VOLUME 11 ISSUE 2 2025

ISSN 2454 – 3055

INTERNATIONAL JOURNAL OF ZOOLOGICAL INVESTIGATIONS

Forum for Biological and Environmental Sciences

Published by Saran Publications, India

International Journal of Zoological Investigations Vol. 11, No. 2, 424-439 (2025)

International Journal of Zoological Investigations

Contents available at Journals Home Page: www.ijzi.net

Editor-in-Chief: Prof. Ajai Kumar Srivastav

Published by: Saran Publications, Gorakhpur, India

ISSN: 2454-3055

Secondary Metabolites: Sustained Releasing Factor of Glucose in Diabetes Mellitus

Upasana[1], Yadav Latika[2], Yadav Rajesh[3], Arya Pratibha[4] and Maurya Neelesh Kumar[5]*

[1]Department of Home Science, Mahila College Dalmia Nagar, Dehrion Sone, Rohtas, Veer Kunwar Singh University, Ara, Bihar, India

[2]Department of Home Science, Vijay Singh Pathik Government PG College, Karina, Shamli, Uttar Pradesh, India

[3]Department of Dialysis Technology, Sharda School of Allied Health Science, Sharda University, Greater Noida, Uttar Pradesh 201310, India

[4]Department of Home Science, Institute of Home Science, Bundelkhand University, Jhansi, India

[5]Department of Nutrition and Dietetics, School of Allied Health Science, Sharda University, Greater Noida, Uttar Pradesh, India

**Corresponding Author*

Received: 29th September, 2024; **Accepted:** 22nd July, 2025; **Published online:** 9th September, 2025

https://doi.org/10.33745/ijzi.2025.v11i02.040

Abstract: Secondary metabolites are chemical compounds produced by plants through specialized metabolic pathways. These substances play a crucial role in protecting plants from pathogens by functioning as antibiotics, antifungal agents, and antiviral compounds. Due to their protective properties, secondary metabolites are valuable in treating various metabolic disorders, including diabetes mellitus and obesity. Key compounds such as flavonoids, polyphenols, anthocyanins, saponins, tannins, polysaccharides, coumarins, and terpenes are naturally active ingredients found in plants. These compounds may help protect pancreatic beta cells from damage, restore insulin signaling, reduce oxidative stress and inflammation, activate AMP-activated protein kinase (AMPK), and enhance insulin sensitivity. In managing diabetes and obesity, individuals must consume foods rich in secondary metabolites, such as fruits and vegetables. These natural foods may slow down carbohydrate digestion, offering a more sustained release of glucose into the bloodstream. By improving blood sugar regulation and assisting in weight management, the consumption of secondary metabolites can significantly lower the risk of developing diabetes and obesity. Overall, including these plant-derived compounds in the diet can contribute to better metabolic health and enhance global well-being.

Keywords: Secondary metabolites, Blood sugar, Phytochemicals, Flavonoids, Polyphenols, Anthocyanins, Saponins, Tannins, Polysaccharides, Coumarins, Terpenes, Diabetes mellitus

Citation: Upasana, Yadav Latika, Yadav Rajesh, Arya Pratibha and Maurya Neelesh Kumar: Secondary metabolites: Sustained releasing factor of glucose in diabetes mellitus. Intern. J. Zool. Invest. 11(2): 424-439, 2025.

https://doi.org/10.33745/ijzi.2025.v11i02.040

Introduction

Plants are recognized to make a couple distinct types of biochemical compounds: primary and secondary metabolites. Park *et al.* (2021) examined the essential significance of primary metabolites in plant growth and development, asserting that plant survival is unattainable without them. Primary metabolites are important compounds that are part of a cell's core metabolic processes. Proteins, carbs, and lipids are some of them (Jeon *et al.*, 2021). Secondary metabolites are those that don't immediately help with growth and development. For example, alkaloids, resins, gums, latex, and tannins. Various organisms synthesize organic compounds referred to as secondary metabolites (Gajger *et al.*, 2021).These organic compounds are not directly involved in the expansion, development, or reproduction of the organism; however, they are essential to the functioning of the ecosystem and other activities. Some scientists refer to secondary metabolites as specialized metabolites, while others call them natural products. The absence of secondary metabolites has a negligible to nonexistent impact on the organism's ability to live and thrive because these substances do not contribute to the expansion and maturation of the organism. On the other hand, after a sufficiently long period, a few insignificant effects might become apparent. Some secondary metabolites are unique to a species and can only be found in that species (Pagare *et al.*, 2015).

Secondary metabolites may be important for activities such as protection, competition, and species interaction, even though they are not necessary for the organism's continued existence. The metabolic pathway that a secondary metabolite takes allows for its categorization into distinct classes. Several forms of secondary metabolites are derived from primary metabolites depicted in Figure 1.

In most organisms, this type of cell also forms during the stationary phase of the growth cycle. The term "idiophone" refers to this stage of the growth process. Many secondary metabolites tend to operate as a form of defense mechanism against a variety of alien invaders. These are typically made in much smaller quantities and are notoriously difficult to extract. Certain classes of secondary metabolites have been used in a variety of biotechnological processes, which have led to the production of various drugs and other compounds. Because secondary metabolites are unique to each species, different secondary metabolites are necessary for the completion of the various processes. The terms "steroids," "essential oils," "phenolics," "alkaloids," "pigments," and "antibiotics" are all examples of secondary metabolites. Secondary metabolites, produced by plants to aid their survival and growth, often arise from intermediates in metabolic pathways like photosynthesis, glycolysis, and the Krebs cycle (Pagare *et al.*, 2015; Sinha *et al.*, 2022).

Phytomedicine, a branch of complementary and alternative medicine (CAM), involves the use of plant-based remedies. As defined by the World Health Organization (WHO), herbal medicine is aimed to preserve health and address illness (Das *et al.*, 2022; Badilla *et al.*, 2022). Traditional herbal medicines, derived from plants with minimal processing, are used in local or regional healing practices to treat various ailments (Jeon *et al.*, 2021).

Metabolism encompasses the totality of biochemical reactions within an organism. Metabolites, the products and intermediates of these reactions, are generally smaller molecules. The term "secondary," coined by Kossel in 1891, distinguishes these metabolites from primary metabolites, which are universally present in dividing cells. Secondary metabolites, while not essential for immediate survival, can significantly impact an organism's ecological fitness. Their presence or absence can differentiate ecologically disadvantaged species within a phylogenetic group (Badilia *et al.*, 2022). The distinction between primary and secondary metabolites can be challenging, as many intermediates in these

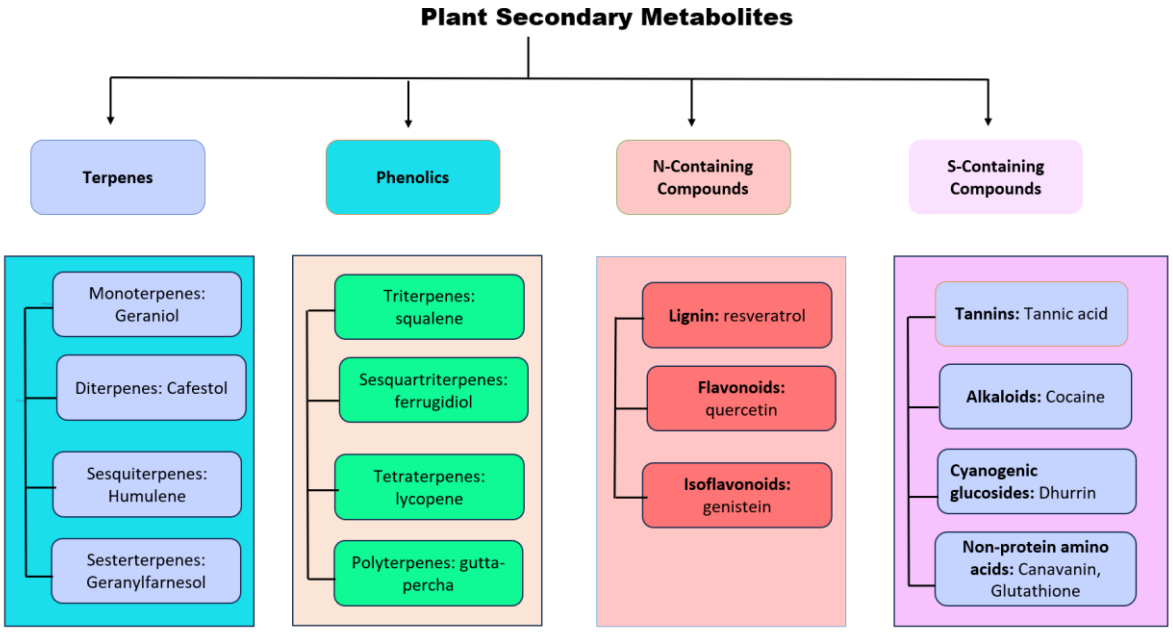

Fig. 1: Classification of plant secondary metabolites (Source: Twaij and Hasan, 2022).

pathways overlap (Sinha *et al.*, 2022). While amino acids are typically considered primary metabolites, they can also be classified as secondary metabolites. Conversely, sterols, essential components of cellular structures, are considered secondary metabolites. The shared biochemical pathways between primary and secondary metabolism highlight their interconnected nature (Gajger *et al.*, 2021). Excess nitrogen and carbon are efficiently transferred into secondary metabolites, which act as a powerful buffer to create an inactive portion of primary metabolism (Twaij and Hasan, 2022). The highly efficient metabolic breakdown of secondary metabolites makes it easy and rapid to turn the stored carbon and nitrogen back into primary metabolites when needed. The balance between the primary and secondary metabolisms is constantly shifting because of growth, tissue differentiation, development, and external stimulation.It is crucial to maintain this balance to achieve optimal health and well-being (Hajam *et al.*, 2022; Thirumurugan *et al.*, 2018).

Classification of secondary metabolites

Figure 1 illustrates that secondary metabolites are classified into about 2,140,000 different types and have varied structures, functions, and production methods. These metabolites can be categorized into five primary types: alkaloids, non-ribosomal polypeptides, fatty acid-derived compounds and polyketides, terpenoids and steroids, and enzyme cofactors (Twaij and Hasan, 2022).

(i) *Terpenoids and steroids*: Terpenoids are the largest group of compounds derived biosynthetically from isopentenyl diphosphate. There are already more than 35,000 recognized steroid and terpene molecules.

(ii) *Alkaloids*: Alkaloids comprise more than 12,000 identified chemicals, which are biosynthetically produced from amino acids and have basic amine groups as part of their structures.

(iii) *Fatty acid-derived substances and polyketides*: The biosynthesis of over 10,000 molecules unequivocally occurs from basic acyl precursors such as acetyl CoA, propionyl CoA, and methyl malonyl CoA.

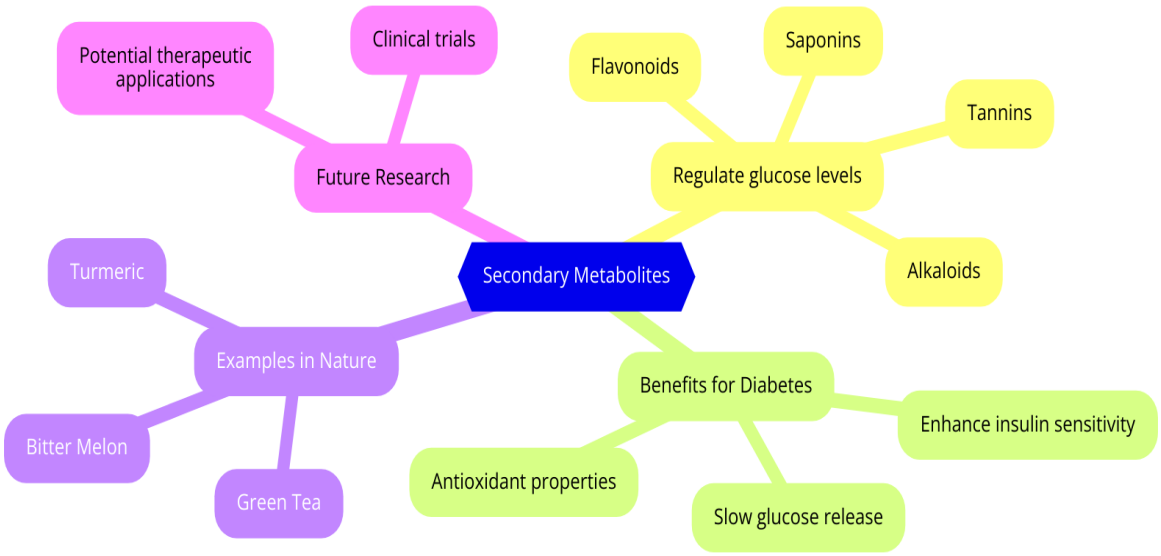

Fig. 2: Secondary metabolites: sustained releasing factor of glucose in diabetes mellitus.

(iv) *Non-ribosomal polypeptides*: Non-ribosomal polypeptides are unique peptide natural products made by huge, multifunctional enzyme complexes known as non-ribosomal peptide synthetases. They are made without mRNA and ribosomes and frequently have cyclic or branched structures, non-proteinogenic and D-amino acids, and several types of tailoring (methylation, glycosylation, halogenation). They are the building blocks of numerous antibiotics, siderophores, poisons, and immunosuppressants.

(v) *Enzyme co-factor*:

Enzyme cofactors refer to low-molecular, nonprotein components of an enzyme that help in catalytic activity.

Functions of secondary metabolites

Antibiotics and other secondary metabolites serve the following main purposes: (i) defense response, i.e., competitive weapons meant to destroy other living organisms, including plants, animals, insects, and microbes; (ii) transporting metals; (iii) symbiotic agents; (iv) reproductive agents; (v) effectors of differentiation; and (vi) agents of interspecies communication. Additional roles of secondary metabolites include interference with spore formation and germination, acting as antimicrobial agents (Thirumurugan *et al.*, 2018).

Figure 2 depicts that numerous historically employed plants treating viral infections have been investigated. It has been discovered that some extracted substances, such as flavonoids, phenols, polyphenols, and terpenes (such as mono-, di-, and tri-), are effective against the HSV virus (Park *et al.*, 2021). People use plant-derived flavonoids for their health advantages, and research has demonstrated that these compounds have viral activity against HCMV. From *Cladosporium* species (spp.) PJX-41 fungi, 14 novel alkaloids were extracted that show inhibitory efficacy against the influenza virus A (H1N1) (Jeon *et al.*, 2021).

Recent research has revealed that numerous naturally occurring chemicals found in plants possess antidiabetic properties and offer multiple health benefits, making them a highly promising alternative therapeutic approach. These bioactive chemicals are readily available and cost-efficient, making them an attractive option for developing novel medication treatments. It is important to emphasize that consuming these chemicals regularly poses no health hazards. Therefore, it is imperative to consider these compounds' low cost and numerous benefits while exploring new therapeutic avenues. They have proven to be effective in treating a wide range of ailments and

reducing the chance of contracting new ones (Sinha *et al.*, 2022). In vitro and in vivo studies have shown that bioactive compounds isolated from plants can have beneficial effects, including lowering cholesterol, blood pressure, blood sugar, and oxidative stress (Lomartire *et al.*, 2022). Apart from these benefits, the bioactive substances have demonstrated their ability to lower blood glucose levels. This review aims to summarize various studies showing the anti-diabetic properties of flavonoids obtained from plants with detailed mechanisms. Because of its interactions with these molecules, the blood's secondary metabolite functions as a sustained realizing factor (Twaij and Hasan, 2022).

(a) *Inhibitors of α-Glucosidase*:

α-glucosidase is acrucial enzyme found in the small intestinal epithelium that plays a pivotal role in breaking down carbohydrates. It is tightly correlated with two other enzymes known as sucrase-isomaltose (SI) and maltase-glucoamylase (MGAM), both of which are also found in the intestinal brush boundary. α-glucosidase functions by breaking down linear α 1 ⟶4 and branching α 1 ⟶ 6 oligo linkages to release glucose from the non-reducing end (Adisakwattana, *et al.*, 2017; Kadar *et al.*, 2021). By significantly slowing down the absorption of glucose in the small intestine and delaying the breakdown of complex carbohydrates into glucose, inhibiting α-glucosidase can effectively and gradually lower postprandial blood sugar levels(Barber *et al.*, 2021).

(b) *Inhibitors of Glucose Co-transporter*:

Glucose, a crucial metabolic fuel derived from carbohydrate-rich meals, is absorbed from the intestinal brush border into the bloodstream. Specialized transport proteins facilitate the movement of glucose across cell membranes. Two groups of these glucose cotransporters can be distinguished (Barber *et al.*, 2021): (i) Glucose transporters reliant on sodium (SGLT), and (ii) Transporters of glucose that facilitate (GLUT).

(c) *Flavonoids as Hyperglycemia Regulators*:

It is a fact that dietary flavonoids play a crucial role in glucose metabolism. Numerous studies have demonstrated that flavonoids can effectively regulate insulin release through various signaling pathways and also inhibit glucose absorption after digestion (Thirumurugan *et al.*, 2018). This is made possible by flavonoids' simple inhibition of glucose transporters and enzymes that break down carbohydrates, which helps the blood circulation reach normoglycemia. These processes play a significant role in diabetes mellitus treatment strategies. Flavonoids improve growth and development, and enhance the defense mechanism of plants (Hasnat *et al.*, 2024).These are divided into six subclasses and share fifteen carbon skeletons. Flavonoids are used to treat diabetes and have antioxidant and health-promoting effects. They affect protein tyrosine phosphatase, insulin receptors, adenosine monophosphate-activated protein kinase, and peroxisome proliferator-activated receptor-gamma. They control glucose and fat metabolism along with insulin signaling pathway (Joshi *et al.*, 2024).

The bioavailability of flavonoids can be increased by using advanced delivery techniques such as enzymatic methylation, microencapsulation, nanosystems, and microemulsions. The ideal level of daily ingestion of flavonoids has not been established because of divergent molecular architectures and uneven bioavailability studies. The mutagenicity and genotoxicity of flavonoids were documented in mammalian investigations. Meals high in flavonoids would not cause them (Tungmunnithum *et al.*, 2018). However, consuming individual flavonoids did not seem to affect diabetes, and in fact, clinical trials indicated a higher risk. To better understand the efficacy, pharmacokinetics, and safety of individual flavonoids or standardized flavonoid combinations, further clinical trials are required (Yen *et al.*, 2021).

(i) *Quercetin*: Quercetin, a naturally occurring flavonoid found in various plant-based foods, has been shown to effectively lower blood glucose

levels in numerous studies. This compound interacts with multiple molecular targets in the body's skeletal muscles, pancreas, small intestine, and liver to regulate glucose absorption, promoting glucose homeostasis. Quercetin mediates hypoglycemia by inhibiting intestinal glucose metabolism, hepatic glucose transporter function, peripheral tissue glucose utilization, and protecting against pancreatic islet damage (Shehadeh *et al.*, 2021).

(ii) *Kaempferol*: Kaempferol is a prominent flavonoid found in plants. This compound exhibits potent antioxidant, anti-inflammatory, anticancer, and antidiabetic properties. The small intestine absorbs kaempferol and metabolizes it into conjugated forms, including glucuronide and sulfate. Kaempferol may control blood glucose levels, reduce the small intestine's absorption of glucose, and increase insulin levels (Yang *et al.*, 2022).

(iii) *Rutin*: The glycoside known as natural rutin (3′,4′5,7-tetrahydroxy-flavone-3-rutinoside) is a citrus flavonoid, widely distributed in plants. Rutin is also known as sophorin, rutoside, and quer-cetin-3-rutinoside. The term "rutin" originates from the plant Rue (genus Ruta), where it was initially isolated (Sok *et al.*, 2021). Rutin has been widely utilized in health supplements and medications in recent years. Numerous health benefits of rutin include strong antioxidants, the ability to scavenge free radicals, antidiabetic effects, and anti-inflammatory properties. Antioxidants have a key role in avoiding diabetes mellitus (DM), and low blood antioxidant levels are generally associated with an increased risk factor for the onset of chronic disease. Intestinal bacteria could break down rutin into smaller metabolites.Rutin is degraded and transformed into leucocyanidin (Shehadeh *et al.*, 2021).

(iv) *Naringenin*: Naringenin, a dietary flavonoid abundant in citrus fruits and grapefruits, has been shown to have antidiabetic, anti-dyslipidemic, anti-atherogenic, and anti-inflammatory properties. The results of *in vivo* and *in vitro* investigations have shown that naringenin lowers blood sugar levels. *In vitro*, naringenin improved glucose uptake in L6 myotubes and skeletal muscles by stimulating insulin signaling and translocating the glucose transporter GLUT4 through AMPK activation, thereby ameliorating insulin resistance (Natsume *et al.*, 2014). The antidiabetic activity of naringenin has been reported. It was found that naringenin enhanced skeletal muscle glucose uptake via AMPK activation (Shehadeh *et al.*, 2021).

(v) *Fisetin*: Fisetin, also known as 3,3′, 4′,7-tetrahydroxy flavone, is a flavan-3-ol with structural similarities found in cucumber, onion, strawberry, grape, apple, and persimmon plants, at concentrations ranging from 2 to 160 µg/g. Fisetin has anti-inflammatory and anti-hyperglycemic along with antiproliferative properties. Additionally, it is a potent compound with scientifically demonstrated antidiabetic effects. It efficiently minimizes methylglyoxal-dependent protein glycation and mitigates the risk of diabetes-related problems (Shehadeh *et al.*, 2021).

(vi) *Morin*: Morin is a naturally produced flavonoid that is an important ingredient of traditional medicinal herbs, especially those from the Moraceae family. It is a light-colored pigment that can be found in many plants, fruits, and wines (Shehadeh *et al.*, 2021). Additionally, morin can also be found in *Psidium guajava* or Indian guava. Guava is historically thought to be an effective plant for diabetes because it has antioxidant properties. In addition to its various health benefits for humans, morin has been shown to possess potent antioxidant, anti-allergic, anti-inflammation, and cardioprotective properties. It has been demonstrated that morin, an antioxidant that mimics insulin, has anti-diabetic properties (Paoli *et al.*, 2013; Verma *et al.*, 2024).

(d) *Tannins*:

Tannins are multifaceted polyphenolic compounds with a wide range of molecular weights. These compounds function as antioxidant enzyme activators and free radical scavengers, offering

potential health benefits. Studies have suggested that tannins prevent chronic diseases such as diabetes. By stimulating insulin signaling pathways, including GLUT-4 translocation, PI3K activation, and p38 MAPK activation, tannins can enhance glucose uptake. Furthermore, they promote the regeneration of beta cells, lower the quantity of glucose and other nutrients absorbed by the intestinal tract, and increase insulin action on adipose cells. The role of tannin has also been seen in neuropathic pain in diabetes (Omar *et al.*, 2022). Few studies investigated the potential benefits of phytochemical tannins on Diabetic neuropathic pain.

(e) *Dietary polysaccharides*:

Dietary polysaccharides are vital nutritional components present in different parts of plants. Sugars are another term for dietary polysaccharides. Dietary polysaccharides have extensively investigated due to low toxicity and wide range of pharmacological activity, they were studied. Dietary polysaccharides have numerous beneficial effects on human health, antioxidants, serum cholesterol reduction, and the management of diabetes(Indra Kusuma *et al.*, 2021; Shehadeh *et al.*, 2021).

(f) *Anthocyanins*:

A class of naturally occurring polyphenolic pigments known as anthocyanins is present in many kinds of plants. Many anthocyanidins have been investigated. The seventh kind of anthocyanidin is called petunidin. Table 1 summarizes several believed mechanisms for anthocyanins' antidiabetic benefits. Several studies, both *in vivo* and *in vitro*, have demonstrated their beneficial benefits on health. They have an impact on various signaling pathways involved in glucose metabolism (Sok *et al.*, 2021; Shehadeh *et al.*, 2021). Anthocyanins have been demonstrated to have anti-diabetic benefits due to their antioxidant and anti-inflammatory qualities, as well as their ability to inhibit the activity and overexpression of PTP1B protein, -amylase, -glucosidase, and DPP-IV enzymes. Anthocyanins can also block the enzymes amylase and glucosidase. The extract and its isolated components significantly improved insulin sensitivity as well as insulin resistance. Conversely, meals of anthocyanin-rich content were provided to individuals with type 2 diabetes. Across all research, there was a noteworthy reduction in insulin resistance and an enhancement in the lipid profile (Twaij and Hasan, 2022).

Retinol-binding protein 4 (RBP4), an adipocytokine that promotes insulin release, enhances insulin sensitivity, and preserves cell viability, is suppressed by anthocyanins. Furthermore, they trigger the AMPK pathway, which raises the expression of GLUT4 in skeletal muscle and adipose tissue.They can increase the expression of the adiponectin gene while decreasing that of the plasminogen activator inhibitor-1 and interleukin-6 genes. Additionally, they alter and activate those genes that are unique to adipocytes (lipoprotein lipase), PPAR expression, and insulin-glucose signaling pathways (Shehadeh *et al.*, 2021).

(g) *Alkaloids*:

In the plant kingdom, particularly among angiosperms, alkaloids are a collection of nitrogen-containing chemicals that are uncommonly distributed. This is particularly true of the alkaloid family. They are categorized as pyrrolidine, pyridine, quinoline, isoquinoline, indole, quinazoline, steroidal, diterpenoid, and other types of alkaloids depending on whether or not they include one or more nitrogen atoms within a heterocyclic ring. They exhibit a broad range of biological actions, including some that have a hypoglycemic effect. The therapeutic actions of alkaloids against diabetes involve multiple pathways and signaling cascades, which are comprehensively outlined in Tables 2 and 3.

When treating type-2 diabetes, alkaloids such as broussonetine and radicamine are regarded as excellent inhibitors of the enzymes α-glucosidase and α-amylase which are among the most efficient

Table 1: Effects of various plant secondary metabolites

Name of compound	Mechanism	References
Cyanidin	Activates AMPK and GLUT-4 translocation Reduces gluconeogenesis via inhibiting the gene expression of PEPCK and G6Pase. prohibit -glucosidase and -amylase. Enhance antioxidant status. Inhibit pancreatic apoptosis via stimulating insulin receptor phosphorylation	Shehadeh *et al.* (2021)
Delphinidin	Anti-inflammatory action. Defends against oxidative stress. Inhibits the activation of the NF-B and JNK signaling pathways. Protein tyrosine phosphatase 1B PTP1B expression is inhibited.	Xu *et al.* (2022)
Pelargonidin	Reduces the effects of oxidative stress. Raises the quantity of insulin released into the body.	Karim *et al.* (2014)
Apigenin	Speeds up the synthesis of glycogen and the release of insulin. Increases the translocation of glucose transporter 4 (GLUT4). Assists in keeping beta cells healthy. Enhances the parameters of antioxidants.	Shehadeh *et al.* (2021)
Baicalein	Turns on the AMPK pathway. Reduces inflammatory response and insulin resistance via phosphorylating IRS-1, Akt, and dephosphorylating JNK, NF-κB, ERK, and extracellular signal-regulated kinase (ERK).	Park *et al.* (2022)
Chrysin	Lessens the quantity of oxidative lipid damage. Reduces both inflammation and oxidative damage. Increase the blood's insulin concentration.	Shehadeh *et al.* (2021).
Diosmin	Lessens the body's exposure to oxidative damage. Encourages the synthesis of glycolytic enzymes, such as glucose-6-phosphate dehydrogenase and hexokinase. Prevents fructose and glucose-6-phosphatase, two gluconeogenic enzymes, from acting correctly.	Shehadeh *et al.* (2021)
Daidzein	Increases the phosphorylation of AMPK in muscles. Increases insulin sensitivity. Restricts the activity of G6Pase, PEPCK, and other enzymes to prevent the production of gluconeogenesis. Encourages the liver to process fats more healthfully. Suppresses the glucosidase and amylase enzymes' activity.	Laddha *et al.* (2024)
Eriodictyol	Increases glucose absorption in tissues and improves insulin secretion and PI3K/Akt pathway function. Mitigates the effects of oxidative stress. Up-regulates mRNA expression of PPARγ. Facilitates PI3K/Akt signalling pathways. Increases insulin sensitivity and secretion. Promotes an increased absorption of glucose in tissues. Mitigates the effects of oxidative stress. The action of results in an increase in PPARγ mRNA expression.	Shehadeh *et al.* (2021)
Genistein	Boost β-cell quantity. Reduces the activity of G6Pase, PEPCK, and other enzymes	Shehadeh *et al.* (2021)

	to inhibit gluconeogenesis. Improves the hepatic lipid metabolism's efficiency. Tyrosine kinase activity is stifled as a result of this compound's presence. Targets the production of AKT and ERK1/2 to protect Langerhans islet cells, and it protects the pancreas by lowering caspase-3 levels and increasing levels of the anti-apoptotic Bcl-2 protein, cAMP, and protein kinase. A route activation causes the blood's glucose level to drop.	
Fisetin	Reduces the amount of glycogen that is broken down. Reduces gene expression of gluconeogenic genes such phosphoenol pyruvate carboxykinase. Inhibits gluconeogenesis. Increases plasma insulin.	Qin *et al*. (2022)
Kaempferol	Boosts the body's ability to absorb glucose. Boosts the generation of antioxidants. Inhibit apoptosis. cAMP signaling is improved, and there is an increase in insulin production and secretion. Decreases the amount of caspase-3 activity in cells.	Shehadeh *et al.* (2021).
Luteolin	PPAR transcriptional activation is increased as a result. Increases the amount of insulin that is secreted.	Shehadeh *et al.* (2021).
Neohesperidin	Has properties that act as antioxidants as well as anti-inflammatory agents. Activates PPAR in the body. Promotes higher levels of GLUT4 expression in adipose tissue. Suppresses the expression of PEPCK and G6Pase, resulting in a decreased glucose production from the liver.	Dinda *et al.* (2022)
Naringenin	Inhibits the -glucosidase in the gut. Minimizes the quantity of gluconeogenesis that takes place and enhances the level of antioxidants. Improves the absorption of glucose. Leads to an increase in GLUT-4 translocation. Leads to an increase in AMPK activation. Results in increased insulin synthesis.	Shehadeh *et al.* (2021).
Naringin	Activates the PPAR receptor. Increases AMPK activity and has a stimulatory effect on glucose absorption. Inhibits DPP-4 enzyme. Safeguards the system of antioxidant defense. Suppresses the expression of PEPCK and G6Pase, resulting in a decreased glucose production from the liver. Reduce the generation of cytokines that promote inflammation.	Bahmani *et al.* (2014)
Morin	Increases the amount of phosphorylation at the insulin receptor, as well as at Akt and FOXO1 Boosts the body's ability to produce glycogen; Improves the antioxidant activity of the body. Hinders gluconeogenesis. Decreases the levels of the pro-inflammatory cytokines IL-1 and IL-6. Both leptin and hepatic insulin sensitivity are restored to normal.	Shehadeh *et al.* (2021).

Quercetin	Reduces the damaging effects of free radicals and oxidative stress. Increases the amount of glucose transporter type 4 (GLUT4) that is translocated in skeletal muscle. Stops the hepatocyte cells' glucose-6-phosphatase, or G6Pase, from functioning. GLUT2 inhibition leads to a decrease in glucose absorption in the intestinal tract.	Indrakusuma *et al.* (2014)
Rutin	Anti-apoptotic activity. Effects on the activities of G6Pase and glycogen phosphorylase. Activates the production and translocation of GLUT-4 in the muscle. The expression of PPAR- is stimulated as a result. Reduces the overall amount of oxidative stress in the body. Inhibit both glucosidase and alpha-amylase. Causes an increase in insulin secretion. Raise the level of hexokinase activity in the liver. Helps to improve the overall morphology of Langerhans islets. Activation of mitogen-activated protein kinase increases the amount of glucose taken in by tissues (MAPK).	Indrakusuma *et al.* (2014)
Resveratrol	Reduces the production of cytokines that contribute to inflammation. Boosts the activity of antioxidant enzymes; Accelerates the burning of fatty acids in the body. Results in an increase in the activity of pyruvate kinase and hexokinase. Activates glycogen synthase while suppressing glycogen phosphorylase, which increasesincreases the amount of glycogen found in the liver. PI3K-AKTsignaling is increased, which leads to an increase in GLUT-4 translocation in muscle. Inhibits the activities of glycogen-6-phosphatase, phosphoenolpyruvate carboxykinase, and lactate dehydrogenase.	Indrakusuma *et al.* (2014)
Pterostilbene	Improves insulin sensitivity. Reduces levels of gluconeogenic enzymes. Lowerlevels of proinflammatory cytokines. Encourages the growth of signaling pathways associated with antioxidants. Hexokinase expression is stimulated, which is a benefit to the glycolytic pathway.	Bahmani *et al.* (2014)

strategies to reduce blood glucose levels (Thirumurugan *et al.*, 2018). Dipeptidyl peptidase-4 (DDP-4) (GIP) is blocked by alkaloids like bebeerine, which breaks down gut incretin hormones like glucagon-like peptide-1 (GLP-1) and stomach inhibitory polypeptide. Increased insulin production and release, inhibition of stomach emptying, which immediately lowers food intake, and prevention of glucagon release from -cells in the islets of Langerhans are the outcomes of inducing cell differentiation. Adenosine monophosphate (AMP) stimulated protein kinase regulates the glucose transporter and acts as a fuel sensor within cells. It accomplishes this by promoting the absorption of glucose and regulating insulin secretion. Because certain alkaloids operate as allosteric activators of AMPK, their presence can enhance the enzyme's enzymatic activity (Indrakusuma *et al.*, 2014).

(h) *Dietary Phenols*:

Natural antioxidants are a diverse group of

Table 2: Alkaloid and terpenes alkaloids act as a sustained releasing factor

Name of compound	Type of Alkaloid	Mechanism	References
Berberine	Isoquinoline	AMPK is activated, which results in increased glucose uptake. Protein tyrosine phosphatase 1B is inhibited, which results in decreased glucose uptake (PTP1B). Inhibits DDP-4 enzyme. Improves insulin sensitivity by inducing a rise in the synthesis of glucagon-like peptides peptide 1 (GLP-1) via the interaction of leptin and adipokines. Increases the expression of the glucose transporter GLUT-1, which in turn stimulates glucose absorption. Suppresses oxidative stress	Shehadeh *et al.* (2021)
Evodiamine	Quinolone	Enhances insulin resistance by influencing PPAR-γ and AMPK.	Zhang *et al.* (2014)
Glycosin	Quinazoline	Proven to interact with PPAY, PTP-1B, the insulin receptor, and DPP-IV.	Shehadeh *et al.* (2021).
Lupanine	Quinolizidine	Blocks KATP channels while simultaneously boosting the production of the INS-1 gene. Increases the amount of insulin that is secreted in response to glucose.	Indrakusuma *et al.* (2014)
Neferine	Isoquinoline	Enhances the body's insulin-responsiveness.	Shehadeh *et al.* (2021)
Piperine	Piperidine	Insulin resistance decreases to baseline values. Adiponectin and AMPK levels are impacted, which restores the plasma insulin concentration. Reduces the amounts of NF-kB and inflammatory cytokines including TNF- and IL-1.	Ramírez-Moreno *et al.* (2014)
Oxymatrine	Quinolizidine	This protein protects the architecture of pancreatic tissue from harm.	Shehadeh *et al.* (2021)
Trigonelline	Pyridine	Raises the ratio of glucose phosphatase to glucose kinase (G6Pase). Increase GLUT4 expression Elevates the levels of serum insulin. Promote cellregeneration and lessencell damage. Inhibits oxidative stress.	Dabur *et al.* (2018)
Vidoline	Indole	Boosts the release of insulin. The activity of protein tyrosine phosphatase-1B (PTP1B) is reduced.	Shehadeh *et al.* (2021)

Table 3: Terpenes alkaloid acts as a sustained releasing factor

Name of compound	Mechanism	References
Basicacid	Increases the flow of insulin from the pancreas.	Indrakusuma *et al.* (2014)
Limonene	Increase the body's natural ability to fight free radicals. Stimulates a higher level of activity in the glycolytic enzyme. Encourages the production of insulin.	Shehadeh *et al.* (2021)
Stevioside	Insulinotropic. Glucagonostatic. Maintains β-cells.	Shehadeh *et al.* (2021)
Rebaudioside	Insulotropism-related activities. Intensifies the process of glycolysis. Gluconeogenesis is inhibited.	Indrakusuma *et al.* (2014)
Lupeol	Lowers the body's level of oxidative stress. Limits the ability of PTP1B to perform its duties. Inhibits the action of glucosidase and alpha-amylase.	Shehadeh *et al.* (2021)
Betulin	Inhibits α-glucosidase. Activates the AMPK pathway, which results in increased glucose absorption. Increases the amount of glucose transporter-4 mRNA that is produced. Insulin production is stimulated as a result. Encourages the build-up of muscle glycogen. Enhances the function and quantity of beta cells.	Indrakusuma *et al.* (2014)

bioactive secondary metabolites derived from the acetate and shikimate pathways. They include simple phenols such as phenolic acids, coumarins, lignans, lignins, stilbenes, hydrolyzable and condensed tannins, and flavonoids, which encompass isoflavones, anthocyanins, flavans, flavonols, flavones, and flavanones (Thirumurugan *et al.*, 2018; Shehadeh *et al.*, 2021). While there are two distinct kinds of hydroxyl derivatives from simple phenols, hydroxybenzoic acid, and hydroxycinnamic acid derivatives are the only aromatic carboxylic acid that may be produced from them. The antidiabetic potential of a few distinct simple phenolic acids was investigated *in vivo* and in clinical settings. Several hydroxycinnamic acid derivatives, listed in Table 4, showed significant hypoglycemic effects (Shehadeh *et al.*, 2021).

Food-based phenols shield pancreatic islet cells, lessen beta-cell apoptosis, promote beta-cell growth, mitigate oxidative stress, trigger insulin signaling, cause the pancreas to release insulin, hinder the absorption of glucose, control gut microbiota, alter the inflammatory response, and prevent the development of advanced glycation end products (Shehadeh *et al.*, 2021).Consuming phenol-rich foods also lowers the chance of cardiovascular disease. The mechanism of phenol-based food depends on bioavailability and their metabolism. Phenolic compounds, known for their potent antioxidant properties, have shown promise in disease prevention. They exert direct and indirect antioxidant effects by activating protective enzymes and modulating signaling pathways. The presence of esterified or glycosylated groups influences their ability to neutralize free radicals. Phenolic acids may help manage diabetes by preventing postprandial hyperglycemia and reducing oxidative stress, a hallmark of the disease (Gupta *et al.*, 2018).

(i) *Stilbenoids*:

Stilbenoids are antibacterial chemicals that are synthesized to protect plants from fungi and poisons (Shehadeh *et al.*, 2021). They have distinct

Table 4: Phenols and Coumarins (sustained-release modulators)

(A) Phenolic acids and related phenols

Name of Compound	Mechanism	References
Caffeic acid	Raises insulin levels; increases cell viability; suppresses hepatic glucose synthesis	Ghazaly *et al.* (2025)
p-Coumaric acid	Activates AMPK; antioxidant and anti-inflammatory effects; increases insulin sensitivity; inhibits adipogenesis and gluconeogenesis; enhances cell function; modulates glucose-metabolism enzymes; reduces intestinal carbohydrate absorption; stimulates insulin secretion	Shehadeh *et al*. (2021)
Cinnamic acid	Reduces DPP-4 and PTP-1B activities; inhibits α-amylase and α-glucosidase; reduces gluconeogenesis; enhances glycolysis; upregulates PPARγ; raises adiponectin; stimulates insulin secretion	Adisakwattana (2017); Shehadeh *et al.* (2021)
Chlorogenic acid	Reduces gastrointestinal glucose absorption; activates AMPK; enhances insulin sensitivity; reduces oxidative stress	Shehadeh *et al.* (2021)
Ellagic acid	Increases insulin gene expression in β-cells; reduces oxidative stress and inflammation	Manhivi *et al.* (2022)
Ferulic acid	Decreases hepatic glucose-6-phosphatase and PEPCK; increases glucokinase activity	Shehadeh *et al.* (2021)
Gallic acid	Reduces gluconeogenesis; increases insulin secretion (via oxidative-stress alleviation); enhances glycolysis and cell regeneration; promotes GLUT4 translocation; inhibits NF-κB activity and pro-inflammatory cytokines	Indrakusuma *et al.* (2014)
Hydroxycinnamic acid (class)	Reduces gluconeogenesis; increases insulin secretion (via oxidative-stress alleviation); enhances glycolysis and cell regeneration; promotes GLUT4 translocation; inhibits NF-κB activity and cytokines	Shehadeh *et al.* (2021)
Protocatechuic acid	Inhibits α-amylase and α-glucosidase; promotes GLUT4 translocation; increases adiponectin secretion; upregulates PPARα/PPARγ; increases hexokinase activity; reduces G6Pase, fructose-1,6-bisphosphatase, and sorbitol dehydrogenase activities	Seliem *et al.* (2022)

(B) Coumarins

Name of Compound	Mechanism	References
Esculetin	Stimulates fructose-1,6-bisphosphatase and glucose-6-phosphatase; enhances glucokinase activity	Shehadeh *et al.* (2021)
Fraxetin	Increases hepatic glycogen; inhibits gluconeogenesis; enhances glucokinase; stimulates glucose-6-phosphate dehydrogenase	Shehadeh *et al.* (2021)
Umbelliferone	Activates PPARγ, increasing insulin sensitivity and promoting GLUT4 translocation; increases insulin sensitivity and secretion; inhibits α-glucosidase; modulates hepatic lipid metabolism; reduces adiponectin	Fiorito *et al*. (2019)

replacements on the aromatic rings, but they have the same backbone, which is a C6-C3-C6 structure. Except for resveratrol, pterostilbene, and polydatin, dietary stilbenoids are rarely mentioned as potential anti-diabetic drugs (Indrakusuma *et al.*, 2014).

(j) *Saponins*:

Bioactive steroidal or triterpenoid glycosides, known as saponins, exhibit a diverse range of biological activities, one of which is their potent inhibition of hyperglycemia. Saponins sourced from a diverse range of plants have proved their antihyperglycemic activity in both *in vitro* and *in vivo* conditions (Choudhary *et al.*, 2021). It alters the insulin signaling pathway and enhances the level of insulin by stimulating the pancreas B cell. In this way, It regains insulin sensitivity, promotes glycogen synthesis, blocks gluconeogenesis, and glucosidase activity, and suppresses mRNA expression. These are only a few of the hypothesized methods they employ to reduce blood sugar levels. The main ways that astragaloside IV lowers blood glucose levels significantly are by reducing insulin resistance in adipocyte cells and blocking glycogen phosphorylase and G6Pase (Indrakusuma *et al.*, 2014).

Conclusion

Plant secondary metabolites are beneficial for people and animals. Alkaloids have pharmacological effects and contain anticancer, antibacterial, antiviral, antioxidant, and antifungal properties. In excessive amounts, secondary metabolites might be poisonous and lethal. Some alkaloids cause paralysis, suffocation, and death. Recent research has focused on developing novel derivatives of isolated secondary metabolites to create more efficacious, safer, and microbe-resistant therapies State-of-the-art methodologies, sophisticated procedures, and computational methods may make developing novel strong pharmaceuticals from natural compounds faster and easier. Nowadays people avoid physical exercise in the age of automation, resulting in obesity and metabolic syndrome. It is recommended to adopt an active lifestyle, engage in physical activity, and consume foods that sustain and retard the process of glucose breakdown. Further study is needed to evaluate and optimize multi-target hypoglycemia therapeutic targets, pharmacokinetic investigations, and clinical trials. Computer-aided research may help produce effective and selective plant-based antidiabetic compounds.

Ethical Statement

This is a review article hence no Ethical Approval needed.

Author Contributions

Each author has contributed equally to the study's planning, analysis, writing, and editing. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

References

Abdul Kadar M, Ahmad NN, Teoh F and Yahaya SL. (2021) Caffeic acid on metabolic syndrome: A review. Molecules 26: 4408.

Adisakwattana S. (2017) Cinnamic acid and its derivatives in diabetes prevention and management. Nutrients 9: 163.

Badilla JG and Fiangaan MLC. (2022) Pharmacognostic evaluation and acute toxicity of formulated tisane powder of *Galinsoga parviflora*. Pharmacogn J. 14: 193-204.

Bahmani M, Golshahi H, Saki K, Rafieian-Kopaei M, Delfan B and Mohammadi T. (2014) Medicinal plants and secondary metabolites for diabetes mellitus control. Asian Pac J Trop Dis. 4: S687-S692.

Barber E, Houghton MJ and Williamson G. (2021) Flavonoids as human intestinal α-glucosidase inhibitors. Foods 10: 1939.

Choudhary N, Khatik GL and Suttee A. (2021) Possible role of saponin in type-II diabetes: A review. Curr Diabetes Rev. 17: 107-121.

Dabur R, Sharma B and Mittal A. (2018) Mechanistic approach of anti-diabetic compounds identified from natural sources. Chem Biol Lett. 5: 63-99.

Das T, Dey A, Pandey DK, Panwar JS and Nandy S. (2022) Fungal endophytes as biostimulants of secondary metabolism in medicinal crops. In: New and Future Developments in Microbial Biotechnology and Bioengineering, Elsevier, pp. 283-314.

Dinda B and Dinda S. (2022) Pharmacology of anti-obesity and antidiabetic phytochemicals from natural sources. In: Natural Products in Obesity and Diabetes, Springer, pp. 277-467.

Fiorito S, Ianni F, Preziuso F, Bucciarelli T and Genovese

S. (2019) Quantitative analysis of hydroxylated and O-prenylated coumarins in pomegranate seed extracts. Molecules 24: 1963.

Gajger T and Dar I. (2021) Plant allelochemicals as sources of insecticides. Insects 12: 301.

Ghazaly MM, Lee GE, Ma NL, Heděnec P, Hassan NR, Zulkifli MF, Mohammed A and Ghazali MS. (2025) A review and a bibliometric analysis of tropical herbs and their bioactive compounds for modulating gut microbiota function and glucose regulation in type 2 diabetes. Food Med Homology 2: 3006-4252.

Gupta N, Gudipati T and Prasad GBKS. (2018) Plant secondary metabolites of pharmacological significance in diabetes mellitus: An update. Int J Curr Microbiol Appl Sci. 7: 3409-3448.

Hajam YA, Rani R, Sharma P, Khan IA and Kumar R. (2022) Role of plant secondary metabolites in metabolic disorders. In: Plant Secondary Metabolites, Springer Nature, pp. 241-280.

Hasnat H, Shompa SA, Islam MM, Alam S, Richi FT, Emon NU, Ashrafi S, Ahmed NU, Chowdhury MNR, Fatema N, Hossain MS, Ghosh A and Ahmed F. (2024) Flavonoids: A treasure house of prospective pharmacological potentials. Heliyon 10(6): e27533.

Indrakusuma AABP, Wahyuni LPS, Wiguna IGWW, Devy AAT, Sasmana IGAP and Indrayani AW. (2021) Secondary metabolites in *Persea americana* seeds as α-amylase inhibitor on T2DM. Intisari Sains Medis 12(3): 886–896.

Jeon JS, Carreno-Quintero N, van Eekelen HDLM, De Vos RCH, Raaijmakers JM and Etalo DW. (2021) Impact of root-associated *Paraburkholderia* strains on metabolism of *Brassica oleracea*. Sci Rep. 11: 2781.

Jiyad HM and Al-Dulaimi LHA. (2022) Effect of *Abelmoschus esculentus* bioactives on blood parameters and renal histology in diabetic rats. Intern J Zool Invest. 9(2): 33-43.

Joshi N, Jadhav A, Godhamgaonkar A, Sundrani D, Randhir K, Pisal H, Wagh G, Krishnaveni G, Gupte S and Joshi S. (2024) Fatty acids and their metabolites (resolvins) are altered in women with gestational diabetes mellitus (GDM). Food Funct. 15(6):3023-3035.

Karim N, Shishir MRI, Li Y, Zineb OY, Mo J, Tangpong J and Chen W. (2022) Pelargonidin-3-O-glucoside nanoliposomes recover palmitic acid-induced hepatocyte injury. Antioxidants 11: 623.

Laddha AP and Kulkarni YA. (2022) Daidzein attenuates urinary bladder dysfunction in diabetic rats by NOX-4 and RAC-1 inhibition. Naunyn-Schmiedeberg's Arch Pharmacol. 395: 975-986.

Lomartire S, Cotas J, Pacheco D, Marques JC, Pereira L and Gonçalves AMM. (2021) Environmental impact on seaweed phenolic production and activity. Mar Drugs 19: 245.

Manhivi VE, Slabbert RM and Sivakumar D. (2022) Co-ingestion of natal plums and marula nuts: Effects on phenolics and bioactivities. Molecules 27: 310.

Mi J, He W, Lv J, Zhuang K, Huang H and Quan S. (2019) Berberine effects on HPA-axis and skeletal muscle GLUT4 in T2DM rats. Diabetes Metab Syndr Obes. 12: 1717-1725.

Natsume N, Yonezawa T, Saito Y, Woo JT and Teruya T. (2021) Prenylflavonoids from *Macaranga tanarius* promote glucose uptake via AMPK. J Nat Med. 75: 813-823.

Pagare S, Bhatia M, Tripathi N, Pagare S and Bansal YK. (2015) Secondary metabolites of plants and their role: Overview. Curr Trends Biotechnol Pharm. 9: 293-304.

Paoli P, Cirri P, Caselli A, Ranaldi F, Bruschi G, Santi A and Camici G. (2013) Insulin-mimetic effect of Morin: A promising molecule in diabetes treatment. Biochim Biophys Acta 1830: 3102-3111.

Park CH, Yeo HJ, Kim YJ, Van Nguyen B, Park YE, Sathasivam R, Kim JK and Park SU. (2021) Profiles of secondary metabolites during flower development in *Lycoris radiata*. Biomolecules 11: 248.

Park MY, Ha SE, Kim HH, Bhosale PB, Abusaliya A, Jeong SH, Park JS, Heo JD and Kim GS. (2022) Scutellarein inhibits LPS-induced inflammation via NF-κB/MAPKs in RAW264.7 cells. Molecules 27: 0001.

Qin H, Song Z, Zhao C, Yang J, Xia F, Wang L, Ali A and Zheng W. (2022) Liquiritigenin inhibits lipid accumulation via mTOR-mediated autophagy. Nutrients 14: 1287.

Ramírez-Moreno E, Arias-Rico J, Jiménez-Sánchez RC, Estrada-Luna D, Jiménez-Osorio AS, Zafra-Rojas QY, Ariza-Ortega JA, Flores-Chávez OR, Morales-Castillejos L and Sandoval-Gallegos EM. (2022) Role of bioactive compounds in obesity: Inflammation-focused mechanisms. Foods 11: 1232.

Seliem EM, Azab ME, Ismail RS, Nafeaa AA, Alotaibi BS and Negm WA. (2022) Green coffee bean extract normalizes obesity-induced metabolic parameters via adiponectin/GLUT4. Life 12: 693.

Shehadeh MB, Suaifan GA and Abu-Odeh AM. (2021) Plant secondary metabolites as blood glucose-lowering molecules. Molecules 26: 4333.

Sinha R, Anand S, Singh D, Tripathi S, Shukla P, Singh S and Srivastava P. (2022) Bioprocessing strategies for microbial production and purification of immunosuppressants. Chem Eng Processing Process

Intensif. 172: 108797.

Sok Yen F, Shu Qin C, Tan Shi Xuan S, Jia Ying P, Yi Le H, Darmarajan T, Gunasekaran B and Salvamani S. (2021) Hypoglycemic effects of plant flavonoids: A review. Evid Based Complem Alternat Med. 2021: 2057333.

Thirumurugan D, Cholarajan A, Raja SSS and Vijayakumar R. (2018) An introductory chapter: Secondary metabolites. In: Secondary Metabolites – Sources and Applications. doi:10.5772/intechopen. 79766

Tungmunnithum D, Thongboonyou A, Pholboon A and Yangsabai A. (2018) Flavonoids and other phenolic compounds from medicinal plants: An overview. Medicines (Basel) 5(3): 93.

Twaij BM and Hasan MN. (2022) Bioactive secondary metabolites from plant sources: Types, synthesis, and therapeutic uses. Int J Plant Biol. 13: 4-14.

Verma VK, Malik S, Mutneja E, Sahu AK, Prajapati V, Bhatia J and Dharamveer Singh A. (2024) Morin ameliorates myocardial injury in diabetic rats via modulation of inflammatory pathways. Lab Anim Res 40: 3.

Xu Q, Cao Z, Xu J, Dai M, Zhang B, Lai Q and Liu X. (2022) Natural plant active compounds for osteoclast-mediated bone destructive diseases. J Drug Target 30: 394-412.

Yang Y, Chen Z, Zhao X, Xie H, Du L, Gao H and Xie C. (2022) Mechanisms of kaempferol in the treatment of diabetes: A comprehensive review. Front Endocrinol (Lausanne) 13: 990299.

Zhang X, Gao R, Zhou Z, Sun J, Tang X, Li J, Zhou X and Shen T. (2022) Mechanism of Huanglian–Wuzhuyu herb pair in NASH: Network pharmacology and validation. J Ethnopharmacol. 296: 115405.