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A scoping review on the anti-diabetic potential of *Urtica dioica*

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Introduction

Diabetes, a persistent metabolic disorder characterized by elevated blood sugar levels, represents a significant global health challenge, affecting around 422 million people worldwide. The escalating figures of diabetes patients can be attributed to factors such as aging populations, urbanization, and the growing occurrence of obesity and insufficient physical activity. The administration of diabetes typically entails lifestyle modifications, blood glucose monitoring, and medications to regulate blood sugar levels. However, these conventional treatments often have adverse effects and can be costly, prompting researchers to investigate alternative and complementary therapies [1] Studies have indicated that

diabetes mellitus is a metabolic condition marked by inadequacies in insulin secretion or utilization, resulting in persistent hyperglycemia.[2]. This condition is associated with a range of complications, including diabetic foot ulcers, peripheral artery disease, and diabetic neuropathy, cardiomyopathy, and peripheral neuropathy, are significant and affect approximately 50% of individuals with diabetes. Furthermore, diabetes is a contributing risk factor for cardiovascular diseases, which highlights the importance of implementing effective management strategies. [3-6].

Oral hypoglycaemic agents and insulin, which are synthetic drugs, are commonly prescribed for the treatment of diabetes. The management of diabetes through the use of synthetic drugs and insulin may result in a range of adverse effects.[7-9]. Insulin therapy has several significant side effects, including weight gain, exacerbation of diabetic retinopathy, alterations in the refractive properties of the lens, dizziness, and difficulty breathing. Moreover, this therapy can lead to increased insulin secretion, which may result in weight gain, hypoglycaemia, anaemia, weight gain, and in some cases heart failure [10-12]. Insulin is a highly effective therapy for diabetes, however, its use has been linked to side effects such as weight gain and hypoglycaemia [13, 14]. Alternative therapies that are natural for diabetes have been investigated, such as medicinal plants, stem cell therapy, and photobiomodulation [15-18]. These alternative therapies have demonstrated effectiveness in regulating glucose homeostasis and improving oxidative stress in the context of type 2 diabetes, as well as in regulating insulin signalling pathways and potentially facilitating the activation of specific receptors in the management of diabetes. [19, 20]. Stem cell therapy presents a novel approach for treating diabetes-associated critical limb ischemia and promoting revascularization in vascular disorders [21]. Additionally, photobiomodulation has been investigated for improving insulin therapy in diabetic mice through modulating microglia and the brain drainage system [15]. Complementary and alternative medicine (CAM) approaches such as reflexology, massage, and acupressure, have also been studied for their effectiveness in reducing pain in diabetic neuropathy [22-24]. Moreover, dietary interventions and physical activity have been considered as alternative or adjunct therapies for diabetes management, with evidence suggesting their potential to reduce the need for medication and improve glycaemic control [25].

Urtica dioica (UD), belonging to the Urticaceae family commonly referred to as stinging nettle, has a long and storied history in traditional medicine across numerous cultures. This plant, notable for its stinging hairs and extensive distribution in Europe, Asia, Africa, and North America, has been revered for its diverse range of health benefits. From the Ancient Egyptians to Medieval Europe, UD has been utilized for its therapeutic properties in treating a range of conditions, including arthritis, skin diseases, and notably, diabetes [26, 27]. Research has demonstrated the therapeutic potential of UD, emphasizing its capacity to modulate the immune system, reduce inflammation, provide antioxidant effects, exhibit antimicrobial properties, inhibit ulcer formation, alleviate pain, and suppress allergic reactions [28]. The usage of UD has been conventionally practiced for its therapeutic qualities, particularly in the administration of diseases such as hypertension and diabetes. Moreover, investigations have uncovered its potential in wound healing proces. [29, 30]. UD is notable for its antioxidant

activity, which has been attributed to its bioactive components. These antioxidants play a crucial role in combating oxidative stress and may have implications in the fight against specific types of cancer. Furthermore, UD has demonstrated promise in protecting against liver and kidney damage caused by harmful substances, reinforcing its potential as a therapeutic agent [31, 32]. The plant demonstrates medicinal properties that are beneficial in the management of diabetes, with research studies indicating its potential antidiabetic effects [33]. The potential of UD as a natural alternative for individuals with diabetes has been investigated due to its capacity to mimic insulin. Furthermore, research has explored its role in reducing urinary oxalate levels, which may have implications for conditions such as hyperoxaluria and kidney calculi [34, 35]. In addition, UD has been acknowledged for its ability to promote growth and stimulate the immune system in farmed fish, demonstrating its versatile applications that extend beyond human health [27, 36]. In short we can day that, UD is a versatile herbal remedy that has a long history of traditional medicinal use and is supported by a growing body of scientific evidence that highlights its therapeutic potential. This herbal drug has been found to have a range of health benefits, including antioxidant and anti-inflammatory properties, wound healing, and antidiabetic effects. Due to its wide range of benefits, UD is an herbal remedy that warrants further exploration and utilization in modern medicine.

The purpose of this manuscript is to provide a detailed comprehensive overview of UD's antidiabetic effects, examining its, mechanisms of action, highlighting the metabolic pathway its bioactive constituent may regulate in the management of diabetes.

Morphological features of UD

UD, commonly referred to as stinging nettle, is a perennial herbaceous plant that belongs to the Urticaceae family. The plant typically thrives in moist and fertile soils and can grow up to 0.5-1 metre in height. It is characterised by its fleshy, serrated, and heart-shaped leaves as well as stems covered in stinging hairs, which give rise to its common name. The leaves of UD have a distinct macroscopic appearance, with an ovate to lanceolate shape, serrated margins, a medium to large size, rough texture due to stinging hairs, red-tinged petioles, an acute apex, a rounded base, and prominent parallel veins [37]. Research has shown that the roots of UD contain various compounds, such as ferulic acid, homovanillyl alcohol, and p-coumaric acid [38]. The leaves have also been reported to have a diverse array of phytochemicals including phenolic compounds, hydroxycinnamic acids, sterols, fatty acids, alkaloids, terpenoids, flavonoids, and lignans. The major flavonoids reported are such as kaempferol, isorhamnetin, quercetin, isoquercitrin, and rutin, as well as phenolic acids like caffeic acid and chlorogenic acid. Additionally, carotenoids such as β-carotene, hydroxyl-β-carotene, luteoxanthin, lutein epoxide, and violaxanthin are present in these leaves, along with essential oils, fatty acids, minerals, and vitamins [39, 40]. The leaves have also been reported to have calcium (Ca), potassium (K), and magnesium (Mg). with Ca forming the predominant macro-nutrient in nettle herbal infusion [41].

Methods:

This scoping review was compiled following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and following an all-inclusive methodological critical appraisal, we compiled the scoping review in an attempt to critically explore the

potential of *UD* in diabetes management [42]. A total of 525 articles were retrieved from the database, which were subjected to a first level of screening. During this process, 246 articles were automatically excluded due to their nature as review articles, chapters, short communications, and letters, or because they failed to meet the aims of our study. Subsequently, a further 100 papers were removed from the field, as they were identified as communications, conference papers, or did not align with the objectives of our investigation. After a detailed screening process based on titles and abstracts, a total of 125 articles remained following the removal of 54 duplicates. At this stage of our review, 91 articles were excluded for the following reasons: review papers (n = 7), systematic reviews (n = 5), incorrect drug (n = 5), incorrect outcome (n = 34), accidental duplicates (n = 8), publications older than 2004 (n = 12), or because they were considered to be outside the scope of current relevance. Consequently, the rigorous application of our predefined inclusion and exclusion criteria allowed for a focused selection of studies that were directly relevant to the research question at hand. The screening was assisted by Endnote and Rayyan [43]. Out of the 125 articles that we screened, we were able to select 31 studies that satisfied our rigorous criteria for data extraction. Our systematic review, which is currently in progress and is being conducted by two independent reviewers, ensures objectivity and minimizes any potential bias. In the event of any disagreements, they will be resolved through consensus or with the intervention of a third reviewer if necessary. Our review aims to provide an comprehensive overview of the evidence-based therapeutic benefits of UD in the treatment of diabetes, with a particular focus on its effects on glucose metabolism and insulin resistance/sensitivity. We will present our findings in a transparent and organized manner, as they offer significant insights into UD's potential as a natural remedy for diabetes management. We hope that our research will encourage other researchers to continue exploring this area.

S. No	Name of the Author	Objective	Results with Data	Insights	Major Chemical Constituents Identified	References
1	Mohamed Bnouham, et al. (2003)	This study aims to evaluate UD's antihyperglycemic effect on hyperglycemia alloxan indued diabetes in rats.	UD (250 mg/kg) showed a 33% glucose lowering effect vs. control.	UD has a significant antihyperglycemic as it reduces intestinal absorption of glucose.	Not specified but the effect may be due to phenolics.	[44]
2	Akbar Aliasgarzadeh, et al. (2012)	To study the mechanisms of UD on RIN5F rat pancreatic beta cells.	Alcoholic extract of UD did not significantly change insulin and C-peptide secretion from RIN5F pancreatic beta cells.	The hypoglycemic effects of UD are not based on enhancement of insulin secretion.	Not specified	[45]
3	Mahmood Abedinzade, et al. (2019)	Evaluating the effects of UD and Lamium Album on the serum level of K-Ras and GSK-3 beta in diabetic rats	Both extracts reduced GSK-3 beta levels and increased blood K-Ras level. They also significantly decreased blood glucose levels.	UD and Lamium Album improve blood glucose level by regulating GSK-3 beta and K-Ras.	Not specified	[46]
4	Sabzar Ahmad Dar, et al. (2012)	To describe the antidiabetic, antiinflammatory, antibacterial activity, and toxicological studies of UD	The aqueous extract of U. dioica significantly reduced the blood glucose level during GTT in Wistar rats. HF2 exhibited both antiinflammatory and potent antibacterial activities	U. dioica leaves are an interesting source of bioactive compounds, justifying their use in traditional medicine to treat various diseases	Fatty acid esters, terpenes, neophytadiene	[47]

5	A.R. Carvalho, et al. (2017)	Polyphenol characterization of Urtica spp. and their antioxidant activity	UD exhibited the highest amount of phenolic compounds, primarily hydroxycinnamic acids. All Urtica species showed significant antioxidant activities	The high phenolic content, particularly hydroxycinnamic acids, is responsible for the antioxidant/antiradical activities of Urtica species	Caffeic acid derivative, p-Coumaric acid, Chlorogenic acid, Caffeoylquinic acid, 2-O-Caffeoylmalic acid, Peonidin 3-O-rutinoside, Rosinidin 3-O-rutinoside, Rutin, Quercetin p-coumaroyl glucoside, Isorhamnetin 3-O-rutinoside	[48]
6	M.J. Golalipour, et al. (2011)	Study the effect of UD extract on liver of diabetic rats	Diabetic morphometric parameters in hepatocytes reduced in periportal zone and increased in perivenous zone. U. dioica extracts caused an increase in main morphometric indices in periportal zone and a decrease in perivenous zone	U. dioica leaf extracts can modify morphometric indices of hepatocytes in diabetic rats, indicating potential therapeutic effects on liver structure	Not specified	
7	Das, et al. (2009)	To assess the antidiabetic and antilipidemic effects of an aqueous extract of UD in a type 2 diabetic rat model.	UD water extract significantly reduced fasting glucose levels in type 2 diabetic rats after 14 days (14.05 ± 3.4 mmol/l in control vs 8.3 ± 1.4 mmol/l in treated group, p = 0.04).	UD exhibits both hypoglycemic and hypolipidemic which may be attributed to the enhancement of β-cells' functional characteristics,	Not specified in the provided content.	[49]

				resulting in improved insulin control.		
9	Golalipour, et al. (2007)	Study protective activity of UD leaves on blood glucose concentration and β-cells in diabetic Rats	Animals receiving U. dioica extract showed a decrease in blood glucose levels and protective effects on pancreatic β-cells against STZ-induced damages	Suggests U. dioica possesses protective effects against hyperglycemia and pancreatic cell damage in STZ-induced diabetic models	Not specified	[50]
11	Minaei, eta al. (2012)	Protective effect of extract of UD leaf on small intestine structure in diabetic rats.	Blood sugar decreased significantly in the therapeutic group. Necrosis and infiltration by mononuclear cells were notably reduced in the therapeutic group treated with UD.	UD demonstrates protective qualities for the mucous lining of the small intestine in diabetic rats, likely through mechanisms involving the decrease of blood glucose levels and anti-inflammatory responses.	UD constituents: Tanin, Musylar, Formic acid, a Phytosterin, Potassium Nitrate, Ferriferouscompounds, a kind of Glucoside with skin reddening effect.	[51]
12	Golalipour, et al. (2009)	Effect of UD leaf hydroalcoholic extract on liver parenchymal cell changes in STZ-induced diabetic rats.	The mean size of hepatocytes, as well as their nuclei and nucleolus, decreased in the periportal zone and increased in the perivenous zone for both the diabetic and treatment groups.	The use of extracts from the leaves of UD can result in minor fluctuations in of liver morphology, particularly in terms of the size of hepatocytes, nuclei, and nucleolus. This	Presence of high percentages of tannins and steroids, and low percentage of flavonoids, carotenoids, and saponins in U. dioica leaves.	[52]

				finding suggests that there may be a protective effect on liver parenchymal cells in diabetic conditions.		
13	Golalipour, et al. (2010)	The protective effect of UD leaves hydroalcoholic extract on diabetic rats' liver morphometric changes was assessed.	In the diabetic + UD group, the mean surface area of hepatocytes in the periportal zone was higher compared to the diabetic and control groups.	UD leaf extract administration before diabetes induction shows protective effects on morphometric alterations of hepatocytes, suggesting a modulation of diabetes-induced liver changes.	Presence of high percentages of tannins and steroids, and low percentage of flavonoids, carotenoids, and saponins in U. dioica leaves.	[53]
15	Haouari, et al. (2007)	To investigate the effects of UD extract on platelet hyperaggregability in type 2 diabetes .	UD extract displayed a marked decrease in thrombin-induced platelet aggregation in a concentration-dependent manner.	UD extract exhibits antiaggregant properties which would prevent cardiovascular complications associated with type 2 diabetes mellitus due to its ability to reduce intracellular calcium and exert antioxidant	None reported	[30]

				actions in human platelets.		
16	Khanaki, et. al. (2017)	Effect of UD and *Lamium album* extracts on serum IGF-1 and fasting blood glucose (FBS) levels .	Diabetic rats treated with U. dioica and *L. album* showed a significant decrease in FBS and an increase in serum IGF-1 levels compared to untreated diabetic rats.	The findings suggest that U. dioica and *L. album* could have beneficial effects in managing diabetes mellitus by modulating serum IGF-1 and glucose levels.	Not specified in the provided content.	[54]
17	Khanaki, et. al. (2019)	Study the effects of U. dioica and *L. album* extracts on COX-2 and CASP-3 expression in the liver and kidney of diabetic rats.	Liver COX-2 mRNA expression was significantly higher in diabetic rats compared to controls. Both U. dioica and *L. album* significantly decreased liver COX-2 mRNA in diabetic rats.	U. dioica and *L. album* might reduce liver inflammation in diabetic rats by decreasing COX-2 expression.	Not specified in the provided content.	[54]
18	Korani,et al. (2016)	Study the effect of UD on glycemic index. a	Substantial reduction in fasting blood glucose (FBG) levels and a rise in Quantitative Insulin Sensitivity Check Index (QUICKI) in the treatment group relative to the placebo group.	UD has the potential to decrease glucose levels and improve insulin release, possibly by increasing AMPK activity..	Not specified in the provided content.	
19	Mehran, et al. (2015)	To compare the effects *of Lamium album* and UD on serum glucose, lipids, and hepatic enzymes.	Both U. dioica and *L. album* significantly reduced serum glucose, cholesterol, and hepatic enzymes levels.	U. dioica may elevate insulin secretion, increase glucose uptake through the	Not specified in the provided content.	[55]

				creation of individual glucose-permeable pores, reduce insulin resistance, and enhance activity of glucose sensors such as Acetyl coenzyme A carboxylase and Nucleoside diphosphate kinase.		
20	Mukundi, et. al. (2017)	To determine the anti-diabetic effects of aqueous extracts of UD in alloxan induced mice and the safety of U. dioica on mice models.	U. dioica extracts showed insulin-like anti-diabetic activity and were safe up to 1000 mg/kg, with no significant changes in hematological, liver, kidney, and lipid profiles.	The plant extracts exhibited effects on the activity of pancreatic β-cells, including an increase in inhibitory activity against insulin enzymes and sensitivity to insulin, increased peripheral glucose utilization, increased glycogen synthesis in the liver, decreased glycogenolysis, inhibition of intestinal glucose absorption, reduction of carbohydrate glycemic	Phenols, alkaloids, flavonoids, tannins, saponins	[56]

				index, and reduction of glutathione's impact.		
21	Patel, et al (2014)	Study the effect of UD leaves extract on the muscarinic cholinergic system.	Diabetic mice experienced a decrease in hippocampal muscarinic acetylcholine receptor-1 and choline acetyltransferase, an increase in acetylcholinesterase, and oxidative stress in the hippocampus.	UD leaves extract has potential to reverse diabetes-induced alterations in the muscarinic cholinergic system in the hippocampus, thereby improving memory functions.	Scopoletin, gentisic acid, protocatechuic acid, quinic acid, esculetin, quercetin, and rutin identified in UD leaves extract.	[57]
22	Patel, et al. (2013)	effect of UD (UD) extract against memory dysfunction and hypoalgesia in a mouse model diabetic neuropathy.	UD significantly reduced blood glucose and polydipsia, improved body weight, insulin level, cognition, and insensate neuropathy. Results were comparable to those of rosiglitazone.	UD exhibited protective effects against neuronal dysfunction in long-standing diabetic conditions, suggesting its potential as a therapeutic agent for diabetic neuropathy.	Scopoletin, 5-HT, and various phytochemicals including coumarin glycosides.	[58]
23	Patel, et al. (2014)	effects of UD on depressive-like behavior and cognitive dysfunction in diabetic mice.	UD reduced hyperglycemia, corticosterone, oxidative stress, and depressive-like behavior, and improved associative memory and GLUT4 mRNA expression in the hippocampus, similar to rosiglitazone.	UD shows promise for treating diabetes and depression due to its ability to improve hyperglycemia and related complications, including cognitive dysfunction and	Scopoletin, quercetin, carvacrol, 5-hydroxy tryptamine (5HT), acetylcholine, choline acetyltransferase.	[59]

				depressive-like behavior.		
24	Patel, et al. (2016)	Examine UD extract's impact on memory impairment and uncover the underlying mechanism in diabetic mice induced by streptozotocin.	Diabetic mice experienced cognitive dysfunction and reduced mobility due to impaired insulin signaling and GLUT4 translocation in the hippocampus. UD treatment improved insulin signaling, glucose tolerance, and recognition memory performance, comparable to rosiglitazone.	UD leaf extract improves memory function and modulates insulin signaling and GLUT4 translocation in the hippocampus to treat diabetes-related central nervous system complications via the insulin signaling pathway.	Scopoletin, gentisic acid, protocatechuic acid, quinic acid, caffeic acid, ferulic acid, quercetin, 5-O-caffeoylquinic acid, esculetin, rutin	[60]
25	Qujeq, et. al. (2011)	The effect of UD leaf extracts on ACC, NDPK, insulin, and glucose levels were examined.	U. dioica lowered glucose and elevated insulin in rats, both extracts increased ACC and NDPK activity.	U. dioica leaf extract reduced hyperglycemic rats' glucose levels and increased insulin secretion.	Not specified in the provided content.	[61]
26	Damola, et al. (2009)	To study the effect of UD (UD) extracts on blood glucose	UD extracts, especially UD-1, did not promote insulin secretion, but they did enhance glucose uptake in L6-GLUT4myc myoblast cells. Studies have shown that cyclical peptides in UD-1 facilitate glucose uptake by	UD-1's antidiabetic effect is due to cyclic peptides that increase glucose uptake, suggesting a new mechanism for lowering blood glucose levels without	Cyclical peptides that form glucose permeable pores.	[35]

			forming unique, glucose-permeable pores.	affecting insulin secretion.		
27	Nassiri-Asl et al. (2009)	the study effects of UD extract on the lipid profile	UD extract improved lipid profiles in hypercholesterolemic rats, indicating its potential for managing cholesterol levels.	UD's potential to lower cholesterol levels could provide a natural option for managing high cholesterol.	Not specified in the provided content.	[62]
28	Ranjbari, et al. (2016)	Study the effect of UD extract on diabetic parameters	UD improved glucose control and beta cell health through insulin sensitivity and resistance and regeneration in pancreatic tissue, and increased insulin secretion and glucose uptake in cells.	UD extract and swimming exercise synergistically improved diabetic parameters, indicating a potential approach to managing diabetes.	Propylene Glycol, Diethylene Glycol, 1,8-Cineole, Ethyl Benzoate, Gamma-Dodecalactone, Di iso-Butyl Phthalate, Palmitic Acid, Dibenzosuberone, Ethyl Palmitate, 4-methyl-2,6-di-t-butyl Phenol, Methyl Oleate, Stearic acid, Ethyl Stearate, Tricosane, Di-(2-ethylhexyl) Phthalate	[63]
29	Shokrzadeh, et al. (2018)	Evaluate UD and pioglitazone's impact on diabetic mice neurotoxicity and oxidative stress.	UD and PIO improved oxidative stress markers and mitochondrial damage in diabetic mice. The combination showed synergistic effects, and the	The study demonstrates the therapeutic potential of UD and PIO in attenuating diabetic-induced neurotoxicity	Not specified in the provided content.	[64]

			treatment also reduced elevated pain scores, indicating neuroprotective effects.	through antioxidative mechanisms and mitochondrial protection, suggesting their use as a co-treatment in managing diabetic neurotoxicity.		

Author Name	Objective	Type of Clinical Trial	Population Size	Control Drug with Dose	Sample Drug with Dose	Data Obtained	Insights	Conclusion	Reference
Md Alin Korani, et al. (2017)	To determine the effect of UD hydro-alcoholic extract on glycemic index and AMPK levels in diabetic patients.	Randomized Single-Blind Clinical Trial	60 diabetic patients, divided into two groups: drug (n = 30) and control (n = 30). After exclusions, included in analysis: drug group (n = 22) and placebo group (n = 22).	Placebo, administered three times a day for 8 weeks	20 mg/kg/day of hydro-alcoholic Utrica dioica extract, administered three times a day for 8 weeks	- FBG levels significantly decreased in the drug group compared with the placebo group (P = 0.032). - QUICKI increased significantly in the drug group compared with the placebo group (P < 0.001). - Insulin levels increased by 62.5%, and AMPK levels increased by 8.0% in the drug group, although not statistically significant compared with the placebo group.	UD extract may decrease glucose levels and improve insulin release in T2DM, potentially through a minor increase in AMPK activity, suggesting its anti-hyperglycemic effect could be mediated by insulin secretion and modulation of AMPK levels.	UD has the potential to decrease glucose levels and improve insulin release in Type 2 Diabetes Mellitus, possibly through a minor increase in AMPK activity.	[65]

Mehrizi, et al. (2021)	To evaluate the protective effect of UD (Nettle) on lipid profile in patients with type 2 diabetes (T2D).	Randomized Double-blinded Clinical Trial	60 men and women with T2D (49 participants completed the study).	Placebo, given in three portions after each of the 3 main meals daily for 8 weeks.	100 mg/kg/day extract of UD, given in three portions after each of the 3 main meals daily for 8 weeks.	No significant difference between the UD group and placebo group in total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDLc) levels. A significant increase in high-density lipoprotein cholesterol (HDLc) levels was observed in the UD group compared to the placebo group.	Consumption of UD extract resulted in an increase in HDLc concentration, which may decrease the risk of cardiovascular disease in patients with T2D.	UD extract consumption for 8 weeks led to an improvement in HDLc levels without significant changes in other lipid profile parameters, suggesting potential cardiovascular benefits for patients with T2D.	[66]

Disucssion

GSK-3 beta is a vital enzyme that regulates glycogen synthesis by phosphorylating and inactivating glycogen synthase, the enzyme responsible for the final step in glycogen synthesis, thereby modulating glucose production and insulin signalling [67]. Selective GSK3 inhibitors, particularly in the liver, have been demonstrated to enhance insulin activation of glucose transport and utilisation, highlighting the significance of GSK3 in glucose homeostasis [68]. UD (stinging nettle) is rich in phenolic compounds, flavonoids, lignans, and polysaccharides, which have been shown to exhibit various biological activities, including anti-inflammatory and antioxidant effects. The kinases present in UD that regulate Glycogen Synthase Kinase-3 (GSK3) include Protein Kinase B (PKB/Akt), MAPK-activated protein kinase-1 (MAPKAP-K1 or RSK), p70 ribosomal S6 kinase-1, and protein kinase A (PKA). These kinases can phosphorylate GSK3 at specific sites, such as serine 21 for GSK3α or serine 9 for GSK3β, leading to the inactivation of GSK3 [69]. Additionally, the phosphoinositide 3-kinase (PI3K)/phosphoinositide-dependent kinase-1 (PDK1)/Akt relay pathway can catalyse the serine-phosphorylation and subsequent inactivation of GSK3 [70]. The regulation of GSK3 by these kinases is crucial for various cellular functions and signalling pathways, including those related to glucose metabolism and energy homeostasis [71]. The extract is also known to increase blood K-Ras levels significantly, thereby regulating the insulin signalling pathway, which could improve insulin sensitivity and further facilitate glucose uptake by cells. These findings suggest that UD and Lamium Album may improve diabetic conditions by modulating GSK-3 beta and K-Ras levels, although further research is needed to fully understand the mechanisms involved. This dual mechanism of action, involving both GSK-3 beta inhibition and K-Ras enhancement, contributes to the observed hypoglycaemic effects of the extracts in diabetic conditions [46, 72]. The activation of Kras levels may also protein phosphatase 2A (PP2A) and thereby further enhancing insulin sensitivity and glucose uptake [73].

The PI3K/Akt pathway and the MAPK/ERK signaling pathway are crucial in the regulation of diabetes by controlling cellular processes that are related to glucose metabolism, insulin sensitivity, and diabetic complications. The PI3K/Akt pathway plays a vital role in glucose homeostasis, insulin signaling, and metabolic regulation. Research has demonstrated that this pathway is involved in mediating the actions of insulin and leptin in the hypothalamus, which affects food intake and energy balance [74]. Additionally, the PI3K/Akt pathway regulates genes that are involved in gluconeogenesis, fatty acid synthesis, and glucose transport, highlighting its importance in metabolic processes [75]. In diabetic complications such as osteoporotic fractures, the PI3K/Akt signaling pathway is implicated, suggesting its role in diabetic skeletal fragility [76]. Furthermore, the PI3K/Akt pathway has been linked to the regulation of autophagy, cell survival, differentiation, proliferation, and migration, indicating its broad impact on cellular functions [77].

On the contrary, the MAPK/ERK signaling pathway plays a role in cell proliferation, growth, survival, and angiogenesis. In diabetic cardiomyopathy, it has been demonstrated that inhibiting the activation of the PI3K/Akt signaling pathway can result in a reduction of oxidative stress, improvement of cardiac function, and diminution of pathological changes, such as fibrosis. Furthermore, the MAPK/ERK pathway has been connected to the regulation of synaptic plasticity, cognitive function, and neuronal protection in diabetes.[78]. Additionally, the MAPK/ERK pathway is involved in the development of cancer by controlling proliferation, migration, differentiation, and apoptosis.[79]. Urosolic acid (UA) has been identified as one of the key chemical constituents in the UD plant.[80]. UA exerts its influence on glucose uptake in these cells by activating the phosphatidylinositol 3-kinase (PI3K) pathway. In particular, when UA is administered, it increases the activity of PI3K pathway proteins, such as phosphoinositide-dependent kinase (PDK) and AKT, thereby stimulating the movement of glucose transporter 4 (GLUT4) from the cytoplasm to the cell membrane. This process enhances glucose uptake from the bloodstream into the adipocytes, thereby lowering blood glucose levels. The study concludes that UA's action on the PI3K pathway and its enhancement of GLUT4's function contribute significantly to its anti-diabetic effects. [81]. Furthermore, it has also been reported that UA possesses insulin secretagogue and insulinomimetic properties, as it resulted in a sustained decrease in blood glucose levels from 15 to 180 minutes post-treatment, demonstrating its potent antihyperglycemic effect. The study reports that UA promotes glucose uptake through classical insulin signaling pathways associated with GLUT4 translocation to the plasma membrane and GLUT4 synthesis. This process involves the activation of DNA transcription, increased GLUT4 mRNA expression, and the modulation of calcium, phospholipase C, protein kinase C, and CaMKII, indicating a complex interaction between calcium and kinase pathways in UA's action. Additionally, UA did not alter serum lactate dehydrogenase and calcium balance, highlighting its safety profile. The insulin secretory activity was further validated through the use of a TLC isolate of UD, as well as by conducting perifusion experiments with isolated Langerhans Islets that were exposed to the selected TLC isolate. These experiments demonstrated enhanced insulin secretion, which was accompanied by a decrease in glucose levels in both normal and streptozotocin-induced diabetic rats. The intraperitoneal injection of F1 in these rats resulted in a marked increase in serum insulin levels, as well as a significant decrease in blood glucose levels. [82].

β-amyrin acetate is a pentacyclic triterpenoid compound discovered in the roots of UD. This compound has been found to activate the AMP-activated protein kinase (AMPK) pathway, which is a significant regulator of energy balance and plays a crucial role in the modulation of glucose and lipid metabolism. Once activated, AMPK can increase insulin sensitivity and glucose uptake in muscle and adipose tissue, leading to a decrease in blood glucose levels. Additionally, amyrin has been observed to modulate the activity of enzymes involved in carbohydrate metabolism, such as α-glucosidase and α-amylase, which are essential for carbohydrate digestion and postprandial blood glucose regulation.[83]. α-amyrin is a bioactive molecule that has the potential to induce GLUT4 translocation in myoblasts through AK and PPARδ/γ activation, which suggests an insulinmimetic action. This property suggests that α-

amyrin could be a promising candidate for the development of multarget drugs for type 2 diabetes and other metabolic disorders.[84].

Rosamainiric acid (RA), a major constituent of UD is also known increases glucose uptake in L6 rat muscle cells by activating AMP-activated protein kinase (AMPK), a crucial enzyme in regulating glucose homeostasis. Unlike insulin, which promotes glucose uptake through the PI3K-Akt signaling pathway leading to GLUT4 translocation, RA's mechanism of action does not involve Akt phosphorylation. Instead, RA stimulates glucose uptake independently of the PI3K-Akt pathway, primarily through AMPK activation. This activation of AMPK by RA leads to an increase in cellular glucose uptake to levels comparable to those achieved with insulin and metformin treatment, indicating its potential as a pharmacological intervention for managing insulin resistance and type 2 diabetes mellitus (T2DM) [85, 86].

Chlorogenic acid is a major phenolic compound that forms a substantial part of plant foods and is an ester of caffeic acid and quinic acid [87]. results revealed that both phenolic acids inhibited α-amylase and α-glucosidase activities in a dose-dependent manner [88]. Chlorogenic acid was found to significantly suppress the postprandial rise in blood glucose levels when rats were administered maltose or sucrose, indicating its potential to manage Type II diabetes. This effect is attributed to chlorogenic acid's strong inhibitory action on α-glucosidase, an enzyme responsible for the breakdown of carbohydrates into glucose, thereby delaying glucose absorption in the intestine. chlorogenic acid inhibited the absorption of glucose from disaccharides in an everted gut sac model, which supports the hypothesis that chlorogenic acid exerts its antihyperglycemic effect by interfering with carbohydrate digestion and glucose absorption [89-91]. Chlorogenic acid (CGA) also stimulates glucose transport in skeletal muscle by activating AMPK, a key regulator of cellular energy homeostasis, leading to increased glucose uptake, is supported by various studies. reported that CGA maximizes the potential of insulin action, similar to the therapeutic action of metformin, indicating its influence on glucose metabolism[92]. Chlorogenic acid is also reported to influence lipid metabolism by modulating the expression of hepatic PPAR-α, leading to decreased hepatic glucose production. The PPAR-α plays a crucial role in intracellular lipid and carbohydrate metabolism by directly controlling the transcription of genes involved in pathways such as peroxisomal and mitochondrial β-oxidation, fatty acid uptake, and triglyceride catabolism[93, 94]. Another study Hemmerle et al., 1997 reported that chlorogenic acid also inhibits hepatic glucose output by targeting glucose-6-phosphatase (G-6-Pase), thereby contributing to lower blood glucose levels [95, 96].

Quercetin, a flavonoid commonly found in plant foods such as apples, onions, and tea, has been the subject of extensive research for its potential impact on glucose levels in the body. According to scientific studies, quercetin has been found to affect glucose metabolism through a variety of mechanisms. Specifically, quercetin has been shown to regulate blood glucose levels, alter lipid metabolism, and prevent liver injury.[97]. It has been claimed that it inhibits intestinal glucose absorption, stimulates insulin secretion and sensitivity, and augments

glucose utilization in peripheral tissues. [98]. Moreover, it has been demonstrated that quercetin stimulates the expression of the glucokinase (GCK) protein in the liver, thereby enhancing hepatic glycogen synthesis and improving glucose metabolism disorders.[99]. Furthermore, the findings suggest that quercetin exhibits anti-diabetic properties by preventing injury to the pancreas, promoting regeneration of pancreatic islets, and maintaining normal blood glucose levels in animal models of diabetes.[100]. Quercetin has demonstrated the ability to shield against harm caused by high glucose levels by stimulating the upregulation of endothelial nitric oxide synthase (eNOS) via Sirt1-dependent mechanisms. This suggests its potential use as a therapeutic agent for patients with diabetes. [101]. Moreover, there is evidence to suggest that quercetin supplementation can lead to improvements in insulin resistance, gut microbiome restoration, and glucose tolerance in multiple experimental models.[102-104]. The effects of quercetin on glucose metabolism involve multiple pathways, including the activation of AMP-activated protein kinase (AMPK), modulation of gene expression related to hepatic glucose metabolism, and inhibition of hepatic gluconeogenesis [102, 105, 106]. Quercetin is believed to enhance lipid metabolism through the SCAP-SREBP2-LDLr signalling pathway, as well as regulate glucose and lipid metabolism via the GPRC6A/AMPK/mTOR signalling pathway.[103, 107]. Moreover, it has been observed that quercetin supplementation results in changes to adipose tissue and hepatic transcriptomes, thereby leading to improvements in adiposity, dyslipidemia, and glucose intolerance.[108].

Research indicates that caffeic acid exhibits significant potential as an antidiabetic agent by enhancing adipocyte glucose uptake, insulin secretion, and antioxidant capacity [109]. Research indicates that caffeic acid possesses the ability to mitigate insulin resistance, improve glucose uptake, and regulate glucose metabolism.[110]. Furthermore, it has been demonstrated that caffeic acid has the ability to decrease blood glucose levels in diabetic rats, which indicates its possible use as an anti-diabetic agent.[111]. Moreover, caffeic acid has been demonstrated to enhance glucose metabolism by encouraging glycogenesis and suppressing gluconeogenesis in insulin-resistant mouse hepatocytes. [112]. Furthermore, studies have suggested that caffeic acid can stimulate the uptake of glucose in cells [1]. Additionally, caffeic acid has been associated with a reduction in plasma glucose levels, indicating its potential to lower blood glucose levels. [113]. The mechanism through which caffeic acid influences glucose metabolism involves the activation of AMP-activated protein kinase (AMPK) and insulin-independent glucose transport in skeletal muscle [114]. This activation of AMPK in the intestine has been suggested to enhance net glucose uptake, contributing to the regulation of whole-body energy metabolism [115].

Kaempferol, a flavonoid prevalent in the UD extract, has been the subject of extensive research for its potential to modulate various metabolic pathways and exert antidiabetic effects. Kaempferol treatment resulted in a decrease in hepatic gluconeogenesis, thereby lowering glucose output in diabetic mice. Additionally, kaempferol significantly suppressed elevated PC activity in these mice, which led to a reduction in the conversion of pyruvate to oxaloacetate and ultimately decreased glucose production through the gluconeogenesis

pathway.[116]. Kaempferol facilitates glucose metabolism by promoting hexokinase activity in the liver and muscle tissues, leading to a reduction in hyperglycemia [117].

The effects on blood sugar and metabolism observed in the study were likely due to the combined actions of the plant compounds. For example, flavonoids and phenolic compounds have antioxidant properties, which may improve insulin sensitivity and affect glucose metabolism. To precisely identify the plant compounds responsible for the anti-diabetic effects observed, further research focusing on the isolation and characterization of specific active components from these extracts would be required.

Conclusion:

In conclusion, our study unveils the multifaceted mechanisms through which UD exerts its antidiabetic effects. Central to these mechanisms is the inhibition of Glycogen Synthase Kinase-3β (GSK-3β), a pivotal enzyme in the regulation of glycogen synthesis and glucose production. The selective inhibition of GSK-3β, particularly in the liver, not only enhances insulin's action on glucose transport and utilization but also underscores the enzyme's crucial role in maintaining glucose homeostasis. Our findings illuminate the rich pharmacological landscape of UD, characterized by an abundance of phenolic compounds, flavonoids, lignans, and polysaccharides. These compounds contribute to a comprehensive modulation of metabolic pathways pivotal in diabetes management.

The kinases present in UD, including Protein Kinase B (Akt), MAPKAP-K1 (RSK), p70 ribosomal S6 kinase-1, and Protein Kinase A (PKA), play a crucial role in phosphorylating and inactivating GSK-3, thereby regulating glucose metabolism and energy homeostasis. Furthermore, our study highlights the significance of the PI3K/Akt and MAPK/ERK signaling pathways in diabetes by regulating cellular processes related to glucose metabolism, insulin sensitivity, and the mitigation of diabetic complications. UD, enriched with bioactive compounds like ursolic acid, β-amyrin acetate, rosmarinic acid, and chlorogenic acid, showcases a broad spectrum of actions, from enhancing insulin sensitivity and glucose uptake to inhibiting gluconeogenesis and promoting glycogen synthesis.

The comprehensive analysis presented in this manuscript not only underscores the potential of UD as a natural antidiabetic agent but also paves the way for future research into its application in diabetes management. Through a dual mechanism involving the inhibition of GSK-3β and the enhancement of K-Ras levels, along with the modulation of crucial metabolic pathways, UD presents a promising therapeutic avenue for improving diabetic conditions. Further research is warranted to unravel the full therapeutic potential and molecular intricacies of UD in diabetes care.

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