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Exploring the Potential Synergistic Effect of Bioactive Compounds from Ziziphus Spina Christi in the Management of Type 2 Diabetes Mellitus

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Abstract
Ziziphus spina-christi commonly known as Christ's Thorn Jujube, is a deciduous or evergreen tree and shrub found throughout the world. The review explored the synergistic effects within the diverse array of phytochemicals present in the plant, aiming for a profound impact on diabetes management. The synergistic effects allow for the exploration of potential interactions between different bioactive compounds in Ziziphus spina christi leading to the identification of combinations that work together synergistically, enhancing the overall therapeutic efficacy compared to individual compounds. Understanding the synergistic effects in Ziziphus spina christi bioactive compounds is important for advancing diabetes management strategies.

Keywords: Synergy, Diabetes, Bioactive compounds, *Ziziphus spina Christi*, Antioxidant

INTRODUCTION
Ziziphus spina christi, commonly known as Christ's Thorn Jujube in English or Kurna in Hausa is a resilient and fruit-bearing tree found in various regions, particularly in the Middle East, North Africa, and parts of Asia (El-Shahir *et al.,* 2022). This species belongs to the family Rhamnaceae. The tree is recognized for its distinctive thorny branches, small yellow flowers, and round edible fruits (Hanoon *et al.*, 2017; Sakna *et al.,* 2022).

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The fruits of *Ziziphus spina christi* have traditionally been used to address gastrointestinal issues (Mahmoud *et al.,* 2022; Sehrish *et al.,* 2023). They are believed to have mild laxative properties and are used to alleviate constipation. Various parts of the plant, including leaves and fruits, are known for their anti-inflammatory properties (Asgarpanah *et al.,* 2012; Sehrish *et al.,* 2023). Infusions or extracts are used in traditional medicine to alleviate inflammatory conditions. The plant is a source of natural antioxidants, which are essential for neutralizing harmful free radicals in the body. This aspect is valued in traditional medicine for promoting overall health and well-being (Mahmoud *et al.,* 2022; Sehrish *et al.,* 2023).Extracts from *Ziziphus spina christi* have been applied topically in traditional remedies for skin conditions (Ibrahim *et al.,* 2015). It is believed to have soothing and healing properties. In some traditional practices, parts of the *Ziziphus spina christi* plant have been explored for their potential in managing diabetes (Mahmoud *et al.,* 2022; Sehrish *et al.,* 2023). The plant's bioactive compounds, including alkaloids and flavonoids, are of interest for their potential antidiabetic effects (Mahmoud *et al.,* 2022; Nuru *et al.,* 2022; Sehrish *et al.,* 2023).

In recent years, there has been a growing interest with the bioactive compounds derived from *Ziziphus spina christi* due to their potential health benefits, with a particular focus on diabetes management (Sukhikh *et al.,* 2023). The bioactive compounds within *Ziziphus spina christi*, such as flavonoids and alkaloids, exhibit antioxidant and anti-inflammatory properties. This dual action is of great interest in combating oxidative stress and inflammation, which are key contributors to diabetes complications (Mesmar *et al.,* 2022; Sehrish *et al.,* 2023).Studies have suggested that certain bioactive compounds in *Ziziphus spina christi* may possess antidiabetic properties. This has spurred interest in exploring their mechanisms of action and potential application as complementary or alternative therapies for diabetes (Mahmoud *et al.,* 2022; Gallardo-Villanueva *et al.,* 2024).The traditional use of *Ziziphus spina christi* in managing diabetes in folk medicine has sparked curiosity among researchers. Validating these traditional claims through scientific investigation adds credibility to the potential health benefits associated with the plant (Mahmoud *et al.,* 2022). Similarly the trend towards natural product-based therapies has brought *Ziziphus spina christi* into the spotlight. As individuals seek alternatives to synthetic medications, the exploration of plant-derived compounds aligns with the growing interest in holistic and natural approaches to health (Sakna *et al.,* 2022; Sukhikh *et al.,* 2023).The diverse array of phytochemicals found in *Ziziphus spina christi* contributes to its appeal for health research. Researchers are delving into these compounds to understand their specific actions and potential synergies that could enhance their overall therapeutic effects (Mesmar *et al.,* 2022; Mahmoud *et al.,* 2022; Sehrish *et al.,* 2023).With an increasing emphasis on preventive health, the investigation of *Ziziphus spina christi* bioactive compounds aligns with the broader goal of identifying natural substances that may contribute to preventing or mitigating chronic conditions, including diabetes (Mahmoud *et al.,* 2022).This collective interest underscores the potential of *Ziziphus spina christi* bioactive compounds as a valuable resource for advancing our understanding of their health benefits, especially in the context of diabetes management. As research continues, the hope is to translate this interest into practical applications for improved health outcomes.

The primary aim of this review is to unlock the full therapeutic potential of *Ziziphus spina christi* bioactive compounds with a specific focus on enhancing antidiabetic activity. The overarching goal is to systematically explore synergistic effects within the diverse array of phytochemicals present in the plant, aiming for a profound impact on diabetes management.

Synergistic Effects in *Ziziphus spina christi* Bioactive Compounds

Ziziphus spina christi is known to contain various bioactive compounds that contribute to its potential health benefits. While the specific composition can vary, common bioactive compounds found in this plant include: alkaloids, flavonoids, terpenoids, Saponins, tannins and the health benefits attributed to these bioactive compounds are often based on traditional uses and preliminary scientific studies (Mahmoud *et al.,* 2022; Nuru *et al.,* 2022). There are several biochemical mechanisms underlying the synergistic effects among bioactive compounds from *Ziziphus spina christi* for antidiabetic activity based on the known properties of various bioactive compounds. These mechanisms involve interactions with key molecular pathways related to diabetes.

Table 1: *Ziziphus spina christi* Bioactive compounds

Compound	Health benefits	Reference
Flavonoids	Flavonoids exhibit antioxidant activity, helping to neutralize harmful free radicals in the body. Contributing to the reduction of inflammation, which is linked to various chronic diseases.	Aba and Asuzu,(2018)
Alkaloids	Alkaloids may possess antimicrobial activity, aiding in the prevention of certain infections. Some alkaloids have been studied for potential neuroprotective properties.	Aba and Asuzu,(2018)
Saponins	Saponins may contribute to the regulation of cholesterol levels in the body. Some saponins exhibit immune-modulating effects.	Mariangela *et al.,*(2016) Aba andAsuzu(2018)
Triterpenoids	Triterpenoids may help reduce inflammation, providing potential benefits for conditions associated with chronic inflammation. Some triterpenoids have been studied for their potential anticancer effects.	Aba and Asuzu,(2018)
Phenolic Compounds	Phenolic compounds may contribute to cardiovascular health by promoting blood vessel health and reducing oxidative stress. Certain phenolic compounds have been investigated for their potential in managing diabetes.	Aba and Asuzu,(2018)
Vitamins and Minerals	*Ziziphus spina christi* may contain essential vitamins (such as vitamin C) and minerals that contribute to overall health and well-being.	Aba and Asuzu,(2018)
Essential Oils	Essential oils found in the plant may have aroma therapeutic properties, promoting relaxation and stress relief.	
Fatty Acids	Fatty acids contribute to skin health and may be beneficial for conditions like dermatitis.	Aba and Asuzu,(2018)

Antioxidant

Antioxidant potential can be increased by the synergistic interactions between different antioxidant compounds. The synergistic interactions decrease the requirement of doses of different bioactive compounds in combination thus reducing the side effects caused by the high concentrations of a single one (Sonam and Guleria, 2017). Different antioxidants follow different mechanisms or pathways under various stress conditions in order to show their antioxidative response. The main mechanisms involve: inhibiting free radical oxidation reactions (preventive oxidants), interruption of propagation of the autoxidation chain reaction (chain breaking antioxidants); inhibiting formation of free lipid radicals; quenching single oxygen species; reducing hydro peroxides converting them into stable compounds; inhibiting prooxidative enzymes; chelating metals and converting metalpro-oxidants into stable products and through synergism with other antioxidants (Sonam and Guleria, 2017; Arabshomali *et al.,* 2023)

Phenolic and flavonoid compounds are secondary metabolites of plants which possess various activities such as anti-inflammatory, analgesic, anti-diabetes and anticancer effects. It has been established that these compounds can scavenge free radicals produced in the body (Hajimehdipoor *et al.,* 2014). Among different secondary metabolites of the plants, phenolics and flavonoids are the main compounds with considerable antioxidant activity (Hajimehdipoor *et al.,* 2014). They are the main components of many products and are sometimes used in combinations. Study by Hajimehdipoor *et al.* (2014) reported the synergistic antioxidant effects in binary and ternary mixtures of compounds indicating that concurrent usage has increased the antioxidant activity more than twice resulting in the possibility of decreasing the required amounts of a certain material along with maintaining the desired antioxidant activity which is economically important. The binary combination of gallic acid and caffeic acid (137.8%), gallic acid and rosmarinic acid (19.7%), gallic acid and chlorogenic acid (27.9%), rosmarinic acid and caffeic acid (27.0). The combination of quercetin, gallic acid and caffeic acid (59.4%), quercetin, gallic acid, and rutin (55.2%), quercetin, rutin, and rosmarinic acid (27.7%), quercetin, rutin and chlorogenic acid (6.6) showed reliable synergistic effects. In another similar study, the binary mixture of rosmarinic acid and quercetin, and that of rosmarinic acid and caffeic acid, in the 2,2′-azobis (2-amidinopropane) dihydrochloride (AAPH)-induced oxidation shows an effective antioxidant activity (Peyrat-Maillard *et al.,* 2013).

The synergistic antioxidant activity was also observed in model oil-in-water emulsions containing combination of bovine serum albumin (BSA) and catechins [epicatechingallate (ECG), EGCG, EC and epigallocatechin (EGC)]. Although BSA had very little antioxidant activity in the absence of phenolic antioxidants, the combination of BSA with each of the catechins showed strong antioxidant activity after 45 days storage (Almajano *et al.,* 2007). In a related study three different antioxidant assays (FRAP, DPPH, and Briggs–Rauscher reaction) were used to study the interaction between resveratrol and other phenolics (gallic acid, caffeic acid, catechin, quercetin) in equimolar binary mixtures. The obtained results indicated that there are differences in the activity of mixture of phenolic compounds and resveratrol depending on mechanism of the used method. All three methods confirmed the synergistic effect between catechin and resveratrol. The reducing activity of the mixture of caffeic acid and resveratrol was almost 10.0% higher than the activity of the individual compounds. Briggs- Rauscher reaction detects that inhibition time is significantly prolonged and the effect was greatly enhanced in the mixtures of gallic acid and resveratrol and of catechin and resveratrol, by 45.5% and 53.3% respectively (Ng *et al.,* 2022). The obtained results confirmed that the activities of the tested compounds vary depending on their structure, concentration, time and the used method, but generally, like in previous studies, similar rank of activities was obtained (Katalinic, 2015; Sonam and Guleria, 2017). Regarding the findings of present review, mixtures of some phenolic and flavonoid compounds could increase the antioxidant effects. The synergistic effect of binary combination of gallic acid, rosmarinic acid, caffeic acid, chlorogenic acid, rutin and quercetin has more synergistic effect than their ternary combination.

Anti-Inflammatory

Inflammation is an important factor in the development of diabtetes. Studies have shown that chronic inflammation can lead to insulin resistance, which is a major risk factor for type 2 diabetes. The synergistic effect of flavonoids and triterpenoids on reducing inflammation may

have implications for the treatment of diabetes. By reducing inflammation, these compounds may improve insulin sensitivity and help to prevent the progression of diabetes.
Flavonoids are group of compounds that have been shown to have antioxidant and anti-inflammatory properties. Triterpenoids have also been reported to have anti-inflammatory properties. An in vitro study was carried out that investigated the synergistic anti-inflammatory effects of flavonoids and triterpenoid (Yanhong *et al.,* 2017). They found that the combination of the two compounds had a greater effect on reducing inflammation than either compound alone. In a related study by Li *et al.* (2020) on binary combination of luteolin (flavonoid) and oleanolic acid (triterpenoid) had a synergistic effect on reducing inflammation in a mouse model of colitis. The percentage synergy was found to be 62.5%.

Lipid profile regulation
Lipid-regulating herbs include those rich in saponin fractions, their mechanisms of action range from appetite regulation, and the inhibition of pancreatic lipase to effects on triglyceride absorption, retrosynthesis, and adipog enesis (Pachura *et al.*, 2022)

Glucose Modulation Synergy
The synergistic effect of caffeic acid and genistein was studied on glucose regulation by Xiaomin *et al.,* (2017). The study was carried out on rats that had been fed a high-fat diet to induce obesity and insulin resistance. They suggested that the combination of the compounds significantly reduced fasting blood glucose levels an improved insulin sensitivity as well as reduced body weight and liver fat content. The study also suggested that the combination of caffeic acid and genistein increased the expression of genes that promote glucose uptake, while decreasing the expression of genes that promote glucose production. These changes are thought to contribute to the observed improvement in glucose regulation (Xiaomin *et al.,* 2017). The synergistic glucose regulation was also observed by the combination of quercetin and resveratrol (Choi *et al.,* 2014). The study was conducted in rats, they found that the synergy of these compounds improved glucose regulation by reducing insulin resistance and increasing insulin sensitivity.

Table 2: summary of synergistic effects of the bioactive compounds

Synergy	Bioactive Compounds	Synergistic Effects
Antioxidant	Flavonoids and phenolic compounds.	Protection against oxidative stress. Oxidative stress is implicated in diabetes, and mitigating it can contribute to improved insulin sensitivity.
Anti-Inflammatory	Flavonoids and triterpenoids	May synergistically reduce chronic inflammation associated with insulin resistance, a hallmark of type 2 diabetes.
Glucose Modulation	Alkaloids and triterpenoids	Alkaloids may contribute to glucose regulation, and their synergy with triterpenoids could enhance this effect, possibly through improved insulin sensitivity or modulation of glucose uptake.
Lipid Profile Regulation	Saponins and fatty acids.	Saponins may contribute to lipid profile regulation, and their synergy with fatty acids could further support cardiovascular health and mitigate lipid-related complications in diabetes.
Insulin Sensitivity	Multiple compounds across different classes	Combining bioactive compounds with various mechanisms of action may lead to a synergistic improvement in insulin sensitivity, a key factor in diabetes management.
Beta-Cell Protection	Phenolic compounds and essential oils	Protecting pancreatic beta-cells, responsible for insulin production, is crucial. Phenolic compounds and essential oils, in synergy, might contribute to beta-cell health and preservation.
Glycemic Control	Various compounds targeting different pathways	A combination of bioactive compounds may exert synergistic effects on multiple pathways involved in glycemic control, leading to better overall management of blood glucose levels.

Table 3: Summary of Synergistic Mechanism of Action of the Bioactive Compounds

Synergy	Bioactive compounds	Mechanisms
Antioxidant	Flavonoids and phenolic compounds	Synergistic antioxidant effects neutralize reactive oxygen species (ROS), reducing oxidative stress. This works by enhancing insulin signaling pathways and protecting pancreatic beta-cells from oxidative damage, promoting overall glycemic control.
Anti-Inflammatory	Flavonoids and triterpenoids	Combining anti-inflammatory compounds inhibit pro-inflammatory cytokines, reducing chronic inflammation associated with insulin resistance. There by improving insulin sensitivity and contributing to better glycemic control.
Glucose Modulation	Alkaloids and triterpenoids	Alkaloids influence glucose metabolism, and their synergy with triterpenoids enhance glucose uptake by cells or regulate hepatic glucose production, contributing to improved glycemic control.
Lipid Profile Regulation	Saponins and fatty acids.	Synergistic effects on lipid metabolism lead to improved regulation of cholesterol and triglyceride levels. This may positively impact cardiovascular health and reduce complications associated with dyslipidemia in diabetes.
Insulin Sensitivity	Multiple compounds targeting different pathways.	Synergy among various bioactive compounds may enhance insulin signaling pathways, leading to increased insulin sensitivity in target tissues. This could result in improved glucose uptake and utilization.
Beta-Cell Protection	Phenolic compounds and essential oils	Synergistic protection of pancreatic beta-cells involves anti-inflammatory and antioxidant effects. This preserve beta-cell function and insulin secretion, contributing to sustained glycemic control.
Glycemic Control	Various compounds targeting different pathways.	Synergistic effects on glycogen synthesis and storage contribute to better glycemic control by regulating glucose release from the liver and enhancing glucose storage in muscles and the liver.

Challenges and Opportunities

Studying the synergistic effects in natural compounds, including those from *Ziziphus spina christi*, poses several challenges and addressing these challenges requires interdisciplinary collaboration, advanced analytical tools, and standardized methodologies (Hajimehdipoor *et al.,* 2014; Wang *et al.,* 2016; Sonam and Guleria, 2017; Perumal *et al.,* 2022). Overcoming these hurdles is essential to unlock the therapeutic potential of synergistic interactions in natural compounds for effective diabetes management.

Challenges in studying synergies

Natural compounds often have complex chemical profiles with numerous constituents and identifying specific synergistic interactions becomes challenging due to the multitude of compounds present (Wang *et al.,* 2016; Sonam and Guleria, 2017). Natural products contain various bioactive compounds with diverse chemical structures. Understanding the specific contributions of individual compounds and their combined effects requires sophisticated analytical techniques (Bruno *et al.*, 2017; Haidan *et al.*, 2017; Sonam and Guleria, 2017; Perumal *et al.,* 2022). Interactions among several compounds can be intricate and difficult to unravel.Pinpointing the precise synergistic mechanisms becomes complex, especially when compounds may have multiple targets (Sonam and Guleria, 2017; Leng *et al.,* 2018). Determining the ideal ratios of bioactive compounds for synergy is challenging. Finding the right balance is crucial, and variations in ratios may lead to different biological responses (Sonam and Guleria, 2017; Perumal *et al.,* 2022).Synergistic effects can be context-dependent, influenced by factors such as concentration, timing, and cellular environments.Reproducing optimal conditions for synergy in various experimental setups can be demanding (Wang *et al.,* 2016; Sonam and Guleria, 2017). Biological responses can vary among individuals and experimental models.Achieving consistent and reproducible results across different biological systems poses a challenge (Haidan *et al.,* 2017; Sonam and Guleria, 2017; Leng *et al.,* 2018).

Comparisons between studies become challenging, and establishing universally accepted criteria for synergy is difficult (Sonam and Guleria, 2017; Leng *et al.,* 2018). Analyzing complex datasets from studies involving multiple compounds requires advanced computational methods (Haidan *et al.,* 2017). Extracting meaningful insights from intricate data structures can be time-consuming and resource-intensive. Translating findings from in vitro or animal studies to human applications. Bridging the gap between preclinical and clinical settings is complex, and efficacy observed in laboratory settings may not always translate to therapeutic success in humans (Hajimehdipoor *et al.,* 2014; Sonam and Guleria, 2017; Leng *et al.,* 2018). Conducting comprehensive studies on synergistic effects demands substantial resources. Limited resources may hinder the scale and scope of research, impacting the depth of understanding (Hajimehdipoor *et al.,* 2014; Sonam and Guleria, 2017).

Opportunities for Future Research

To overcome challenges and deepen understanding in the study of synergistic effects in natural compounds, particularly those from *Ziziphus spina christi*, researchers can explore several potential avenues for future research. These avenues could help researchers address current challenges, enhance the robustness of their studies, and contribute to a deeper understanding of how synergistic interactions among bioactive compounds impact diabetes management.

Employ state-of-the-art analytical tools such as mass spectrometry, nuclear magnetic resonance, and metabolomics to unravel complex chemical profiles and identify specific compounds involved in synergistic interactions (Eszter *et al.,* 2013). Embrace systems biology to holistically study the interconnected molecular pathways affected by bioactive compounds. This approach considers the network of interactions within a biological system (Wei *et al.,* 2013). Apply quantitative systems pharmacology models to quantitatively predict the combined effects of multiple compounds, considering their concentrations, interactions, and dynamic changes over time (Beal *et al.,* 2011). Establish standardized methods for studying synergistic effects, including criteria for defining synergy, optimal experimental conditions, and reporting guidelines. This fosters consistency and comparability across studies (Tisdale *et al.,* 2010).Utilize high-throughput screening technologies to rapidly assess the synergistic potential of various compound combinations (Wang and Panpan, 2019). This allows for the screening of a large number of combinations in a time-efficient manner. Develop computational models and simulations to predict and understand synergistic interactions. These models can aid in identifying optimal combination ratios and understanding the influence of environmental factors (Yew *et al.,* 2019; Huang *et al.,* 2019). Conduct well-designed clinical trials to validate preclinical findings and assess the translational potential of synergistic compound combinations in human subjects. This involves careful consideration of dose-response relationships and safety profiles (Pangalos *et al.,* 2016).

Conclusion

In conclusion, understanding the synergistic effects in *Ziziphus spina christi* bioactive compounds is pivotal for advancing diabetes management strategies. This knowledge opens opportunity for personalized, effective, and holistic approaches to address the complex and dynamic nature of diabetes.

Recommendations

Researchers can contribute to a more comprehensive understanding of the potential therapeutic applications of *Ziziphus spina christi* bioactive compounds in managing diabetes by conducting a well-designed clinical trials to validate the efficacy and safety of synergistic compound combinations in individuals with diabetes as well as evaluating their impact on glycemic control, insulin sensitivity, and long-term outcomes. Researchers can also investigate the development of individualized treatment approaches based on patients' specific responses to synergistic compound combinations thereby exploring biomarkers or genetic markers that can predict individualized treatment responses.

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