

MULTIFACETED ROLES OF *ZIZIPHUS MAURITIANA* IN DIABETES MANAGEMENT: A REVIEW OF *IN VITRO* AND *IN VIVO* STUDIES

*(Pelbagai Peranan Ziziphus mauritiana dalam Pengurusan Diabetes: Satu Ulasan
Kajian In Vitro dan In Vivo)*

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ABSTRACT

Diabetes Mellitus (DM) is a long-term condition characterized by the body's inability to maintain normal blood glucose levels, leading to chronic symptoms. Worldwide, approximately 537 million adults aged 20 to 79 years are diagnosed with diabetes. Given its rising prevalence and global health impact, alternative therapeutic strategies with fewer side effects and greater accessibility are needed. Therefore, this review focuses on the therapeutic potential of *Ziziphus mauritiana* (ZM) in the management of DM. Focusing on in vitro and in vivo research, a comprehensive literature review was conducted up to 2025 to explore ZM and identify its active constituents and

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their mechanisms of action, with particular focus on α -amylase and α -glucosidase inhibition in the regulation of carbohydrate digestion and glycemic control. Supplementary searches were also conducted to evaluate the safety and toxicology of the plant, ensuring thorough coverage of potential adverse effects. ZM exhibits strong antidiabetic potential by inhibiting carbohydrate-hydrolyzing enzymes, thereby slowing carbohydrate breakdown and postprandial glucose spikes. The presence of bioactive compounds such as saponins, alkaloids, flavonoids, and terpenoids modulates glucose absorption and insulin sensitivity by directly or indirectly interacting with the enzyme active site. ZM also possesses strong antioxidant potential, scavenging oxygen radicals and reducing oxidative stress associated with pancreatic β -cell damage and DM progression. ZM has a significant effect on blood glucose management due to its ability to inhibit α -amylase and α -glucosidase and its rich profile of bioactive compounds. As for safety, ZM demonstrates a favorable safety profile at acute doses, though prolonged high-dose administration may warrant caution. Ultimately, the current lack of extensive clinical evidence necessitates further studies on effective dosing and cytotoxicity for its development as an herbal DM therapy.

Keywords: Bioactive compounds; diabetes mellitus; enzyme inhibition; hyperglycemia; *Ziziphus mauritiana*

ABSTRAK

*Diabetes Mellitus (DM) merupakan satu keadaan jangka panjang yang dicirikan oleh ketidakupayaan tubuh untuk mengekalkan paras glukosa darah yang normal, yang seterusnya menyebabkan pelbagai simptom kronik. Di seluruh dunia, dianggarkan sekitar 537 juta orang dewasa berumur antara 20 hingga 79 tahun telah didiagnosis dengan diabetes. Seiring dengan peningkatan prevalens penyakit ini serta impaknya terhadap kesihatan global, strategi terapeutik alternatif yang mempunyai kesan sampingan yang lebih rendah serta lebih mudah diakses amat diperlukan. Oleh itu, ulasan ini memberi tumpuan kepada potensi terapeutik *Ziziphus mauritiana* (ZM) dalam pengurusan DM. Dengan memfokuskan kepada kajian *in vitro* dan *in vivo*, satu tinjauan literatur yang komprehensif telah dijalankan sehingga tahun 2025 bagi meneliti ZM untuk mengenal pasti komponen aktifnya serta mekanisme tindakannya, dengan penekanan khusus terhadap penghambatan enzim α -amilase dan α -glukosidase dalam pengawalan pencernaan karbohidrat dan kawalan glisemik. Carian tambahan turut dijalankan untuk menilai aspek keselamatan dan toksikologi tumbuhan, bagi memastikan liputan yang menyeluruh terhadap potensi kesan buruk. ZM menunjukkan potensi antidiabetik yang kuat melalui penghambatan enzim yang menghidrolisis karbohidrat, sekali gus memperlahankan pemecahan karbohidrat dan*

peningkatan glukosa selepas makan. Kehadiran sebatian bioaktif seperti saponin, alkaloid, flavonoid dan terpenoid membantu memodulasi penyerapan glukosa serta sensitiviti insulin melalui interaksi secara langsung atau tidak langsung dengan tapak aktif enzim. Selain itu, ZM juga mempunyai potensi antioksidan yang tinggi dengan keupayaan menyahtoksik radikal oksigen serta mengurangkan tekanan oksidatif yang berkaitan dengan kerosakan sel β -pankreas dan perkembangan DM. Secara keseluruhannya, ZM menunjukkan kesan yang signifikan dalam pengawalan glukosa darah melalui keupayaannya menghambat enzim α -amilase dan α -glukosidase serta kandungan sebatian bioaktif yang kaya. Dari segi keselamatan, ZM menunjukkan profil keselamatan yang baik pada dos akut, namun penggunaan berpanjangan pada dos tinggi mungkin memerlukan perhatian. Secara keseluruhannya, kekurangan bukti klinikal yang meluas pada masa ini menuntut kajian lanjut mengenai dos berkesan dan sitotoksiti bagi pembangunan ZM sebagai terapi herba untuk DM.

Kata kunci: *Sebatian bioaktif; diabetes mellitus; penghambatan enzim; hiperglisemia; Ziziphus mauritiana*

INTRODUCTION

Diabetes Mellitus (DM) encompasses metabolic disorders characterized by chronically high blood sugar (hyperglycemia) due to inadequate insulin production, insulin resistance, or a combination of these factors. The most common forms of DM are type 1 DM (T1DM) (insulin-dependent diabetes) or type 2 DM (T2DM) (non-insulin-dependent diabetes) (Seetaloo et al. 2019). In T1DM, the beta cells in the pancreas do not produce insulin, while in T2DM, the body cannot utilize insulin (Ahmad Jan et al. 2017). The 10th edition of the International Diabetes Federation (IDF) Diabetes Atlas reported that approximately 537 million adults aged 20 to 79 years worldwide had diabetes (International Diabetes Federation, 2021). By 2030, this is expected to reach 643 million, increasing further to 783 million by 2045. In Malaysia, the National Health and Morbidity Survey (NHMS) 2023 found that around 3.6 million adults have diabetes. Worryingly, 40% of them are unaware of the symptoms and conditions. Even among those who have been diagnosed, around 56% find it difficult to maintain blood glucose at an appropriate level (CodeBlue 2023). Diabetes can be fueled by urbanization, economic growth, and modern lifestyles that include less physical activity and unhealthy eating habits. These factors contribute to the ongoing increase in diabetes cases worldwide as countries develop (Magliano et al. 2021; Akhtar et al. 2022).

However, diabetes is a significant public health problem not only because of its increasing prevalence, but also because of its serious complications. Chronic

hyperglycemia can lead to target organ damage by elevating the risk of both microvascular complications (e.g., diabetic neuropathy and diabetic retinopathy) and macrovascular complications (e.g., peripheral vascular and cardiovascular diseases) (Lu et al. 2024). Cardiovascular complications are now the most common cause of death in diabetes. More than 75% of diabetics over the age of 40 are likely to die from cardiovascular consequences and are at a higher risk of experiencing a first cardiovascular event than non-diabetics (Damaskos et al. 2019). A primary factor in these complications is oxidative stress, characterized by redox dysregulation driven by excessive production and accumulation of reactive oxygen species (ROS). ROS are generated by the transfer of electrons to oxygen from mitochondrial activity. In patients with diabetes, ROS damage vascular endothelial cells, enhance intravascular permeability, disrupt endothelial junctions, and lead to microvascular and macrovascular complications (An et al. 2023).

Several studies have highlighted the role of enzyme inhibitors in the management of DM (Kumar et al. 2011; Nair, Kavrekar & Mishra 2013; Agarwal & Gupta 2016). A promising approach in treating the disease involves reducing postprandial hyperglycemia (PPHG) by blocking carbohydrate-hydrolyzing enzymes such as α -amylase and α -glucosidase (Rozenan et al. 2021). α -amylase facilitates the cleavage of α -D-(1-4)-glycosidic bonds in carbohydrates, resulting in the formation of oligosaccharides, while α -glucosidase operates in the final stage of the digestion to facilitate the transformation of complex carbohydrates and disaccharides into absorbable monosaccharides. Inhibitors of these enzymes can slow glucose hydrolysis, thereby reducing PPHG (Lordan et al. 2013).

Current diabetes treatments primarily focus on regulating and lowering blood glucose levels to within the normal range. However, many modern treatments are associated with side effects that can lead to other health problems over time. Acarbose, for example, is often used as an α -amylase and α -glucosidase inhibitor but often causes adverse effects in diabetic patients, such as bloating, diarrhea, and flatulence (Ojah, Moronkola & Akintunde 2020). In addition, Rosiglitazone, a thiazolidinedione, can cause leg and ankle swelling, while Glibenclamide, a sulfonylurea, may lead to weight gain and skin irritation (Watts 2019).

Conversely, traditional medical systems from diverse cultures have recognized the healing properties of natural substances, particularly herbs, in promoting health and addressing illnesses. Notably, approaches such as Prophetic medicine have historically emphasized the use of plant-derived remedies within holistic healing practices (Masruri et al. 2017). This enduring dependence on traditional medicine continues to generate interest in alternative and complementary therapies for contemporary health issues

(Tran, Pham & Le 2020). One such plant is *Ziziphus mauritiana* (ZM), which shows significant potential for application in both nutrition and phytomedicine. However, there is a need for comprehensive studies evaluating the therapeutic metabolic profiles and enzyme-inhibitory activities of ZM across varying solvent concentrations to optimize extraction methods and determine its full medicinal properties.

Ziziphus mauritiana

ZM has been cultivated across the Indian subcontinent for centuries, particularly in arid and semi-arid states such as Gujarat, Rajasthan, and Uttar Pradesh. Beyond India, ZM has spread globally, thriving in tropical and semi-tropical regions of Africa, Australia, Southeast Asia, and the Caribbean (O'Brien et al. 2023). It has become an essential food source in resource-limited populations in these arid regions. In Australia, it was brought to northern Queensland for its ornamental and agricultural potential (Bancé, Bationo & Ouedraogo 2022). Today, ZM's distribution in Australia is concentrated in Northern Queensland, the Northern Territory, and Western Australia (O'Brien et al. 2022).

In Southeast Asia, particularly Malaysia, it is recognized for its rich tropical biodiversity, including numerous medicinal plants that are shaped by religions, traditional beliefs, and practices. In this study, a local plant was selected to investigate its antidiabetic properties. ZM belongs to the Rhamnaceae family and is also known as “Bidara” in Malaysia (Mohd Jailani et al. 2020), “jujube” or “ber” in India, “nabk” in Arab countries, and “tsao” in China, reflecting its widespread traditional uses across various cultures (Koley et al. 2016). This tree is found in warm climates, is highly adaptable, and can thrive in harsh conditions, including salinity, drought, and waterlogging.

Its resilience enables it to grow across different soil types (Mohd Jailani et al. 2020). Due to its adaptability to climates, low production cost, and high nutritional value, it is often called a poor man's apple or the king of arid zone fruit (O'Brien et al. 2023). This tree is medium-sized, reaching 9 to 16 meters in height. It features spreading branches with dark brown bark and zigzag branches that are initially covered with white hair. The tree has glossy green, egg-shaped leaves with jagged edges and three prominent veins near the tips. The flowers have yellow and green petals, and the oval fruits contain hard seeds. The size of the fruits can vary from 1.5 to 2 cm or 4 to 6 cm (Hussain et al. 2021).

Traditionally, different parts of ZM are employed to address various health issues, such as the roots for fever, wounds, and ulcers; the bark for diarrhea and boils; the seeds for vomiting and insomnia; the leaves for asthma and leucorrhea; and the fruits

for fatigue and itching (Naaz, Agari & Singh 2020). In addition to its widespread use as a medicinal plant, this tree is also used for various religious purposes (Yusri, Salleh & Hassan 2017).

Phytochemicals of *Ziziphus mauritiana* on Glucose Regulation

ZM is a plant that contains a high concentration of bioactive compounds, making it a promising candidate for multiple medicinal uses. Different parts of the plant, including fruits, seeds, leaves, roots, and stems, contain a range of compounds, including alkaloids, flavonoids, saponins, mucilages, glycosides, polyphenols, vitamins, and resins (Hidajati & Rokhmania 2019).

Phytochemical analyses of this fruit have identified the presence of glycosides, phenols, lignins, flavonoids, saponins, and tannins. In addition, the ethanol extract from the seeds was found to contain tannins, terpenes, flavonoids, alkaloids, glycosides, essential oil, and saponins (Tran, Pham & Le 2020). These saponins, which were extracted from the seeds of ZM, include jujubosides A, B, A1, B1, C, and acetyljujuboside B. Jujubosides have hemolytic, sedative, anxiolytic, and antacid effects. Jujuboside A, for example, specifically inhibits calmodulin, a protein that regulates various cellular functions, including inflammation, metabolism, muscle contraction, and memory (Goyal, Sasmal & Nagori 2012).

Further analyses using gas chromatography-mass spectrometry (GC-MS) provide a comprehensive phytochemical profile of the n-hexane, chloroform, and methanol extracts of ZM leaves. Some important compounds, such as methyl stearate (15.59%), α -linolenic acid (14.21%), and squalene (12.09%), along with palmitic acid, phytol, and vitamin E are identified in the leaves. The methanol extract is mainly rich in phenolic compounds, while the chloroform extract contains mainly palmitic acid (38.55%), E-15 heptadecenal (12.31%), and α -tocopherol (10.09%) (Butt, Hussain & Munawar 2021). Similarly, the n-hexane extract is rich in α -linolenic acid (26.45%), squalene (12.83%), and palmitic acid (16.26%). The chloroform extract contains the highest concentration of phenolic compounds, whereas flavonoids were identified as the main component in the methanol extract (Butt, Hussain & Munawar 2021). Aqilah et al. similarly employed the same solvents for the extraction of twigs and leaves of ZM (Aqilah, Yusof & Saat 2017). It was reported that almost all secondary metabolites, such as alkaloids, flavonoids, glycosides, phenols, steroids, sterols, tannins, and terpenoids except saponins, are present in the leaves, while the twigs contain all these secondary metabolites.

In addition to leaves and twigs, phytochemical compounds were detected in the roots by GC-MS analysis (Pauloi et al. 2024). Based on the relative peaks, three main compounds are conspicuous: Dimyristyl thiodipropionate, propanoic acid 3, 3'-thiobis-, ditetradecyl ester, and 2-propenoic acid, pentadecyl ester. Among these, dimyristyl thiodipropionate was observed at retention times of 23.97 and 27.85 minutes with considerable peak areas of 5.83% and 64.65%, respectively. The second compound is propanoic acid 3,3'-thiobis-, ditetradecyl ester, which eluted at 23.88 and 24.06 minutes, with peak areas of 10.52% and 13.89%, respectively. Ranking third in significance, 2-propenoic acid, pentadecyl ester, exhibited a retention time of 11.279 minutes. Dimyristyl thiodipropionate is often used as an antioxidant and stabilizer to inhibit or delay oxidation, which can cause deterioration of materials such as plastics and polymers. In addition, 2-propenoic acid, pentadecyl ester possesses anticancer potential (Sahu et al. 2024).

Analysis of the ZM stem yields a similar result, identifying dimyristyl thiodipropionate as the major compound based on GC-MS chromatogram analysis, with a peak area of 96.21%. In addition, the identified compound octadecane, 1,1'-[1, 3-propanediylbis(oxy)] bis exhibits significant biological activities. The strain of ZM is rich in phytochemicals, including octadecane, which contribute to the medicinal properties, namely antioxidants, cytotoxic, and immunomodulatory effects (Pauloi et al. 2024). Overall, many compounds have been identified across different parts of ZM, suggesting that ZM is involved in various biological activities, including anti-inflammatory, antioxidant, and other pharmacological properties. However, deeper research is needed to understand the interactions among these compounds and their other health benefits, and to further explore DM.

METHODOLOGY

A comprehensive review of the existing literature was conducted to identify studies on the effects of ZM on DM, using biochemical and enzymatic evaluations. The scientific studies were retrieved from reliable databases, including Google Scholar, PubMed, ScienceDirect, BASE, SpringerLink, and LENS.ORG, as shown in Figure 1. The search strategy included specific keywords such as “therapeutic potential of *Ziziphus mauritiana*”, “enzyme inhibition potential of *Ziziphus mauritiana*”, “ α -amylase inhibition potential of *Ziziphus mauritiana*”, “ α -glucosidase inhibition potential of *Ziziphus mauritiana*”, “*in vivo* diabetes studies of *Ziziphus mauritiana*”, “*in vitro* diabetes studies of *Ziziphus mauritiana*”, and “phytochemicals of *Ziziphus*” with combined Boolean operators of “OR” or “AND” to refine the results.

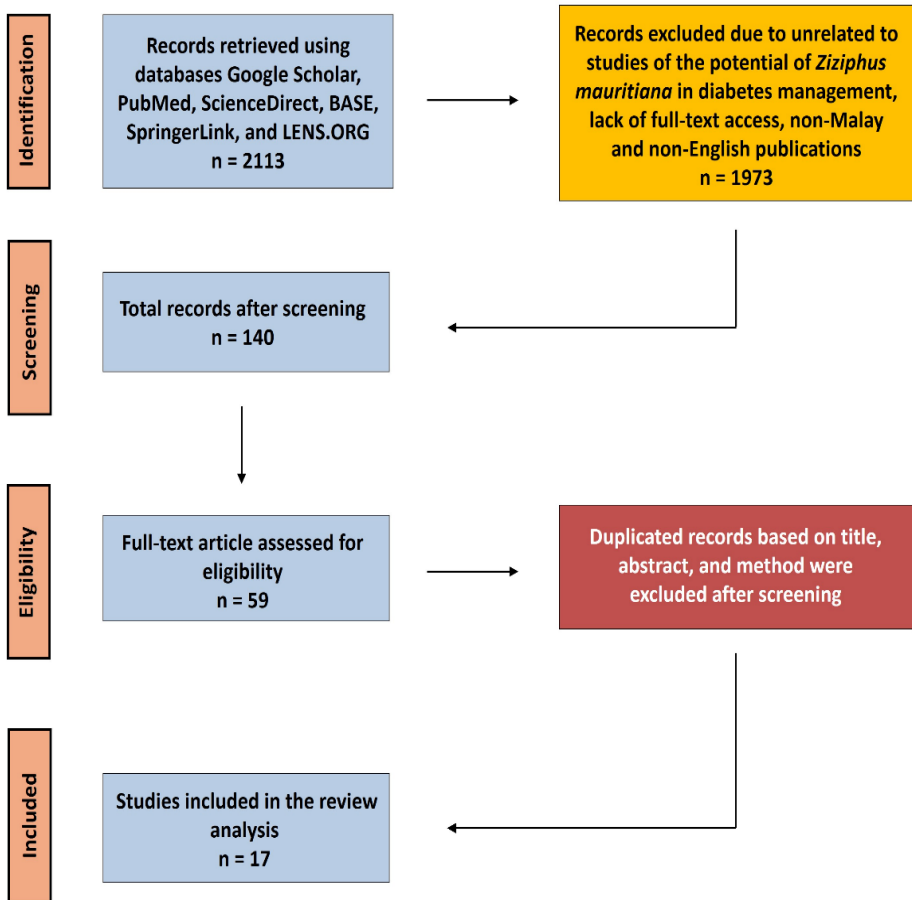


FIGURE 1 Flow diagram of the search strategy used. A total of 2113 records were identified from databases, and 1973 were removed prior to screening. Of the remaining 140 records, 59 were eligible for full-text review, and 17 studies were included in the final analysis. In addition to these records, supplementary searches were also conducted to assess the safety and toxicology of ZM, ensuring comprehensive coverage of potential adverse effects and safety considerations for the plant.

Most of the included studies on ZM and DM that dealt with *in vitro* research were published between 2015 and 2025, whereas the *in vivo* studies were conducted over a broader period, from 2010 to 2025, due to the scarcity of relevant studies. Studies were included based on applicability to diabetes management, phytochemical compounds, and biochemical mechanisms. These selected studies provide deeper insights into the antidiabetic potential of ZM, including its mechanisms of action and its enzyme-inhibitory effects.

RESULTS AND DISCUSSION

Antidiabetic properties of *Ziziphus mauritiana*

The antidiabetic potential of ZM has been examined through both *in vitro* and *in vivo* models. *In vitro* testing plays an important role in discovering the biochemical mechanisms of action by investigating how plant compounds interact with enzymes and influence cellular functions related to glucose metabolism and oxidative stress. Such studies are essential for identifying the central bioactive constituents and for understanding specific modulatory effects and molecular-level inhibition. On the other hand, *in vivo* studies validate these findings in biological systems by evaluating the extract's overall impact on metabolic balance, blood glucose regulation, and oxidative markers in diabetic models. The principal findings from both *in vitro* and *in vivo* investigations conducted on ZM are highlighted in Table 1, which presents the experimental models, plant parts analyzed, extract administration, and resulting data.

***In vitro* Studies of *Ziziphus mauritiana* on Enzyme Inhibition, Antioxidant Potential, and Cellular Glucose Uptake**

A recognized strategy for preventing diabetes involves minimizing the rise in blood glucose levels caused by dietary intake. This can be achieved by inhibiting dietary carbohydrate digestion in the gastrointestinal (GI) tract by suppressing digestive enzymes, namely α -amylase and α -glucosidase (Kim et al. 2005). The methanolic extract from the leaves of ZM is rich in saponins, the principal bioactive constituents, which are present at high concentrations and confirmed by qualitative colorimetric tests (Abdallah, Elsharkawy & Ed-dra 2016). Based on this, Dubey et al. showed that saponins isolated from the ZM extract exhibit antidiabetic potential via an α -amylase inhibition assay, with inhibition percentages ranging from 21.2% to 97.09% and a mean inhibitory concentration (IC_{50}) of 82.12 g/ml (Dubey et al. 2019). The inhibitory mechanism involves saponins occupying the α -amylase active site, thereby preventing substrate binding and starch hydrolysis.

Similarly, the aqueous leaf extract of ZM has the highest α -amylase inhibitory activity among the other solvent extracts. This indicates that aqueous extraction is most effective for isolating α -amylase-inhibitory compounds from these plants (Sarfraz, Hassan & Murtaza 2018). In addition, the study by Prathyusha & Velraj showed that the leaf extract of ZM exhibited the highest IC_{50} of 63.7 μ g/ml in an α -amylase inhibition assay, compared to *Scoparia dulcaris* (whole plant) and *Michelia champaca* (bark) (Prathyusha & Velraj 2022). This suggests that ZM is a potent antidiabetic agent. In a comparable study using ZM root, Diarra et al. identified that

the ethanolic extract possesses the strongest inhibitory effect, surpassing ethyl acetate, aqueous extract, and acarbose (Diarra et al. 2024).

In addition to its α -amylase inhibitory effect, ZM also exhibits a strong α -glucosidase inhibitory effect. Prathyusha & Velraj analyzed the methanolic extract of ZM leaves for α -glucosidase. This plant extract showed a dose-dependent inhibition (Prathyusha & Velraj 2022). At 100 $\mu\text{g/ml}$, the inhibition rate was 70.10%, and the IC_{50} value is 67.10 $\mu\text{g/ml}$. The IC_{50} value was the lowest among *Scopus dulcaris* and *Michelia champaca*, but slightly higher than acarbose, the control, indicating the strongest inhibition. Notably, the ZM leaf extract possesses α -glucosidase inhibitory activity five times greater than *Ziziphus jujube* (Sakna et al. 2019). While many researchers have used leaves for inhibition trials, Pratiwi used fruit extract instead (Pratiwi 2023). The results showed ZM ethanol extract at its highest concentration demonstrated 90.97% inhibition of α -glucosidase. However, the inhibition rate remains lower than that observed with acarbose, which is used as a benchmark for comparing ZM's inhibition potential.

Contributing to this inhibitory effect is Betulinic Acid (BA), a naturally occurring lupine-type pentacyclic triterpenoid identified and isolated from *Ziziphus spp* (Sareen et al. 2022). Studies by Chen et al. demonstrated that BA has a strong affinity for α -glucosidase, binding tightly to its active center and forming a BA- α -glucosidase complex (Chen et al. 2022). Key amino acids in the enzyme's binding pocket include ASP347, TYR311, PHE155, PHE175, and HIE277. This inhibition of α -glucosidase activity reduces postprandial hyperglycemia, making BA a promising candidate for diabetes management.

In addition to enzyme inhibition, oxidative stress also plays a crucial role in T2DM. Disruption of redox reactions activated by ROS leads to β -cell dysfunction and insufficient insulin production (Vassalle, Maltinti & Sabatino 2020). Therefore, Teh et al. reported that the ZM fruit extract demonstrated antioxidant activity via its bioactive compounds, suggesting that it can help mitigate oxidative stress and support the β -cell cycle (Teh et al. 2022). The compound from the fruit of ZM was extracted using supercritical fluid extract (SFE) to analyze the antioxidant activity through the 2, 2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity and total phenolic content (TPC) of the fruit extract. Based on the studies, the fruit extract of ZM contains 539.18 mg GAE/100 g phenol and inhibits the free DPPH radical by 16.65%. These values are consistent with a previous research by Adilah et al., who found a much higher phenolic content (1690 mg GAE/100 g) in the fruit juice extract of ZM (Adilah et al. 2022). Phenolic compounds, classified as secondary metabolites, are recognized for exhibiting potent antioxidant activity (Ha et al. 2020). Therefore,

ZM fruit extract can counteract pancreatic β -cell destruction and help sustain β -cell mass. This directly stimulates insulin production, which is needed to regulate blood sugar, thereby improving blood sugar control.

To further explore the antidiabetic mechanism of ZM, Xie et al. investigated the impact of BA on hyperglycemia-induced oxidative damage, inflammation, and metabolic dysfunction in cells (Xie et al. 2022). The results showed that BA reverses hyperglycemia-induced oxidative stress by restoring endothelial nitric oxide synthase (eNOS) expression, thereby reducing ROS levels and restoring endothelial function. BA also decreases nuclear factor κ B (NF κ B) p65 activity, thereby reducing inflammation and DNA damage, and enhances nuclear factor erythroid 2-related factor 2 (Nrf2) activation to boost the antioxidant response by upregulating genes such as glutathione peroxidase (GPx) and superoxide dismutase 2 (SOD2) (Li et al. 2019). In muscle cells, BA can fully restore glucose transporter 4 (GLUT4) expression and glucose uptake, counteracting epigenetic repression that impairs glucose metabolism.

Similarly, four major flavonoids were found to be present in the peel of ZM, namely naringin triglycoside, quercetin-3-O-pentosylhexoside, quercetin-3-O-[(2-hexosyl)-6-rhamnosyl]-hexoside, and quercetin-3-O-(2-pentosyl-rhamnoside)-4'-O-rhamnoside, which were identified as potent glucose modulators (Wang et al. 2023). Dhanya et al. previously demonstrated that 100 μ M quercetin enhances glucose uptake in L6 myotubes under oxidative stress induced by tertiary butyl hydrogen peroxide (Dhanya et al. 2014). Therefore, Dhanya et al. sought to understand the molecular mechanism by which quercetin acts on the skeletal muscle cell lining, owing to its antidiabetic effects (Dhanya et al. 2017). Inhibitor studies on L6 myotubes showed that quercetin does not affect the wortmannin (phosphoinositide 3-kinase (PI3K)) pathway but can reduce glucose uptake by up to 80% in the presence of an adenosine monophosphate kinase (AMPK) inhibitor, revealing its role in the AMPK pathway. This was confirmed by increases in all three molecules: adenosine monophosphate (AMP), adenosine diphosphate (ADP), and adenosine triphosphate (ATP). Importantly, the ratios of AMP to ATP and ADP to ATP both doubled, indicating increased ATP usage within the cells. Since the AMP: ATP ratio is a key signal for AMPK activation and is mathematically related to the ADP: ATP ratio, the researchers used the ADP: ATP ratio as an indirect indicator of AMPK activation. Analysis of real-time polymerase chain reaction (qPCR) showed that GLUT4 mRNA expression of calcium/calmodulin-dependent protein kinase (CaMKK), mitogen-activated protein kinase (MAPK), and AMPK increased 14-fold compared to the control condition. Insulin receptor substrate (IRS) expression increased slightly, as confirmed by Western blot, suggesting that quercetin regulates glucose metabolism primarily through AMPK rather than insulin signaling.

***In vivo* Studies of *Ziziphus mauritiana* on its Hypoglycemic Effects in Diabetic Models**

ZM's effectiveness in treating diabetes and promoting wound healing has been well documented in numerous studies. The most important property of ZM is its antidiabetic potential, which demonstrates how various plant extracts help lower blood sugar levels. For instance, a study by Abubakar et al. showed that hydro-methanolic fruit extracts from ZM and *Ziziphus spina-christi* were effective in lowering blood glucose levels in diabetic rat models (Abubakar et al. 2018). In this study, both *Ziziphus* species, especially at higher doses, significantly lowered blood glucose levels without harming the rats, indicating that *Ziziphus* holds promise as a safe antidiabetic treatment.

Similarly, Bhatia & Mishra studied the antihyperglycemic activity of ZM seed extract alone and in combination with glyburide in diabetic and non-diabetic mice (Bhatia & Mishra 2010). Approximately 800 mg/kg of seed extract showed the greatest reduction in blood glucose levels in mice. However, the greatest reduction was achieved through the synergistic effect of glyburide and the extract. The extract improved glucose clearance within 30 minutes and showed a positive effect on glucose metabolism as measured by the oral glucose tolerance test (OGTT). It also maintains weight and improves the survival rate of mice. According to Gaur et al., the ZM seed extract effectively reduced blood glucose levels and increased body weight (Gaur, Mishra & Jain 2024). Notably, both the seed and stem bark of ZM showed a dose-dependent response, with the extract of stem bark demonstrating a greater reduction in blood glucose in Swiss albino mice than the seed extract (Akanda & Hasan 2021). In addition to the fruits, seeds, and stem bark, the ethanol extract of ZM leaves was also found to reduce glucose levels in male rats in a dose-dependent manner. Histopathological analysis demonstrated that 300 and 500 mg/kg of the ZM leaf extract reduced pancreatic necrosis and preserved the Langerhans islets of the pancreas (Nasution, Nasution & Mutia 2024). Approximately 400 mg/kg of ZM leaf extract, which is considered the highest dose able to drastically reduce blood glucose and restore the body weight of diabetic rats (Wahyuni, Mawardika & Sabbab 2024).

This glucose-lowering effect is also supported by Indrianti et al., who observed a notable decline in blood glucose levels in rats treated with ZM leaves from day 6 onwards (Indrianti et al. 2024). The most effective doses are 300 mg/kg and 500 mg/kg, which have effects proportional to those of metformin. The phytochemical analysis identified saponins, flavonoids, and alkaloids that may be involved in antidiabetic activity by activating AMPK and maintaining glycogen synthase kinase-3 (GSK3) levels, as shown in Figure 2. Compounds of these phytochemical groups are

also involved in other mechanisms, including glucokinase (GK), protein of tyrosine phosphatase-1B (PTP1B), and sterol regulatory element binding protein 1 (SREBP1). Rajan et al. also reported that flavonoids, namely flavones, increase AMPK phosphorylation at Thr 172, leading to GSK3 β phosphorylation and inactivation (Rajan et al. 2021). Inactivation of GSK3 β promotes glucose storage by allowing glycogen synthesis. Structurally, the γ -subunit of AMPK contains four cystathionine β -synthase (CBS) domains that are known as binding activators. When flavones were docked into CBS1, CBS3, and CBS4 domains, high binding affinity was detected, almost comparable to or exceeding that of AMP, the natural activator. The formation of more hydrophobic interactions and hydrogen bonds indicates stable binding with these domains.

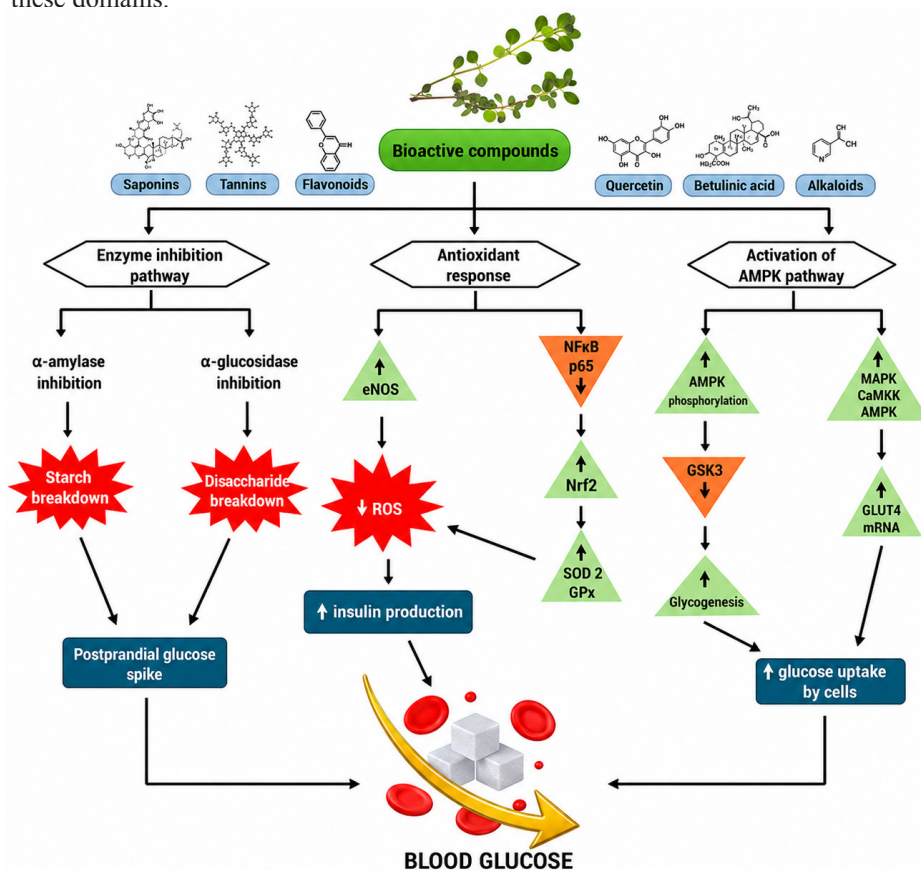


FIGURE 2 The mechanism of blood glucose reduction by bioactive compounds in *Z. mauritiana* involves enzyme inhibition, antioxidant activity, and enhanced cellular glucose uptake through the AMPK activation.

Table 1 shows the overview of the *in vitro* and *in vivo* research on ZM.

TABLE 1 Summary of the *in vitro* and *in vivo* research on *Z. mauritiana*

Type of Model	Dosage & Duration of Treatment	Observation	Reference
<i>In vitro studies</i>			
Enzyme assay	50, 75, 100, 125, 150 µg/ml of saponin extract (within 24 hours)	<ul style="list-style-type: none"> - Isolated saponin from ZM leaf showed α-amylase inhibition (21.2% - 97.09%). - Competitive inhibition at the α-amylase binding site. - IC₅₀: 82.1243 ± 1.811 g/ml. 	(Dubey et al. 2019)
Enzyme assay	Aqueous, 100% methanol, 50% aqueous methanol, 100% ethanol, and 50% aqueous ethanol extract of leaf (within 24 hours)	<ul style="list-style-type: none"> - Aqueous extract of ZM leaf showed the highest α-amylase inhibition. - IC₅₀: 90.46 ± 0.23 µg/ml. 	(Sarfraz, Hassan & Murtaza 2018)
Enzyme assay	20, 40, 60, 80, 100 µg/ml methanolic extract of ZM leaf (within 24 hours)	<ul style="list-style-type: none"> - ZM leaves showed the highest α-amylase inhibition when compared to <i>Scoparia dulcis</i> whole plant and <i>Michelia champaca</i> bark. - IC₅₀: 63.7µg/ml. - ZM leaves showed the highest α-glucosidase inhibition when compared to <i>Scoparia dulcis</i> whole plant and <i>Michelia champaca</i> bark, with a percentage inhibition of 70.10% at 100 µg/ml. - IC₅₀: 67.10 µg/ml. 	(Prathyusha & Velraj 2022)

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Enzyme assay	20, 40, 80, 160, 320 $\mu\text{g/ml}$ of ethanol, ethyl acetate, and aqueous root extract (within 24 hours)	<ul style="list-style-type: none"> - The strongest α-amylase inhibitory activity is possessed by the ethanolic extract of the ZM root (72.48 $\mu\text{g/ml}$) and leaves (71.51 $\mu\text{g/ml}$). - Flavonoids and polyphenols may contribute to the hypoglycemic effect, which showed a strong correlation (R^2: 0.94) with enzyme inhibition. 	(Diarra et al. 2024)
Enzyme assay	30, 90, 150, 210, 270 ppm of ethanol fruit extract (within 24 hours)	<ul style="list-style-type: none"> - α-glucosidase activity at 270 ppm: 90.97%. - Flavonoids and alkaloids are responsible for the antidiabetic effects observed in most plants. 	(Pratiwi 2023)
Enzyme assay	1) 10 μl BA solution 2) 50 μl of pNPG (2.5 mM) acts as substrate (within 24 hours)	<ul style="list-style-type: none"> - BA can inhibit the α-glucosidase activity in a dose-dependent manner. - Structural modification of BA at C-3 and C-28 might influence the inhibitory activity. - ZM contains BA, suggesting it may have similar activity. 	Chen et al. 2022)
Phytochemical screening (TPC, DPPH)	1 mg of fruit extract (within 24 hours)	<ul style="list-style-type: none"> - Fruits of ZM extracted using SFE showed 539.18 mg GAE/100 g of phenol and the DPPH free radical inhibition by 16.65%. 	(Teh et al. 2022)
Phytochemical screening (TPC)	1 ml of fruit extract (within 24 hours)	<ul style="list-style-type: none"> - The fruit juice of ZM showed 1690 mg GAE/100 g of total phenol. 	(Adilah et al. 2022)

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HUVEC, HASMC	LG (5 mM) HG (25 mM) HG + 20 μM of BA	<ul style="list-style-type: none"> - HUVEC: ↑ eNOS expression, ↓ NFκB p65, ↑ Nrf2 activity, ↓ ROS. - HASMC: ↑ GLUT4 mRNA & protein expression, ↑ glucose uptake in the cell. - ZM contains BA, suggesting it may have similar activity on HUVEC and HASMC cells. 	(Xie et al. 2022)
Fully differentiated L6 myotubes	Quercetin (10 and 100 μm) (within two days)	<ul style="list-style-type: none"> - Quercetin's effect on glucose uptake was unaffected by the PI3K inhibitor, suggesting the PI3K pathway is not involved in the insulin signaling pathway. - Treatment of quercetin with an AMPK inhibitor ↓ glucose uptake up to 80%, indicating the AMPK pathway is involved. - ↑ AMP: ATP and ADP: ATP ratios. - ZM contains quercetin, suggesting it may have similar activity on L6 myotubes. 	(Dhanya et al. 2017)

In vivo studies

Male albino rats were induced with diabetes using a single intraperitoneal injection of alloxan monohydrate (360 mg/kg in normal saline).	200, 400 mg/kg of ZM fruit (14 days)	<ul style="list-style-type: none"> - ↓ blood glucose from 241.83±40.81 to 78.67±15.01, triglyceride, cholesterol, LDL, and HDL levels. - ↑ total protein and albumin levels. - Dose-dependent response. 	(Abubakar et al. 2018)
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<p><i>Swiss albino</i> mice (25-30 g) were induced with diabetes using alloxan monohydrate in acetate buffer (0.15 M, pH4.5).</p>	<p>100, 400, 800 mg/kg of seed extract of ZM (acute study – within 10 hours, subacute study – 28 days)</p>	<ul style="list-style-type: none"> - The maximum glucose-lowering effect at the extract dose of 800 mg/kg. - Synergistic treatment of glyburide (10 mg/kg) and extract (800 mg/kg) showed the greatest glucose-lowering effect after 2 hours: Acute: 26% ± 2.5%, subacute: 169.97 ± 2.1 mg/dL, body and spleen weight maintained, 0% mortality. - 800 mg/kg bw extract treatment showed ↓ mortality rate (33.3%). - ↑ glucose tolerance based on OGTT for extract, glyburide, and combination treatment. - Triterpene BA was identified as a marker compound. 	<p>(Bhatia & Mishra 2010)</p>
<p>Wistar rats were induced with diabetes using STZ 2% solution mixed in 0.9% NaCl.</p>	<p>200, 400 mg/kg ethanol extract of the seed of ZM (21 days)</p>	<ul style="list-style-type: none"> - ↓ blood glucose with values of 130.36 ± 2.97 mg/dL at 200 mg/kg and 112.69 ± 3.06 mg/dL at 400 mg/kg. - Dose-dependent response. - Greater ↓ at the higher dose. 	<p>(Gaur, Mishra & Jain 2024)</p>
<p><i>Swiss albino</i> male mice were not induced but were fasted overnight.</p>	<p>200, 400 mg/kg methanol extract of seed and stem bark of ZM (within one day)</p>	<ul style="list-style-type: none"> - The 400 mg/kg doses of seed (41.49%) and stem bark (44.27%) extracts were effective in ↑ the percentage of blood glucose reduction. - Dose-dependent response. 	<p>(Akanda & Hasan 2021)</p>

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Male Wistar rats were induced with diabetes using alloxan.	50, 150, 300, and 500 mg/kg ethanol extract of ZM Lamk. leaf (28 days)	<ul style="list-style-type: none"> - A 500 mg/kg dose is the most effective ↓ blood glucose (p-value of 0.004). - Dose-dependent response. - 50 & 150 mg/kg ↑ pancreatic damage and ↑ necrosis (80%). - 300 & 500 mg/kg ↑ number of Langerhans islets, ↑ pancreatic health, and ↓ necrosis (50%). 	(Nasution, Nasution & Mutia 2024)
Rats were induced with diabetes using STZ	100, 200, 300, and 400 mg/mL leaf extract of ZM	<ul style="list-style-type: none"> - 400 mg/mL showed the highest glucose ↓, decreasing from 300 mg/mL to 100.1 mg/mL by day 42. - Dose-dependent response. - 100 mg/ml showed the highest ↑ in body weight recovery in the rat (316.4 g) by day 42. 	(Wahyuni, Mawardika & Sabban 2024)
Male rats (<i>Rattus norvegicus</i>) were induced with diabetes using alloxan (130 mg/kg).	50, 150, 300, and 500 mg/kg ethanol extract of ZM leaf (28 days)	<ul style="list-style-type: none"> - ↓ blood glucose from day 6 for all the treatments. - 300 mg/kg and 500 mg/kg showed a notable ↓ amount of glucose. - A 50 mg/kg dose is ineffective. - Key compounds were detected: saponins, flavonoids, and alkaloids. 	(Indrianti et al. 2024)

ZM, *Ziziphus mauritiana*; BA, Betulinic Acid; IC₅₀, Mean inhibitory concentration; GAE, Gallic Acid Equivalents; DPPH, 2, 2-diphenyl-1-picrylhydrazyl; TPC, Total phenolic content; P13K, Phosphoinositide 3-kinase; AMPK, Adenosine monophosphate kinase; AMP, Adenosine monophosphate; ATP, Adenosine triphosphate; ADP, Adenosine diphosphate; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; OGTT, Oral glucose tolerance test; STZ, Streptozotocin; ↑, increase; ↓, decrease.

SAFETY AND TOXICOLOGICAL CONSIDERATIONS OF ZIZIPHUS MAURITIANA

Previous *in vivo* studies have generally shown that ZM is safe for short-term use and exhibits very low acute toxicity, with median LD50 values greater than 5,000 mg/kg and even exceeding 20,000 mg/kg in animal models without causing death (Attemene et al. 2017; Owolarafe et al. 2022). Massive acute doses of up to 50 g/kg in mice and rats caused no toxic symptoms (Kumar & Kumar 2023), and supplementing the diet of pregnant cows with its leaves demonstrated no detrimental health effects during pregnancy or lactation (Barkakati & Kalita 2020). However, constant administration of high doses of this plant in rat models (ranging from 28 to 180 days) resulted in notable nephrotoxicity and hepatotoxicity, evidenced by elevated serum creatinine and urea levels, alongside histopathological damage such as tubular cystic degeneration, interstitial edema, vacuolation, and liver inflammation (Attemene et al. 2017; Owolarafe et al. 2022; Yahaya et al. 2022). Furthermore, long-term exposure may also alter hematological parameters, potentially causing thrombocytosis, mild anemia, or alterations in white blood cell counts (Attemene et al. 2017; Yahaya et al. 2022), and moderate cytotoxicity in Brine Shrimp Lethality Assays (Pushpanathan et al. 2022).

As a whole, this medicinal plant has also been shown to be safe in acute toxicity studies, with no adverse effects observed even at high doses, supporting its traditional use. Nevertheless, while acute safety is established, the safety profile shifts drastically with chronic consumption. where the continuous accumulation of its bioactive compounds over an extended period can lead to severe cumulative damage. Further comprehensive long-term toxicological, genotoxicity, and clinical safety evaluations are needed to ensure its broader therapeutic application, particularly for DM.

CONCLUSIONS AND FUTURE DIRECTIONS

In conclusion, maintaining good health is an ongoing journey that necessitates a focus on fundamental needs, with nutrition being a pivotal component. Food not only fuels the body's physiological functions but also significantly affects physical and cognitive development (Mohd Nor et al. 2023). While a balanced diet enhances overall well-being, poor dietary choices are linked to the onset of various diseases (Hilmi & Kadir 2013; Abdul Hamid 2021), including diabetes. In this regard, ZM has emerged as a noteworthy natural food source, particularly for its potential advantages in blood glucose management and metabolic health support. Based on the comprehensive review, ZM is rich in vitamins, minerals, and various bioactive compounds, including

phenols, flavonoids, and saponins. This review suggests that many indirect studies of ZM in the mechanism of DM exist. Therefore, further in-depth studies are required to clarify how the bioactive constituents of ZM function in diabetes therapy.

Future studies should focus on the molecular mechanisms underlying DM. These include the plant's role in improving insulin sensitivity, stabilizing insulin secretion, and reducing oxidative stress. Some other advanced techniques, such as proteomics and metabolomics, are useful for studying specific genes and proteins affected by ZM extracts. Molecular docking studies can unravel the mechanism of ZM enzyme inhibition.

Toxicity studies are also important for future research. While ZM has shown promising antidiabetic potential, its long-term safety and cytotoxicity should be evaluated before future use. Toxicity studies can determine the IC_{50} using cell viability or enzyme inhibition assays, while the LD50 is analyzed using *in vivo* models. In addition, clinical studies are crucial for substantiating findings from *in vitro* and animal models. These studies should be conducted in the human population, considering lifestyle, genetic factors, and diet, to better understand the plant compound's side effects and efficacy.

To summarize, this plant is highly beneficial due to its high nutritional value, medicinal properties, and economic value. Despite its numerous benefits, its susceptibility to diseases and pests may pose a challenge to the widespread utilization of this plant. Continued research into ZM, with advances in technology, can unlock many more potential applications and overcome the obstacles that make the plant even more valuable in agriculture, healthcare, and industry. Promoting the cultivation and use of ZM can maximize the benefits by strengthening rural economies, improving food security, and promoting global health.

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