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Anti-diabetic Benefits from *Morus alba* Fruits

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Review Article

Abstract:
The aim of this review was to highlight the therapeutic potential of *Morus alba* fruits in managing type 2 diabetes mellitus (T2DM). This review examining studies sourced from databases including Scopus, PubMed, ScienceDirect, and Google Scholar. Key search terms such as *Morus alba*, mulberry, hypoglycemic, antioxidant and antidiabetic guided the literature search. Inclusion criteria encompassed studies involving the administration of *Morus alba* fruit extracts on HepG2 cells and the related bioassays; studies that included antidiabetic enzymatic assays; studies that included fasting glucose, postprandial glucose, and insulin resistance; and also studies involving comparison of *Morus alba* and other *Morus sp.* in terms of their antioxidant contents and properties. Overall, *Morus alba* fruit extracts exhibit promising effects at the phytochemical level, specifically enhancing glucose uptake. Significant components found in *Morus alba* fruits, such as anthocyanins, demonstrate hypoglycemic properties and contribute to mitigating diabetic nephropathy. The pharmacological profile of *Morus alba* is multifaceted, encompassing attributes like improved glucose absorption, enhanced insulin secretion, antioxidant and anti-inflammatory properties, as well as activities against hyperglycemia, hyperlipidemia, and obesity. In conclusion, *Morus alba* fruits exhibit various pharmacological effects in managing T2DM, encompassing improvements in glucose absorption, insulin secretion, antioxidative properties, and activities against high blood sugar and high lipid levels, as well as potential benefits in obesity control. Despite these positive outcomes, the current existed research falls short in exploring the full potential and synergistic effects of *Morus alba* fruit components. This gap limits the exploration of more potent therapeutic strategies utilizing the comprehensive properties of the plant's fruits.
Keywords: Antidiabetic; Antioxidant; *Morus alba* fruits; Phytochemicals; Type 2 diabetes mellitus

1. INTRODUCTION

Diabetes is a metabolic disease that causes high blood sugar that results from disruptions in carbohydrate, lipid, and protein metabolism. Oxidative stress and insulin production issues, particularly damage to pancreatic beta cells, lead to unstable glucose levels. The rise in oxidative free radicals is linked to diabetes causes. According to IDF Diabetes Atlas (1), diabetes cases are increasing globally, with estimates reaching 463 million in 2019 and expected to hit 700 million by 2045. The common complication of diabetes includes cardiovascular disease (heart disease and stroke), nephropathy (chronic kidney or renal disease), peripheral neuropathy (nerve damage), lower extremity amputations, retinopathy (visual problem), hearing problem, oral health and mental health. Antidiabetic drug demand is soaring, with market reports predicting significant growth. Functional foods, rich in bioactive compounds, contribute to overall well-being and can aid in preventing and treating chronic diseases like diabetes.

Plant-based functional ingredients, especially those in mulberries, are gaining attention for their potential health benefits. Mulberries, from the *Morus* genus, come in three main variations: white, red, and black. They are rich in bioactive compounds like phenolics, flavonoids, anthocyanins, etc. These compounds have antioxidant properties, combating oxidative stress and promoting health. *Morus sp.* leaves are popular for treating type 2 diabetes mellitus (T2DM) due to the good content of alkaloids such as DNJ. However, *Morus sp.* fruits are also rich in functional ingredients useful for T2DM and other diseases (2). Typically, those mulberry fruits in dark color have good potential due to the presence of anthocyanins which is one of the components that has been proven contributing to the anti-diabetic properties. Other than the typical black mulberry fruits (*Morus nigra*), anthocyanins can be found in *Morus alba* (commonly known as white mulberry which some of its varieties have white fruits even during fully matured stage) fruits as well because the ripening process is accompanied by the darken of color due to the accumulation of anthocyanins. This review aims to provide a comprehensive understanding of the intricate relationship between diabetes mellitus, the burgeoning market for

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antidiabetic drugs, the rising demand for functional foods, and the promising role of mulberry-derived functional ingredients. The exploration of potent components in mulberries and their mechanisms in combating diabetes underscores the potential for natural, plant-based interventions in the management of this global health concern.

2. DIABETES MELLITUS

Diabetes (or diabetes mellitus) is a metabolic disease resulting in high blood sugar and causing hyperglycemia due to the changes in metabolism of carbohydrates, lipids and proteins. Patients will experience increased oxidative stress and abnormal or malfunction of insulin production due to the damage of pancreatic beta cells, which could interfere with the stable levels of glucose in the body. In other words, the cause of diabetes is the occurring of oxidation process that can produce free radicals, which has been reported that an increase in oxidative free radicals in the body is one of the several causes of diabetes (3). Insulin resistance, dysfunction of islet cells and mitochondria and decrease of glucose tolerance can be resulted in an oxidative stress environment (4, 5). Nowadays, diabetes cases are rising globally, causing unsustainable demands on individuals, carers, health systems and society (6). The International Diabetes Federation (IDF) (1) revealed that there were 540 million people worldwide who have diabetes. It is reported that 10.5 % (approximately 537 million adults, higher than the reported 463 million in 2019) of the adult population aged from 20 to 79 suffering from diabetes in 2021, with almost half unaware with their condition. The number is expected to reach 643 million by 2030 and 783 million by 2045, an increase of 46 %. Additionally, about 75% of the adult diabetic patients are from low- and middle-income countries. The southeast Asia region is expected to have a 68 % increase, from 90 million in 2021 to 152 million in 2045 (7). According to World Health Organization (WHO) (7), diabetes is now one of the leading causes of death and disability worldwide. As one of the top 10 killers, the deaths caused by diabetes increased 70% globally between year 2000 and 2019. In 2019 and 2021, IDF reported that diabetes has caused 4.2 million and 6.7 million adults' deaths respectively. The southeast Asia region is responsible for 747,000 deaths in 2021 (7).

Generally, diabetes mellitus can be categorized as 3 types, which are Type I, Type II and Gestational. Type II is the most prevalent, posing risks like coronary diseases and stroke. A patient who diagnosed as Type I diabetes, his body can only generate minimal or no insulin as the immune system attacks and destroys the insulin producing cells in the pancreas. Insulin is a hormone produced by the pancreas that acts as a gateway to allow glucose from food to transfer from the bloodstream through the body's cells to generate energy. The typical treatment to maintain the blood glucose level is daily insulin injection. On the other hand, for the Type II diabetes patient, his body is unable to utilize the insulin produced. Ones will need to adopt a healthy balanced diet and do physical exercises regularly. Gestational diabetes (GDM) is diagnosed among women during the pregnancy by showing symptoms of high blood glucose levels. GDM can affect both the mother and the baby. Family history, advanced maternal age, polycystic ovarian syndrome, sedentary lifestyle, obesity, and environmental pollutants are examples of risk factors that can influence GDM (8). According to IDF (1), there were more than 1.1 million children and adolescents diagnosed with Type 1 diabetes and more than 20 million live births (1 in 6 live births) affected by diabetes during pregnancy. Based on the market reports by Ugalmugle and Swain (9) and Fior Markets (10), both predicted that the antidiabetic drug will have high demand in the market and the demand will continue growing in the forecast period of future 6 to 7 years. Moreover, among the 3 types of diabetes, Type 2 diabetes mellitus (T2DM) is the most common and the prevalence is increasing worldwide (1, 10). As a result, the risk of coronary heart diseases, vascular diseases and stroke will also increase. The older diabetes patients will have a high possibility of suffering from sarcopenia and physical disability.

Based on the market report by Ugalmugle and Swain (9), the antidiabetics drug market size was USD 65.5 billion in 2019 and will grow at a CAGR of 10.7 % from 2020 to 2026. The market report was based on the coverage of regions including United States, Canada, United Kingdom, Germany, Spain, Brazil, Italy, France, Mexico, Australia, China, Japan, Saudi Arabia, South Africa and India. The increasing prevalence of diabetes across the globe will stimulate the market potential for anti-diabetic drugs during the forecast period. Another report published by Fior Markets (10) expected that the global antidiabetics market will grow from USD 61.8 billion in 2019 to USD 130.56 billion by 2027, at a CAGR of 9.8 % during the forecast period 2020-2027. On the basis of application, the global market which segmented according to the types of diabetes, T2DM dominated the market with USD 44.1 billion in 2019. The key drivers for the growth of this segment in the upcoming years will be increasing awareness of T2DM through campaigns, advertisements and electronic social media, growing adoption of e-commerce (or online stores) and increasing trend of unhealthy lifestyle and eating habits.

According to another market report by Straits Research across the forecast period (2022 to 2030), Asia Pacific is the fastest growing diabetes supplement market, where there is the highest population suffering from diabetes and prediabetes diseases. China and India are the major contributors for this region (11). For the time being, the only available biguanides in most countries for preventing and delaying T2DM is metformin. It is a common oral antihyperglycemic agent used in conjunction with lifestyle modifications such as diet and exercise. The continued loss of pancreatic beta-cell function and insulin production are the symptoms of T2DM, hence optimal glycemic control is important. Metformin as the common diabetic medicine, functions to enhance the hepatic adenosine monophosphate-activated protein kinase activity, consequently reducing hepatic gluconeogenesis and lipogenesis and increasing insulin-mediated uptake of glucose in muscles. Another example of oral hypoglycemic medication is α-glucosidase inhibitors such as acarbose, miglitol and voglibose. The main function of α-glucosidase inhibitors is to inhibit alpha-glucosidase enzymes in the intestinal brush border cells that digest the dietary starch, thus inhibiting the polysaccharide reabsorption and the metabolism of sucrose to glucose and fructose. The hypoglycemic drugs often bring adverse effects which the severity of the symptoms differ from individual to individual. For example, the common effects of metformin are diarrhea, nausea and vomiting, headache, skin rash, vitamin B12 deficiency, etc. The minority of the patients who consume this drug may suffer from lactic acidosis, which can be a medical emergency. For alpha-glucosidase inhibitors, the effects can be flatulence, diarrhea, abdominal pain and increased serum transaminases. There are many other oral medications with similar functions but with different adverse effects, such as sulfonylureas, meglitinides, thiazolidinediones, DPP-4 inhibitors, SGLT2 inhibitors and cycloset

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(12). Hence, more research is required on the natural sources to explore the potential ingredients for developing the suitable anti-diabetic supplements and drugs for the patients, especially for those who always have obvious side effects after consuming the current existed drugs or medicine during the treatment.

3. PLANT BASED FUNCTIONAL INGREDIENTS FOR ANTI-DIABETIC PREVENTION AND MANAGEMENT

Foods that contain bioactive compounds or ingredients and are physiologically beneficial to health are often known as functional foods. The natural contents of nutraceuticals in foods, such as polyphenols, alkaloids, flavonoids, sterols, terpenoids, pigments, and unsaturated fatty acids, are referred to as functional ingredients which have health-promoting effects (13). Nowadays, it is a norm that humans suffer from various diseases due to unhealthy eating habits and sedentary lifestyles. Regular consumption of functional foods is good for maintaining our health as well as preventing and treating chronic diseases, like T2DM, by improving the antioxidant, insulin sensitivity, anti-cholesterol and anti-inflammatory functions (13). Also, since the use of antioxidants is the best remedy to combat oxidative stress by inhibiting and scavenging free radicals, medicinal plants could be the commercial source of antioxidants as which diet is also the major source of antioxidants (3). As the development of functional food industry, it can be seen that the health benefits beyond individual nutrients present challenges to the traditional ‘nutrition’ approach to foods (14).

A global market report that investigated global functional food ingredients throughout the forecast period from 2024 to 2029, expected the market value to reach USD 165.8 billion by 2029 (from USD 119.2 billion in 2024, at a CAGR of 6.8 %). The major factor that is driving the market growth is the increasing of health and nutrition awareness among the people which leading to the increased demand for functional foods. The scopes of the market distribution are such as by source (natural functional food ingredients, synthetic functional food ingredients and hybrid or blended sources), type (probiotics, protein & amino acids, phytochemicals & plant extracts, prebiotics, omega-3 fatty acids, carotenoids, vitamins), application (food, beverages, nutraceutical and dietary supplements), etc. (15).

In today’s society, the awareness and concern of people towards their health have increased, particularly the relationship between diet and diseases. People are starting to pay more attention to their eating habits and lifestyles. Nevertheless, people’s change in mindset has prompted the increasing demand of functional foods and dietary supplements. People would prefer foods that offer longer-term prevention of chronic diseases, no matter is the ageing population or the category that lives fast-paced lifestyles. Among the plant-based functional ingredients, fruit-based functional ingredients are one of the sub-branches. Epidemiological studies suggest that people can reduce the risk of chronic diseases, also boost health and well-being by consuming fruits regularly and sufficiently (14). Consequently, there are a wide range of research related to the application of goodness of fruits into food products being carried out amongst the academic, industry and government institutes, directly prompt the development of fruit-based functional ingredients. In 2015, US imported nearly 3.4 million pounds of frozen mulberries worth $2.6 million for the business year for the production of functional food products. The mulberry fruit manufacturing industry grows fast due to the development of the functional food industry (16).

4. MULBERRY

Mulberry comes from a genus of flowering plant known as *Morus* in the family Moraceae. Mulberry plants can be grown under cultivation and even grow wild in many regions with temperate climates. For example, in China, Japan, India, southern Europe, North Africa, Arabia, and among other regions (17). Traditionally, the mulberry leaves, typically *Morus alba*, are commonly used as natural remedy to manage diabetes. *Morus alba* leaves are also the main well-known food source when mass rearing silkworms. People utilized the leaves for anti-diabetic supplements, whereas the fruits are being disposed of, in fact, *Morus* fruits also contain high phytochemicals which beneficial to health. Basically, the most recognized mulberry plants can be categorized in 3 variations based on the fruit colors, which are white (*Morus alba*), red (*Morus rubra*) and black (*Morus nigra*) (Figure 1). *Morus alba* exist in dark purple as well other than the commonly known white color. Various types of mulberry fruits can be found on hypermarket shelves or in nursery farms. Ones should be careful while handling the mulberry fruits as it is easy to get bruised when exposed to heat or when stored due to its fragile physiognomy. Mulberry plants are fast and easy growing. Figure 2 shows the parts of a *Morus alba* plant.

Figure 1. Most common species of genus *Morus*, (a) *Morus alba*, (b) *Morus nigra*, and (c) *Morus rubra.*

White mulberry has 16 recognized species and dozens of cultivars. Mulberry is easy to plant and does not require low temperatures to survive. Mulberry plant is a kind of medium-sized tree which the height range is around 10 to 20 m, depending on the environmental conditions. It has branches from the main trunk forming a spreading canopy. The twigs are often slender and grayish brown, with a zigzag pattern. The leaves are typically lobed and alternate, with serrated margins. They are generally heart-shaped or broadly ovate, usually about 5 to 15 cm long. Both top and underneath of the leaves are hairy. The fruits can be found in two colors, which are white and dark purple or black. The maturity of the fruits can be identified through observing the fruit color. For the dark purple fruit, it turns from pink to red then dark purple or black while ripening (Figure 3). Whereas another is white or pink color at its fully ripe stage and can be found in both irregular subglobose and long oblong (around 6cm) shapes. The fully ripe fruit gives a sweet taste while the unripe one gives a sour taste. The fruits are very juicy, and the juice can leave stains on our fingers and clothes.

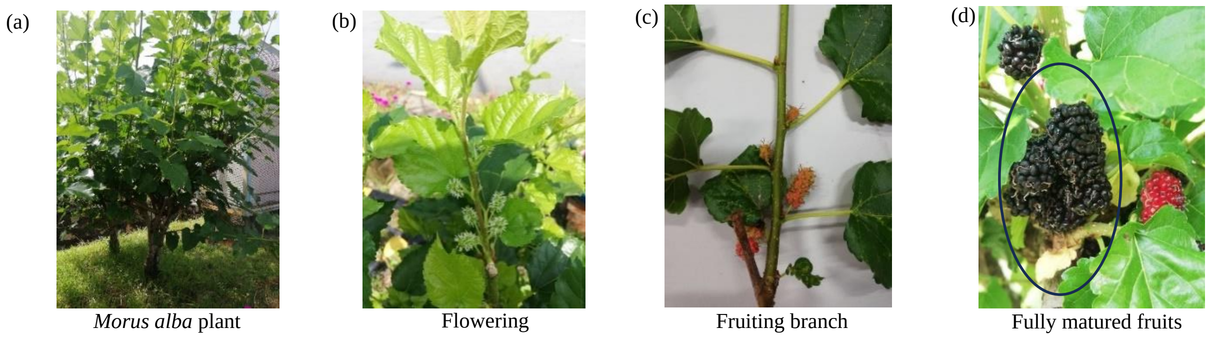

Figure 2. Parts of dark fruited *Morus alba* plant.

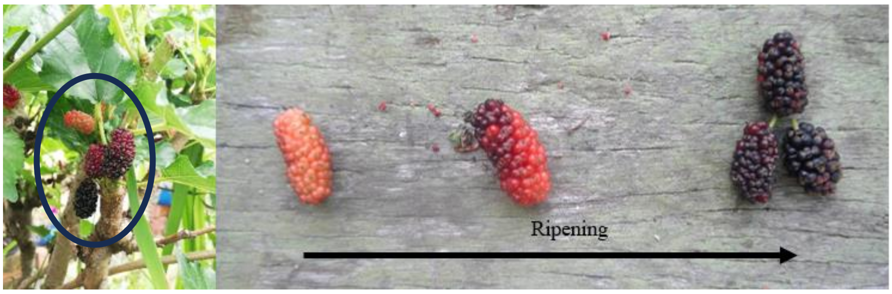

Figure **3.** Maturity level of local *Morus alba* fruits.

Mulberry fruits have low glycemic index and only cause slower rise in blood glucose levels compared to high glycemic foods. Mulberries are also rich in dietary fiber, including soluble fiber like pectin, which can help to slow down the absorption of sugars from the digestive tract, contributing to more stable glucose levels after meals. Diverse bioactive compounds is one of the most criteria making mulberry fruits as a valuable source of ingredients. Mulberries usually contain anthocyanins, flavonoids, vitamin C, alkaloids, polysaccharides, etc. which are beneficial in managing diabetes by protecting cells from damage caused by high blood sugar levels. Those components collectively contribute to its antidiabetic properties by targeting various pathways involved in glucose metabolism and insulin sensitivity. The related information is further discussed in the section afterwards.

Furthermore, the natural sweetness of mulberry fruits makes it a healthier alternative to refined sugar for diabetes patients. Mulberries provide sweetness without causing rapid spike in blood glucose levels. Also, the versatility and palatability of mulberry fruits are important as well. Mulberries can be consumed fresh, dried, juice, jams, desserts, etc. They can be easily incorporated into a diabetic diet while giving a pleasant flavor. Generally, mulberry fruits are always considered safe for consumption and are available in many regions. While mulberry fruits are beneficial and possessing good potential as functional ingredient for antidiabetic purpose, it is important to note that research specifically focusing on different varieties and species of mulberry fruits from different regions is limited compared to mulberry leaves as mentioned previously. Therefore, further studies are required to fully understand and harness the potential benefits of different mulberry fruits in diabetes management.

5. PHYTOCHEMICALS IN MULBERRY FRUITS THAT CONTRIBUTING TO ANTI-DIABETIC AND ANTIOXIDANT PROPERTIES

Mulberry fruits contain an abundance of phytochemicals or known as phenolics that contribute to the antidiabetic and antioxidant properties, such as including various flavonoids, stilbenes, phenolic acids and alkaloids.

5.1 Phenolics

Generally, phenolic compounds are widely distributed in the plant kingdom, and it is the largest category of phytochemicals, which is about 45% (18). Phenolic compounds are known as primary antioxidants, which are mainly free radical scavengers that able to delay or even inhibit the initiation step or interrupt the propagation step of lipid oxidation, therefore the formation volatile decomposition products like aldehydes and ketones that can cause rancidity can be reduced (19). Polyphenols (PPs) can be defined as a large group of complex natural chemical compounds in plants as secondary metabolite compounds (18). Polyphenols influence an extensive range of biochemical properties such as antioxidant, anti-diabetic, and anti-hypertensive properties, as well as anti-aging (20). Based on the color and flavor of vegetables and fruits, there are exceeding 8000 phenolic compounds that have been identified in various plant species. Fruits (e.g. grapes, apples, pears, cherries, and berries) and beverages (e.g. tea, red wine, and coffee) are essential sources of PPs, with can contain up to 200 to 300 mg PPs per 100 g fresh weight and around 100 mg of PPs, respectively. Leguminous plants, cereals, and Brassica crops are examples of PPs source for vegetables (18). Table 1 highlights the category of phenolics, and Table 2 described the phytochemicals in fruits of the species *Morus alba, Morus nigra and Morus rubra*.

Table 1. Classification of natural phenolic antioxidants (19).

Phenolics		
Class	**Subclass**	**Example of Compounds**
Phenolic acids	Hydroxybenzoic acid derivatives	Gallic, p-Hydroxybenzoic, Vanillic, Syringic, Protocatechuic, Ellagic
	Hydroxycinnamic acid derivatives	*p*-Courmaric, Caffeic, Ferulic, Sinapic, Chlorogenic
Flavonoids	Flavanols	Quercetin, Kaempferol, Isorhamnetin
	Flavones	Apigenin, Chrysin, Luteolin, Rutin
	Flavanols (Catechin)	(+)-Catechin, (-)-Epicatechin, (-)-Epicatechin-3-gallate, (+)-Gallocatechin, (-)-Epigallocatechin, (-)-Epigallocatechin-3-gallate
	Flavanones	Eriodictyol, Morin, Naringenin
	Isoflavonoids	Daidzein, Formononetin, Genistein, Glycitein
	Anthocyanidins	Cyanidin, Delphinidin, Leucocyanidin, Leucodelphinidin, Prodelphinidin, Propelargonidin
Stilbenes	Resveratrol	
Tannins	Hydrolysable	Ellagitannins, Gallotannins
	Condensed	Monomers, Dimers, Trimers, 4-6mers, 7-10mers, Polymers

Mulberry fruits contain a variety of biologically active compounds. Examples are phenols, flavonoids, anthocyanin, carotenoids, essential fatty acids, ascorbic acid, and some other organic acids**.** According to Rodrigues et al. (17), black mulberry (*Morus nigra*) tends to be the richest in phenolics (1422 mg GAE/100g) and flavonoids (276 mg GAE/100g) as compared to *Morus alba* (181 mg GAE/100g of phenolics and 29 mg GAE/100g of flavonoids) and *Morus rubra* (1035 mg GAE/100g of phenolics and 219 mg GAE/100g of flavonoids). *Morus alba* fruits showing the anthocyanins compounds are not detected, which indicated that the results are referring to white fruits of *Morus alba*. There are many existing studies related to *Morus alba* fruits having similar results due to the variety that they worked on. *Morus nigra* shows the high content of phytochemicals mainly due to its good content of anthocyanins. As mentioned in the previous section, *Morus alba* fruits can also be found in dark color, which can be indicated that it can be having abundance of anthocyanins which is a potential antioxidant and anti-diabetic compound as described in the section afterwards.

Additionally, according to Gundogdu et al. (21), *Morus alba* with white fruits has more vitamin C compared to deep-colored mulberry. Dietary antioxidants including Vitamins E, C, and carotenoids are known to be effective in the prevention of oxidative stress-related diseases, such as diabetes and cardiovascular disease. However, according to the review done by Memete et al. (2), *Morus alba* showed greater content of total phenols (60.4 to 663 mg GAE/100 g fw) and flavonoids, (217 to 370 mg GAE/100 g fw). In terms of quercetin and kaempferol which are often found in mulberry leaves, Memete et al. (2022) stated that both were identified in white and black mulberries, and in general, agreed that both variation of mulberries are potential sources of phytochemical which can be utilized the development of food supplements or functional foods that useful for preventing or ameliorating various chronic diseases. In conclusion, the bioactive compounds and their functionality found in mulberry vary depending on the variety or genetic factor, and also external factors, such as climate, geography (includes soil), agricultural and processing conditions (2, 21).

5.2 Flavonoids

As stated in the previous section, some of the main bioactive compounds from plant foods are polyphenols. They are essential for their antioxidant capacity in oxidative stress conditions and ageing. Anthocyanin is considered as one of the polyphenols of the flavonoid group (22, 23) although it has a positive charge at the oxygen atom of the C-ring of basic flavonoid structure (19). It is also called the flavylium (2-phenylchromenylium) ion.

Table 2 shows the common anthocyanins and anthocyanidins (sugar-free counterparts of anthocyanins) found in mulberries. Anthocyanins are water-soluble pigments (purple, red and blue) belonging to the phenolic group (23, 24). The pigments are in glycosylated forms. Anthocyanins, which consist of glycosylated polyhydroxy and polymethoxy, is a by-product of 2-phenylbenzopyrylium salt, natural pigments that are commonly found in nature and are manifested in the colors of countless edible fruit. Unlike other flavonoids, anthocyanins can form a resonance structure through pH alteration to produce a range of distinguishing colors. Anthocyanins can be found in plants like in fruits, flowers, vegetables and tubers. In terms of fruits, berries, currants, grapes, and some tropical fruits have high anthocyanins content. For instance, a darker black mulberry color indicates a higher anthocyanin level. The colored anthocyanin pigments have been traditionally used as a natural food colorant. The color and stability of these pigments are influenced by pH, light, temperature, and structure. In acidic conditions, anthocyanins appear as red, whereas blue in alkaline conditions.

Table 2**.** Common anthocyanidins and anthocyanins found in berries.

Anthocyanidin	**Anthocyanin**
Cyanidin ($C_{15}H_{11}O_6^+$)	Cyanidin-3-O-rutinoside ($C_{27}H_{31}O_{15}^+$)
Delphinidin ($C_{15}H_{11}O_7^+$)	Delphinidin-3-O-rutinoside ($C_{27}H_{31}ClO_{16}$)
Malvidin ($C_{17}H_{15}O_7^+$)	Malvidin-3-O-glucoside ($C_{23}H_{25}O_{12}^+$)
Pelargonidin ($C_{15}H_{11}O_5^+$)	Pelargonidin-3-O-glucoside ($C_{21}H_2O_{10}^+$)
Peonidin ($C_{16}H_{13}O_6^+$)	Peonidin-3-O-glucoside ($C_{22}H_{23}O_{11}^+$)
Petunidin ($C_{16}H_{13}O_7^+$)	Petunidin-3-O-glucoside ($C_{22}H_{23}O_{12}^+$)

Ripen mulberry fruits which its deep dark color is mainly due to the anthocyanin, the natural pigment. The natural color pigments, anthocyanidins and anthocyanins are not only can be utilized as natural dyes, but also can be served as potential pharmaceutical ingredients that give various beneficial health effects. Scientific studies, including cell culture studies, animal models, and human clinical trials, show that anthocyanidins and anthocyanins possess anti-oxidative and anti-microbial activities, improve visual and neurological health, and protect against various non-communicable diseases (24). According to Les et al. (22), human interventional studies have shown that high doses of anthocyanins have potential in the prevention or treatment of T2DM.

Several studies have claimed that polyphenols derived from berries can be a great anti-diabetic agent. These polyphenols affect the gastrointestinal tract. Polyphenols, specifically anthocyanin, could regulate nutrients such as glucose via the inhibition of digestive enzymes involved in carbohydrate breakdown and assimilation, which would result in blood glucose control (25, 26, 27). Studies on animals and healthy humans have shown that anthocyanin extracted from mulberry leaf hindered the rise of postprandial blood glucose levels (26). The compound was also able to suppress the action of α-glucosidase, α-mannosidase, and β-galactosidase, which are the enzymes required to break down carbohydrates. Thus, this study proves that anthocyanin can indeed control glycemic levels in the blood (28).

According to Rodrigues et al. (17), black mulberry consists of anthocyanins and flavonoid mainly rutin. The fruit of the black mulberry has high anthocyanin, which is more concentrated at the fruit than the leaves, stem, or bark. Basically, *Morus nigra* fruits consist of four major forms of anthocyanin, which are cyanidin-3-O-glucoside, cyanidin-3-O-rutinoside, pelargonidin-3-O-glucoside and pelargonidin-3-O-rutinoside (16). Unlike the summary tabulated by Rodrigues et al. (17) which claiming that anthocyanin is not detected in *Morus alba* fruits, Memete et al. (2) agreed the presence of anthocyanins in some varieties of white mulberry as the change of fruit color can be observed in corresponding to the ripening process due to the accumulation of anthocyanins. Based on the research done by Kim and Lee (29), the *Morus alba* L. grown in 6 different cultivars in Korea showed different ability on their antioxidant properties. All the investigated *Morus alba L.* contain noticeable amount of cyanidin-3-O-glucoside and cyanidin-3-O-rutinoside, while the pelargonidin-3-O-glucoside showed relatively lower content in them.

Rutin (5,7,3′,4′-OH, 3-rutinose) is a strong antioxidant that can scavenge free radicals and inhibit lipid peroxidation. Its antidiabetic and anti-inflammatory properties include lowering blood glucose levels, modulating insulin secretion, improving dyslipidaemia conditions, inhibiting advanced glycation end-products (AGEs) formation, and positively influencing IRS-2/PI3K/Akt/GSK-3β signalling pathways. Another common flavonoid that possesses antidiabetic properties found in mulberry fruit extract is quercetin (3,5,7-trihydroxy-2-(3,4-dihydroxyphenyl)-4Hchromen-4-one). Quercetin has demonstrated the ability to boost glucose uptake through an MAPK insulin-dependent mechanism and enhance the phosphorylation of PI3K/Akt signaling pathways. These actions promote the translocation of glucose transporter 4 and reduce the activity of gluconeogenesis enzymes in the liver. Additionally, quercetin interacts with the PPARγ receptor, improving β-cell function and proliferation while inhibiting alpha-glucosidase and alpha-amylase activities. Moreover, quercetin shows promise in ameliorating diabetic bone disorders in patients with type 2 diabetes mellitus.

Kaempferol (3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one) is an important regulator of lipid metabolism. Kaempferol shows potential in managing diabetes includes preventing hyperglycemia development and suppressing hepatic gluconeogenesis by decreasing pyruvate carboxylase activity. Additionally, it might enhance insulin sensitivity by inhibiting pro-inflammatory cytokines, thereby reducing inflammatory responses and hepatic inflammatory lesions (30).

5.3 Stilbenes

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) belongs to polyphenols' stilbenoids group, having an ethylene bridge linked in between the two phenol rings. (Figure 4) The *trans*-form is more common and attributed different biological activities, like inducing cellular responses such as cell cycle arrest, differentiation, apoptosis, and to enhance cancer cells anti-proliferation. Its antioxidant, anticarcinogenic, antitumor and estrogenic or antiestrogenic activity are also widely reported (31).

Resveratrol was being discovered in more than 70 plant species, primarily found in the grape skin. There are also discrete amounts of resveratrol being found in red wines and some foods. Wine grape (*Vitis vinifera*) consists of high concentrations of resveratrol due to the response to fungal infection or injury. In plants, resveratrol acts as a phytoalexin (antimicrobial and often antioxidative substances synthesized) for fungal infection, mechanical injury, and UV irradiation. In the industry, resveratrol is obtained from yeasts *Saccharomyces cerevisiae* through chemical or biotechnological synthesis (31).

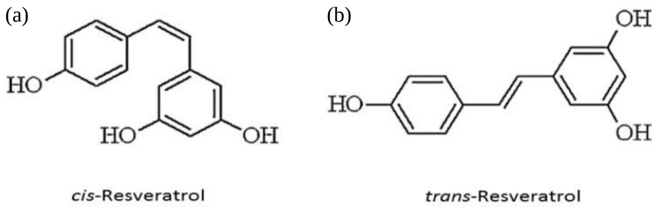

Figure 4. Resveratrol chemical structure.

As a natural food ingredient, resveratrol possesses many biological properties, such as its antitumor and anticancer potential. There are many *in vivo* and *in vitro* studies being done to confirm its anticancer properties. Resveratrol is able to inhibit all carcinogenesis stages including from initiation, promotion and to progression stages. The other reported bioactive effects, including anti-inflammatory, anti-carcinogenic, cardioprotective, neuroprotective, phytoestrogenic, and vasorelaxant. However, the most remarkable is its high antioxidant potential that is hampered by its low bioavailability, in which attempts have been made to enhance their lipophilicity. Resveratrol derivatives can be used as potential antioxidants in food and biological system. In addition, resveratrol also exhibits antidiabetic effects. Resveratrol has been shown to enhance insulin sensitivity in individuals with type 2 diabetes mellitus (T2DM), diet-induced obese mice and rats, and Zucker diabetic fatty (ZDF) rats. It activates sirtuin deacetylases 1–7, particularly SIRT1, which is a highly conserved NAD+-dependent lysine deacylase known for its potential as a pharmacological target against insulin resistance in T2DM. Additionally, resveratrol exhibits antioxidant properties that shield β-cells from oxidative stress. It also mitigates the risk of diabetic neuropathy and aids in preventing bone loss among diabetic patients (30). The poor solubility and bioavailability, as well as adverse effects of resveratrol causes its application in the pharmaceutical industry to be remained as a major challenge. Currently, resveratrol is marketed as nutritional supplement with various pharmacological benefits, such as cellular defensive action against oxidative stress (31).

5.4 Phenolic Acids

Chlorogenic acid (CGA) is a type of phenolic acid, which has similar therapeutic action as metformin that used as prescription drug to treat T2DM by controlling the high blood sugar. CGA at a dose of 5 mg/kg body weight would possess antidiabetic potential in streptozotocin (STZ) nicotinamide induced diabetic rats (45 mg/kg bw) (31). According to the study reported by Pehluvan et al. (33), chlorogenic acid was major phenolic acid in white and black mulberries. The study found that chlorogenic acid concentration to be higher in black mulberry fruit (35.8 mg/kg fresh weight) than that of the white mulberry fruit (5.4 mg/kg fresh weight), which the finding was different in other way as compared to the other previous reports. This can be due to genotypic or climatic factors.

5.5 Alkaloids

Alkaloids are referred to the organic compounds which containing at least one nitrogen atom, such as DNJ and fagomine. According to D'urso et al. (34), the N-containing sugars such as 1-DNJ, N-nonil DNJ and fagomine, which were reported for *Morus alba* leaves for inhibiting α-glucosidase and possessing anti-hyperglycemic effect, can be found in black mulberry fruits as well. These components contribute to the anti-diabetic potential of the black mulberry fruits and are useful in amelioration of insulin resistance, other than contributing to anti-obesity, antiviral and also anti-carcinogenic.

According to Truzzi et al. (35), 1-DNJ concentration in white mulberry fruits ranged from 0.65 ± 0.04 to 2.70 ± 0.23 μg/g, different from the results obtained by Wang et al. (36), 1-DNJ ranged from 5 to 126.3 μg/g in fresh fruits of *M. alba.* Truzzi et al. (35) mentioned that the study done by Wang et al. (36) on the *Morus alba* fruits grown in Asia and South America has proved that the plant variety having the greatest impact on the expression of the iminosugar. There is also study done by Song et al. (37) claimed that the 1-DNJ was not detectable under their experimental conditions in all white mulberry fruits. The varies of results done by different researchers can be concluded that both the genetic and geographical factors strongly affect iminosugar expression and thus affecting the properties that can be possessed by the alkaloid content in the fruits.

Iminosugars can inhibit enzymes like α-glucosidase and α-amylase in the intestines. These enzymes break down complex carbohydrates into simpler sugars (glucose), which are then absorbed into the bloodstream. By inhibiting these enzymes, iminosugars can slow down digestion and absorption of carbohydrates, thereby reducing the postprandial (after-meal) increase in blood glucose levels. This mechanism is similar to the action of drugs like acarbose, which is used to treat type 2 diabetes. The detailed mechanism of action for α-glucosidase inhibitors is explained in the following section.

Besides, iminosugars can inhibit enzymes involved in glycoprotein processing and modification within cells. These enzymens are crucial to produce glycoproteins such as insulin receptors and glucose transporters (like GLUT proteins). By altering the glycosylation patterns of these proteins, iminosugars may enhance insulin sensitivity and glucose uptake into cells. This could potentially improve blood glucose control in individuals with diabetes. Furthermore, iminosugars have also been investigated for their anti-inflammatory properties and their ability to modulate lipid metabolism. Inflammation and dyslipidemia are common complications associated with diabetes, and drugs that can mitigate these effects may provide additional benefits in managing the disease. Overall, iminosugars represent a promising avenue for diabetes treatment due to their multiple mechanisms of action targeting carbohydrate metabolism, glycoprotein processing, and potentially other pathways relevant to diabetes pathology. However, further research is essential to fully understand their efficacy and safety profiles in clinical applications.

6. ANTI-DIABETIC POTENTIAL OF MULBERRY FRUIT EXTRACT

Mulberry fruits extract possesses antidiabetic potential by various phytochemicals content. This potential can be evaluated by enzymatic assay involving alpha-glucosidase inhibitory activity and also cells assay such as glucose uptake assay, glycogen content assay, and glucose production assay.

6.1 Alpha-glucosidase Inhibition

There are a variety of epideomiology studies have shown the health effects of mulberry plant extract and anthocyanin consumption in treating T2DM. Berries may positively affect glycemic levels via their polyphenolic mechanisms. The polyphenols from the berries have the ability to enhance the insulin production, reduce apoptosis, and stimulate the proliferation of pancreatic beta-cells, which possess the great anti-diabetic potential of the fruits (25, 28).

Alpha-glucosidase inhibitors such as acarbose, miglitol, and voglibose have been identified as an alternative treatment for T2DM. Across the regions, there are many plants that have α-glucosidase inhibitory mechanism, which are especially useful to be developed to counter T2DM. α-Glucosidase slows down the absorption of carbohydrates and the uptake of glucose, thereby reducing blood glucose levels and mitigating hyperglycemia in diabetic patients. These hydrolase enzymes break down the glycosidic bond, releasing glucose from the non-reducing end of oligosaccharides. This enzymatic process supports carbohydrate metabolism and the processing of glycoproteins. Essentially, α-glucosidases catalyze the hydrolysis of α-glucopyranosidic bonds to liberate glucose. (28). After playing its part, α-glucosidase will continue the degradation process. Located in the small intestine, this enzyme is in charge of the hydrolysis of terminal non-reducing 1,4 linked α-glucose leading to the discharge of monosaccharide, which enables it to be absorbed into the blood. Hence, the inhibition of these enzymes can delay the digestion of carbohydrates; hence causing a reduction in the rate of glucose absorption and consequently suppressing postprandial hyperglycemia (38). All the above health benefits, which are also contained in mulberry, must be driven out through extraction processes such as ultrasonic extraction. Memete et al. (2) highlighted that among various methods, ultrasonic extraction using diluted ethanol solvent proves most effective for extracting compounds from mulberry fruits. This method enhances mass transfer, facilitating deeper penetration of the solvent into mulberry cells. Figure 5 shows the mechanism of α-glucosidase inhibitors.

The ability of white mulberry fruit extract to inhibit the carbohydrate digestive enzyme (α-glucosidase) can be used as one of the indicators to evaluate its potential as an anti-diabetic agent. The inhibition of α-glucosidase results in reduction of blood glucose levels, so the inhibitors can be indicated as important for controlling type 2 diabetes mellitus (T2DM). According to Chen et al. (39), antioxidant content in mulberry inhibited between 30% and 90% of α-glucosidase. It showed that the antioxidants in the mulberry fruits could still serve as a potential inhibitor for α-glucosidase although the inhibitory effect shown was lower than the anti-diabetic drug, acarbose.

6.2 Glucose Metabolism

Bioassays are mainly categorized into *in vivo* and *in vitro* types. According to Kamiloglu et al. (40), bioassay method evaluates the potency of substances by observing their pharmacological effects on living animals (*in vivo*) or isolated tissues (*in vitro*), comparing them to a standard of known potency. In the pharmaceutical industry, *in vitro* assays are commonly utilized.

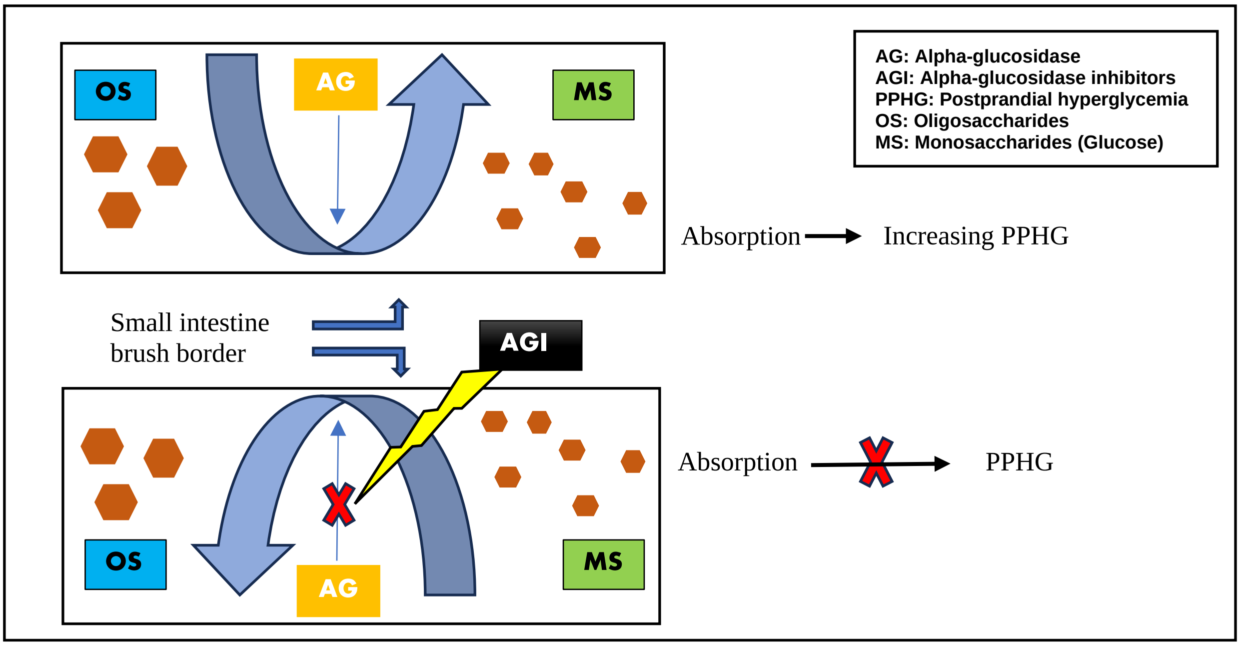

Figure 5. Mechanism of α-glucosidase inhibitors.

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To assess the *in vitro* antidiabetic properties of an extract, experiments may involve monitoring glucose uptake in HepG2 cells and examining the inhibition of carbohydrate and lipid metabolizing enzymes (41, 42). The antidiabetic effect of extract is related to its ability to improve glucose utilization and preservation of pancreatic β-cell populations, while also preventing fat accumulation in adipocytes (43). The antidiabetic potential of an aqueous extract sample can be investigated using various cell-based bioassays, such as rat insulinoma (INS-1) cells, murine pre-adipocytes (3T3-L1), rat skeletal muscle (L6 myotubes), and human hepatocellular carcinoma (HepG2) cells (43). Among all, HepG2 or commonly known as human liver cancer cell line, is the most often used cell line for investigating the antidiabetic effect of a plant extract. Other than glucose uptake or consumption assay, glycogen content assay and glucose production assay are also related assays that often used in evaluating the antidiabetic property of mulberry fruit extracts.

Table 3 shows the summary of glucose metabolism. Each of the mechanisms is a potential target for therapeutic interventions aimed at managing blood glucose levels and improving overall health outcomes in diabetic patients. It is important to monitor and achieve optimal glucose control in the body of a diabetic patient to prevent other possible complications that might occur associated with the disease itself.

Table 3. Summary of glucose metabolism.

Mechanism	Description
Insulin production and secretion	In type 1 diabetes, there is a deficiency in insulin production due to autoimmune destruction of pancreatic β cells. In type 2 diabetes, there is often impaired insulin secretion from β cells in response to elevated blood glucose levels (glucose-stimulated insulin secretion). Treatment strategies aim to either replace insulin (exogenous insulin therapy) or enhance insulin secretion using medications like sulfonylureas or incretin mimetics.
Insulin sensitivity	Insulin sensitivity refers to how effectively cells respond to insulin to take up glucose from the bloodstream. In type 2 diabetes, there is often insulin resistance, where cells become less responsive to insulin. Medications such as metformin, thiazolidinediones, and GLP-1 receptor agonists work to improve insulin sensitivity in various tissues, particularly muscle and liver cells.
Glucose uptake/ consumption	Glucose uptake into cells, particularly muscle and adipose tissue, is facilitated by glucose transporters (GLUT proteins). Insulin promotes glucose uptake by increasing the translocation of GLUT4 transporters to the cell membrane. Some treatments, such as sodium-glucose co-transporter 2 (SGLT 2) inhibitors, act independently of insulin by blocking glucose reabsorption in the kidneys, leading to increased urinary glucose excretion and reduced blood glucose levels.
Glycogen synthesis and storage	Glycogen is a polysaccharide composed of glucose units and serves as a storage form of glucose in the body. Insulin promotes glycogen synthesis in the liver and muscle, which helps to remove excess glucose from bloodstream and store as glycogen for future energy needs. Drugs like insulin and sulfonylureas can enhance glycogen synthesis, thereby lowering blood glucose levels.
Gluconeogenesis/Glucose production	This is the process by which the liver produces glucose from non-carbohydrate sources (such as amino acids and glycerol). Glucose production is tightly regulated to maintain blood glucose levels within a normal range (70-130 mg/dL or 3.9-7.2 mmol/L). When blood glucose levels drop during fasting or between meals, the body stimulates gluconeogenesis to produce glucose and prevent hypoglycemia. In diabetes, excessive gluconeogenesis can contribute to elevated fasting blood glucose levels (hyperglycemia), Medications such as metformin primarily reduce hepatic gluconeogenesis, helping to lower blood glucose levels.
Intestinal glucose absorption	Inhibiting intestinal glucose absorption can help reduce postprandial blood glucose spikes. Alpha-glucosidase inhibitors, such as acarbose, slow down carbohydrate digestion and absorption in the gut, thereby reducing the rise in blood glucose after meals.
Regulation of hormones	Besides insulin, other hormones such as glucagon, cortisol, and incretins (like GLP-1) play roles in glucose metabolism. Medications targeting these hormones, such as GLP-1 receptor agonists and DPP-4 inhibitors, can help regulate blood glucose levels in diabetic patients.

7. POTENTIAL HEALTH SUPPLEMENTS MADE FROM MULBERRY

Mulberry fruits can be consumed fresh or as ingredients in processed food and beverage products, such as juices, tea, jams, soft drinks, yogurts, cakes, pasta, etc. It can be modified into various forms in the industries, such as frozen, dried, powdered, and syrup, before being added into the products. In the nutraceutical industries, mulberries can also be utilized as functional ingredients for producing a variety of human health supplements targeting different health benefits. The supplements can be in pills, capsules, or liquid forms. Depending on the extraction process, different biocomponents can be obtained and concentrated and made into supplements that help with different health functions. Other than product composition with purely mulberry fruit extracts, there are also products with different formulations using mulberry extracts and other possible ingredients being commercialized in the markets. Each of them functions differently based on their composition. The existing brands on the market are GreenSilk, Nature's, WellBetX, etc. There is a formulation under GreenSilk utilizing mulberry extract, wolfberry extract, safflower extract and so on and that product is functioning to lower

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blood sugar, improving cholesterol, and helping in weight loss (44). Based on the present studies, mulberry possesses biological activities, such as antioxidant, anti-diabetic, anti-microbial, hyperlipidemia, anti-inflammatory, anti-cancerous, etc., and thus can be potentially helping with different health problems. The supplements can be consumed for prevention of diseases or as an aid during the treatment process of a patient, following the instructions of pharmacists and doctors.

8. FUTURE PERSPECTIVES

Research on the bioavailability of key bioactive compounds from white mulberries, particularly those grown in different countries and regions, is essential. Geographical and weather factors can affect the availability of biocomponents found in the fruits. Furthermore, determining the optimal dosage for maximum therapeutic benefits and minimal side effects is crucial for practical dietary recommendations.

Apart from that, a more in-depth exploration of the underlying mechanisms involved in white mulberries' anti-diabetic effects is needed. Undertaking mechanistic studies at the cellular and molecular levels is important to understand how mulberry compounds interact with key pathways involved in diabetes. Consequently, the studies can guide targeted antidiabetic drug development and potentially offer innovative therapeutic solutions for individuals with diabetes.

Future research should also prioritize large-scale clinical trials involving diverse populations, long-term observational studies, bioavailability research, mechanistic elucidation, and comparative effectiveness studies. These efforts will collectively contribute to a more comprehensive understanding of mulberries' potential role in diabetes management.

9. CONCLUSION

The global prevalence of diabetes is escalating, posing significant challenges to individuals, healthcare systems, and societies worldwide. The surge in diabetes cases, particularly type 2 diabetes mellitus (T2DM), is associated with an increased risk of cardiovascular diseases and other complications. The escalating demand for antidiabetic drugs reflects the urgency to address the growing burden of diabetes globally. In this context, the review explores the potential of plant-based functional ingredients, with a focus on *Morus alba* fruits, as a natural remedy for diabetes management. The bioactive compounds present in *Morus alba* fruits, particularly the dark purple fruits, such as phenolics, flavonoids, stilbenes, phenolic acids, and alkaloids, contribute to its anti-diabetic and antioxidant properties. The inhibitory effect on alpha-glucosidase, a key enzyme in carbohydrate metabolism, further supports the potential therapeutic role of black mulberry in regulating blood glucose levels. Functional foods, enriched with bioactive compounds, offer a preventive and therapeutic approach to combat chronic diseases like diabetes. The rising awareness of the link between diet and health has fuelled the demand for functional foods and dietary supplements. The functional food industry's growth reflects the shift in consumer preferences toward long-term health benefits. As individuals become more conscious of their health, the demand for functional foods, including those derived from plant-based sources like mulberry, is expected to continue growing. In conclusion, the review underscores the potential of *Morus alba* fruits as a valuable plant-based functional ingredient with anti-diabetic and antioxidant properties. The diverse array of bioactive compounds present in the *Morus alba* fruits contributes to its effectiveness in managing diabetes, for instance, through the inhibition of alpha-glucosidase. As the global burden of diabetes continues to rise, exploring natural and sustainable solutions, such as incorporating mulberry fruits into functional foods, holds promise for improving public health and mitigating the impact of this metabolic disorder.

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CONFLICT OF INTEREST

All authors have no conflict of interest.

REFERENCES

(1) International Diabetes Federation. IDF diabetes atlas 2021. 10th ed. 2021.
(2) Memete AR, Timar AV, Vuscan AN, Miere F, Venter AC, Vicas SI. Phytochemical composition of different botanical parts of Morus species, health benefits and application in food industry. Plants. 2022; 11(2):152. https://doi.org/10.3390/plants11020152.
(3) Ranjan B, Kumar R, Verma N, Mittal S, Pakrasi P, Kumar R. Evaluation of the antidiabetic properties of S-1708 mulberry variety. Pharmacogn Mag. 2017; 13(2):S280–S288. https://doi.org/10.4103/pm.pm49016.
(4) Liu CH, Liu F, Xiong L. Medicinal parts of mulberry (leaf, twig, root bark, and fruit) and compounds thereof are excellent traditional Chinese medicines and foods for diabetes mellitus. J Funct Foods. 2023; 106:105619. https://doi.org/10.1016/j.jff.2023.105619.
(5) Tangvarasittichai S. Oxidative stress, insulin resistance, dyslipidemia and type 2 diabetes mellitus. World J Diabetes. 2015; 6(3):456–480. https://doi.org/10.4239/wjd.v6.i3.456.
(6) Forouhi N, Wareham N. Epidemiology of diabetes. Medicine. 2019; 47(1):22–27. https://doi.org/10.1016/j.mpmed.2018.10.004.
(7) World Health Organization. 2020. WHO reveals leading causes of death and disability worldwide: 2000-2019 [internet]. World Health Organization [cited 2024 Aug 3]. Available from: https://www.who.int/news/item/09-12-2020-who-reveals-leading-causes-of-death-and-disability-worldwide-2000-2019.

(8) Antar AS, Ashour NA, Sharaky M, Khattab M, Ashour NA, Zaid RT, Roh EJ, Elkamhawy A, Al-Karmalawy AA. Diabetes mellitus: Classification, mediators, and complications; A gate to identify potential targets for the development of new effective treatments. Biomed Pharmacother. 2023; 168:115734. https://doi.org/10.1016/j.biopha.2023.115734.
(9) Ugalmugle S, Swain R. Antidiabetics market size by product (insulin {rapid acting, long acting, premixed insulin, short acting, intermediate acting}, drug class {alpha-glucosidase inhibitors, biguanides, sulphonylureas, glp-1 agonist, meglitinides, dpp-4 inhibitors, sglt-2, thiazolidinedione}), by patient population (pediatric, adult, geriatric), by route of administration (insulin syringe/insulin pen, insulin pump, intravenous infusion, oral), industry analysis report, regional outlook, application potential, price trends, competitive market share & forecast, 2020 – 2026 [internet]. Global Market Insights Inc. 2020 [cited 2024 Aug 3]. Available from: https://www.gminsights.com/industry-analysis/antidiabetics-market.
(10) Fior Markets. Antidiabetics market by product (insulin, short-acting, intermediate-acting, long-acting, premixed, premixed analog, GLP-1 agonist, biguanides, SGLT-2, alpha-glucosidase inhibitors, meglitinides, sulphonylureas, thiazolidinediones, DPP-4 inhibitors, other), application (type I diabetes, type II diabetes, gestational diabetes), region, global industry analysis, market size, share, growth, trends, and forecast 2020 to 2027 [Internet]. Pharmaceuticals and Healthcare [cited 2024 Aug 3]. Available from: https://www.fiormarkets.com/report/antidiabetics-market-by-product-insulin-short-acting-intermediate-acting-long-acting-418887.html.
(11) Straits Research. Global diabetes supplement market share, demand to 2030 [Internet] [cited 2024 Aug 3]. Available from: https://straitsresearch.com/report/diabetes-supplement-market.
(12) Ganesan K, Rana MBM, Sultan S. Oral hypoglycemic medications. In: StatPearls. StatPearls Publishing: United States; 2024. https://www.ncbi.nlm.nih.gov/books/NBK482386/.
(13) Alkhatib A, Tsang C, Tiss A, Bahorun T, Arefanian H, Barake R, Khadir A, Tuomilehto J. Functional foods and lifestyle approaches for diabetes prevention and management. Nutrients. 2017; 9(12):1310. https://doi.org/10.3390/nu9121310.
(14) Sun-Waterhouse D. The development of fruit-based functional foods targeting the health and wellness market: A review. Int. J. Food Sci. 2011; 899–920. https://doi.org/10.1111/j.1365-2621.2010.02499.x.
(15) Markets and Markets. 2024. Functional food ingredients market by type (probiotics, protein & amino acids, phytochemicals & plant extracts, prebiotics, omega-3 fatty acids, carotenoids, vitamins), application, source, form, health benefits and region [Internet]. Global Forecast to 2029 [cited 2024 Aug 3]. Available from: https://www.marketsandmarkets.com/Market-Reports/functional-food-ingredients-market-9242020.html.
(16) U.S. Department of Agriculture (USDA). Economic research service (ERS). Fruit and tree nuts data: Market segment. [Internet] [cited 2024 Aug 3]. Available from: https://data.ers.usda.gov/reports.aspx?programArea=fruit&groupName=Noncitrus&ms_key=Z&ID=17887#P71a7d9231a9c47c593517c6216bda704_7_613iT0R0R0x9.
(17) Rodrigues E, Marcelino G, Silva G, Figueiredo P, Garcez W, Corsino J, Freitas K. Nutraceutical and medicinal potential of the morus species in metabolic dysfunctions. Int J Mol Sci. 2019; 20(2):301. https://doi.org/10.3390/ijms20020301.
(18) Zuiter A. Proanthocyanidin: Chemistry and biology: From phenolic compounds to proanthocyanidins. In: Reference Module in Chemistry, Molecular Sciences and Chemical Engineering. Elsevier: Netherlands; 2014. https://doi.org/10.1016/B978-0-12-409547-2.11046-7.
(19) Shahidi F, Ambigaipalan P. Phenolics and polyphenolics in foods, beverages and spices: Antioxidant activity and health effects – A review. J Funct Foods. 2015; 18:820–897. https://doi.org/10.1016/j.jff.2015.06.018.
(20) Shih PH, Chan YC, Liao JW, Wang MF, Yen GC. Antioxidant and cognitive promotion effects of anthocyanin-rich mulberry (Morus atropurpurea L.) on senescence-accelerated mice and prevention of Alzheimer's disease. J Nutr Biochem. 2010; 21 (7):598–605. https://doi.org/10.1016/j.jnutbio.2009.03.008.
(21) Gundogdu M, Muradoglu F, Gazioglu Sensoy RI, and Yilmaz H. Determination of fruit chemical properties of Morus nigra L., Morus alba L. and Morus rubra L. by HPLC. Sci Hortic. 2011; 132:37–41. https://doi.org/10.1016/j.scienta.2011.09.035.
(22) Les F, Casedas G, Gomez C, Moliner C, Valero M, Lopez V. The role of anthocyanins as antidiabetic agents: from molecular mechanisms to in vivo and human studies. J Physiol Biochem. 2021; 77(1):109–131. https://doi.org/10.1007/s13105-020-00739-z.
(23) Zhang H, Ma Z, Luo X, Li X. Effects of mulberry fruit (Morus alba L.) consumption on health outcomes: A mini-review. Antioxidants. 2018; 7(5):69. https://doi.org/10.3390/antiox7050069,
(24) Khoo H, Azlan A, Tang S, Lim S. Anthocyanidins and anthocyanins: Colored pigments as food, pharmaceutical ingredients, and the potential health benefits. Food Nutr Res. 2017; 61(1). https://doi.org/10.1080/16546628.
(25) Edirisinghe I, Burton-Freeman B. Anti-diabetic actions of berry polyphenols – Review on proposed mechanisms of action. J Berry Res. 2016; 6(2):237–250. https://doi.org/10.3233/JBR-160137.
(26) Jeszka-Skowron M, Flaczyk E, Jeszka J, Krejpcio Z, Król E, Buchowski MS. Mulberry leaf extract intake reduces hyperglycaemia in streptozotocin (STZ)-induced diabetic rats fed high-fat diet. J Funct Foods. 2014; 8:9–17. https://doi.org/10.1016/j.jff.2014.02.018.
(27) Li AN, Li S, Zhang YJ, Xu XR, Chen YM, Li HB. Resources and biological activities of natural polyphenols. Nutrients. 2014; 6(12):6020–6047. https://doi.org/10.3390/nu6126020.
(28) Promyos N, Temviriyanukul P, Suttisansanee U. Investigation of anthocyanidins and anthocyanins for targeting α-glucosidase in diabetes mellitus. Prev Nutr Food Sci. 2020; 25(3):263–271. https://doi.org/10.3746/pnf.2020.25.3.263.

(29) Kim IH, Lee JH. Variations in anthocyanin profiles and antioxidant activity of 12 genotypes of mulberry (Morus spp.) fruits and their changes during processing. Antioxidants (Basel). 2020; 9(3):242. https://doi.org/10.3390/antiox9030242.

(30) Blahova J, Martiniakova M, Babikova M, Kovacova V, Mondockova V, Omelka R. Pharmaceutical drugs and natural therapeutic products for the treatment of type 2 diabetes mellitus. Pharmaceuticals. 2021; 14(8):806. https://doi.org/10.3390/ph14080806.

(31) Salehi B, Mishra A, Nigam M, Sener B, Kilic M, Sharifi-Rad M, Sharifi-Rad, J. Resveratrol: A double-edged sword in health benefits. Biomedicines. 2018 ; 6(3):91. https://doi.org/10.3390/biomedicines6030091.

(32) Meng S, Cao J, Feng Q, Peng J, Hu Y. Roles of chlorogenic acid on regulating glucose and lipids metabolism: A review. Evid Based Complement Alternat Med. 2013;2013:801457. https://doi.org/10.1155/2013/801457.

(33) Pehluvan M, Tuncay K, dogru B, Lara I. The effect of frozen storage on the phenolic compounds of Morus nigra L. (black mulberry) and Morus alba L. (white mulberry) fruit. Fruits. 2015; 70(2):117–122. https://doi.org/10.1051/fruits/2015004.

(34) D'urso G, Mes J, Montoro P, Hall R, de Vos R. Identification of bioactive phytochemicals in mulberries. Metabolites. 2020; 10(1):7. https://doi/org/10.3390/metabo10010007.

(35) Truzzi E, Marchetti L, Gibertini G, Benvenut S, Cappellozza S, Giovannini D, Saviane A, Sirri S, Pinetti D, Assirelli A, Bertelli D. Phytochemical and functional characterization of cultivated varieties of Morus alba L. fruits grown in Italy. Food Chem. 2024; 431:137113. https://doi.org/10.1016/j.foodchem.2023.137113.

(36) Wang Z, Dai F, Tang C, Xiao G, Li Z, Luo G. Quantitative determination of 1-deoxynojirimycin in 146 varieties of mulberry fruit. Int J Food Prop. 2021; 24(1):1214–1221. https://doi.org/10.1080/10942912.2021.1955923.

(37) Song W, Wang HJ, Bucheli P, Zhang PF, Wei DZ, Lu YH. Phytochemical profiles of different mulberry (Morus sp.) species from China. J Agric Food Chem. 2009; 57 (19):9133–9140. https://doi.org/10.1021/jf9022228.

(38) Trinh BT, Staerk D, Jäger AK. Screening for potential α-glucosidase and α-amylase inhibitory constituents from selected Vietnamese plants used to treat type 2 diabetes. J Ethnopharmacol. 2016; 186:189–195. https://doi.org/10.1016/j.jep.2016.03.060.

(39) Chen C, You L, Abbasi A, Fu X, Liu R. Optimization for ultrasound extraction of polysaccharides from mulberry fruits with antioxidant and hyperglycemic activity in vitro. Carbohydr Polym. 2015; 130:122–132. https://doi.org/10.1016/j.carbpol.2015.05.003.

(40) Kamiloglu S, Tomas M, Ozdal T, Yolci-Omeroglu P, Capanoglu E. Bioactive component analysis - Chapter 2. In: Innovative Food Analysis. Academic Press: United States; 2021: p. 41–65. https://doi.org/10.1016/B978-0-12-819493-5.00002-9

(41) Odeyemi S, Dewar J. In vitro antidiabetic activity affecting glucose uptake in HepG2 cells following their exposure to extracts of Lauridia tetragona (L.f.) R.H. archer. Processes. 2020; 8(1):33.https://doi.org/10.3390/pr8010033

(42) Yan FJ, Zhang J, Zhang LX, Zheng XD. Mulberry anthocyanin extract regulates glucose metabolism by promotion of glycogen synthesis and reduction of gluconeogenesis in human HepG2 cells. Food Funct. 2016; 7:425–433; https://doi.org/10.1039/c5fo00841g.

(43) Akinrinde A, Koekemoer T, Van De Venter M, Bradley G. In vitro investigation of potential anti-diabetic activity of the corm extract of Hypoxis argentea harv. ex baker. Acta Pharm. 2018; 68(4):389–407. https://doi.org/10.2478/acph-2018-0023

(44) Jan B, Parveen R, Zahiruddin S, Khan MU, Mohapatra S, Ahmad S. Nutritional constituents of mulberry and their potential applications in food and pharmaceuticals: A review. Saudi J Biol Sci. 2021; 28(7):3909–3921. https://doi.org/10.1016/j.sjbs.2021.03.056.