia are unclear, but hypothalamic-pituitary-adrenal axis (HPA axis) function, neurotransmitter mechanisms, and inflammatory responses are thought to be involved. Furthermore, the condition serves as a criterion in the diagnosis of depression and has shown comorbidity with other mood disorders. Around 90% of patients with depression have symptoms of insomnia and of insomnia patients around 5%-30% have a form of depression or anxiety. Insomnia can lead to more serious physical and psychological diseases, which has effects on daily quality of life and physical and mental health (Shen et al. 2022). Jujube as a food and medicine has shown consistent results of intervention to improve measures of sleep and, the biological mechanisms outlined above contribute to Jujube's potential as a natural intervention for insomnia with low side effects or risk of toxicity. Emerging methods such as metabolomics could enhance

the study of such TCM ingredients and formulations that could provide clinical medicine with more holistic food based, medicinal treatments.

Conclusion

Overall, Jujube (Ziziphus jujuba) is a remarkable fruit with profound therapeutic potential, particularly in addressing insomnia and its related comorbidities. Through its rich array of bioactive compounds, including flavonoids, saponins, and polysaccharides, jujube exerts neuroprotective, antioxidant, and anti-inflammatory effects that support neurotransmission and neuroplasticity. Traditional Chinese Medicine underscores its value as a safe and effective herbal remedy, offering unique advantages over conventional treatments for mood disorders and sleep disturbances. Future research could further elucidate the precise mechanisms underlying its benefits, paving the way for its integration into modern therapeutic approaches.

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