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REVIEW ARTICLE

Perilla frutescens and Blood Sugar Balance: A Functional Perspective on Diabetes Management - A Review

Medha Singh and Shikha Saxena*

School of Health Science and Technology, UPES, Dehradun - 248007, Uttarakhand, India; shikha.saxena@ddn.upes.ac.in

Abstract

Perilla frutescens, a cherished herb native to Uttarakhand, India, has been a part of traditional medicine for generations. It is now gaining recognition for its potential in managing Type II Diabetes Mellitus (T2DM). This review closely examines the herb's antidiabetic properties and the bioactive compounds- such as rosmarinic acid, luteolin, and perillaldehyde- that contribute to its therapeutic effects. These compounds are known for their antioxidant, anti-inflammatory, and blood sugar-lowering capabilities. In Uttarakhand, *P. frutescens* has traditionally been used to treat various metabolic disorders, including diabetes, reflecting the community's deep-rooted knowledge of natural remedies. Combining this traditional wisdom with modern scientific evidence allows us to explore innovative, holistic strategies to manage T2DM more effectively. This integrated approach highlights the importance of acknowledging and valuing traditional practices while building on them with contemporary research to provide better care for individuals with diabetes.

Major Findings: This review highlights the impressive anti-diabetic potential of Perilla frutescens due to its high content of polyphenols, flavonoids, and omega-3 fatty acids. It shows promise in regulating blood glucose levels, reducing oxidative stress, and improving insulin response. It is a valuable functional food candidate for managing Type 2 Diabetes and supporting palliative care.

Keywords: Antidiabetic Properties, Perilla Frutescens, Traditional Medicine, T2DM

1. Introduction

Diabetes Mellitus (DM) is a chronic metabolic disorder that has become a global health concern, afflicting millions across the globe[1]. This disorder is caused by tissue Insulin Resistance Syndrome (IRS), which impairs insulin secretion by β-cells[2]. The prevalence of diabetes is no longer confined to developed countries. Diabetes has become an increasingly pressing global health issue, with the number of people affected rising sharply over the past few decades[1]. According to the World Health Organization (WHO), the number of individuals living with diabetes jumped from 200 million in 1990 to a staggering 830 million in 2022. What is particularly concerning is that the rise has been much steeper in low- and middle-income countries compared to wealthier nations. In 2022 alone, 14% of adults aged 18 and above were living with diabetes worldwide. Even more troubling is the fact that more than half of adults over 30 with diabetes- around 59%- were not on any form of medication. This treatment gap is widest in countries with fewer resources, where access to healthcare remains a significant challenge due to limited infrastructure[4,5]. Supporting this, the International Diabetes Federation noted that over 81% of people with diabetes now live in low- and middle-income regions[6]. In the United States, the Centers for Disease Control and prevention (CDC) reported that by 2021, about 38.4 million people- roughly 11.6% of the population had diabetes.

*Author for correspondence

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While 29.7 million of these cases had been diagnosed, a concerning 8.7 million people were living with the condition without knowing it, highlighting a critical need for better awareness and early detection[5]. It can decrease life expectancy by 5 to 10 years and is projected to become the seventh leading cause of death worldwide by 2030[7,8]. Maintaining blood glucose levels within a normal range is essential for metabolic stability, as persistent hyperglycemia can lead to complications such as retinopathy, nephropathy, cardiovascular disease, and impaired wound healing. Chronic hyperglycemia also increases oxidative stress and systemic inflammation, which further exacerbate insulin resistance and organ dysfunction[9].

One such natural candidate is the herb *P. frutescens*, which is abundantly harvested and utilized in the Uttarakhand region of India. *P. frutescens*, commonly known as the "*Perilla*" plant, has long been used in traditional Asian medicinal systems because of its therapeutic properties. The leaves of the *P. frutescens* plant are particularly rich in nutrients, boasting a crude protein content of 27.8%, which is significantly higher than that found in ordinary vegetable leaves. In addition, we investigated its potential as an antidiabetic agent[10]. Various herbs such as *Gymnema sylvestre*, *Trigonella foenum-graecum*, *Momordica charantia*, and *Cinnamomum verum* have demonstrated antidiabetic properties by inhibiting carbohydrate-digesting enzymes, enhancing insulin sensitivity, and modulating inflammatory pathways involved in glucose metabolism[11]. Recent studies have highlighted the antidiabetogenic and antioxidant effects of *P. frutescens* extracts in animal models of diabetes. The bioactive compounds present in the *P. frutescens* plant, such as flavonoids, have been shown to possess potent antioxidant properties, which can help alleviate oxidative stress, a hallmark of diabetes and its complications[12]. *P. frutescens*, also known as the "purple mint", has a rich history of traditional *Ayurvedic* medicine, with its leaves and seeds utilized for various therapeutic purposes[13]. Beyond its antidiabetic effects, Perilla has shown potential as a neuroprotective, cardioprotective, anti-inflammatory, and anti-obesity agent. Its bioactive constituents are reported to modulate key signaling pathways such as AMPK, NF-κB, and MAPKs, contributing to its wide range of therapeutic actions[14]. This review will explore *P. frutescens* as a potential natural alternative for managing T2DM.

Despite the promising antidiabetic potential of *P. frutescens*, its public health significance lies in its potential to provide a natural, cost-effective supplement for diabetes management. Validating its efficacy through clinical trials could support its integration into public health strategies, improving accessibility to alternative diabetes care, particularly in resource-limited settings[15]. While preclinical studies demonstrate the plant's ability to regulate glucose metabolism through mechanisms such as α-amylase and α-glucosidase inhibition, antioxidant activity, and modulation of the gut microbiome, these findings need to be validated in human populations to confirm their translational relevance. Additionally, the optimal dosage, bioavailability, and long-term safety profile of *P. frutescens* remain largely unexplored[16,17]. There is also a need to investigate its synergistic effects when combined with other functional foods or conventional diabetes treatments. Future research should focus on well-designed clinical trials to establish standardized formulations and validate their therapeutic potential, ultimately paving the way for their incorporation into dietary guidelines for diabetes management[18].

Integrating *P. frutescens* into diabetes management strategies has profound public health implications. Given the rising prevalence of T2DM, especially in regions with limited access to advanced healthcare, utilizing locally available, culturally accepted functional foods can provide cost-effective, sustainable interventions. Leveraging traditional dietary practices in Uttarakhand, where *Perilla* is already consumed, can help improve community health outcomes[19,20]. Developing *Perilla*-based food formulations with other anti-diabetic ingredients like fenugreek and Kodo millet can enhance dietary diversity and nutritional security. Moreover, integrating these functional foods into public health nutrition programs can promote preventive healthcare, reducing the burden of diabetes-related complications. Future efforts should focus on public awareness, policy integration, and large-scale human clinical trials to validate its benefits and encourage widespread adoption. By merging traditional wisdom with modern science, we can create scalable, accessible, and culturally relevant solutions for diabetes prevention and management[21].

Currently, globally, 1 in 11 adults have diabetes, of which Type 2 accounts for 90-95% of cases, with 50% of undiagnosed diabetes. The mechanisms that should be considered in the management of T2DM are represented in Figure 1. It is important to note that diabetes is commonly treated with medications such as sulfonylureas, biguanides, thiazolidinediones, and metformin. However, these medications can lead to side effects, including abdominal bloating, diarrhea, flatulence, and a delay in the action of pancreatic enzymes[22-24]. The inhibition of starch-hydrolyzing enzymes (α-amylase and α-glucosidase) represents a prevalent therapeutic strategy for managing Type II diabetes mellitus[25-28]. This approach effectively decelerates or obstructs the hydrolysis of starch by directly inhibiting the active sites located at various sub-sites of the enzymes, thereby prolonging the overall process of digestion and the transformation of carbohydrates or starch into glucose[2]. Consequently, the rate of glucose absorption is diminished, and the elevation of blood glucose levels postprandial is attenuated[24,28]. Acarbose and Miglitol are pharmacological agents that exert inhibitory effects on α-glucosidase and α-amylase activity. Nonetheless, their application among individuals with diabetes is constrained due to adverse effects, including diarrhea, abdominal distension, and flatulence[27-29].

Alternative methods such as exercise, diet, and maintaining a healthy gut microbiome are cost-effective tools for managing T2DM without side effects[24,30-32]. The gut microbiome affects host metabolism and produces beneficial metabolites, such as SCFA, that offer an indirect solution to fight diabetes[32,33]. This approach has led to a global shift to plant-based remedies as an alternative treatment for diabetes. The International Diabetes Federation (IDF) states that the primary contributor to the onset of T2DM is lifestyle choices, typically linked to unhealthy eating habits such as consuming processed foods and high-fat foods[9]. The World Health Organization (WHO) emphasizes the necessity of establishing a strategy by endorsing initiatives that encourage nutritious diets[34]. According to a study, the whole food plant-based diet improves insulin resistance and glycemic control in T2DM through various mechanisms[35]. A plant-based diet, being higher in fiber content, reduces the postprandial blood glucose response and promotes satiety. A recent trial reported the effects of a Whole Food Plant-Based diet (WFPB) versus a DASH diet on insulin doses in 15 T2DM patients, revealing significant reductions in insulin needs with a remarkable 39% drop

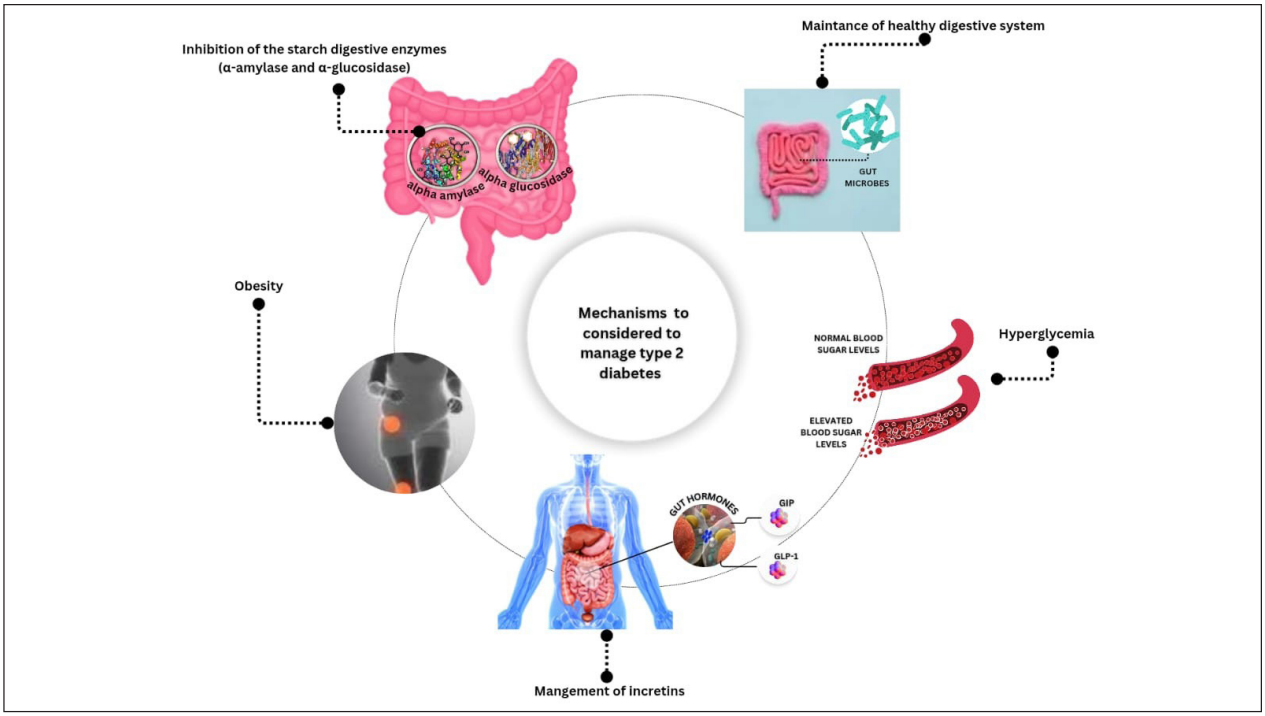


Figure 1. Illustration of the vital mechanisms essential for effectively managing Type 2 diabetes mellitus (T2DM).

after the WFPB diet[36]. Studies have shown that a plant-based diet can improve overall quality of life and reduce chronic diabetic neuropathy. Maintaining a healthy weight and digestive system is crucial for managing T2DM. Obesity is closely linked to insulin resistance, a critical factor in the development of the condition. Even modest weight management can significantly enhance the body's sensitivity to insulin, leading to more effective regulation of blood sugar levels[37]. Furthermore, weight loss can potentially decrease chronic inflammation, which worsens insulin resistance. While it may not be immediately evident, a healthy digestive system is supportive by ensuring proper absorption of nutrients, including glucose, which is crucial for controlling blood sugar levels[38]. Recent research also suggests that the gut microbiome may impact insulin sensitivity and inflammation, underscoring the potential benefits of a well-balanced diet for gut health. To sum up, managing weight and promoting digestive health is crucial for managing T2DM. Lifestyle changes, such as adopting a nutritious diet and engaging in regular exercise, can lead to significant enhancements in blood sugar control and overall health[39].

2. *Perilla frutescens*

Perilla seeds, a versatile and underutilized superfood, have been traditionally valued in several Asian cultures for their exceptional nutritional composition[40]. These seeds are particularly rich in Polyunsaturated Fatty Acids (PUFAs), especially Alpha-Linolenic Acid (ALA), a precursor to essential omega-3 fatty acids[41]. Perilla seed oil comprises approximately 40% lipids, dominated by neutral lipids (91.2-93.9%), followed by glycolipids (3.9-5.8%) and phospholipids (2-3%). Within the neutral lipid fraction, triacylglycerols constitute 88.1-90%, sterol esters 4.1-6.2%, and hydrocarbons 1.9-2.7%. The oil also contains a variety of saturated fatty acids, including lauric, myristic, palmitic, and stearic acids, which together account for 7-9% of the total oil content[14]. This beneficial fatty acid profile has been associated with improved cardiovascular function, reduced inflammation, and the prevention of metabolic and chronic diseases.

Perilla seeds are also abundant in micronutrients. They provide essential vitamins, including B-complex vitamins and vitamin E (especially γ-tocopherol), as well as minerals like calcium, magnesium, and iron, which are critical for various physiological processes[42]. Their mineral content supports protein and carbohydrate metabolism. Moreover, the seeds are a significant source of dietary fiber, ranging from 23% to 41%, contributing to gastrointestinal health, enhanced satiety, and improved glycemic control[40,43].

Beyond their rich nutritional profile, Perilla seeds also offer considerable therapeutic potential, particularly in the management of Type 2 diabetes mellitus. They are rich in bioactive compounds such as rosmarinic acid, luteolin, quercetin, and perillaldehyde-phytochemicals known for their hypoglycemic, antioxidant, and anti-inflammatory activities[14]. These compounds contribute to glucose regulation and help reduce oxidative stress, making *P. frutescens* a promising complementary approach for diabetes management[44,45].

Studies have shown that Perilla seed extracts significantly lower blood glucose levels, enhance insulin sensitivity, and protect pancreatic β-cells in animal models. Such properties underline the therapeutic relevance of both the seeds and leaves of *P. frutescens*. Similar to other traditional medicinal plants used in diabetes treatment, incorporating Perilla into daily diets could provide a safer, more holistic alternative to synthetic medications[46]. However, further research is essential to fully elucidate the underlying mechanisms of its antidiabetic activity and to optimize the formulation and delivery of its bioactive components.

In addition to lipids, Perilla seeds are a good source of high-quality plant-based proteins, mainly prolamins, which contribute to overall health[20]. As shown in Table 1, Perilla seeds exhibit superior protein quality and content compared to conventional oil seeds such as mustard, cotton, linseed, and sunflower. Their protein content ranges from 15.7% to 23.9%, primarily located in the seed kernel. Hulling the seeds can further increase protein concentration, as the hull contains only ~5% protein. Notably, 39% of the total amino acids in Perilla seeds are essential amino acids, with lysine being the limiting amino acid. Perilla seed meal protein also shows potent antioxidant properties, attributed to its low molecular weight and specific amino acid profile. Additionally, ground Perilla cake, containing 31.54% crude protein and a rich amino acid spectrum, serves as a valuable protein source. Its by-products can be repurposed as natural antioxidants or incorporated into animal feed[40,47,48].

Table 1. Comparison of Perilla seeds proximate composition of nutritional content to other oilseeds

Nutrient	Perilla	Mustard	Groundnut	Flaxseed	Sunflower	Sesame
Moisture (%)	7.4	8.5	5.5	6.5	5.5	-
Protein (%)	17.4	20	18.3	20.3	19.8	23.53
Fat (%)	51.7	39.7	43.3	37.1	52.1	52.86
Ash (%)	3.6	4.2	5.2	2.4	3.7	4.75
Carbohydrate (%)	20.3	23.8	25	28.9	17.9	14.52
Energy (Kcal)	615	541	563	28.9	620	-
Phosphorus (mg)	710	700	570	530	670	--
Magnesium (mg)	275	-	-	370	118	52.53
Calcium (mg)	269	490	1450	-	64	45.33
Iron (mg)	9	7.9	9.3	170	5.6	3.78
Manganese (mg)	4.8	2.56	1.32	2.7	-	0.23
Zinc (mg)	4.7	4.8	12.2	-	3.78	1.46
Copper (mg)	0.18	0.83	2.29	-	1.74	0.73
Chromium (mg)	20	63	87	-	-	-
Fatty acids (g)						
ω-3/ω-6	0.2	1	32	2	68	84
SCFA:MUFA:PUFA*	1:1.6:8.7	1:22.6:9.6		1:2.1:6.9	1:1.6:5.8	1:2.2:2.1

*SCFA-Short Chain Fatty Acids, MUFA-Monounsaturated Fatty Acids, PUFA-Polyunsaturated Fatty Acids[40,47,48].

3. Biological Activities of *P. frutescens*

Perilla seeds have been widely studied for their diverse biological properties, attributed to a rich composition of polyunsaturated fatty acids, flavonoids, and phenolic compounds. As highlighted in Figure 2, these seeds exhibit antioxidant, anti-hyperglycemic, anti-inflammatory, anti-adipogenic, cardioprotective, anticancer, antimicrobial, and neuroprotective potentials. The underlying mechanisms and associated biomarkers linked to these effects- such as reductions in oxidative stress, modulation of lipid metabolism, and improvements in insulin sensitivity- are elaborated in the following section.

3.1 Antidiabetic Activity of *P. frutescens*

Various bioactive substances identified in *P. frutescens* are responsible for inhibiting enzymes. Research has indicated that obstructing the starch digestive enzymes (α-amylase and α-glucosidase) is a conventional approach for managing T2DM, as illustrated in Figure 1[26,28,49]. This entails directly impeding the active center of the enzymes at diverse sub-sites, which prolongs or postpones the overall digestion of starch and its conversion to glucose. This process has the potential to decelerate or halt the breakdown of carbohydrates. The α-glucosidase is an enzymatic catalyst that facilitates the hydrolysis of glucose molecules through its action on α (1-4) glycosidic linkage, thereby promoting the assimilation of starches within the intestinal tract, resulting in a drastic blood sugar levels spike, post-meal in diabetic patients. The inhibitors consequently postpone the assimilation of simple sugars in the intestines, thereby averting heightened postprandial glucose levels. In a study by, 5 bioactive compounds isolated from *P. frutescens* seeds showed α-glucosidase inhibitory activity[50]. Luteolin was found to be a potent α-glucosidase inhibitor with an IC_{50} value of 45.4 µM. Caffeic acid-3-O-glucoside, rosmarinic acid, rosmarinic acid-3-O-glucoside, and apigenin also exhibited α-glucosidase inhibitory activity at concentrations higher than 100µM. These findings suggest the potential use of these compounds in developing oral antidiabetic medications[13,51,52]. Several *in vitro* and *in vivo* studies are demonstrating the anti-diabetic effects of *P. frutescens* in Tables 2 and 3.

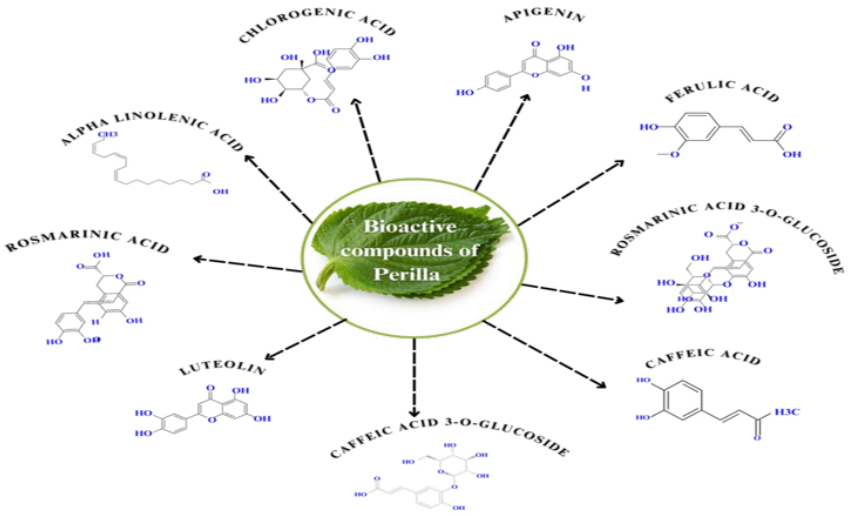


Figure 2. An illustrated overview of the bioactive compounds found in *P. frutescens*, highlighting their significant roles in various biological activities and health benefits.

Table 2. Summary of *in vitro* studies evaluating the anti-diabetic potential of *P. frutescens*, including enzyme inhibition, phytochemical profiling, and insulin signaling activity

Extract Type or Compounds	Assay or Model	Key Findings	Anti-diabetic Implications	References
75% ethanolic extract	α-amylase and α-glucosidase inhibition assay	Strong inhibition: α-amylase IC_{50} = 5196.62 ± 248.38; α-glucosidase IC_{50} = 361.28 ± 2.01	Comparable α-glucosidase inhibition to acarbose.	[16]
Methanolic and ethanolic extracts	HPTLC (High Performance Thin Layer Chromatography) and enzyme inhibition	Highest peak at Rf 0.64 (ethanolic). α-amylase inhibition 28.21% to 68.01% (IC_{50}: 1.15 mg/mL). Acarbose IC_{50}: 0.575 mg/mL	Identified 17 phenolic constituents with potential anti-diabetic activity.	[53]
Ethyl acetate fraction	Antioxidant and *in vivo* assay	Highest antioxidant activity (IC_{50} = 190.03 µg/mL); improved glucose and lipid profile in diabetic rats	Supports antioxidant-driven hypoglycemic potential.	[54]
Leaf extract pre- and post-digestion	TPC (Total phenolic content) / TFC (Total flavonoid content) and DPPH (2, 2-diphenyl-1-picrylhydrazyl)/ABTS assay (2,2 ′-azino-bis (3-ethylbenzthiazoline-6-sulphonic acid)	TPC decreased 53%, TFC 40%; DPPH IC_{50} +23%, ABTS +56%; reduced α-glucosidase, acetyl cholinesterase, and MCF-7 cell proliferation.	Maintained bioactivity post-digestion; indicates gastrointestinal stability.	[48]
Stem extract	SHP-1 inhibition and insulin signaling in HepG2	SHP-1 IC_{50}: 4 µg/mL; increased IR/ERK phosphorylation.	Promotes insulin sensitivity *via* SHP-1/IR pathway activation.	[56]
Caffeic acid-3-O-glucoside, rosmarinic acid, luteolin, apigenin	α-glucosidase inhibition	Luteolin IC_{50}: 45.4 µM	Luteolin is a potential bioactive anti-diabetic compound.	[57]

Table 3. Summary of *in vivo* studies evaluating the anti-diabetic potential of *P. frutescens* using animal models

References	Extract Type or Model	Key Findings	Anti-diabetic Implications
[21]	Perilla oil extract in KKAy mice model	FPG >10 mM in model group; Perilla oil significantly reduced FPG (Fasting Plasmaglucose) to normal levels by day 28 ($p < 0.01$).	Demonstrated hypoglycemic effect in a diabetic mouse model.
[45]	PF sprout extract in db/db mice; gene expression in liver and HepG2 cells	RA (Rosmarinic acid): 15.239 mg/g; caffeic acid and apigenin-7-O-glucoside detected; improved AMPK(*AMP*-activated protein kinase), PEPCK (Phosphenol pyruvate carboxykinase), G6Pase expression (Glucose-6-phosphatase).	Suggests insulin sensitization and improved glucose metabolism.
[17]	Wistar rats on HFD (High fat diet) + PSO (Perilla Seed Oil) or metformin	Gut dysbiosis, inflammation, insulin resistance improved; gut barrier integrity enhanced.	PSO showed metabolic benefits, though less potent than metformin.
[58]	Perilla oil in diabetic KKAy mice; gut microbiota, triglyceride profile	Lowered triglycerides; improved liver and adipocyte health; reduced Blautia.	Modulation of gut microbiota and lipid metabolism.
[59]	Perilla leaf powder in SHR-cp rats	Reduced BP, triglycerides, lipid peroxides; increased beneficial fatty acids.	Cardiovascular protection and antioxidative effects.
[60]	Ethyl acetate extract of *P. frutescens* in Sprague-Dawley rats lens model	IC_{50} = 190.03 µg/mL; improved glucose, lipid profile, glycogen storage, body weight	Strong anti-diabetic and antioxidant potential *in vivo*.

3.2 Antioxidant Property of *P. frutescens*

The antioxidant properties of Perilla have been extensively studied, demonstrating its potential as a natural source of bioactive compounds for various therapeutic applications[61-64]. The well-documented antioxidant activity of Perilla is largely attributed to its polyphenolic compounds, such as rosmarinic acid and luteolin[65]. Analysis of Perilla seeds reveals that they are a rich source of potent antioxidant compounds, including phenolic acids like rosmarinic, caffeic, and ferulic acids, as well as flavonoids like apigenin and luteolin. These bioactive constituents contribute significantly to the antioxidant properties of Perilla seeds in various studies, as represented in Table 4[63]. Furthermore, these compounds have shown the ability to inhibit important enzymes involved in carbohydrate metabolism, such as α-glucosidase and aldose reductase, which are linked to the development of diabetic complications[61,63,65]. The methanol extract (80%) of Perilla seeds has demonstrated strong antioxidant activities in various radical assays, including the 2, 2-Diphenyl-1-Picrylhydrazyl (DPPH) and 2,2 ′-Azino-bis (3-Ethylbenzthiazoline-6-Sulphonic acid) (ABTS) assays. *P. frutescens* is recognized for its remarkable antioxidant properties, evaluated using diverse assays such as DPPH, ABTS, and Ferric Reducing Antioxidant Power (FRAP)[66]. These tests measure the plant's ability to scavenge free radicals and reduce oxidative stress, primarily due to its high content of phenolic and flavonoid compounds. Research indicates that methanolic extracts from the leaves and seeds of *P. frutescens* exhibit notable antioxidant activity, as evidenced by their strong free radical scavenging potential and specific IC_{50} values reported by[67,72]. Moreover, ethanol extracts of Perilla show potent DPPH scavenging activity, with an IC_{50} of 0.27 mg/mL, underscoring the efficacy of ethanol as an extraction solvent[68,69]. The ABTS assay reveals that ethyl acetate fractions derived from the leaves of *Perilla frutescens* exhibit superior radical scavenging activity, surpassing standard controls as noted by[11]. Similarly, ethanol extracts of Perilla nutlets demonstrate significant ABTS scavenging activity, further supporting the plant's antioxidant potential with an IC_{50} of 3.43 mg/mL[12]. The FRAP assay

evaluates the reducing power of antioxidants and indicates that extracts obtained through pressurized liquid extraction possess enhanced ferric-reducing antioxidant power compared to traditional methods[13]. High ferric reducing power is also observed in ethyl acetate fractions of Perilla leaves[11]. While the antioxidant properties of *P. frutescens* are well-established, their effectiveness can vary depending on extraction methods and conditions. Future research is encouraged to optimize these parameters to maximize antioxidant potential. Additionally, the presence of other bioactive compounds, such as rosmarinic acid and flavonoids, enhances its health benefits, suggesting that *P. frutescens* could serve as a functional food or nutraceutical[68,69]. Overall, the antioxidant capacity of *P. frutescens* positions it as a valuable resource for natural antioxidant properties.

3.3 Neuroprotective Property *of P. frutescens*

Perilla, a genus of herbs belonging to the mint family, has garnered significant attention in recent years due to its potential neuroprotective properties. The bioactive compounds in *P. frutescens*, such as luteolin, rosmarinic acid, and Perilla ketone, exhibit neuroprotective effects through various mechanisms. Luteolin has been shown to counteract ROS-induced cytotoxicity in cerebral nerve cells, enhancing the viability of primary neurons exposed to peroxide toxicity[82]. Rosmarinic acid, another constituent of Perilla, has demonstrated the ability to mitigate neuroinflammation and protect against neurotoxicity in various experimental models. Its anti-inflammatory properties and capacity to modulate neurotransmitter systems contribute to its neuroprotective potential[83]. Additionally, Perilla ketone, a component of essential oils, has been found to exert neuroprotective effects by inhibiting acetylcholinesterase activity and enhancing cholinergic function, which is crucial for cognitive performance and memory formation. Furthermore, luteolin has been shown to alleviate oxidative stress in primary cortical neurons by increasing the levels of antioxidant enzymes such as catalase and glutathione, suggesting its potential as a suitable dietary supplement to aid in the prevention of neurodegenerative conditions like Alzheimer's disease, Parkinson's disease, and cerebral ischemia[84].

3.4 Cardio Protective Property of *P. frutescens*

The cardioprotective properties of *P. frutescens* can be attributed to its diverse array of bioactive compounds, such as phenolic acids, flavonoids, and omega-3 fatty acids. These compounds have been shown to exhibit potent antioxidant and anti-inflammatory activities, which are crucial in preventing and managing cardiovascular diseases[10,63]. One of the key bioactive compounds found in *P. frutescens* is rosmarinic acid, a phenolic acid that has been extensively studied for its cardioprotective effects. Rosmarinic acid has been demonstrated to possess the ability to modulate various signaling pathways involved in the regulation of oxidative stress and inflammation, which are known to be significant contributors to the development of cardiovascular diseases[85]. In addition to rosmarinic acid, *P. frutescens* also contains a rich array of other phenolic compounds, such as apigenin, luteolin, and scutellarein-7-O-glucuronide, which have been shown to exhibit similar cardioprotective properties[87]. Interestingly, *P. frutescens* is also a rich source of omega-3 fatty acids, particularly α-linolenic acid, which has been widely recognized for its beneficial effects on cardiovascular health[63,87]. These omega-3 fatty acids have been shown to exert anti-inflammatory and antioxidant effects, as well as to modulate lipid profiles and improve endothelial function[87].

3.6 Hepato-protective Property of *P. frutescens*

Rosmarinic acid, a major polyphenolic component of P. *Frutescens*, reduces lipopolysaccharide-induced liver injury in d-galactosamine-sensitized mice. The mechanism of action of Perilla-derived rosmarinic acid, in reducing liver injury induced by DGalN and LPS, is mainly attributed to the scavenging of superoxide or peroxynitrite[88]. In addition, the antioxidant and anti-inflammatory properties of P. *frutescens* have been linked to its ability to modulate oxidative stress and inflammation, which play crucial roles in the pathogenesis of various liver diseases[89]. The hepatoprotective potential of *P. frutescens* has been demonstrated in multiple *in vitro* and *in vivo* studies. Extracts of the plant have been shown to exhibit protective effects against acetaminophen-induced liver injury by reducing oxidative stress, inhibiting

Table 4. Compilation of experimental approaches and antioxidant outcomes in *P. frutescens* research

Research Theme	Methods Used	Key Findings	References
Essential oils and extraction methods	Essential oil extracted by steam distillation. Antioxidant assays: DPPH scavenging and reducing power.	Methionine (150 mg/L) with double spray significantly enhanced plant yield, essential oil content, and antioxidant activity.	65
Polyphenol extraction and optimization	Polyphenols extracted using Box-Behnken design (temperature, time, pH). Antioxidant activity *via* FRAP (Feric Reducing Antioxidant Power) assay and DNA protection assay.	Optimal extraction: 70° C, 60 min, pH 7.0; polyphenol content ranged 6.056-9.630 mg GAE/g. Improved DNA protection and reducing power under specific pH and temperature.	73
Tissue culture and phenolic acid induction	Hairy roots induced with Agrobacterium rhizogenes (C58C1). Phenolic acids quantified by HPLC (High Performance Liquid Chromatography) post-SA(salicylic acid) and MeJA (Methyl Jasmonate) elicitation.	Max Rosmarinic Acid (RA) production: 20.92 mg/g (DW) with SA and 17.36 mg/g with MeJA. C58C1 line showed highest yield.	74
Seed meal antioxidant and enzyme inhibition	Ethanol (25-100%) used for extracting seed meal. Antioxidant potential and enzyme inhibition (α-glucosidase, α-amylase) evaluated.	75% ethanol extracts yielded high phenolic (105.58 mg GAE/g) and flavonoid (66.52 mg QE/g) content.	16
Whole plant antioxidant capacity and trace elements	DPPH assay on methanolic extracts from leaves, seeds, roots, stems, flowers. ICP-MS (Inductively Coupled Plasma Mass Spectrometry) for zinc detection.	Leaves and seeds showed strong DPPH activity (IC_{50}: 5.95 µg/mL and 8.28 µg/mL). Zinc content confirmed (17.20-33.56 ppm), supporting antioxidant potential.	53
Cytoprotection and radical scavenging (nutlets)	ABTS, DPPH, hemolysis inhibition, and MTT (Methyl Thiazolyl Tetrazolium) assays conducted on ethanol extract. Constituents identified by HPLC.	Strong ABTS (IC50: 3.43 mg/mL) and DPPH (IC50: 0.27 mg/mL) scavenging. Extract inhibited AAPH (2,2′-Azobis(2-amidinopropane) dihydrochloride)-induced hemolysis effectively.	15
Anti-hemolytic and iron chelating activity	DPPH, ABTS, iron chelation assays. Evaluated anti-hemolytic effect using RBCs under AAPH-induced stress.	Potent antioxidant capacity (DPPH IC50: 34.3 µg/mL, ABTS IC50: 9.69 µg/mL). Moderate iron chelation and reduced lipid peroxidation and ROS (Reactive Oxygen Species).	69
Cosmeceutical and anti-inflammatory potential	DPPH, ABTS, NO inhibition in LPS-induced macrophages, and cytotoxicity via MTT assay.	70% ethanol extract had highest antioxidant activity and strong NO inhibition (>90%). Non-toxic across tested concentrations.	16
Analytical fingerprinting and quality control	Phenolic profiling (caffeic acid, rosmarinic acid, luteolin, apigenin) *via* HPLC. Antioxidant efficacy *via* TBARS, peroxide, hexanal analyses.	Strong phenolic-antioxidant correlation (r = 0.876). Extracts (320 ppm) comparable to BHA (20 ppm) in oxidative inhibition.	17
Application in food systems	Polyphenolic profile *via* HPLC; antioxidant capacity *via* ABTS, ORAC, FRAP assays; oxidative stability tests.	Perilla extract (320 ppm) matched BHA in preventing hydroperoxide formation and oxidative degradation.	78
Comparative analysis of plant parts	GC-MS identified volatile compounds from different plant parts. *In vitro* antioxidant assays performed.	Leaves had highest oil yield and DPPH scavenging; seeds showed strongest OH scavenging.	54
Neuroprotection via enzymatic extracts	DPPH, hydroxyl, and alkyl radical scavenging *via* ESR. Extracts prepared using carbohydrases and proteases.	Alcalase and Promozyme had strongest DPPH IC50 (77.25–109.66 µg/mL). Pepsin extract protected PC12 cells from oxidative damage.	79
Hepatoprotective potential in vivo	Rats pretreated with extract (250-1000 mg/kg), then challenged with tBHP. Biomarkers and histological damage assessed.	Extract reduced AST, ALT, LDH levels, improved glutathione, and mitigated oxidative liver damage.	80
Phenolic acid profiling and antioxidant assays	Methanolic extracts of perilla leaves analyzed for antioxidant activity (DPPH, ABTS) and phenolic content *via* HPLC.	Two major compounds identified (2.98 mg/g and 2.26 mg/g). Moderate to strong radical scavenging *in vitro*.	81

apoptosis, and regulating inflammatory responses[10,63]. Similarly, *P. frutescens* has been found to ameliorate alcohol-induced liver damage in rodent models, potentially through its ability to suppress oxidative stress, inhibit inflammatory pathways, and modulate lipid metabolism[76,90].

3.7 Anti-inflammatory and Anti-allergic Properties of *P. frutescens*

Perilla frutescens exerts its anti-allergic properties through its ability to modulate the immune system. Specifically, compounds found in *P. frutescens*, such as rosmarinic acid and luteolin, have been shown to inhibit the release of histamine and other inflammatory mediators from mast cells, which play a crucial role in developing allergic reactions[91,92] Additionally, these bioactive compounds have been found to suppress the production of pro-inflammatory cytokines, such as interleukin-4 and interleukin-5, which are involved in the pathogenesis of allergic diseases[93].

3.8 Hypolipidemic Properties

The hypolipidemic (cholesterol-lowering) effect of *P. frutescens* has been a topic of growing research, particularly in managing obesity. Several studies have investigated the effects of extracts from *P. frutescens* on lipid profiles and obesity-related factors in both animal models and human subjects[94]. A recent study demonstrated that the administration of *P. frutescens* extracts to mice resulted in a significant reduction in triglyceride and cholesterol levels, along with noticeable decreases in body weight and fat accumulation[92]. The authors suggest the cholesterol-lowering effects may stem from *P. frutescens* ability to regulate genes involved in lipid metabolism and fat cell formation. Similarly, a study on people with high cholesterol showed that consuming *P. frutescens* supplements substantially decreased total cholesterol, LDL-cholesterol, and triglycerides, while increasing HDL-cholesterol[10]. These findings indicate that *P. frutescens* could be a promising natural option for managing obesity and related lipid disorders.

4. Challenges and Limitations

Despite the growing interest in *P. frutescens* as a potential functional food for Type 2 Diabetes Mellitus (T2DM), several challenges need to be addressed before it can be recommended widely. A major limitation is the absence of human clinical trials. While preclinical studies suggest it can help regulate blood sugar and support metabolic health, we need clinical evidence to determine optimal dosages and any interactions with conventional treatments. Another concern is bioavailability- the ability of the body to absorb and utilize its beneficial compounds. Although rosmarinic acid and luteolin show promise in laboratories, their effectiveness in humans is still unclear, necessitating further research[95,96].

Additionally, while *P. frutescens* is consumed in Uttarakhand, its full potential as a functional food remains underexplored. Combining it with other diabetes-friendly ingredients could enhance its effects, but requires understanding its interactions. Finally, consumer acceptance is crucial. Identifying health benefits is not enough; we need to develop appealing and convenient food products that encourage people to incorporate *P. frutescens* into their diets[14].

5. Future Directions

To bridge these gaps, future research must focus on clinical validation, formulation innovations, and public awareness. Large-scale, randomized controlled trials are essential to determine the efficacy, safety, and long-term benefits of *P. frutescens* for diabetes management. Human clinical trials will provide the necessary scientific evidence to support its integration into mainstream healthcare. Additionally, leveraging traditional consumption patterns in Uttarakhand, researchers can develop innovative dietary formulations by combining *P. frutescens* with other functional ingredients to enhance its antidiabetic potential.

Beyond formulation, improving the bioavailability and stability of active compounds in *P. frutescens* is crucial. Research should explore novel food processing technologies, such as microencapsulation, fermentation, or lipid-based delivery systems, to enhance the absorption and stability of its bioactive compounds. Furthermore, public education on the benefits of *P. frutescens* and its role in traditional medicine could encourage wider adoption. Integrating it into nutrition policies

and dietary guidelines for diabetes management could further support its inclusion in evidence-based dietary interventions.

By addressing these challenges and advancing research in these key areas, *P. frutescens* has the potential to move beyond traditional use and emerge as a scientifically validated, culturally relevant, and accessible functional food for diabetes management.

6. Conclusion

The rising prevalence of Type 2 Diabetes Mellitus (T2DM) underscores the urgent need for comprehensive and sustainable management strategies beyond conventional pharmacological approaches. Although medications play a key role in blood sugar regulation, their side effects and limitations create a need for safer, food-based interventions. Traditionally consumed in Uttarakhand as a condiment, *P. frutescens* holds significant potential for diabetes management, yet its benefits remain underexplored in human clinical settings.

By addressing the root causes of T2DM- including obesity, insulin resistance, and gut microbiome imbalances- through functional nutrition and lifestyle modifications, we can complement medical therapies and reduce long-term reliance on medications. However, to fully harness the benefits of *P. frutescens*, further research is needed to validate its clinical efficacy, optimize bioavailability, and explore its synergy with other functional foods, other seeds, and millets.

Bridging traditional wisdom with modern scientific validation will be key to integrating *P. frutescens* into evidence-based dietary strategies for diabetes management. By promoting education, accessibility, and policy inclusion, we can pave the way for more sustainable, culturally relevant, and effective interventions, ultimately improving metabolic health and quality of life for individuals with diabetes worldwide.

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8. Author Contribution

Conceptualization: Medha Singh; Literature search and data compilation: Medha Singh; Writing- original draft preparation: Medha Singh; Writing- review and editing: Shikha Saxena and Medha Singh; Supervision: Shikha Saxena. All authors have read and agreed to the published version of the manuscript.

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