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Foeniculum vulgare (Fennel): A comprehensive review of its anti-diabetic properties

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ABSTRACT

Type 2 diabetes mellitus (T2DM) emerges as a global health crisis and is characterized by hyperglycemia, insulin resistance, and oxidative stress. Conventional treatments for T2DM often have limitations, thus prompting interest in natural alternatives like fennel. This review explores fennel's potential anti-diabetic properties, focusing on its antioxidant and anti-inflammatory effects. Fennel contains various bioactive compounds, including flavonoids, phenolic acids, and volatile oils, known for their antioxidant properties. These compounds can neutralize free radicals and reduce oxidative stress, which plays a crucial role in T2DM. Additionally, fennel's anti-inflammatory effects may help mitigate the chronic inflammation associated with T2DM. Preclinical studies have demonstrated fennel's ability to lower blood glucose levels, improve insulin sensitivity, and reduce oxidative stress in diabetic animals. These findings suggest that fennel may be a promising natural agent for managing T2DM. However, further research is needed to fully understand its mechanisms of action and to evaluate its efficacy and safety in human clinical trials.

KEYWORDS: *Foeniculum vulgare*; Fennel; Diabetes; *Trans-anethole*; Oxidative stress

1. Introduction

The International Diabetes Federation reports that from 2000 to 2021, the number of adults with diabetes mellitus (DM), including type 1 (T1DM) and type 2 (T2DM), rose from 151 million to 537 million. T2DM, the most common chronic metabolic condition, results in elevated blood glucose levels due to poor insulin management[1]. Chronic high blood sugar leads to increased production of advanced glycation end products, which can cause inflammation and oxidative stress[2]. The exact causes of

inflammation in T2DM are not fully understood, but inflammation may contribute to the disease and worsen insulin resistance[3]. Studies have linked inflammatory biomarkers like TNF- α , IL-6, *etc.* to T2DM and its complications[4]. Adipose (fat) tissue plays a crucial role in producing these biomarkers due to interactions between fat cells, macrophages, and other immune cells[5].

Oxidative stress also significantly contributes to T2DM. People with T2DM often show increased oxidative stress and reduced antioxidant levels[6]. High blood sugar can exacerbate oxidative stress through several pathways, resulting in increased reactive oxygen species (ROS). These ROS can cause harm by reducing insulin secretion, damaging DNA, and increasing vascular

Summary

Question: Can fennel (*Foeniculum vulgare*) serve as an effective natural adjunct therapy for type 2 diabetes mellitus due to its antioxidant and anti-inflammatory properties?

Findings: This review synthesizes preclinical findings on fennel's bioactive compounds, which show potential in reducing blood glucose, improving insulin sensitivity, and mitigating oxidative stress in diabetic models. However, clinical studies on humans are limited.

Meaning: Fennel demonstrates promise as a natural supplement for managing type 2 diabetes mellitus, but further human trials are essential to validate its clinical efficacy and safety.

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permeability. They also promote the formation of advanced glycation end products, which can lead to complications affecting blood vessels[7]. Given the harmful effects of oxidative stress on T2DM and its complications, antioxidant therapy is being explored as a potential treatment strategy[8].

Foeniculi fructus refers to the fruit of *Foeniculum vulgare* (*F. vulgare*) Mill., commonly known as fennel or sweet anise. This fruit has a long history of medicinal use, particularly as a carminative (to relieve gas) and galactagogue (to promote milk production). Research suggests that fennel has various effects, including antibacterial, antioxidant, anti-inflammatory, and hepatoprotective properties[9,10]. The European Medicines Agency recognizes fennel fruits as effective carminatives and expectorants[11]. Fennel contains both volatile and non-volatile compounds. The non-volatile components mainly include phenolic compounds like hydroxycinnamic acid and flavonoids[12]. The main volatile compounds in fennel essential oil are *trans*-anethole (TA), estragole, and fenchone, which can vary by geographic origin[13].

Fennel has potential protective effects against diabetes through various mechanisms. Fennel's volatile oils may enhance insulin release from pancreatic cells. Flavonoids and phenolic compounds in fennel can reduce oxidative stress in pancreatic cells and improve insulin sensitivity. Alkaloids in fennel may help reduce chronic inflammation related to diabetes. While much evidence is from preclinical studies, clinical trials show that fennel can improve blood sugar control and reduce complications like neuropathy and nephropathy[2,14].

Fennel is generally safe when consumed in moderation, but it is important to monitor for potential side effects, especially in individuals with allergies or those on medications. Research on long-term safety, optimal formulations, and dosages is needed. Future studies should focus on understanding fennel's mechanisms, conducting larger clinical trials, and exploring its potential in diabetes prevention among high-risk groups. Given the above, this review aimed to examine how *F. vulgare* and its constituents affect diabetes and its complications and what safety measures are required to use fennel as an anti-diabetic agent.

2. Current approaches to diabetes management

The global increase in T2DM has led to various prevention efforts[15,16], including successful strategies like the U.S. Diabetes Prevention Program, a national initiative launched in 1990 aimed at preventing type 2 diabetes in high-risk individuals. Diabetes Prevention Program was based on a major clinical trial showing that lifestyle changes—such as increased physical activity and healthier eating—could reduce diabetes risk by up to 58% and lower cardiovascular disease risk factors, along with decreasing reliance on medications[17]. While medications like metformin[18], acarbose[16],

and thiazolidinediones[19] can reduce diabetes risk, lifestyle changes and metformin are preferred due to their favorable risk-benefit profiles; metformin is especially effective in individuals under 60 with a BMI of 35 or higher[18]. Various lifestyle modification programs have been launched[20], and bipartisan support exists for enhancing the National Diabetes Prevention Program. Encouragingly, annual incidence rates of type 2 diabetes in the U.S. are declining for the first time in thirty years[21].

Over the past 20 years, the number of medications for lowering blood sugar has significantly increased, resulting in complex management strategies and the development of guidelines to assist general practitioners[22]. These guidelines vary in strictness, addressing both treatment options and cost considerations[23]. Despite the trend toward personalized medicine, reliable information for selecting appropriate medications remains scarce. The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study project is investigating glucose-lowering drugs as co-treatments with metformin[24], but until results are available, physicians must rely on limited data.

Most type 2 diabetes treatment occurs in primary care, despite the complexity of managing the condition. Referrals to specialists may be necessary when treatment complexity exceeds primary care capabilities, particularly with insulin administration or complications. As metabolic dysfunction progresses, more complex medication regimens are required to maintain glycosylated hemoglobin A1c (HbA1c) levels below 7%. Lifestyle interventions, such as those in the Diabetes Prevention Program[18], can help control blood glucose and reduce medication needs.

Metformin is typically the first medication prescribed due to its safety, effectiveness, affordability, and lack of hypoglycemia risk. Most experts support this choice, although direct evidence comparing metformin to other drugs is limited[18]. Starting metformin alongside intensive lifestyle modifications is advisable[23], and it is usually continued throughout treatment unless contraindicated.

Choosing a second medication to complement metformin is less clear due to limited comparative efficacy studies. Many trials on newer medications focus on cohorts with lower baseline HbA1c values, complicating comparisons. The Food and Drug Administration does not require a significant HbA1c reduction for drug approval, leading to less effective medications entering the market[25]. However, the Food and Drug Administration mandates post-marketing studies for new diabetes drugs to evaluate cardiovascular safety.

Clinicians must choose an additional drug to pair with metformin and lifestyle changes, aiming for an HbA1c of no more than 7%. Key factors in this decision include efficacy, patient acceptability, safety, tolerance, side effects, and cost, particularly in lower-income nations[25,26]. Insulin and sulfonylureas are traditional medications for type 2 diabetes, supported by long-term evidence. While often viewed as a last resort, insulin should be considered earlier due to

its proven efficacy, ability to achieve remission[27], and consistent glycemic control, despite the risk of hypoglycemia being lower in T2DM than in T1DM. Many patients can achieve target glycemia with simple, single-dose regimens.

The following safety concerns are common for the current anti-diabetic drugs.

2.1. Thiazolidinediones

Thiazolidinediones activate peroxisome proliferator-activated receptors (mostly gamma)[28]. Troglitazone was withdrawn due to rare but severe liver failure (1 in 20000 cases). While pioglitazone and rosiglitazone are not linked to liver issues, they are associated with increased risks of cardiovascular disease and bladder cancer[28], though the latter risk is now considered unlikely. These concerns have led to decreased use of thiazolidinediones, especially of rosiglitazone, which is further limited by adverse effects such as fluid retention, congestive heart failure, and bone loss.

2.2. Glucagon-like peptide (GLP-1) therapy

Researchers developed GLP-1 analogs that resist breakdown by dipeptidyl peptidase-4. Current GLP-1 receptor agonists reduce HbA1c by about 1% when combined with metformin. Benefits include a low risk of hypoglycemia and weight loss, unlike insulin, which can cause weight gain[29]. However, challenges include the need for injections, short study durations, gastrointestinal discomfort, and high costs. Evidence linking GLP-1 agonists to pancreatitis and pancreatic cancer is still lacking but raises concerns[30].

2.3. Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 inhibitors increase endogenous GLP-1 levels but not as significantly as GLP-1 agonists, lowering HbA1c by 0.6% to 0.8% and also decreasing glucagon levels[31]. They are widely used despite modest efficacy and high cost, partly due to weight-neutral options like saxagliptin and alogliptin, which do not cause significant hypoglycemia. Saxagliptin has been linked to an increased risk of chronic heart failure, but no dipeptidyl peptidase-4 inhibitors have shown benefits for cardiovascular disease[32].

2.4. Sodium-glucose transporter inhibitors

Sodium-glucose transporter inhibitors are the latest class of blood sugar-lowering drugs, increasing glycosuria by blocking glucose reabsorption in the kidneys[33]. They lower HbA1c by about 1% and generally do not cause hypoglycemia or weight gain. However, they are associated with a twofold increase in genital and urinary tract infections and may raise insulin resistance in some patients[34].

Although synthetic medications have made progress in managing

DM, many have long-term side effects. Therefore, the World Health Organization advocates for the development of herbal medicine as a safer alternative[35]. Dried herbs are known to offer various physiological benefits, including anti-diabetic effects[36]. Several spices, such as fenugreek seeds (*Trigonella foenum-graecum*), garlic (*Allium sativum*), onion (*Allium cepa*), and turmeric (*Curcuma longa*), have been shown in studies to possess anti-diabetic properties. Additionally, some studies have reported hypoglycemic effects about cumin seeds (*Cuminum cyminum*), ginger (*Zingiber officinale*), mustard (*Brassica nigra*), curry leaves (*Murraya koenigii*), and coriander (*Coriandrum sativum*)[37].

3. Botanical overview of *F. vulgare*

F. vulgare Mill, known as fennel in English and fenouil in French, belongs to the Apiaceae family. This fragrant, herbaceous plant grows 1 to 2 meters tall and is found across Asia, the Mediterranean, and various parts of Europe[38]. Fennel is a perennial herb with grooved stems and dark green, feathery leaves that have sheathed petioles. Its flowers can be bisexual and are typically yellow, forming umbrella-like clusters. The small seeds are about 8 mm long and 3 mm wide, have a cylindrical shape, and are known for their aromatic scent and pleasant flavor, with sizes varying based on plant growth[39].

Fennel has been used in traditional medicine to treat various conditions related to the reproductive, endocrine, digestive, and respiratory systems. With over forty recognized ailments treated, *F. vulgare* is among the most popular herbal remedies, supported by both scientific and traditional use. Phytochemical studies have identified valuable compounds, including volatile chemicals, flavonoids, phenolic compounds, fatty acids, and amino acids. Studies have isolated lipids, aromatic compounds, petroleum products, volatile chemicals, and other secondary metabolites from various parts of *F. vulgare* (Table 1). Most of these phytochemicals are found in its essential oil. Some phytoconstituents from *F. vulgare* are used as pigments and anti-aging agents[40]. Additionally, they have notable pharmacological and biochemical properties.

3.1. Volatile compounds

Guillén and Manzanos[41] studied the volatile substances in pentane extracts of *F. vulgare*'s leaves, stems, and seeds, identifying 37 compounds using gas chromatography (GC) and gas chromatography-mass spectrometry (GC-MS). The hydro-distilled fennel oil had 19 compounds, while supercritical CO₂ (SC-CO₂) seed extracts contained 28, primarily TA (about 75%), fenchone (8%-15%), and methyl chavicol (5%-9%)[42]. Liu *et al.* analyzed 76 volatile components in fennel essential oil using steam distillation and solid-phase microextraction methods[43]. Tognolini *et al.* found

Table 1. Chemical composition of *Foeniculum vulgare* (fennel).

Category	Study/Source	Extraction method	Number of compounds identified	Key compounds	Notes
Volatile compounds	[40]	Pentane extraction	37	N/A	Studied leaves, stems, and seeds; identified using GC and GC-MS.
	[41]	Hydro-distillation	19	N/A	Fennel oil analysis.
	[41]	Supercritical CO ₂	28	<i>Trans</i> -anethole (75%), fenchone (8%-15%), methylchavicol (5%-9%)	-
	[42]	Steam distillation, SPME	76	N/A	Analyzed fennel essential oil.
	[43]	N/A	18	Anethole	The most common compound in fennel oil.
	[44]	N/A	28	<i>Trans</i> -anethole (72.2%)	Essential oil concentration decreases with maturation.
	[45]	GC and GC-MS	60	<i>Trans</i> -anethole (58.8% to 90.4%)	Analyzed two fennel cultivars (Aurelio and Sparta).
	[46]	GC-MS of hexane extracts	78	Estragole, limonene	Chemical makeup varies among cultivars.
	[47]	N/A	28	<i>Trans</i> -anethole (68.53%)	Identified in fennel oil.
Flavonoids	[48]	Various	Various	Rosmarinic acid, quercetin-3-rutinoside, eriodictyol-7-rutinoside	Important antioxidants found in the Apiaceae family.
	[49]	Various	Various	Kaempferol, quercetin isorhamnetin glucoside, kaempferol derivatives	Show anti-inflammatory and immunomodulatory effects.
Phenolic chemicals	[50]	Water extract	Various	Flavonoid glycosides, hydroxyl cinnamic acid derivatives	Linked to hepatoprotective and antioxidant properties.
	[49]	Methanolic extract	N/A	Chlorogenic acid (14.9%), rosmarinic acid (6.8%)	Total phenolic content higher than flavonoid content.
	[49]	Isolated from wild fennel	2	3',8'-binaringenin (2.4%), 3,4-dihydroxyphenethylalcohol-6- <i>O</i> -caffeoyl-β- <i>D</i> -glucopyranoside (1.2%)	Found in lower concentrations compared to cultivated fennel.

SPME: solid-phase microextraction methods; GC: gas chromatography; GC-MS: gas chromatography-mass spectrometry.

anethole to be the most common among 18 compounds detected in fennel oil[44].

Telci *et al.* reported that essential oil concentration decreases with plant maturation, identifying 28 constituents that made up 98.0% of the oil, with TA at 72.2%[45]. In two fennel cultivars, Aurelio and Sparta, GC and GC-MS analysis revealed 60 components, with TA ranging from 58.8% to 90.4%[46]. A comparative study showed that the chemical makeup of Algerian fennel differed from other cultivars in Turkey, Serbia, India, and China. GC-MS analysis of hexane extracts found 78 compounds, including estragole and limonene[47]. Diao *et al.* identified 28 components in fennel oil, with TA being the primary component (68.53%)[48].

Flavonoids are important antioxidants, and the Apiaceae family, including fennel, has many. *F. vulgare* contains flavonoids like rosmarinic acid, quercetin-3-rutinoside, and eriodictyol-7-rutinoside[49]. Other common flavonoids include isorhamnetin glucoside and kaempferol derivatives[50]. Methanol extracts revealed additional flavonoids including quercetin 3-*O*-β-glucoside. Ethyl acetate extracts contained flavonoids like kaempferol and quercetin. These flavonoids have strong anti-inflammatory properties and show immunomodulatory effects[51].

3.2. Phenolic chemicals

Fennel's water extract is rich in phenolics, many of which have hepatoprotective and antioxidant properties. Most enriched ones are flavonoid glycosides, hydroxyl cinnamic acid derivatives, and flavonoid aglycones[52]. These compounds are linked to preventing oxidative stress-related conditions like cancer, inflammation, and cardiovascular disease. Consequently, they have attracted interest from nutritionists, food scientists, and consumers.

A methanolic extract of fennel seeds shows 14.9% chlorogenic acid and 6.8% rosmarinic acid as major phenolic compounds, along with 17.1% quercetin and 12.5% apigenin as primary flavonoids. Overall, the total phenolic content is higher than that of flavonoids[50]. *F. vulgare* contains various phenolic acids, such as di-caffeoylquinic acids[53]. Additionally, two new compounds isolated from wild fennel, 3',8'-binaringenin, and 3,4-dihydroxyphenethylalcohol-6-*O*-caffeoyl-β-*D*-glucopyranoside, were found in lower concentrations (2.4% and 1.2%) compared to cultivated fennel, which has total phenolic and flavonoid levels of 3.1% and 1.6%, respectively[50].

4. Properties of *F. vulgare*

4.1. Antioxidant properties of *F. vulgare*

F. vulgare is rich in natural antioxidants, including flavonoids and polyphenols, which helps inhibit free radical production (Table 2). Key phenolic compounds include rosmarinic acid, quercetin 3-*O*-galactoside, kaempferol-3-*O*-glucoside, eriodictyol-7-rutinoside, and caffeoylquinic acid. The volatile oil of fennel demonstrates strong antioxidant properties, while comparative studies show that its aqueous and ethanolic extracts exhibit lower antioxidant activity[54].

Research on fennel seeds has shown significant free radical scavenging capabilities. Studies have evaluated the antioxidant capacity, hydrogen peroxide scavenging, and metal chelation abilities of fennel extracts, comparing their efficacy to well-known antioxidants such as alpha-tocopherol and butylated hydroxyanisole[55]. Results revealed that fennel seed extracts are a rich source of natural antioxidants, with significant activity compared to alpha-tocopherol. In the DPPH antioxidant test, fennel extracts effectively scavenged free radicals, particularly methanol and ethanol extracts, with methanol showing superior efficiency[56]. The essential oil from fennel leaves had a lower scavenging capacity due to lower anethole levels[57], while fennel seed essential oil showed strong DPPH radical activity (0.35-0.04)[58]. Another study found both fennel seed ethanol extracts and essential oils are effective in scavenging DPPH radicals[59]. Methanolic fennel seed extracts exhibited the highest antioxidant activity (IC_{50} =27.17 g/mL) compared to other essential oils[60]. Fennel leaf hydroalcoholic extracts also demonstrated antioxidant activity with a relative antioxidant capacity index value of 0.844[59]. Variations in antioxidant activity may be mainly attributed to *trans*-anethole concentration.

4.2. Anti-inflammatory properties of *F. vulgare*

Research shows that methanol extract from *F. vulgare* has anti-inflammatory properties. This extract can inhibit acute and subacute inflammation, as well as type 4 allergic reactions when taken

orally. It increases plasma high-density lipoprotein cholesterol levels while increasing the activities of catalase and superoxide dismutase. Additionally, it reduces malondialdehyde levels, a marker of lipid peroxidation, indicating effective inflammation mitigation. Mostafa *et al.* found that the methanol extract from fennel seeds also reduces inflammation[61]. Choi *et al.* further explored the anti-inflammatory effects of methanol extract from *F. vulgare*, concluding that its actions involve both central and peripheral pathways[62]. Central pathways of inflammation involve neuroinflammation and cytokine production in the central nervous system, affecting systemic responses, while peripheral pathways include immune cell activation and vascular responses at injury sites. Both pathways interact bidirectionally, influencing inflammation and healing processes in diabetes. The hydromethanolic extract of *F. vulgare* seeds also shows promising anti-inflammatory property and showed significant inhibition of protein denaturation [(35.9±0.4)%], protease activity [(58.1±0.1)%], and heat-induced hemolysis [(9.7±0.3)%] at concentrations of 200, 250, and 200 µg/mL, respectively, compared to the reference drug indomethacin ($P<0.001$). This strong anti-inflammatory activity may be due to the high levels of flavonoids in the extract. GC-MS analysis confirmed the presence of linalool and fatty acids (palmitic and oleic acids), which are known for their potential anti-inflammatory effects[63].

5. Anti-diabetic effects

Research has explored the anti-diabetic effects of aqueous extracts from plants in the Apiaceae family, particularly fennel (*F. vulgare*) (Table 3). These studies suggest that fennel extracts may help diabetic patients regulate their blood sugar levels and could be effective in reducing chronic complications associated with diabetes[64–67]. In diabetic studies, streptozotocin (STZ) is commonly used to induce diabetes in animals, primarily targeting pancreatic β cells[68]. Harmful effects of STZ may be linked to the production of ROS and the suppression of free radical-scavenging enzymes[69,70]. In studies involving rats induced with diabetes using STZ, fennel extract significantly lowered blood sugar levels. This effect is

Table 2. Antioxidant properties of compounds of *Foeniculum vulgare*.

Compound name	Concentration	Antioxidant activity	Reference number
Rosmarinic acid	Not specified	Natural antioxidant; contributes to overall activity	-
Quercetin 3- <i>O</i> -galactoside	Not specified	Natural antioxidant; contributes to overall activity	-
Kaempferol-3- <i>O</i> -glucoside	Not specified	Natural antioxidant; contributes to overall activity	-
Eriodictyol-7-rutinoside	Not specified	Natural antioxidant; contributes to overall activity	-
Caffeoylquinic acid	Not specified	Natural antioxidant; contributes to overall activity	-
Methanol extract	IC_{50} = 27.17 g/mL	Highest antioxidant activity compared to other essential oils	[59]
Fennel seed essential oil	0.35-0.04	Strong DPPH radical activity	[57]
Fennel leaf essential oil	Not specified	Lower scavenging capacity due to lower anethole levels	[56]
Hydroalcoholic extracts	RACI = 0.844	Demonstrated antioxidant activity	[58]
<i>Trans</i> -anethole	Not specified	Variation in activity attributed mainly to its concentration	-

RACI: relative antioxidant capacity index.

Table 3. Potential therapeutic effects of fennel on diabetes management.

Category	Study/Source	Key findings	Notes
Traditional uses	[63]	Fennel has diuretic and carminative effects.	Historically used in Mediterranean medicine.
	[64,65]	Contains about 20% fixed oil; rich in <i>trans</i> -anethole and fenchone. Contributes to antioxidant, anti-inflammatory, and pro-oxidant properties.	Anti-diabetic effects
	[66]	Aqueous extracts may help regulate blood sugar levels and reduce complications in diabetic patients.	Apiaceae family studies focus on fennel.
	[70]	Fennel extract significantly lowered blood sugar levels in STZ-induced diabetic rats.	Antioxidant properties are linked to these effects.
	[68,69]	STZ's harmful effects involve reactive oxygen species production and free radical-scavenging enzyme suppression.	-
Antioxidant mechanisms	[71]	Key enzymes like superoxide dismutase, GPx, and catalase are crucial for oxidative damage mitigation.	GPx activity is reduced in diabetic rats; fennel oil may counteract this decline.
	[72]	Fennel oil helps maintain GPx activity in diabetic rats.	Protects against oxidative stress in β cells.
Renal and pancreatic effects	[75]	Fennel oil consumption can reverse diabetes-induced oxidative stress in renal and pancreatic tissues.	Histological improvements were noted in STZ-induced diabetic rats.
	[76]	Necrotic changes in pancreatic islets noted; fennel shows beneficial effects.	-
Liver health	[79]	Fennel and <i>trans</i> -anethole reduced liver oxidative damage and fibrosis in diabetic rats.	Improved serum lipid profile and liver enzyme levels.
	[80]	Fennel essential oil showed significant hypoglycemic and antioxidant effects in treated diabetic rats.	Notable reductions in serum glucose levels and improvement in pancreatic health.
Ovarian health	[83]	Fennel oil improved ovarian structure and reduced blood glucose levels in diabetic female rats.	Supports traditional use as a fertility enhancer.
	[84]	Both fennel oil and mesenchymal stem cells improved ovarian health and reduced blood glucose levels.	Highlights potential therapies for diabetes-related reproductive dysfunction.
Obesity-related complications	[82]	Fennel treatment reduced serum protein and cholesterol levels, improving liver enzyme activity.	Potential for enhancing liver function in insulin resistance syndrome.
Antioxidant properties	[85]	Evaluation of 23 fennel samples revealed high flavonoids and phenolic compounds in the Kh1 variety from Iran.	Promising antioxidant and antibacterial activity against food-borne pathogens.
Glucose tolerance	[86]	Fennel oil consumption enhances glucose tolerance in animal studies.	Links antioxidant properties to diabetes management.
	[87,88]	Fennel may inhibit nuclear factor-kappa B activation, linked to inflammation in diabetes.	-
Herbal combination studies	[77]	Caraway, coriander, and fennel improve histological changes in the kidneys and pancreatic islets of diabetic rats.	Suggests potential as therapeutic agents for diabetes management.
	[78]	Fennel and senna extracts together improve blood glucose, and lipid profiles, and reduce oxidative stress.	Indicates combined benefits for diabetes and cardioprotection.

STZ: streptozotocin; GPx: glutathione peroxidase.

believed to be linked to fennel's antioxidant properties, making it a candidate for developing anti-diabetic medications[71]. Additionally, a methanolic extract of fennel fruit also showed reductions in both blood sugar and cholesterol levels.

Effective antioxidant defense mechanisms are crucial for mitigating oxidative damage, with key enzymes like superoxide dismutase, glutathione peroxidase (GPx), and catalase playing significant roles[72]. The reduced activity of GPx in diabetic rats suggests a connection to oxidative stress, which fennel essential oil appears to counteract by preventing significant decreases in this enzyme's activity[73]. Moreover, GPx may provide broader protective effects against lipid hydroperoxides beyond hydrogen peroxide, with its upregulation serving as a defense mechanism against oxidative stress in β cells[74]. Fennel oil administration has been shown to mitigate the decline in pancreatic antioxidant enzyme levels in diabetic rats, likely due to its high concentration of phenolic compounds[74,75].

Recent findings suggest that fennel oil consumption can reverse diabetes-induced oxidative stress effects in renal and pancreatic

tissues. Histological analysis of STZ-induced diabetic rats revealed significant kidney damage and changes in renal tubules linked to hyperglycemia[76]. The regenerative capacity of renal tubules may facilitate recovery following fennel oil treatment, underscoring fennel's potential as an anti-diabetic agent that normalizes metabolic functions at the cellular level. Previous studies reported protective effects of fennel against necrotic changes in pancreatic islets due to STZ, further supporting fennel's beneficial effects[77].

The effects of caraway, coriander, and fennel on the kidneys and pancreatic islets in diabetic rats were also examined. Treatment with these herbs improved significant histological changes, such as inflammatory infiltration and cellular degeneration, suggesting they may serve as therapeutic agents in diabetes management[78]. Another study investigated the cardioprotective effects of senna (*Cassia angustifolia*) and fennel in diabetic rats. The combination of these extracts showed significant improvements in blood glucose and lipid profiles while reducing oxidative stress. This indicates that senna and fennel together can provide both anti-diabetic and cardioprotective

benefits[79]. A combined approach using fennel and senna extracts in diabetic rats showed improved hyperglycemia, insulin levels, and overall health markers. This suggests that these herbal treatments could effectively manage diabetes, likely due to their antioxidant properties[79].

Fennel seed extract and its active compound, TA, were also studied for their effects on liver injury in diabetic rats. Both fennel and TA effectively reduced blood glucose levels, food and water intake, and weight loss during treatment. They also improved the serum lipid profile, lowered serum aminotransferases, and reduced liver oxidative damage and fibrosis[80]. Further investigation focused on fennel essential oil, which exhibited significant hypoglycemic and antioxidant effects. In treated diabetic rats, serum glucose levels dropped from 162.5 mg/dL to 81.97 mg/dL, and there was an increase in GPx activity. Improvements in kidney and pancreatic health were also observed, suggesting fennel essential oil may be a promising option for anti-diabetic therapies[81]. A 30-day study on the daily administration of fennel extract in normal and diabetic rats showed significant reductions in blood glucose, cholesterol, triglycerides, and liver enzymes while increasing high-density lipoprotein levels. These results indicate fennel's potential for improving lipid profiles and reducing oxidative stress in diabetic rats, pointing to its possibilities for drug development[82].

Research also looked at how fennel interacts with conventional medications for obesity-related complications, specifically focusing on its effects on insulin resistance syndrome. Fennel treatment led to reductions in serum protein and cholesterol levels while improving liver enzyme activity, indicating its potential to enhance liver function and manage obesity-related complications[83].

In studies assessing the effects of fennel oil on ovarian health in diabetic female rats, results showed that fennel oil improved ovarian structure and reduced blood glucose levels, supporting its traditional use as a fertility enhancer[84]. Similarly, a study involving mesenchymal stem cells and fennel oil indicated that both treatments improved ovarian health and reduced blood glucose levels, highlighting potential therapies for diabetes-related reproductive dysfunction[85].

An evaluation of 23 fennel samples revealed their antioxidant, antibacterial, and antiglycation properties. The Kh1 variety from Iran demonstrated the highest levels of flavonoids and phenolic compounds, showing promising antioxidant activity and antibacterial effects against food-borne pathogens[86].

While limited research exists on fennel oil's direct effects on blood sugar, it has been shown to enhance glucose tolerance in animal studies[87]. The herb's antioxidant properties may link to its effectiveness in managing diabetes, as indicators of oxidative stress correlate with altered glucose and lipid levels[88]. Additionally, fennel may inhibit nuclear factor-kappaB activation, associated with inflammation in diabetes[89]. Overall, the administration of *F. vulgare* essential oil to diabetic rats appears to restore pathological abnormalities and hyperglycemia by re-establishing redox balance

and exerting antioxidant effects, highlighting its potential for integration into anti-diabetic therapies (Figure 1).

5.1. Mechanism of action

In a study involving diabetic rats, it was found that those treated with *F. vulgare* experienced a significant reduction in glycosylated hemoglobin levels, a marker of long-term glucose control. In contrast, untreated diabetic rats showed a notable increase in this marker. The enzyme hexokinase, which plays a crucial role in glucose metabolism, was found to be decreased in the liver and kidneys of diabetic rats; however, pretreatment with *F. vulgare* significantly increased hexokinase levels in these organs. Additionally, diabetic rats exhibited decreased blood and tissue protein levels, while *F. vulgare* treatment led to a substantial increase in these protein levels. The administration of this plant extract also resulted in significant reductions in elevated urea and creatinine levels in the blood of STZ-induced diabetic rats[88].

The study further revealed that succinate dehydrogenase levels were reduced in diabetic rats, but these levels increased significantly following pretreatment with *F. vulgare*. The findings indicate that administering an aqueous extract of this plant before diabetes induction decreased the levels of marker enzymes such as alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase, acid phosphatase, and kidney enzymes in STZ-induced diabetic rats, suggesting a protective effect against tissue damage[88].

Moreover, significant alterations were observed in the blood lipid profiles of diabetic rats, including notable increases in total cholesterol, triglycerides, low-density lipoprotein, and very low-density lipoprotein, alongside a decrease in HDL levels. However, normal lipid levels were restored after pretreatment with the aqueous extract of *F. vulgare*, demonstrating its hypolipidemic effects.

Oral administration of the water-based extract before diabetes induction resulted in substantial increases in both non-enzymatic antioxidants, such as vitamin C, and enzymatic antioxidants like catalase, superoxide dismutase, and GPx[88]. The increase in both enzyme- and non-enzyme-based antioxidants suggests a potential protective effect. These findings indicate that *F. vulgare* exhibits significant anti-diabetic effects in both *in vitro* and *in vivo* diabetic studies. Further research is warranted to isolate and purify the active ingredients responsible for these anti-diabetic properties of *F. vulgare* seed extract.

5.2. Anti-diabetic effects of TA

TA, a terpenoid found in essential oils from various medicinal plants, exhibits hypoglycemic and antioxidant properties (Figure 2). A study evaluating TA's effects on carbohydrate metabolism in STZ-induced type 2 diabetic rats showed that administering TA at 80 mg/kg for 45 d significantly reduced plasma glucose and HbA1c

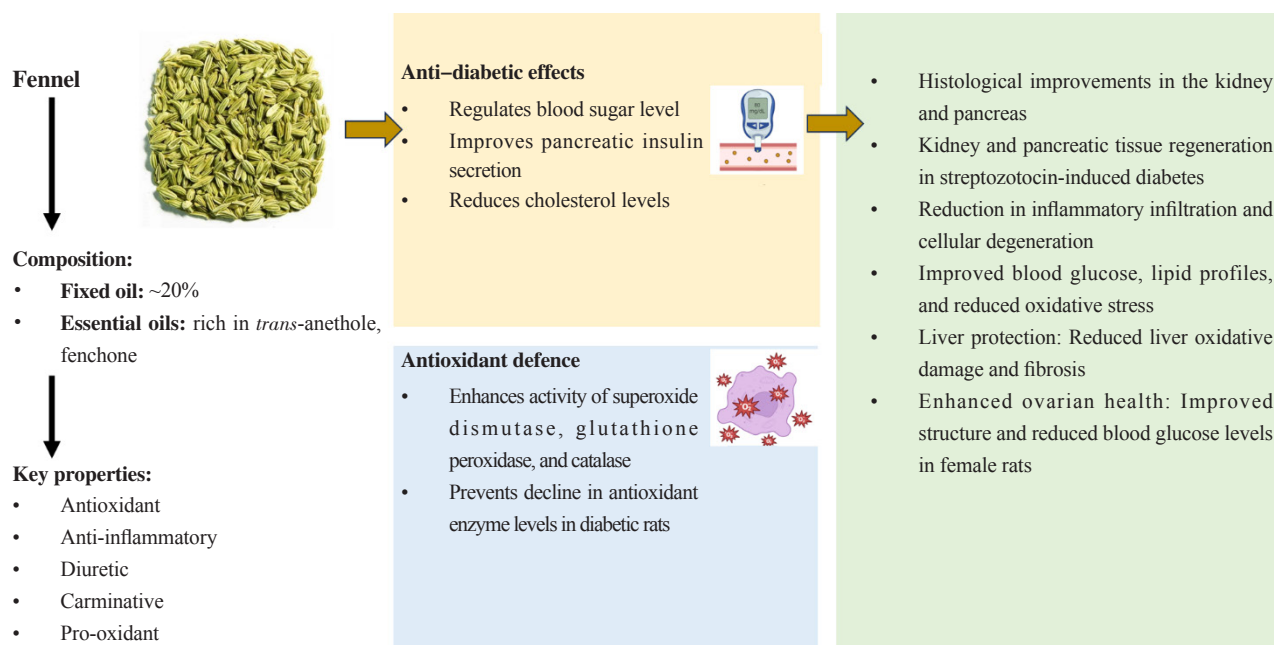


Figure 1. Anti-diabetic effects of *Foeniculum vulgare*. It has antioxidant and anti-diabetic properties, and the ability to improve metabolic markers in diabetic rats.

levels, while increasing insulin and hemoglobin. TA normalized key glycolytic and gluconeogenic enzyme levels and improved glycogen content in liver and muscle tissues, demonstrating protective effects on pancreatic β -cells compared to the standard drug glibenclamide[90]. Research has also identified TA as a potent aldose reductase inhibitor (IC_{50} of 3.8 μ g/mL). Prolonged treatment improved blood glucose levels and lipid profiles in STZ-induced diabetic rats. Additionally, TA exhibited anti-cataract activity by enhancing soluble lens protein and reducing oxidative stress markers during high-glucose conditions, indicating its therapeutic potential for diabetic complications[91].

Another study assessed the protective effects of fennel and TA against liver injury induced by STZ. Male rats received STZ (65 mg/kg) and were treated with fennel (200 and 400 mg/kg), TA (80 mg/kg), or metformin (300 mg/kg) for 35 d. Results indicated that both treatments lowered blood glucose, reduced liver enzyme activity, and improved lipid profiles, while decreasing oxidative stress markers and liver fibrosis, highlighting TA's hypoglycemic and antioxidant properties[92]. A study on non-alcoholic fatty liver disease assessed TA's effects on cellular senescence and lipid metabolism in HepG2 cells. At 2000 μ g/mL, TA maintained high cell viability and reduced senescence, while increasing mitochondrial membrane potential. It upregulated lipolytic gene expression and downregulated lipogenic genes, indicating its potential as a functional food ingredient for preventing fatty liver disease[93]. Similarly, in models of nonalcoholic steatohepatitis, TA demonstrated significant protective effects against liver injury, reducing hepatic steatosis and fibrosis through the inhibition of the transforming growth factor-beta signaling pathway, suggesting its promise as a therapeutic strategy

for nonalcoholic steatohepatitis[94].

In diabetic nephropathy models, a study examined the renoprotective and anti-fibrotic effects of TA alone and with losartan. TA (80 mg/kg) and losartan (10 mg/kg) significantly improved kidney function by reducing blood glucose, urea, and creatinine levels. Both treatments decreased renal fibrosis and oxidative stress markers while downregulating AT1R, TGF- β 1, and collagen IV expression, suggesting TA's effectiveness in mitigating diabetic nephropathy[95]. Research highlighted TA's role in reducing white adipose tissue expansion and promoting brown adipose tissue activation to regulate obesity. In high-fat diet-induced obesity models, TA enhanced the expression of beige-specific genes and regulated lipid metabolism by decreasing adipogenesis and lipogenesis while promoting lipolysis. Molecular docking analyses indicated that TA interacts with key proteins involved in fat browning, suggesting its potential as a therapeutic agent for obesity management[96].

5.3. Safety and adverse effects

To ascertain the safety of spices, medicinal herbs, and their mixtures, further scientific research is required. One of the primary considerations for using herbal remedies in medical contexts is the absence of hazards such as mutagenicity, carcinogenicity, and teratogenicity. Generally, these products should exhibit low levels of toxicity and adverse effects. Individual hypersensitivity is often considered the most common yet manageable risk, and the majority of herbal medicines are generally recognized as safe. However, concerns remain regarding potential harm to humans from specific

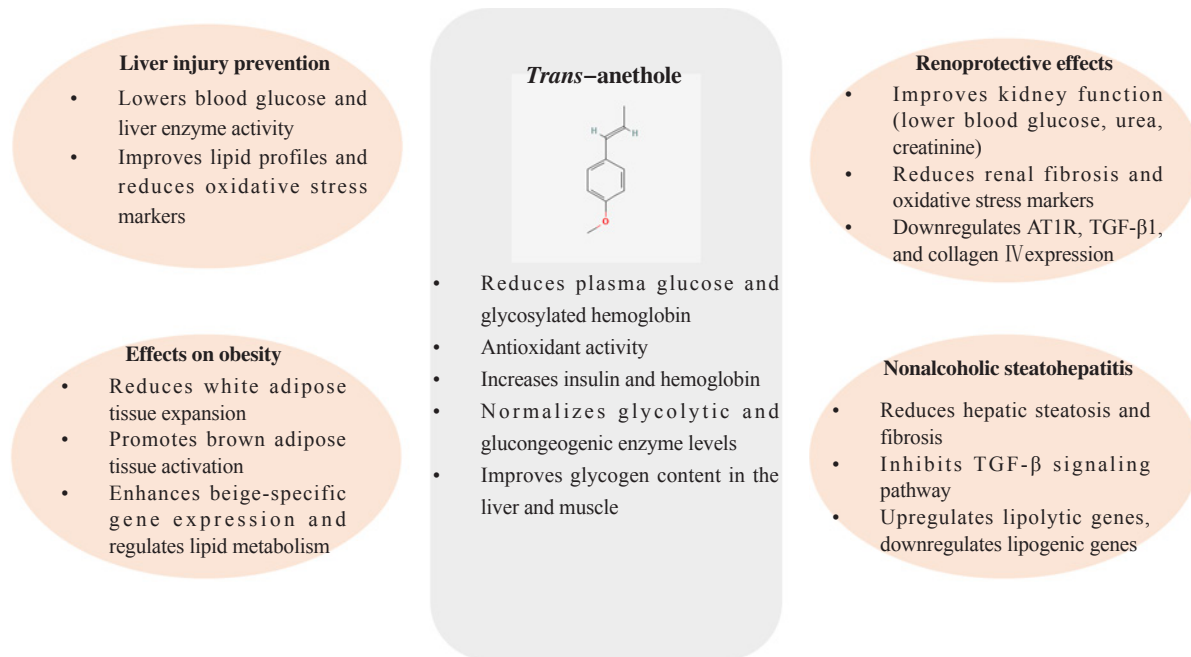


Figure 2. Pharmacological effects of *trans*-anethole (TA). It could reduce blood glucose levels, enhance insulin sensitivity, and protect against liver and kidney damage in diabetic models.

compounds that have shown hazardous effects in laboratory animals. One such compound of interest in the context of *F. vulgare* is estragole.

Estragole, also known as methylchavicol, is one of the primary constituents of *F. vulgare* essential oil. Reports have linked estragole to the development of malignant tumors in rats, which led the Scientific Committee on Food of the European Union to recommend its ban[97]. However, it remains unclear whether estragole poses a cancer risk to humans. Following Drinkwater's original report on estragole's genotoxic and carcinogenic potential[98], several *in vitro* and *in vivo* studies were conducted. These studies revealed that estragole has carcinogenic effects that may be specific to certain tissues, species, and sexes[99].

Recent data suggests that estragole does not directly cause cancer. Instead, its metabolic activation plays a crucial role in determining its carcinogenic potential. This process generates unstable molecules and reactive radicals that can adduct with nucleic acids, leading to DNA damage[100]. The metabolism of estragole is dose-dependent, meaning that higher doses promote its biotransformation, resulting in the production of mutagenic metabolites[101]. In summary, while estragole is associated with potential carcinogenicity, its effects appear to vary based on dosage and specific biological contexts.

6. Future directions and research gaps

Future studies on *F. vulgare* and its potential for managing diabetes present numerous research directions. Mechanistic investigations

are essential to understand how *F. vulgare* exerts its molecular anti-diabetic effects. Clinical trials are needed to confirm its safety and efficacy across diverse populations. Novel formulations and enhanced bioavailability could maximize therapeutic outcomes. Long-term studies are required to assess safety profiles and enduring impacts. Clinical guidelines should be informed by research examining interactions with conventional medications. Targeted studies within specific populations may reveal unique effects and tailored approaches. Investigating new molecular targets and developing standardized methodologies will ensure consistency and reliability. Addressing these research gaps will enhance our understanding and application of *F. vulgare* in diabetes treatment.

7. Conclusion

In conclusion, *F. vulgare*, or fennel, exhibits significant antioxidant and anti-inflammatory properties, making it a promising candidate for therapeutic applications, particularly in the management of diabetes and related complications. Rich in natural antioxidants such as flavonoids and polyphenols, fennel effectively inhibits free radical production, as demonstrated by various studies highlighting its potent free radical scavenging capabilities, particularly through its methanol extracts and essential oils. Moreover, fennel's anti-inflammatory effects are underscored by its ability to modulate key pathways involved in inflammation and oxidative stress, contributing to improved insulin sensitivity and metabolic profiles in diabetic models. The evidence suggests that fennel extracts not only lower

blood glucose levels but also enhance the functioning of antioxidant enzymes, mitigate oxidative damage, and support overall metabolic health.

However, while the therapeutic potential of fennel is promising, concerns regarding certain constituents, like estragole, necessitate further investigation into their safety profiles and potential carcinogenicity. Future research should focus on elucidating the molecular mechanisms underlying fennel's beneficial effects, conducting clinical trials to assess efficacy across diverse populations, and exploring its interactions with conventional diabetes medications. In summary, *F. vulgare* holds great potential as a natural adjunct in diabetes management and other health issues, warranting further exploration to fully harness its therapeutic benefits while ensuring safety and efficacy.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Declaration

During the preparation of this work, the authors used ChatGPT to improve language in some places. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

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Data availability statement

The data supporting the findings of this study are available from the corresponding authors upon request.

Authors' contributions

NHN searched the literature and wrote the manuscript. JG is the guarantor, who reviewed, edited and supervised the entire work.

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