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Anti-diabetic potential of *Rubus* species: linking conventional knowledge with scientific developments: a review

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Abstract

The incidence of diabetes mellitus, a pressing global health concern that is rapidly increasing, has prompted the exploration of medicinal plants for potential remedies, particularly those within the *Rubus* genus. This comprehensive review aims to connect traditional knowledge with scientific insights, shedding light on the antidiabetic properties of various *Rubus* species. An exhaustive exploration of the literature revealed that *Rubus chingii Hu, Rubus idaeus, Rubus ulmifolius, Rubus fruticosus, Rubus amabilis*, and some other *Rubus* species exhibited noteworthy antidiabetic effects, each operating via distinct mechanisms. Furthermore, *Rubus* species serve as abundant reservoirs of bioactive compounds, including flavonoids, phenolic acids, tannins, alkaloids, glycosides, antioxidants, triterpenoids, and sterols. As indicated by various in vivo and in vitro studies, these compounds notably improve insulin secretion, increase hepatic glycogen synthesis, inhibit key digestive enzymes, enhance the functions of β-cells in the pancreas, and effectively reduce blood glucose levels. This review, which describes the antidiabetic potential of *Rubus* species in terms of both pharmacological effects and traditional uses, offers valuable insights for future scientific initiatives in the development of innovative antidiabetic therapies.

Keywords Anti-diabetic, *Rubus*, Diabetes mellitus, Hypoglycemic agents, Therapeutic uses, Antioxidants, Phytotherapy

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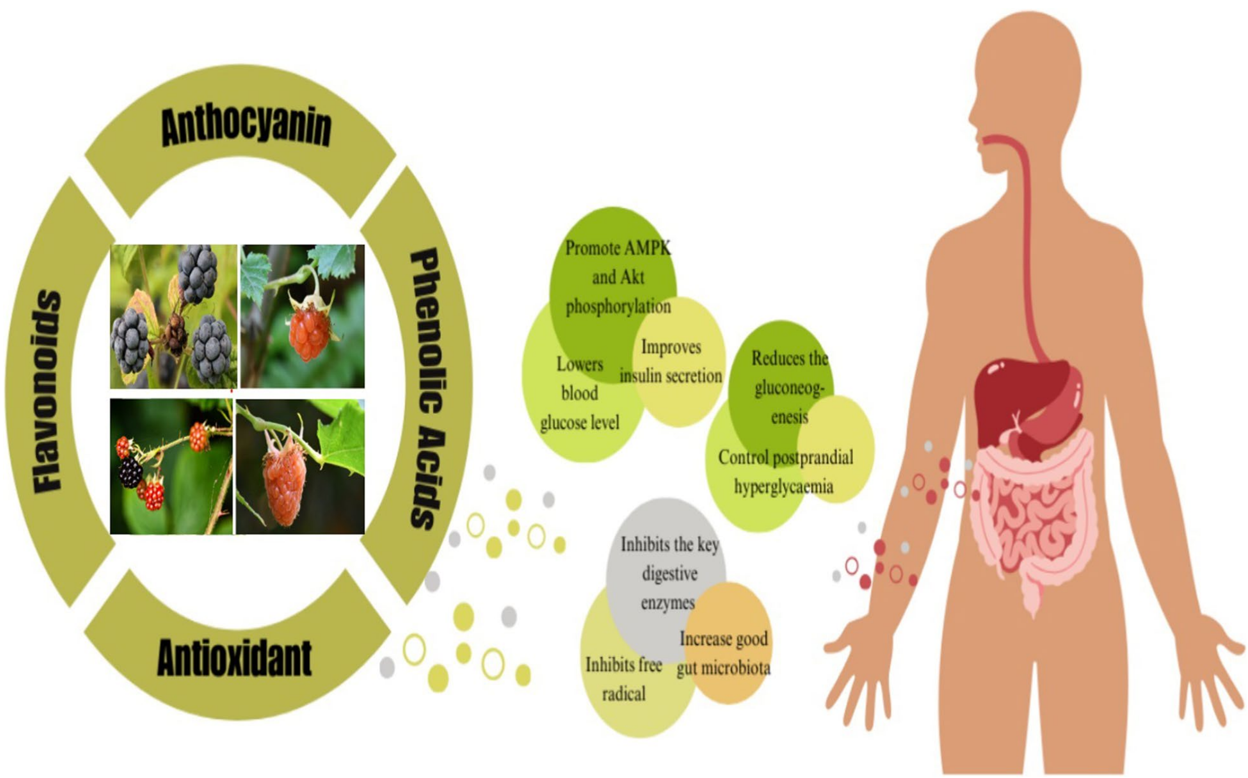
Graphical Abstract



Introduction

Diabetes mellitus is a chronic metabolic disease that has caused great concern among health officials due to its rapid increase in both developing and developed countries. It affects approximately 422 million people worldwide and is responsible for 1.5 million deaths, the majority of which occur in medium- and low-income nations (World Health Organization, 2016). Diabetes mellitus can occur due to several factors, including damage to pancreatic β cells, insulin resistance, or a deficiency in insulin secretion (Padhi et al., 2020). This results in decreased or increased glucose concentrations in the blood (Deshmukh & Jain, 2021). Diabetes mellitus is classified into two types: type 1 diabetes (insulin-dependent) and type 2 diabetes (Moradinazar et al., 2022). In an autoimmune disorder, type 1 diabetes mellitus affects pancreatic cells that impair or reduce the secretion of insulin, while in type 2 diabetes mellitus, pancreatic beta cells become impaired, which results in the inability of individuals to use insulin (Padhi et al., 2020).

In diabetes mellitus type 1, the immune system attacks pancreatic cells (autoimmune disorder), leading to reduced or impaired production of insulin, causing a lifetime need for insulin therapy (Eizirik et al., 2020; Padhi et al., 2020). The development of type 1 diabetes mellitus involves the formation of a complex between macrophages and T cells, leading to the release of cytokines in the islet microenvironment. This, in turn, produces cell-cell pro-apoptotic signals. Furthermore, signals produced either physiologically or by stressed or injured beta cells attract and activate immune cells to islets (Eizirik et al., 2020). According to recent data from the UK Biobank, diabetes mellitus type 1 can occur at any stage of life. The data revealed that during the first six decades of life, 42% of type 1 diabetes mellitus patients are diagnosed after the age of 30, while 58% are diagnosed either before or at the age of 30 (Thomas et al., 2019). There was no significant difference in gender distribution, as both males and females suffer equally.

Individuals with type 2 diabetes mellitus, accounting for 90% of the total

diabetic population, have the greatest influence on diabetes statistics (Standl et al., 2019). It is a progressive ailment associated with early coexisting conditions and complications such as high blood pressure, kidney issues, polycystic ovary syndrome, and abnormal lipid levels

(Jiang et al., 2023). Diabetes is a significant global public health challenge and imposes substantial financial strain on healthcare systems (Khan et al., 2019; Liu et al., 2023). The World Health Organization has found populations at heightened risk for diabetes (Han et al., 2019). Current worldwide assessments reveal that 537 million adults are affected by diabetes, 80% of whom reside in middle-income and low-income countries (Gregg et al., 2023). The incidence of diabetes is experiencing a steady surge on a global scale, with a high rate among adults worldwide reaching 8.8% in 2017. Projections show that this figure is expected to increase to 9.9% by 2045. In 2017, 424.9 million individuals worldwide had diabetes. By 2045, this number is expected to increase by 48% to 628.6 million people with diabetes. The prevalence of diabetes varies according to age, with values of approximately 5%, 10%, 15%, and 20% for the 35–39, 45–49, 55–59, and 65–69 years age groups, respectively. Globally, diabetes affects individuals in the "middle-aged" bracket, typically between 40 and 59 years, with significant social and economic consequences (Standl et al., 2019).

Maintaining a nutritious diet is crucial for managing diabetes with proper medication. Insulin and oral hypoglycemic medicines are safe for older patients but have limitations related to the risk of hypoglycemia and other medical conditions. Approximately 5–10% of patients experience secondary failure, often due to declining beta-cell function, medication adherence, weight gain, reduced activity, dietary changes, or illness (Rahman et al., 2022). In less developed regions, the availability of insulin and diabetes drugs is costly and limited, and these drugs often cause severe side effects. High treatment costs pose a significant barrier, rendering it unaffordable in these developing nations. Therefore, natural substances and phototherapy are commonly used as primary treatments (Chinsembu, 2019). Herbal medicine is a cost-effective way to stabilize the side effects of synthetic drugs. Bioactive compounds are readily available and have fewer side effects (Salehi et al., 2019; Tarafdar et al., 2015).

Diet plays a significant role in insulin resistance development, especially in less active and aging populations. High-calorie processed foods such as fast food, meats, animal fats, and sugary drinks contribute to the global rise in type 2 diabetes patients. Plant-based diets and reduced animal food intake are highly effective at preventing type 2 diabetes and are linked to lower rates of obesity, cancer, hyperlipidemia, cardiovascular-related deaths, and hypertension (McMacken & Shah, 2017). Research shows that consuming natural antioxidants from plant sources reduces the risk of diabetes. These antioxidants can induce epigenetic modifications, such as histone modification and DNA methylation, influencing gene expression related to diabetes. Fruits rich in natural antioxidants are recommended for prediabetic and diabetic individuals (Sun et al., 2021). Ayoub et al., (2015) reported soluble phenolics extracted from berry seed meals. Their study revealed gallic acid and derivatives as major phenolic acids, and quercetin derivatives as major flavonoids in blackberry and black raspberry seeds, while blueberry seeds had procyandin dimer B as dominant flavonoid. Anthocyanins varied by berry type. Blackberry seeds were richest in phenolics. Phenolic compounds, especially insoluble-bound ones, exhibited antioxidant properties. Studies in India have shown that vegetarians are less at risk of type 2 diabetes and obesity than omnivores are. This benefit is attributed to plant-based phytonutrients, the absence of animal fats, and a preference for low glycemic index foods (Thomas et al., 2023).

Rubus species: a diverse genus with medicinal significance

Rubus species belongs to the *Rosaceae* family. This family is located in subtropical and temperate areas of the Northern Hemisphere and has a limited number of species discovered in the Southern Hemisphere, consisting of approximately 3000 species with over 100 genera. In traditional medicine, various parts of plants have been used to address an overall range of health concerns. These include managing stomach pain, fever, diarrhea, skin infections, and joint discomfort; managing diabetes; and promoting wound healing. They also act as anti-fertility agents, provide pain relief, serve as anticonvulsant agents and renal tonics, and treat ulcers (Prakash et al., 2022). In addition, numerous species within this genus are utilized for managing diabetes mellitus (Figs. 1 and 2) (Ayele et al., 2021; Yu et al., 2022). Toshima et al., (2021) reported that *Rubus* is a diverse and large genus in the *Rosoideae* subfamily, with 740 species worldwide. *Rubus* species can be categorized into 12 subgenera, among which *Rubus* (132 species) is the largest, followed by *Idaeobatus* (117 species) and *Malachobatus* (115 species) (Yu et al., 2022). The *Rubus* genus is believed to have two potential regions of origin: North America and southwestern China (Meng et al., 2022). These fruits are also popular in Europe and Asia and, over the years, have a rich tradition of functionality in these regions, particularly in some European countries. Certain native species, such as *Rubus corchorifolius*, are widely grown for their therapeutic, edible, and aesthetic value (Yu et al., 2022).

Rubus is popular because of its inflorescence architecture, reproductive patterns, diversity, and leaf shape. These plants commonly accoutre with prickles, bristles, or hairs for protection. The leaves display simple, pinnate, or palmate shapes, and their flowers are mostly bisexual and pentamerous. The fruits of *Rubus* are drupelets or drupaceous achenes that

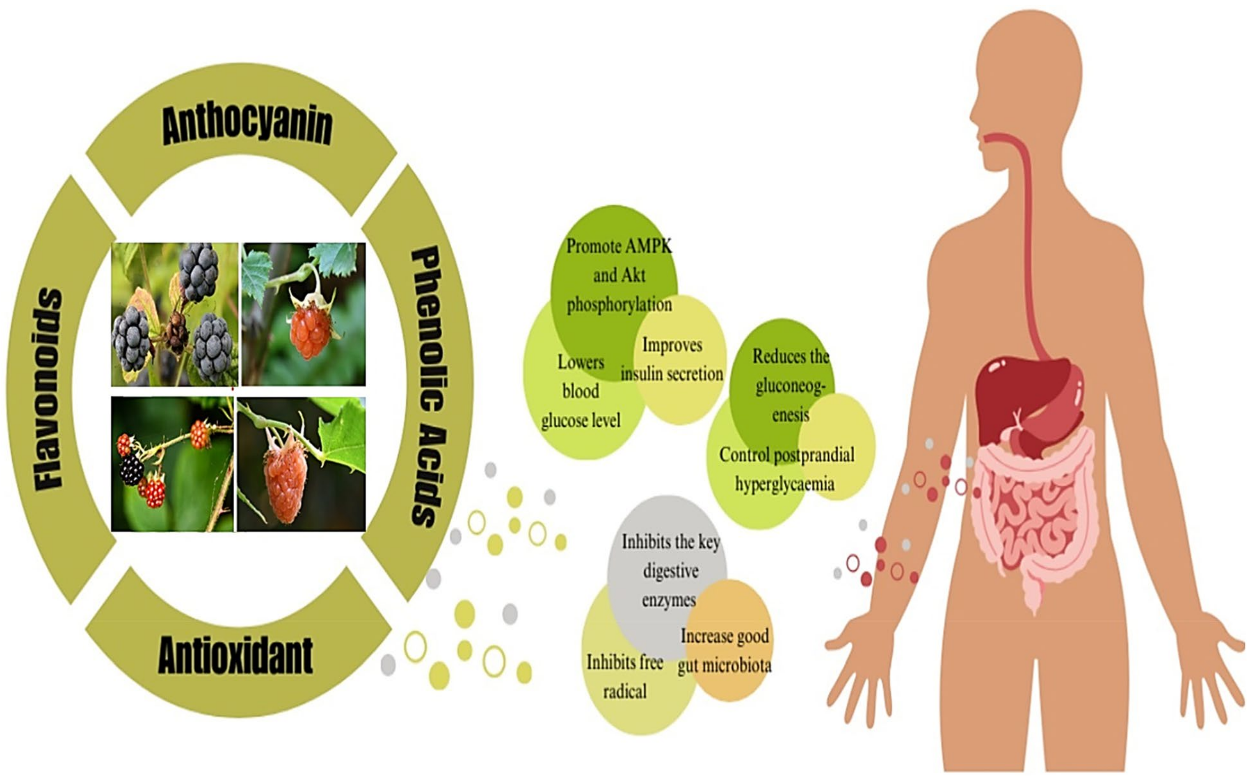


Fig. 1 Impact of bioactive compounds present in *Rubus* species for the management of diabetes mellitus

cluster together on a peduncle, forming cylindrical, semispherical, or conical shapes (Fig. 2). Among the taxa of flowering plants, *Rubus* is the most difficult to classify, as it has highly diverse morphologies and convoluted polyploidy, hybridization, and apomixis (Yu et al., 2022). The availability of *Rubus* species is given in Table 1.

Exploring the antidiabetic capabilities of *Rubus* species

Rubus amabilis

Rubus amabilis is a widely distributed deciduous shrub found in China, especially on the Qinghai-Tibetan Plateau. The fruits of this plant are categorized by their unique and delightful aroma. *Rubus amabilis* fruits serve as a source of sustenance and medicinal remedies for locals. During the season of these fruits, locals consume them in a canned form or as freshly plugged from the plant. In addition, the leaves of *Rubus amabilis* are consumed as tea. The leaves, stems, and roots of *Rubus amabilis are* known for their therapeutic properties, including analgesic, antitumor, antiphlogistic, and antidotal properties.

In vitro studies

Sun et al., (2020) studied the active component present in *Rubus amabilis*, which acts as a hypoglycemic agent, and its primary mechanism. They prepared aqueous extracts of *Rubus amabilis* plant stems and incubated them with MIN6 β-cells. Phosphate-buffered saline was used as a blank control. After incubation, the cells were washed; components that were bound to the cell membrane were separated and found using mass spectrometry/ultra-performance liquid chromatography. The components that are bound to the β-cell membrane include 3 procyanidin C trimers and a B dimer. No significant cytotoxicity was detected for total procyanidins at concentrations up to 100 μg/mL. Treatment with procyanidins reversed the PA-induced impairment of glucose-stimulated insulin secretion and increased the percentage of apoptotic cells. This active component (procyanidins), which is present in *Rubus amabilis,* acts as a hypoglycemic agent. These procyanidins shielded MIN6 cells against palmitate-induced apoptosis by initiating PI3K/FoxO1/Akt signaling.

Fig. 2 Ripened berries of various *Rubus* species; **a** *Rubus caesius* (Photo credit-Janet Graham); **b** *Rubus-corchorifolius* (Photo credit-Ming-I Weng; **c** *Rubus occidentalis* (Photo credit-Dorota); **d** *Rubus fruticosus* (Photo Credit-janhallback); **e** *Rubus corchorifolius* (Photo credit-Ming-I Weng); **f** *Rubus chingii* hu (Photo credit-Pixabay.com); **g** *Rubus ellipticus*; **h** *Rubus rosifolius* (Photo credit-Ming-I Weng)

Rubus anatolicus

Rubus anatolicus is a shrub species commonly grown in the *non-forest* and/or forest edge zones of Iran. This species is also found in the northwestern Himalayas, the Balkan Peninsula, western Asia, Pakistan, the Caucasus, China, Afghanistan, Kashmir, and Turkmenistan. The fruit of the *Rubus anatolicus* plant is utilized as a component in ice creams, jellies, yogurt, fresh fruits, and juices. Roots and leaves are also utilized for treating gynecological disorders, diarrhea, cutaneous conditions, bloody mucus, diabetes, dysphonia, hematuria, and anemia. Research has shown that this species consists of vitamins, tannins, minerals, polysaccharides, ellagitannin, folic acid, anthocyanins, glycosides, and antioxidants (Sahragard & Jahanbin, 2017).

In vitro studies

Safarzad et al., (2020) studied the influence of leaf extracts of *Rubus anatolicus* plants on insulin, glycogen, and glucose levels in different cell lines (mouse pancreatic cells, rat myoblasts, and human liver *cells*). The findings of their research indicate that the use of *a* leaf extract of *R. anatolicus* to treat pancreatic cells, muscle cells, and liver cells was successful. The extract enhanced glucose uptake in all three cell lines and increased the secretion of insulin in mouse pancreatic cell lines. In addition, the cellular content of glycogen in human liver cells (200 μg/mL) and rat myoblasts (100 μg/mL) was measured. According to their findings, they suggested that the leaf extract of *R. anatolicus* can treat diabetes mellitus.

Table 1 Availability of *Rubus* species

***Rubus* Species**	**Common Name**	**Availability**	**Reference**
Rubus amabilis	-	China	Caidan et al., 2015
Rubus anatolicus	-	Western Asia, Chitral, Kashmir, Causasus, Pakistan, north–west of Himalaya, Afghanistan, Turkmenistan, and the Balkan Peninsula, Iran	Mozaffarian, 2009
Rubus chingii Hu	Fu-Pen-Zi/Palm-leaf raspberry	China, particularly in the provinces of Zhejiang, Fujian, Jiangxi, Anhui, and Jiangsu	Li et al., 2021; Tan et al., 2023
Rubus caesius	Blåhallon (blue raspberry)/European dewberry/Salmbär (Solomon berries)	Europe and Asia, including Poland, Baltic Sea islands Gotland and Fårö, Finland	Hering et al., 2022; Svanberg & Ståhlberg, 2021
Rubus corchorifolius	March bubble, raspberry milk bubble or Ci-Hu-Lou	China	Chen et al., 2017; Yang et al., 2019; Sun et al., 2011
Rubus ellipticus	Indian raspberry and yellow Himalayan raspberry	Southern China, Indian Subcontinent, the Philippines, and all continents except Antarctica, mountains, and lowlands of India and Srilanka	George et al., 2015; Lamichhane et al., 2023; Pandey & Bhatt, 2016; Sharma & Kumar, 2011a, b
Rubus erlangeri Engl	-	-	Ayele et al., 2021
Rubus fruticosus	European blackberry, European bramble, vilaayatianchhu, Karwara, Akhara, Baganrra, Ach	Britain, North America, India (Kashmir, Assam, and Tamilnadu), Northern areas of Pakistan	Riaz et al., 2011; Verma et al., 2014
Rubus grandifolius	Amoras	Portugal (the Madeira Archipelago)	Gouveia-Figueira & Castilho, (2015)
Rubus idaeus	Red raspberries	Europe, North America and Asia, Northern Turkey	Çekiç & Özgen, 2010; Wang et al., 2019
Rubus occidentalis	Black raspberry	Eastern North America, Europe, Czech Republic, Slovakia, Russia, Poland, United States including Northwest, Midwest and Northeast	Kula & Krauze-Baranowska, 2015; Willman et al., 2022
Rubus rosifolius	Red mulberry	Jamaica, Brazil, Southeast Asia, Hawaii and the Caribbean, China, the West Indies, Southern and Central America, Africa, and Australia	Campbell et al., 2017; De Quadros et al., 2023; Rambaran & Bowen-Forbes, 2020
Rubus steudneri Schweinf	Gora	Euthopia	Raghavendra et al., 2022
Rubus ulmifolius	Wild blackberry	South American countries like Brazil, North America, Europe, Asia and North Africa	Martins et al., 2014; Schulz et al., 2019

Rubus chingii Hu

Rubus chingii Hu, also known as Palm leaf raspberry or Fu-Pen-Zi in China, originates from China and has a long history of being consumed due to its perceived health advantages (Li et al., 2021; Tan et al., 2023). This species is extensively grown in southeastern and eastern China, particularly in the provinces of Zhejiang, Fujian, Jiangxi, Anhui, and Jiangsu (Tan et al., 2023). Phytochemical studies of *Rubus chingii Hu* fruits and leaves have revealed the presence of phenolics, alkaloids, steroids, flavonoids, phenylpropanoids, terpenoids, and organic acids. The active substances and extracts obtained from these plants show diverse pharmacological properties, such as antithrombotic, anti-inflammatory, antidiabetic, antifungal, antitumor, antiosteoporotic, antioxidant, and central nervous system-regulating properties (Sheng et al., 2020).

In vivo studies

A study by Huo et al., (2021) concluded that *Rubus chingii Hu* has the potential to alleviate various diabetes symptoms in mice induced with STZ. This includes reversing skeletal muscle atrophy and weight loss, reducing hyperglycemia, and protecting the pancreas from streptozotocin-induced destruction. The antihyperglycemic mechanism of *Rubus chingii Hu* involves stimulating the synthesis of hepatic glycogen, decreasing gluconeogenesis, preserving pancreatic β-cell function and integrity, and activating insulin/antibodies against protein kinase B and 5′ AMP-activated protein kinase/liver kinase B1 signaling pathways. These promising findings suggest that *Rubus chingii Hu* could be a valuable component for managing hyperglycemia and diabetes-related symptoms.

Rubus caesius

Rubus caesius is universally recognized as a European dewberry and is broadly distributed in Europe and Asia, including Poland. This plant is commonly found in Poland and is grown along roadsides and forest edges. This plant is characterized by small shrubs with trailing or low-arching shoots. *Rubus caesius* L. produces pruinosa aggregate fruits made up of several drupes. This fruit is consumed directly from the plant. The fruits and seeds of this plant contain significant amounts of flavonoids and anthocyanins, which are beneficial compounds known for their antioxidant properties. *Rubus caesius* L. contains 35 compounds, 35 of which are phenolic acids, flavonoids, and ellagic acid derivatives. Among these compounds, many are antioxidants and are valuable nutritional and medicinal supplements because they have anti-inflammatory, antihyperglycemic, cardioprotective, and anti-gastrointestinal effects (Grochowski et al., 2020; Hering et al., 2022).

In vivo studies

Schädler and Dergatschewa, (2017) conducted their study on *Rubus caesius* leaves to perform a pharmacognostic assay and assess the hypoglycemic activity of these leaves. An alloxan-induced diabetes rat model was used to investigate the hypoglycemic effect of *Rubus caesius* leaf extract. The rats were allocated to four groups (Groups A, B, C, D), each comprising six animals. These four groups had different glycemic statuses and treatment schedules: group A, nondiabetic group (1 mL dw for 10 days); group B, diabetic control group (1 ml of 5% monohydrate alloxan solution at a dosage of 125 mg/kg); group C, diabetic group (for 10 days, glibenclamide was injected at 10 mg/kg); and group D, diabetic group (the *Rubus caesius* leaf aqueous extract was inoculated at 500 mg/kg for 10 days). After 10 days, Group D exhibited a significant effect on the glucose level. In conclusion, alloxan had a considerable hypoglycemic effect on rats treated with an aqueous extract of *Rubus caesius* leaves. In addition, they mentioned that there were some limitations to their study and that further research is needed.

In vitro studies

Grochowski et al., (2018) conducted an in vitro research study on the enzyme inhibitory and antioxidant properties of *Rubus caesius* L. They performed different chemical analyses to assess the antioxidant effect and examined the inhibitory effect of *Rubus caesius* L. extract on enzymes (α-glucosidase, tyrosinase, cholinesterase, and α-amylase). Among the different extracts, the diethyl ether fraction exhibited the greatest inhibitory effects on cholinesterase and α-amylase. The enzyme α-amylase causes a rise in blood glucose levels and postprandial hyperglycemia. For managing and treating postprandial elevations in blood glucose, the use of α-amylase is a renowned therapeutic aim (Kaur et al., 2021). *The* above studies *indicate* that *Rubus caesius* L. has the potential to be used as an *antidiabetic agent* due to the presence of a natural inhibitor in its diethyl ether fraction. Moreover, further research studies are required to confirm whether this species can be used to treat hyperglycemia.

Rubus corchorifolius

Rubus corchorifolius, commonly known as a milk bubble or a March bubble, is a species of the *Rosaceae* genus. It is extensively cultivated in China and used as a traditional Chinese remedy for treating hemorrhages, alcoholic addiction, and diarrhea. *Rubus corchorifolius* is suitable for direct consumption as *a* food because of its distinctive fruity *flavor* combined with *its* sweetness and sourness. It *is rich in* nutrients, including vitamin C, essential amino acids, superoxide dismutase, dietary fiber, and various minerals (Yang et al., 2019). *People* have consumed tea *from Rubus corchorifolius* leaves for a long time.

In vivo and in vitro studies

Tian et al., (2021) extracted and isolated 12 flavonoids from *Rubus corchorifolius,* among *which* six (compounds 2, 4, 9, 10, and 12) were isolated for the first time. They performed both in vitro and in vivo studies on *flavonoids* extracted from *Rubus corchorifolius*. Their findings indicate that among 12 flavonoids, compound 4 exhibits noteworthy α-amylase and α-glucosidase hindering activity. Molecular modeling analysis of compound 4 revealed strong binding of this compound to the active sites of both the α-amylase and α-glucosidase enzymes. Surface plasmon resonance and Lineweaver–Burk plot assays showed the potential binding ability of the enriched flavonoids to α-amylase and α-glucosidase enzymes. In conclusion, flavonoids were found to have potential hypoglycemic activity.

A study on tea manufacture using *Rubus corchorifolius* leaves was conducted by Li et al., (2023). They reported that the 70% ethanol extract of *Rubus corchorifolius* leaf tea *had* powerful inhibitory effects on α-glucosidase and α-amylase. Moreover, *Rubus corchorifolius* leaf tea notably enhanced the consumption of glucose in 3T-3L1 cells. The eight *major* inhibitors are isovitexin, delphinidin-3-O-glucoside, iso-orientin, cyanidin-3-rutinoside, rutin, epigallocatechin gallate, procyanidin C3, and dihydromyricetin, which are found in *Rubus corchorifolius* leaf tea. Currently, researchers have identified natural inhibitors of *α-glucosidase* and α-amylase from tea products, fruits, and cereals. Natural inhibitors have few side effects and are economical and efficacious as antihyperglycemic agents for treating type 2 diabetes (Liao et al., 2017; Yang et al., 2021). The above studies indicate that *Rubus corchorifolius* has the potential to be used as an antidiabetic plant due to the presence of natural inhibitors in its leaf extract.

Rubus ellipticus

Rubus ellipticus, also known as yellow Himalayan raspberry, is a *Rubus* species native to southern China, the Indian Subcontinent, and the Philippines. It has a wide range of traditional uses as a source of food and medicinal herbs. In traditional medicine, all parts of *Rubus ellipticus* have been used to cure gastrointestinal problems, as anti-infective agents, to treat diabetes, and as respiratory ailments. Scientific studies have shown that the fruit of this plant is rich in micronutrients, macronutrients, and minerals, suggesting that it can be used as a nutraceutical. Moreover, this plant has a variety of secondary metabolites, including terpenoids, tannins, polyphenols, anthocyanins, and flavonoids. In addition, it also has several noteworthy compounds, including gallic acid, ascorbic acid, catechin, and kaempferol (Lamichhane et al., 2023).

In vitro studies

Benmohamed et al., (2023) and Papoutsis et al., (2021) reported that α-amylase is the enzyme responsible for breaking down disaccharides and starch into glucose, which plays a crucial role in managing the level of blood sugar. Subba et al., (2019) conducted a study on *Rubus ellipticus* and reported that methanol extracted from its leaves exhibited a moderate level of inhibition of α-amylase, with an approximately 269.94 ± 0.11 μg/mL IC50. The author speculated that the antidiabetic effect of this species might be attributed to its ability to hinder α-amylase and its antioxidant properties. In addition, further research studies are required to understand the presence of bioactive compounds that are responsible for the ability of these compounds to hinder α-amylase activity and the underlying mechanism involved.

In vivo studies

Sharma and Kumar, (2011a, b) conducted a research study to scrutinize the antidiabetic effect of different extracts (ethanol, petroleum ether, and aqueous solution) obtained from the fruit of *Rubus ellipticus*. This study was performed on male Wistar albino rats weighing 150–200 g. After treatment with glibenclamide and *Rubus ellipticus* fruit extracts, blood glucose levels were measured on the 1st, 4th, 7th, and 15th days. These measured values were compared to those of the diabetic control group. A phytochemical assay of *Rubus ellipticus* fruit revealed that it has numerous compounds, such as carbohydrates, steroids, tannins, flavonoids, and phenolic compounds. The study of acute toxicity revealed that the consumption of plant extract at concentrations up to 2000 mg/kg had no effect on behavioral or toxic neurological symptoms. The authors concluded that each extract of *Rubus ellipticus* fruit had a significant antihyperglycemic effect on a diabetes mellitus experimental model. These findings support the use of *Rubus ellipticus* fruit for treating diabetes. However, further biochemical, and pharmacological studies are required for this species. These investigations will illuminate the actual antihyperglycemic mechanism of this species and could help identify this plant as a therapeutic agent for treating diabetes.

Rubus erlangeri Engl

In vitro and in vivo studies

Ayele et al., (2021) studied the antidiabetic activity of *Rubus Erlanrige* Engl leaf extract. The purpose of their investigation was to examine the antihyperglycemic activity of *Rubus Erlanrige* Engl plant extracts first in vitro and then in vivo. An in vitro study was performed using the 2,2-diphenyl-1-picrylhydrazine method to assess the antioxidant effect and the 3,5-dinitrosalicylic acid procedure to assess the α-amylase inhibition properties of this plant. Furthermore, the in vivo experiment was executed on two groups: normoglycemic mice given a 2.5 g/kg glucose load and mice induced with hyperglycemia cured by a single dose of streptozotocin (200 mg/kg). The outcomes of their investigation revealed that the extract is safe at doses of 2 g/kg or higher. In vitro tests revealed that the extract has α-amylase inhibition activity with an IC50 value of 10.38 ± 0.62 μg/ml. However, an in vivo study revealed that the extract effectively lowered the blood glucose level. In streptozotocin-induced diabetic mice, a noteworthy decrease in blood glucose levels was detected. In conclusion, this study revealed that the aqueous extract of *Rubus Erlanrige* Engl leaf effectively reduced blood sugar levels in both orally glucose-loaded mice and mice with STZ-induced diabetes. This decrease in glucose level occurred without increasing the risk of hypoglycemia or loss of body weight. The free radical scavenging activity of the extract and the inhibition of intestinal α-amylase promoted the antidiabetic activity of the plant extract.

Rubus fruticosus

Rubus fruticosus L., a member of the *Rosaceae* family, is a medicinal plant known locally as "fursad". This seasonal tree is renowned for its popular fruits, which can come in various colors, such as red, violet, white, or black, with black fruits being referred to as blackberries due to their dark hue. The plant is highly valued on a global scale due to its delightful taste, pleasant flavor, and nutritional benefits. It is believed to have originated in Armenia and is extensively cultivated in European nations, as well as in the northern regions of Pakistan, Saudi Arabia, and Oman (Weli et al., 2020). The fruit of *Rubus fruticosus* L. comprises vitamins (C, A, E), folic acid, minerals (Co, Al, Fe, Zn, Mn, chloride, Cu), sterols, and several carotenoids (α-carotene, β-cryptoxanthin, lycopene, β-carotene, zeaxanthin, Marinova). These compounds contribute to the protective effects of this fungus against various disorders (Amini et al., 2021).

In vivo studies

Soheilifar et al., (2020) investigated the defensive effects of *Rubus fruticosus* hydroethanolic extract on biochemical factors in diabetic streptozotocin-treated rats. Forty male Wistar rats were divided into 5 groups: diabetic (55 mg/kg/induced STZ), control, and three treatment groups receiving different doses of *Rubus fruticosus* extract (100 mg/kg, 50 mg/kg, and 200 mg/kg, respectively). Four weeks later, blood samples were taken directly from the hearts of the Wistar rats for inflammatory cytokine and biochemical parameter measurements. After the initiation of diabetes, the serum levels of alanine aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, interleukin-6, aspartate aminotransferase, ceruloplasmin, tumor necrosis factor-α, and copper significantly increase. Treatment with a high dose of *Rubus fruticosus* extract, i.e., 200 mg/kg, significantly reduced these parameters, suggesting its potential to ameliorate the adverse effects of STZ-induced diabetes in male rats. He also concluded that the results of this study suggested that the use of *Rubus fruticosus* extract could reduce copper levels and liver enzyme activity in diabetic rats. This effect is attributed to the presence of flavonoids, which appear to enhance the anti-inflammatory mechanisms within the body.

Similar studies were performed by Mirazi and Hosseini, (2020) and Motevalian and Javadpour, (2017), who concluded that the oral administration of *Rubus fruticosus* leaf extract can reduce the serum lipid content and blood sugar-lowering effects on liver function. *Rubus fruticosus* extract decreases inflammation in diabetic rats. These results could be associated with the natural active ingredients in the *Rubus fruticosus* extract that enhance the antioxidative system. Akyüz, (2022) reported the antidiabetic potential of *Rubus fruticosus L.* fruit extracts at different maturity stages. Their results showed significant inhibitory effects on α-glucosidase and α-amylase enzymes which is crucial in postprandial glucose management. Ethanol and water extracts from immature, intermediate, and ripening stages demonstrated varying degrees of inhibition against α-glucosidase, with intermediate stage extracts showed the highest potency. Water extracts exhibited strong inhibition of α-amylase, particularly in the intermediate stage. The findings suggest R. fruticosus L. fruit extracts as promising natural antidiabetic agents, with potency influenced by fruit maturity, highlighting their potential in managing postprandial hyperglycemia.

Rubus grandifolius

Rubus grandifolius is a rare species of the *Rubus* genus found extensively in Portugal (the Madeira Archipelago). It grows in shady and moist areas. This plant has a curved and hard stem with thorn-like structures, and oval-shaped leaves and white-colored flowers grow in clusters on a pyramid-shaped panicle. The berries of this plant are cylindrical to subspherical, and fleshy. The ripened berries are black. These berries are chiefly utilized in food processing industries to manufacture liquor, juice, and jam. Fruits, shoots, and leaves are used in traditional medication as astringents for children. These parts are also utilized as antidotes to ease sore throat and to treat diuretics, diabetes, and diabetes. In addition, it is also used to prepare alcoholic infusions and herbal tea (Gouveia-Figueira & Castilho, 2015).

In vitro studies

Spínola et al., (2019) conducted their research study on *Rubus grandifolius L*. (wildblackberry) and assessed its ability to control obesity and type 2 diabetes through in vitro experiments. In their study, they concluded that extracts of *Rubus grandifolius* exhibited effective β- and α-glucosidase suppression activity but had a moderate influence on lipase and α-amylase. Their study suggested that some particular phenolic compounds might have distinct suppressive effects on some enzymes. Among the 50 polyphenols that were measured, ellagitannins and anthocyanins were the most abundant. Cyanidin-3-glucoside was found to be one of the key hypolipidemic and hypoglycemic agents in all the extracts. In addition, *Rubus grandifolius* acts as a preventing agent for the glycation of bovine serum albumin. It also has powerful radical scavenging activity toward free-tested radicals. Finally, he concluded that the extract of *Rubus grandifolius* had a potential effect on controlling or managing type 2 diabetes.

Rubus idaeus

Rubus idaeus, locally known as red raspberry, is extensively grown in Europe, North America, and Asia. This fruit is munched as fresh fruit, used to make fermented wine, and even used as an ingredient in functional beverages, as it has an appealing color, delightful taste, and notable nutritional value (high levels of phenolic compounds). Additionally, raspberry leaves, which have anti-diabetes, anti-inflammatory, and antioxidant properties, have attracted considerable attention due to their potential health benefits. Leaves are often used to produce tea products, and their intake has been on the rise. Raspberry seeds are valuable resources for the food industry, although there has been limited research on their phytochemical constituents and bioactivities (Wu et al., 2019).

In vitro studies

Zhang et al., (2018) investigated the metabolism of polyphenols in the ripened raspberry *Rubus idaeus*. During their research study, they found that the primary ellagitannins (polyphenols) present in *Rubus idaeus* were cyanidin 3-O-glucoside, cyanidin 3-O-sophoroside, and sanguiin H6. Wu et al., (2019) also conducted a study on the antioxidant properties and ability of phenolic compounds found in various parts of *Rubus idaeus* to inhibit digestive enzymes. According to their study, the leaves of *Rubus idaeus* have the greatest amounts of phenolic and flavonoid compounds. Nineteen different phenolic compounds were detected, of which ellagic acid, procyanidin C3, and gallic acid were the most abundant. Analysis of the chemical composition of *Rubus idaeus* revealed that the leaves had the highest concentrations of total phenolic and flavonoid compounds. These components display antioxidant properties and the ability to hinder digestive enzymes such as α-glucosidase and α-amylase, thereby preventing the formation of monosaccharides. Previous research revealed that phenolic compounds are present in raspberry extracts and exhibit significant anti-diabetic effects (Bobinaitė et al., 2012; Qin et al., 2018; Sun et al., 2020; Zhang et al., 2018).

In vivo studies

Various studies have been conducted on the effects of *Rubus idaeus* on pregnant women diagnosed with gestational diabetes. Their findings revealed that this herb has glycemic control properties. The patient with gestational diabetes experienced low blood sugar levels and required a lowered insulin dosage after consuming raspberry leaf tea for thirty-eight consecutive days, which led to a reduced need for insulin. The patient's self-withdrawal and subsequent reintroduction of the herb further substantiated the causal association. Detailed examinations of the patient's metabolism and fetal well-being showed no abnormalities. However, this particular study established a precedent for *Rubus idaeus* in reducing blood glucose levels in humans. In addition, this plant could indirectly contribute to decreasing the occurrence and severity of gestational diabetes mellitus (Cheang et al., 2016; Zhang et al., 2018).

Rubus occidentalis

Rubus occidentalis is a paltry cultivated yet highly valued crop in the processing and fresh markets of the United States. *Rubus occidentalis* is indigenous to the Eastern part of North America. Currently, this plant is grown for commercial purposes in three regions of the United States, namely, the Northwest, Midwest and Northeast

States (Willman et al., 2022). *Rubus occidentalis* comprises many natural components, such as phytosterols, vitamins, minerals and flavonoids. Due to the presence of these compounds, this plant shows potential health benefits. In *Rubus occidentalis,* ellagitannis and anthocyanins are abundant. Over the past few decades, there has been increasing interest in the potential of ellagic acid and ferulic acid, which are found in *Rubus occidentalis,* as they have anti-inflammatory and antiproliferative properties. Moreover, this plant is a berry that has an abundant number of anthocyanins. This herb exhibits medicinal properties for prostate cancer, colon cancer, and esophageal cancer and has potential for cancer management (Wang et al., 2023). *Rubus occidentalis* also enhances metabolic conditions *such as* insulin resistance and hypertension (Lee et al., 2019).

In vivo studies

Lee et al., (2019) investigated the improvement of hyperglycemia using *Rubus occidentalis*. In this study, they examined the gut microbiota composition in mice treated with *Rubus occidentalis.* This examination was conducted *in* an aged mouse model *of* high-fat-induced diet-*induced* obesity. According to their test results, *Rubus occidentalis* enhanced the glucose profile of mice *by improving* intraperitoneal glucose tolerance and *the* level of serum glucose. Treatment with *Rubus occidentalis* caused the healthy gut microbiota (*Ruminococcus, Bacteroides, Mucispirillum,* and *Butyricimonas*) to flourish. In addition, glucose profiles are correlated with an increase in these gut microbes. Finally, they concluded that these groups of healthy gut microbiota were linked with the patterns of glucose levels. This indicates that the consumption of *Rubus occidentalis* can increase the *abundance* of good microbiota *that* produce short-chain fatty *acids,* resulting in the regulation of glucose levels. The production of beneficial metabolites by *Rubus occidentalis* may be instrumental in glucose regulation in hyperglycemic patients.

A study was conducted by Kim et al., (2018) *on Rubus occidentalis* to confirm its novel potency in *treating* metabolic syndrome. This study was conducted on *mice* with metabolic syndromes. This disorder can be characterized by numerous *combinations* of metabolic syndromes (hyperlipidemic obesity and hyperglycemia). They conducted an experiment in which C57BL/6 N mice were subjected to a high-fat diet for 23 weeks to induce metabolic syndrome. They aimed to examine the potency of *Rubus occidentalis* toward hyperglycemia and hypercholesterolemia. They found that oral administration of *Rubus occidentalis* was effective for 16 weeks. During this time, *Rubus occidentalis* had a positive impact on hyperglycemia. This was shown through a notable decrease in glucose tolerance and a glucose fasting level test. The conclusion of their study suggested that *Rubus occidentalis* exerts an antidiabetic effect in mice with diet-induced metabolic syndromes.

Rubus rosifolius

Rubus rosifolius is a natal plant species of Jamaica, Brazil, Southeast Asia, Hawaii, and the Caribbean. This species commonly originates at elevated levels and relatively cool temperatures. Two distinct varieties of *Rubus rosifolius* (red and wine red) have been described (Rambaran & Bowen-Forbes, 2020).

In vivo studies

Rambaran et al., (2020) investigated the hypoglycemic activity and fatty acid profile of two varieties of *Rubus rosifolius* fruit extract. A Sprague–Dawley rat model was used to conduct this research. Male Sprague–Dawley rats were orally administered two different extracts obtained from *Rubus rosifolius* fruit (50 mg/kg by body weight). This was done to evaluate the potential for lowering levels of blood sugar. For the positive control group, metformin was administered intravenously (15 mg/kg body weight). of the three extracts, n-hexane was more potent. Linoleic acid accompanied by palmitic and oleic acids was identified as the component of the triacylglycerol blend that was isolated as the predominant compound of the n-hexane extract. Among all the extracts, this nonpolar extract exhibited the greatest hypoglycemic effect. Compared with hypoglycemic drugs and metformin, the oxidized triacylglycerol (compound 1) isolated from the n-hexane extract showed greater effectiveness in reducing blood glucose levels and had superior activity after its administration. For the first 30 min, compound 1 showed a significant hypoglycemic effect over metformin. At 120 min, no significant difference was observed. Finally, they concluded that *Rubus rosifolius* red berries may have beneficial effects on human health, and the phytochemicals found in this berry can have potential applications in areas such as pharmaceutical development or the development of functional foods.

Rubus steudneri

Rubus steudneri, also known as Gora by local people, belongs to the genus *Rubus*. This plant is a scandent shrub with stems that are deeply furrowed and enveloped with stellate hairs or prickles. The leaves of this plant are doubly serrate, trifoliate, densely whitish-tomentose below, and glabrate above. Fruits are consumable. *Rubus steudneri* is consumed ethnobotanically as medicine and food. A decoction produced from the roots of *Rubus steudneri* is utilized to cure diarrhea, indigestion, and gastritis. *Rubus steudneri* is also utilized to treat diabetes mellitus. This plant is commonly cultivated in the Ethiopian region (Raghavendra & Kekuda, 2018). *Rubus steudneri* leaf extract contains several phytochemicals, namely, alkaloids, tannins, saponins, and flavonoids. Therefore, the leaves of this plant are traditionally used as an herbal medication for controlling diabetes mellitus (Raghavendra et al., 2019).

In vivo studies

Raghavendra et al., (2019) conducted their research study focused on *Rubus steudneri* leaf extract. The authors used alloxan-induced diabetic rats as their experimental model. Two groups of rats were treated with different doses (150 mg kg^{-1} and 300 mg kg^{-1} based on their body weight). These dosages were given orally to diabetic rats induced by alloxan. Their findings indicated a noteworthy decrease in blood glucose levels in diabetic rats treated with leaf extract compared to those in untreated diabetic rats. Finally, they concluded that the leaf extract of *Rubus steudneri* possesses antidiabetic properties because it helps to modulate glucose metabolism and can control glucose levels in the blood.

Rubus ulmifolius

Rubus ulmifolius is a perennial shrub that originates from North America and Europe. This species is found in various regions globally, including South American countries such as Brazil. The *Rubus ulmifolius plant* yields edible blackberry fruits. These fruits can be characterized by their aggregate nature, round shape, tart taste, and black coloration when fully ripe (Schulz et al., 2019). Tabarki et al., (2017) identified naringenine and kaempferol 3-O-rutinoside as the primary phenolic compounds present in the leaves of *Rubus ulmifolius*. Ali et al., (2017) detected tannins, steroids, alkaloids, and flavonoids in the aerial parts of *Rubus ulmifolius*. However, there is limited research on the nutritional characteristics, polyphenolic components, and antioxidant capacity of *Rubus ulmifolius* fruits (Hajaji et al., 2017; Schulz et al., 2019). The immature fruits of *Rubus ulmifolius* are used as aphrodisiacs, and tonics, roots, and leaves are applied to address skin ailments. In traditional Italian medicine, *Rubus ulmifolius* is used to treat ulcers and abscesses, as well as for diarrhea and vaginal lavages. Furthermore, in traditional Chilean medicine, *Rubus ulmifolius* is recognized for its ability to lower blood sugar levels (Akhtar et al., 2017).

In vivo studies

Akhar et al., (2017) conducted a study on *Rubus ulmifolius*. Their study aimed to assess the antihyperlipidemic and hyperglycemic effects of the aerial part of *Rubus ulmifolius*. The model used for this study was a streptozotocin (STZ)-induced diabetic albino mouse model. They used mice of either sex, aged between 48 and 60 days and weighing 18–25 g, to examine the antihyperglycemic effect. These mice were divided into eight groups, each consisting of 6 mice, and subjected to different treatments (control, 500 μg/kg glibenclamide, 2% Tween-80, 150 mg/kg methanol extract, 300 mg/kg methanol extract, 150 mg/kg ethyl acetate extract, 150 mg/kg chloroform extract and 150 mg/kg butanol extract). These doses were given to the mice orally for 15 days. Blood glucose levels and body weights were measured on the 1st, 4th, 7th, 10th, and 15th days. The results showed that the groups treated with *Rubus ulmifolius extract* [butanol extract], methanol extract (150 and 300 mg kg^{-1}, ethyl acetate extract, and chloroform extract] exhibited a noteworthy decrease in blood glucose levels. In conclusion, extracts of *Rubus ulmifolius* have promising effects on diabetic albino mice, and these extracts can be used for treating diabetes.

Mechanism of antihyperglycemic activity

The bioactive compounds in the *Rubus* species are listed in Table 2. The principal mechanisms of the *Rubus* species that have been investigated include promoting AMPK and Akt phosphorylation, protecting and preserving the function of pancreatic β-cells and insulin secretion, enhancing glucose consumption, inhibiting the digestive enzymes involved in glucose digestion, inhibiting apoptosis, promoting the proliferation of β-cells, reducing postprandial blood glucose levels, and increasing the percentage of good gut microbiota (Fig. 3). *Rubus* species contain numerous bioactive compounds that are responsible for promoting different antidiabetic effects upon consumption (Table 2). These bioactive compounds include procyanidin B dimers and a trimer C, phenolic compounds, phytochemicals, hydrolyzable tannins, flavonoids, alkaloids, terpenoids, quinones, quinones, vitamins A and C, cyanidin-3-glucoside, antioxidant enzymes, and organic acids.

The bioactive components procyanidin C-timers and B-dimers are found in one of the *Rubus* species, *Rubus amabilis*. This compound shows antidiabetic properties when tested in MIN6 cells (Sun et al., 2020). These procyanidins significantly hindered the apoptosis of beta cells, promoted beta-cell proliferation, and restored impaired GSIS. This suggests that the inhibition of apoptosis is due to an increase in procyanidin-induced cell survival and the promotion of cell proliferation. Procyanidins protect beta cells from palmitate-induced apoptosis by activating the Akt/FoxO1 pathway and decreasing the levels of

Table 2 Bioactive compounds in *Rubus* species

Rubus Species	Part Used	Bioactive compounds	Action mechanism	Test model	Reference
Rubus amabilis	Stem	Procyanidin B dimers and a trimer C	Hindered the apoptosis of beta cells, promoted beta-cell proliferation, and restored the impaired GSIS. Activate the PI3K/Akt/FoxO1 signaling pathway, decrease the levels of Ser256-phosphorylated FoxO1 and Ser473-phosphorylated, and maintain Pdx1 levels.	MIN6 cell	(Sun et al., 2020)
Rubus anatolicus	Leaves	Phenolic compounds (such as phenolic acids, flavonols, flavanols, anthocyanins, proanthocyanidins, and ellagitannins)	Promote AMPK and Akt phosphorylation, increase the Glucose transporter 2 expression in β-cells of pancreases, upregulate and promote the alternation of GLUT-4 via AKT/PI3K, CAP/TC10/Cb1 and AMPK pathways	HepG2, CRI-D2 and C2C12 cell lines	Safarzad et al., 2020
Rubus chingii Hu	Fruit	Flavonoids (apigenin-rhamnoside and procyanidin dimmer), Hydrolyzable tannins (including 11 ellagitannins and 4 gallotannins, such as casuariin/pedunculagin isomers, ellagic acid, and its glycosides. Gallotannins with hexahydroxydiphenoyl group), phenolic acids (caffeoylthreonic acid salvianolic acid C, and coumaroylthreonic acid)	Reduces gluconeogenesis, increase glucose uptake and promotes hepatic glycogen, protects and preserves the function of beta-cells and increases insulin secretion, preserves the survival of beta-cells by inhibiting NF-κB signaling, activating the Akt/insulin and LKB1/AMPK signaling pathways in pancreas	mice induced with streptozotocin	Huo et al., 2021
Rubus caesius	Leaves	Hyperoside, ruthin (diglucosidequercetin), kaempferol (isoquercitrin-glycoside), phenolic acids	-	Alloxan induced diabetes rat model	Schädler & Dergatschewa, 2017
	Leaves	Quercetin 3-O-β-D-rutinoside, quercetin 3-O-β-D-glucuronide,, kaempferol 3-O-β-D-glucuronide, methyl brevifolincarboxylate, coumaroyl)-glucoside, kaempferol, kaempferol 3-O-β-D-(6′-O-(E)-p, quercetin, ellagic acid, and pedunculagin	-	-	Grochowski et al., 2020

Table 2 (continued)

***Rubus* Species**	**Part Used**	**Bioactive compounds**	**Action mechanism**	**Test model**	**Reference**
Rubus corchorifolius	Leaves	Phenolic acids, flavonoids, anthocyanins, and their derivatives dihydromyricetin, procyanidin C3, epigallocatechin gallate, rutin, cyanidin-3-rutinoside, and isovitexin	Interaction and formation of H-bonds or van der Waals force with the amino acid remains of α-AMY/α-GLU and inhibit their activity, significantly enhance the glucose consumption capacity of 3T-3L1 cells	3T-3L1 cells	Li et al., 2023
	Fruit	Flavonoids (apigenin-7-*O*-*β*-D-glucopyranuronide, quercetagetin-7-*O*-*β*-D-glucopyranoside, quercetin-3-monomethyl ether, naringenin, kaempferide, L-epicatechin, isorhamnetin-7-*O*-*β*-D-Glucopyranuronide, luteolin, quercetin, apigenin, quercetin-3-monomethyl ether, kaempferol).	Reduce postprandial blood glucose levels, and have inhibiting activity α-glucosidase and α-amylase.	-	Tian et al., 2021
Rubus ellipticus	Fruits	Alkaloids, terpenoids, quinones, quinones, terpenoids, glycosides and flavonoids	-	-	Subba et al., 2019
	Fruit	Flavonoids, carbohydrates, steroids, tannins and phenolic compounds.	-	Alloxan induced diabetic rats	Sharma & Kumar, 2011a, b
Rubus erlangeri Engl	Leaves	Phenols, Flavonoids	It lowers the level of blood glucose, inhibits the α-amylase, and have free radical scavenging activity	Streptozotocin-induced diabetic mice	Ayele et al., 2021
Rubus fruticosus	Fruit	vitamins A, C, antioxidants and flavonoid (ellagitannins)	Significant reduce in the levels of plasma glucose, prevent from increasing the serum level of ceruloplasmin and copper	Male Wistar rats	Soheilifar et al., 2020
	Leaves	Flavonoids, antioxidants, polyphenols (e.g. allagic acid, tannins), anthocyanins, alpha-linolenic acid and linoleic acid, zinc copper, vitamin A, vitamin E, and vitamin C.	Inhibits free radicals, protective effect on pancreatic beta cells, quickens the mending of impaired beta cells and stimulates them for the secretion of insulin, and inhibits, the decrease of blood sugar via absorption of carbohydrates from the intestine,	STZ-induced diabetic rats	Motevalian & Javadpour, 2017
	Plant	-	Reduces interleukin -6, tumor necrosis factor-α, malondialdehyde, and C-reactive protein and increases the levels of glutathione and total antioxidant status, reducing the free radicals	Male Wistar rats	Mirazi & Hosseini, 2020

Table 2 (continued)

***Rubus* Species**	**Part Used**	**Bioactive compounds**	**Action mechanism**	**Test model**	**Reference**
Rubus grandifolius	Fruit and leaves	Phytochemicals, ellagitannins, Casuarinin, Hydroxycinnamic Acid, anthocyanins, other flavonoids, phenolic acids, terpenoids, cyanidin-3-glucoside, and organic acids	Hinder the key enzyme involved in the digestion of glucose. Inhibit (α-, β-) glucosidases, and modest hindering activity toward α- amylase for controlling postprandial hyperglycemia. Strong capability to inhibit the formation of advanced glycation end-products	-	Spínola et al., 2019
Rubus idaeus	Fruits, leaves, pulp	Ellagic acid, procyanidin C3 and gallic acid cyanidin 3-O-glucoside, cyanidin 3-O-sophoroside and sanguiin H6	Hinder digestive enzymes such as α-glucosidase and α-amylase, indirectly contribute to lowering the occurrence and severity of gestational diabetes mellitus	-	Cheang et al., 2016; Wu et al., 2019; Zhang et al., 2018
Rubus occidentalis	Fruit	Phenolic compounds, including anthocyanin, gallic acid, caffeic acid, ferulic acid, p-coumaric acid, rutin, myricetin, luteolin, and kaempferol	Cause a decrease in the Firmicutes/Bacteroidetes ratio. Percentages of Ruminococcus, Bacteroides, and Butyricimonas were increased. This improves metabolic disorders.	aged mouse model of high-fat diet-induced obesity.	Lee et al., 2019
	-	-	Significantly lowers the glucose tolerance test and fasting glucose levels	Mice with Diet-Induced Metabolic Diseases	Kim et al., 2018
Rubus rosifolius	Fruit	Omega-3 α-linolenic acid (32% and 35%) and omega-6 linoleic acid (47% and 50%) (1-hexadecanoyl-2-(9Z,12Z-octadecadienoyl)-3-(9Zoctadecenoyl)-sn-glycerol)	-	Male Sprague–Dawley rats	Rambaran et al., 2020
Rubus steudneri Schweinf	leaves	Antioxidant enzymes (GSH, total thiols, SOD, and catalase)	Increased levels of SOD and catalase antioxidants facilitate the conversion of free radicals (superoxide) into hydrogen peroxide and oxygen molecules. Inhibited the adverse actions of the free radicals, which prevented severe structural changes in the kidney, liver and pancreas.	Alloxan-induced diabetic rats	Raghavendra et al., 2019
	Fruits	Phenolic compounds, Anthocyanins, pyridoxine, niacin and flavonoid	Enhanced the functions of the β-cells in the pancreas. Causing a delay in carbohydrate Digestion and exhibit α-glucosidase inhibitory Activity.	-	Raghavendra et al., 2022
Rubus ulmifolius	Aerial parts	Saponins, flavonoids, glycosides, cardiac anthraquinone glycosides, carbohydrates, terpenoids, phenolic compounds, alkaloids, tannins, proteins and amino acids	Inhibition of carbohydrate digestive enzymes especially of a-glucosidase and pancreatic alpha-amylase	either sex (male and female) albino mice	Akhtar et al., 2017

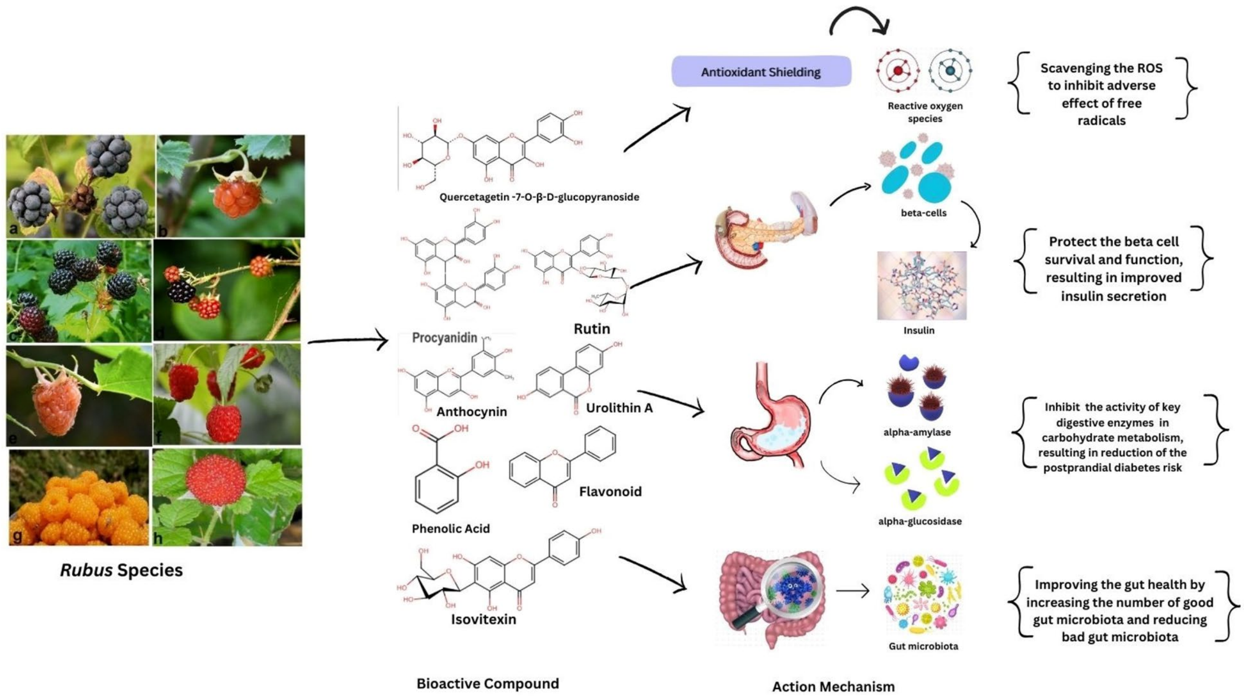


Fig. 3 Antihyperglycemic mechanism of action of bioactive compounds found in *Rubus* species

Ser256-phosphorylated FoxO1 and Ser473-phosphorylated Akt. Procyanidins facilitate the maintenance of Pdx1 levels by affecting FoxO1 (Cox & Kushner, 2017). Sun et al., (2020) reported that after exposure to palmitate, there was an increase in Bax and a decrease in Pdx-1. Procyanidins reversed these effects. This reversal is mediated through the Akt/FoxO1 pathway, confirming that procyanidins can activate the PA-induced suppression of the PI3K/Akt/FoxO1 signaling pathway.

Most *Rubus* species have high concentrations of phenolic compounds. These phenolic compounds (phenolic acids, ellagitannins, anthocyanins, flavanols, proanthocyanidins, flavonols, etc.) help cells increase the consumption and uptake of glucose. A high concentration of phenolic compounds promotes Akt phosphorylation and AMPK. It also activates AMPK through an insulin-independent mechanism. Additionally, it can inhibit the production of hepatic glucose by influencing the regulation of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase. Deactivation of glucose-6-phosphatase and phosphoenolpyruvate carboxykinase expression inhibits gluconeogenesis in hepatocytes. Another phenolic compound found in this plant is flavonoids. Flavonoids increase the expression of GLUT-2 in the beta cells of the pancreas, which helps to regulate glucose levels. Moreover, flavonoids can promote and upregulate the translocation of glucose transporter type 4 through the AMPK, PI3K/AKT, and CAP/Cb1/TC10 pathways. Flavonoids also preserve the survival of beta cells by hindering NF-κB signaling and increasing insulin secretion. Anthocyanina are phenolic compounds found in this species. Anthocyanin can stimulate AMP-activated protein kinase, resulting in an increase in the uptake of glucose in skeletal muscle and liver cells. A major metabolite of ellagitannins, urolithin A, is found in one of the *Rubus* species, *Rubus chingii, and* can enhance the pancreatic function index of HOMA-β, decrease the fasting level of glucose and increase Akt phosphorylation levels (Huo et al., 2021; Safarzad et al., 2020).

Quercetagetin-7-O-β-D-glucopyranoside is a flavonoid compound found in *Rubus corchorifolius*. A molecular docking study was conducted on the flavonoid quercetin-7-O-β-D-glucopyranoside. This study model revealed that this compound had a stable binding configuration within the active site of α-glucosidase. This stability was attributed to interactions with amino acid residues via hydrogen bonds. This binding showed that quercetin-7-O-β-D-glucopyranoside has strong inhibitory effects on α-glucosidase. Similarly, this compound binds to α-amylase and has inhibitory effects. This inhibitory effect of quercetin-7-O-β-D-glucopyranoside was examined by a molecular docking model, which showed that this compound had a high affinity for binding to α-amylase and α-glucosidase. In conclusion, the flavonoids found in *Rubus corchorifolius* can hinder postprandial diabetes via the inhibition of α-amylase and α-glucosidase (Tian et al., 2021; Zhang et al., 2020). Some of the other polyphenols (cyanidin-3-retinoid, epigallocatechin gallate) and flavonoids (procyanidin C3, rutin, isovitexin) were also found in *Rubus corchorifolius* and are also responsible for the inhibition of the activity of the digestive enzymes α-amylase and α-glucosidase by forming stronger hydrogen bonds with the active sites of amino acid residues (Li et al., 2023). In addition, some other *Rubus* species show inhibitory effects on α- and β-glucosidases (Akhtar et al., 2017; Ayele et al., 2021; Spínola et al., 2019).

Future scope

Over the last few decades, there has been a rising awareness of natural remedies and the discovery of their antidiabetic properties for developing natural products and drugs for managing hyperglycemia. There are several reasons why people choose natural remedies as alternatives to conventional diabetic treatments. Compared to pharmaceuticals and conventional medicines, natural remedies are considered more natural and holistic, have fewer adverse effects, and improve general health and blood sugar control because they are high in fiber, antioxidants, and other minerals.

Currently, a plethora of natural remedies, including various fruits and berry products, are readily available. These offerings provide a growing demand for holistic approaches to health and wellness, particularly in managing conditions such as diabetes. Moreover, nature provides us with an abundance of fruit-bearing plants, many of which show remarkable anti-diabetic properties. This diversity in fruit species presents an exciting avenue for research and innovation in the realm of natural remedies, offering the potential for effective and sustainable solutions for individuals seeking to manage their diabetes through dietary and natural means. According to many researchers, extracts and bioactive compounds isolated from different *Rubus* species have shown significant antihyperglycemic effects and can be considered promising approaches for resolving problems related to diabetes management. Research shows that this species contains natural antioxidants (polyphenols, flavonoids, and antioxidant enzymes), which reduce the risk of diabetes. Although this species has remarkable antidiabetic properties, some limitations need further research. These limitations include an insufficient number of clinical studies, the lack of specific active compounds of some of the species, and the lack of knowledge of the mechanism of action of active compounds for some species, for which more in-depth research and development are needed. There are no studies available on the commercial use of *Rubus* extract as an antidiabetic agent.

Future research on the antidiabetic properties of *Rubus* species will integrate cutting-edge scientific discoveries with conventional wisdom. This strategy aims to find the active ingredients as well as the mode of action of *Rubus* plants via clinical research to determine how these plants might effectively control diabetes. Future endeavors will concentrate on tackling current constraints, such as the absence of active ingredients and inadequate clinical evidence. Innovation in the creation of novel, culturally proper antidiabetic treatments derived from *Rubus* species will be fueled by cooperation between traditional healers, scientists, and pharmaceutical corporations. This multidisciplinary strategy, which draws from both conventional wisdom and state-of-the-art research, promises safer and more efficient treatment alternatives for people with diabetes.

Currently, there is limited literature on the potential use of certain *Rubus* species to treat diabetes in ongoing clinical trials or human studies. These plants may have medicinal and nutritional properties that are beneficial for the management of diabetes according to in vivo and in vitro studies or experiments. The bioactive compounds in *Rubus* species, which may influence glucose metabolism, are highlighted by promising findings from studies involving animals or isolated cells. Nevertheless, it is still necessary to examine whether these results can be beneficial in human applications due to the lack of a complete trial in humans. The current literature, despite the lack of directly observed evidence in humans, points to a promising foundation for further studies on the medicinal potential of *Rubus* species and reiterates the need for intense clinical trials demonstrating their efficacy and safety among people with diabetes.

Food supplements and ingredients of *Rubus* species

The various supplements and food ingredients available by different manufacturers are given in Table 3. Berries in the *Rubus* family, which include blackberries, raspberries, and other varieties, are highly valued for their nutritional content and powerful health advantages. Utilizing the antioxidant power of blackberries (*Rubus fruticosus*), Bionutricia Manufacturing Sdn. Bhd. provided a powdered extract of this fruit. The nutritious food supplement Sarandrea *Rubus idaeus* is made from *Rubus idaeus* and is sold by Sarandrea Marco & C. Srl. Raspberry powder from *Rubus idaeus*, a source of essential vitamins and minerals, is sold by Naturmed Scientific. Forza Vitale presents Les *Rubus idaeus* Integratore Alimentare, a nutritional supplement that uses the abundance of nutrients in *Rubus idaeus*. Fruitaco India manufactures

Table 3 Food supplements and ingredients of *Rubus* species

S.No.	Product	*Rubus* species	Manufacturer
1	Blackberry (*Rubus fruticosus*) extract powder	*Rubus fruticosus*	Bionutricia Manufacturing Sdn. Bhd. (915789-W)
2	Sarandrea *Rubus Idaeus* Food Supplement 50 ml Mg	*Rubus idaeus*	Sarandrea marco &c. Srl
3	Raspberry Powder	*Rubus idaeus*	Naturmed scientific
4	Les *Rubus Idaeus* Integratore alimentore	*Rubus Idaeus*	Forza vitale
5	Mala's raspberry mocktail	Species not mentioned	Mala's
6	Fruitaco Teasing Raspberry Syrup	Species not mentioned	Fruitaco India
7	Red raspberry/Palmleaf Raspberry Fruit	*Rubus idaeus*	Top of Form UBNA Distribution LLC Bottom of Form
8	Raspberry Ketones	Species not mentioned	Fresh Healthcare
9	Raspberries dried whole	Species not mentioned	Bakers Fantasy
10	Super Reds Dietary supplement	Raspberry (Species not mentioned)	Windmill Health Products
11	Raspberry Extract	Raspberry (Species not mentioned)	Bulk supplements.com

Fruitaco Teasing Raspberry Syrup, a wonderful fruity delight, while Mala's Raspberry Mocktail entices tastes with the flavor of raspberries. UBNA Distribution LLC utilizes the benefits of *Rubus idaeus* to provide red raspberry/palm leaf raspberry fruit. Because of the health benefits of raspberries, Fresh Healthcare has Raspberry Ketones. With the berries' inherent goodness preserved, Bakers Fantasy offers Dried Whole Raspberries. The Super Reds Dietary Supplement from Windmill Health Products uses the health-promoting properties of raspberries. Raspberry extract, which concentrates the nutritious value of raspberries in a handy form, is offered by Bulk supplements.com. These dietary supplements and culinary ingredients derived from the *Rubus* genus offer a tasty and nourishing approach to promote general health.

Human studies and ongoing trials on *Rubus* species

The study on Rubus occidentalis (RO) extract's impact on metabolic parameters in prediabetic patients through a 12-week, double-blind, placebo-controlled trial (An et al., 2016). Patients ($n = 44$) received either a placebo, low-dose RO extract (LRE), or high-dose RO extract (HRE). HRE significantly reduced postprandial glucose levels compared to placebo ($p < 0.05$) and increased Homoeostasis Model Assessment-B ($p < 0.05$). Additionally, HRE dose-dependently decreased serum levels of monocyte chemoattractant protein-1 and oxidized low-density lipoprotein ($p < 0.05$). These results suggest RO extract's potential in managing glycemia and vascular inflammation in prediabetic patients, supporting further exploration of its therapeutic benefits (An et al., 2016). The study of Gowd et al., (2018) demonstrated that gastrointestinal digestion (GID) and gut microbiota fermentation (GMF) enhance the antioxidant capacities of blackberry (*Rubus* species) polyphenols. Blackberry supplementation increased glucose consumption and glycogen content in HepG2 cells post-GID and GMF. It also mitigated high glucose plus palmitic acid-induced ROS overproduction, restored glutathione, and maintained mitochondrial membrane potential. Their findings suggest blackberry polyphenols possess potent antioxidant and antidiabetic activities even after GID and GMF, promoting their potential as functional foods for maintaining good health. Moreno Uclés et al., (2022) performed a robust experimental design to elucidate the protective effects of (poly)phenols against diabetes, along with identifying potentially implicated metabolites. They administered oral doses of red raspberry (*Rubus idaeus*) (123 g/day for 2 weeks) to patients with type 2 diabetes mellitus (T2DM), monitoring blood samples for insulin resistance (IR) biomarkers and phenolic metabolites pre- and post-feeding. The study revealed a decline in Homeostatic model assessment- Insulin resistant (HOMA-IR) following red raspberry intervention, while several (poly)phenol metabolites were identified, suggesting their ability to penetrate internal tissues.

Moreno Uclés, (2019) reported that red raspberry (RR) extracts, rich in anthocyanins and ellagitannins, were studied for their effects on diabetes biomarkers. In a trial with type 2 diabetes mellitus (T2DM) and prediabetic patients, consuming one RR serving daily for 2 weeks showed promising outcomes. Phenolic metabolites like urolithins were detected post-feeding, indicating RR's potential in diabetes management. While reductions in inflammation (hsCRP, $p = 0.01$) and a trend in insulin resistance (HOMA-IR, $p = 0.0584$) were observed, anthocyanin-derived metabolites showed non-significant increases. Although DOPAC, a RR metabolite, didn't stimulate insulin secretion, the study underscores RR's capacity to modulate diabetes-related biomarkers (Moreno Uclés et al., 2022).

The extensive exploration of various *Rubus* species has unveiled their potential antidiabetic properties in human subjects. However, to comprehensively understand and harness the therapeutic benefits, further investigations across diverse *Rubus* species are imperative. Delving deeper into the antidiabetic activity of these distinct species in human trials promises to unveil novel insights and therapeutic avenues, propelling the quest for effective natural remedies against diabetes to new heights.

Conclusion

Currently, there is increasing interest in the development of natural antidiabetic treatments, particularly from plant sources, to manage the complexities of diabetes and the associated complications. Recent studies have highlighted the potential of active compounds and crude extracts derived from many *Rubus* species to exhibit notable antidiabetic activity in both in vivo and in vitro models. Specifically, compounds isolated from *Rubus* species have been shown to ameliorate diabetes-related complications in animal models induced by agents such as streptozotocin and alloxan. Among the diverse *Rubus* species, those with strong antidiabetic potential include *Rubus chingii Hu*, *Rubus idaeus*, *Rubus ulmifolius*, *Rubus fruticosus*, and *Rubus amabilis*.

These *Rubus* species have been found to exert their antidiabetic effects through several mechanisms, including stimulating insulin secretion, increasing hepatic glycogen synthesis, inhibiting key digestive enzymes, enhancing the functions of β-cells in the pancreas, augmenting peripheral glucose uptake, and improving antioxidant status. This review underscores the need for further scientific exploration and investigation for developing effective antidiabetic medications derived from natural sources, chiefly focusing on *Rubus* species. Although extracts and bioactive compounds from diverse *Rubus* species have demonstrated noteworthy antidiabetic effects, there is insufficient understanding of their mechanism of action and a scarcity of experimental studies. Therefore, additional research involving the isolation, identification, and comprehensive examination of antidiabetic molecules, as well as clinical trials, is urgently needed to facilitate the development of effective antidiabetic drugs derived from *Rubus* species.

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