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Original Article

Teucrium polium Extracts are Used as Antidiabetic Medication

Roohallah Yousefi [1*]

[1] Behbahan Faculty of Medical Sciences, Behbahan, Iran

* **Corresponding Author:** Roohallah Yousefi, Behbahan Faculty of Medical Sciences, Behbahan, Iran. E-mail: ry@behums.ac.ir

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Abstract

Diabetes mellitus is a long-term condition that causes high blood sugar, with type 2 diabetes (T2DM) presenting special problems due to insulin issues. Treatment aims to manage blood sugar through lifestyle changes and medications, but side effects of current drugs have led to interest in new options. Many patients, especially in developing countries, use herbal remedies like *Teucrium Polium* (Tp), which may help but have limited research. Some studies suggest Tp could aid in managing diabetes, though effects are unclear, and safety concerns exist, indicating a need for more research on its effects on insulin and glucose metabolism. To investigate the effectiveness of Tp in treating diabetes mellitus, a literature search was conducted using databases such as PubMed, Science Direct, and Scopus, employing relevant keywords. We analyzed the properties and effects of the antidiabetic compounds in Tp utilizing the SwissADME database. This study aimed to assess the potential of Tp for managing diabetes. The compounds examined include apigenin, quercetin, and cirsimaritin, each with molecular weights around 300 Daltons and containing 20-23 heavy atoms, sharing similar structures but differing in properties that can assist in diabetes treatment. Cirsimaritin can easily penetrate biological membranes, making it effective for high blood sugar, while apigenin is better suited for addressing low blood sugar. All three compounds are well absorbed during digestion, but rutin has lower absorption, diminishing its effectiveness. Further research is necessary to explore their interactions and develop enhanced diabetes treatments.

Keywords: *Teucrium polium*, Hypoglycemic Agents, Apigenin, Quercetin

Introduction

Diabetes mellitus, a multifactorial disorder characterized by chronic hyperglycemia, has gained significant attention due to its increasing prevalence and associated complications. Type 2 Diabetes Mellitus (T2DM), require different management approaches. Conventional treatments for diabetes often come with side effects, leading to the increased use of complementary and alternative medicine, including herbal remedies.[1] Diabetes mellitus, particularly type 2 diabetes, is a global health concern affecting millions of people. It is characterized by hyperglycemia resulting from impaired insulin secretion, insulin action, or both. The prevalence of type 2 diabetes has increased dramatically, leading to a higher burden of disease and complications. COVID-19 patients are also more susceptible to diabetes, and vice versa.[2]

Current Treatment Strategies and Challenges

Current treatment objectives for type 2 diabetes focus on maintaining normal blood glucose levels. Lifestyle changes, such as diet and exercise, are the first approach, followed by pharmacological therapy. Several treatment strategies are available, including medications that improve insulin sensitivity, increase endogenous insulin, or decrease hepatic glucose production. However, these medications may have side effects or limitations, necessitating the search for new antidiabetic drugs.[3]

Medicinal Plants as a Source of Antidiabetic Agents

Many diabetic patients in developing countries use complementary or medicinal natural products with antidiabetic properties. Medicinal plants have provided lead active compounds that can be further developed into antidiabetic medications. For example, the discovery of metformin, a widely used antidiabetic drug, was inspired by natural products. Although there are thousands of medicinal plants with potential antidiabetic activity, only a small percentage have been pharmacologically investigated.[4]

Teucrium Polium, a Medicinal Plant with Antidiabetic Potential

Teucrium polium (Tp) is one such medicinal plant with reported antidiabetic properties. However, a detailed analysis of the extract in relation to type 2 diabetes is not well-documented. Phenolic compounds, found in Tp extracts, are of interest due to their potential antidiabetic effects. These compounds are metabolized quickly after ingestion, and their concentrations in the blood post-ingestion are not well-known. Therefore, it is crucial to evaluate the literature on Tp for treating type 2 diabetes and discuss the assessment strategies of studies examining key phenolic compounds in the aqueous Tp extract.[5]

Flavonoids in Tp, Bioactivity and Bioavailability

Apigenin and quercetin are flavonoids found in Tp extracts and have been suggested to contribute to the plant's traditional use in treating diabetes. Both flavonoids have demonstrated antidiabetic properties in various experimental settings. However, the doses used in studies may be higher than what is actually present in the total Tp extract. The bioavailability of these flavonoids can be influenced by factors such as enzymatic hydrolysis, metabolic conjugation, and the formation of different metabolites in the gut and liver.[6]

Toxicological Studies on Tp Extract and Future Research Directions

Toxicological studies on Tp extract are limited, with some reports suggesting liver toxicity. However, these findings are not conclusive, and further assessments are needed. As we aim to develop new hypoglycemic agents for type 2 diabetes, it is crucial to investigate the mechanistic role of Tp's chemical constituents in insulin secretion and to understand the molecular mechanisms involved in glucose metabolism.[7] In this study, we investigate the physicochemical and pharmacodynamic properties of the plant compounds found in Tp plant.

Tp Extraction

The extraction method for Tp extract was developed based on previous studies of the plant. The Tp used in the previous study was collected from Kerman, Iran and identified by Dr. Mirtjadini, a renowned botanist from the Department of Botany at Bahnar University, Kerman. A voucher specimen (KF1249) was deposited in the Herbarium of the Faculty of Pharmacy at Kerman University of Medical Sciences, Kerman, Iran, to serve as a reference for future research and authentication purposes.[8]

The aerial parts of Tp (100-500 grams) were harvested and dried to remove excess moisture. The dried plant material was then powdered to a uniform size using a mill and passed through a sieve to ensure a consistent particle size of 300 micrometers. The powdered plant material was subjected to sequential extraction using four different solvents: petroleum ether, chloroform, methanol, and water. Each solvent was used to extract the bioactive compounds present in the plant material, with the goal of isolating a wide range of compounds. After each extraction step, the solvent was removed from the plant material using a rotary evaporator set at a temperature of 35 °C. This process helped concentrate the extract and remove any residual solvents. The final extracts were stored at a temperature of 2 °C to preserve their stability and potency. The resulting extracts will be used for further research and analysis to identify the bioactive compounds present in Tp.[8-10]

Materials and Methods

Predicting Physicochemical Properties and Pharmacodynamics

The IUPAC chemical formula of the compounds studied in this research was extracted from the PubChem database. It was then entered into the Swiss ADME software to generate the structure of the sample and perform other measurements. The SwissADME web tool is an essential resource for drug development researchers, providing a convenient and efficient platform for forecasting crucial parameters such as physicochemical properties and pharmacokinetics. With its user-friendly interface and reliable predictive models like BOILED-Egg and iLOGP, this online tool can be accessed without registration at http://www.swissadme.ch.[8-12]

Methods

To determine the efficacy of Tp in managing diabetes mellitus, a comprehensive literature search was conducted using various databases, including PubMed, Science Direct, and Scopus. The search strategy involved incorporating relevant keywords related to herbal and traditional medicine, as well as diabetes. By surveying the main outcomes of these studies, we then calculated the physicochemical properties and pharmacodynamics

of antidiabetic compounds found in Tp using the SwissADME database's online software. This investigation aimed to better understand the potential of Tp for managing diabetes mellitus.

Table 1. Anti-diabetic Natural Herbal Compounds[8-10]

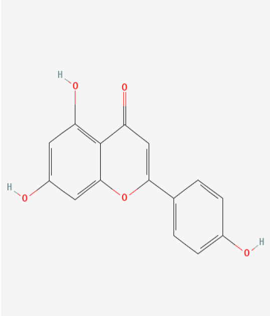
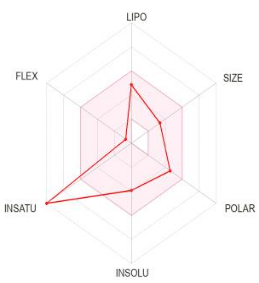
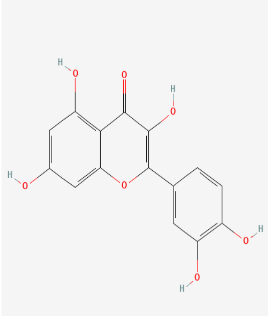
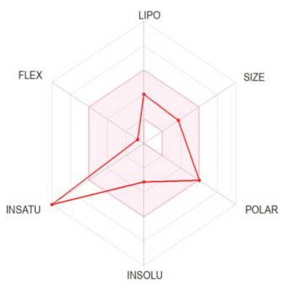
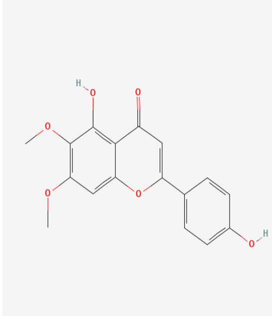
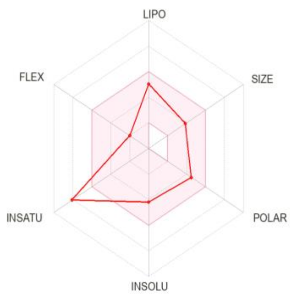
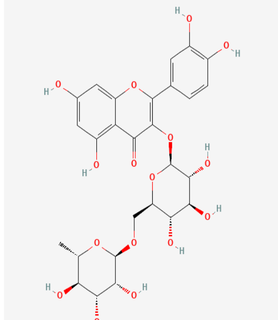
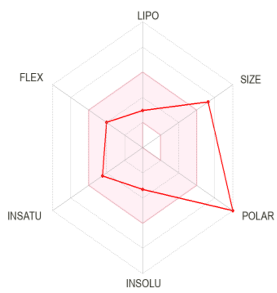
	IUPAC Name	PubChem CID	2D-Chemical structure	Radar scale of physicochemical properties
Apigenin	5,7-dihydroxy-2-(4-hydroxyphenyl)chromen-4-one	5280443		
Quercetin	2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one	5280343		
Cirsimaritin	5-hydroxy-2-(4-hydroxyphenyl)-6,7-dimethoxychromen-4-one	188323		
Rutin	2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-[[(2R,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxymethyl]oxan-2-yl]oxychromen-4-one	5280805		

Table 2. Physicochemical Properties of Apigenin, Quercetin, Cirsimaritin, and Rutin[9,10]

Molecule	Apigenin	Quercetin	Cirsimaritin	Rutin
MW	270.24	302.24	314.29	610.52
Heavy atoms	20	22	23	43
Aromatic heavy atoms	16	16	16	16
Fraction Csp3	0	0	0.12	0.44
Rotatable bonds	1	1	3	6
H-bond acceptors	5	7	6	16
H-bond donors	3	5	2	10
MR (Molar Refractivity)	73.99	78.03	84.95	141.38
TPSA	90.9	131.36	89.13	269.43
iLOGP	1.89	1.63	2.56	0.46
XLOGP3	3.02	1.54	3.32	-0.33
ESOL Log S	-3.94	-3.16	-4.2	-3.3
ESOL Solubility (mg/ml)	0.03070	0.21100	0.02000	0.30800
ESOL Solubility (mol/l)	0.00011	0.00070	0.00006	0.00051
ESOL Class	Soluble	Soluble	Moderately soluble	Soluble

Results

The three compounds, apigenin, quercetin, and cirsimaritin, have molecular weights close to 300 Daltons and possess 20-23 heavy atoms. These compounds share a basic structure but exhibit unique physicochemical properties that make them valuable in the development of drugs for managing diabetes. Among these compounds, cirsimaritin stands out due to its high hydrophobicity, which allows it to easily penetrate biological membranes and maintain relatively good solubility in physiological fluids such as blood and lymph. These properties make cirsimaritin a suitable candidate for designing drug templates to control hyperglycemia, a common issue in diabetes. Cirsimaritin has the highest hydrophobicity, while apigenin demonstrates lower hydrophobicity compared to cirsimaritin. This lower hydrophobicity can be attributed to the presence of hydroxyl and ketone functional groups on its aromatic rings. Consequently, apigenin exhibits higher solubility in physiological fluids. Due to these properties, apigenin serves as an ideal basic compound for designing effective drugs targeting hypoglycemia and diabetes control. The unique physicochemical properties of apigenin and cirsimaritin make them promising candidates for drug design in the context of diabetes management.

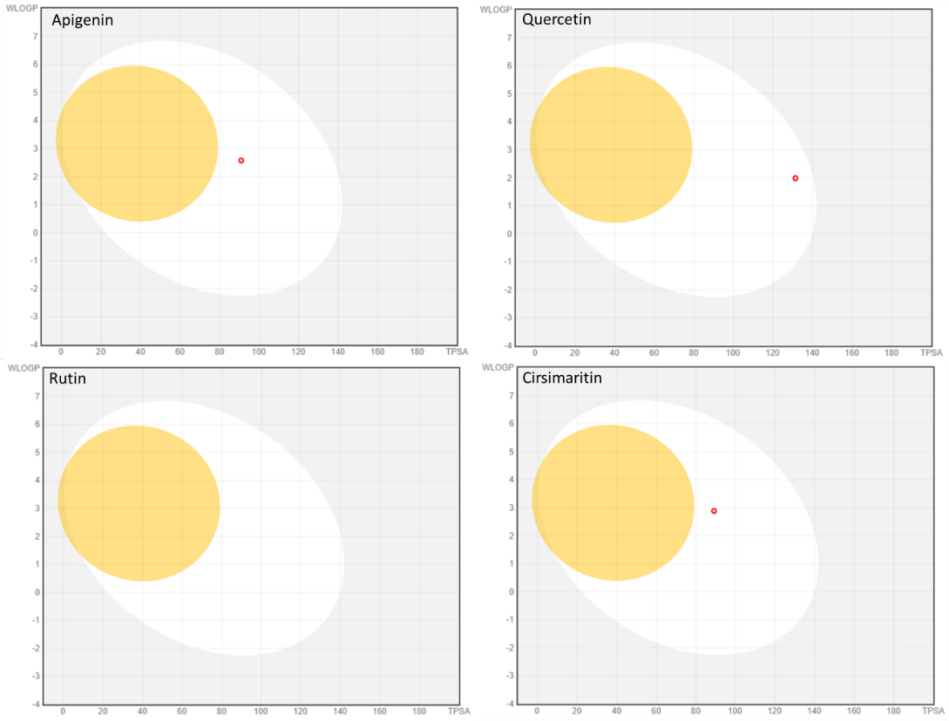


Figure 1. Yellow areas contain compounds that can passively cross the blood-brain barrier. White areas contain compounds that can be passively absorbed by the digestive system. Blue dots indicate compounds that can enter the central nervous system through P-glycoproteins. Red dots signify compounds that can be removed from the central nervous system through P-glycoproteins.[11]

Table 3. Pharmaceutical Properties of Apigenin, Quercetin, Cirsimaritin, Rutin[11,12]

Molecule	Apigenin	Quercetin	Cirsimaritin	Rutin
GI absorption	High	High	High	Low
BBB permeant	No	No	No	No
Pgp substrate	No	No	No	Yes
CYP1A2 inhibitor	Yes	Yes	Yes	No
CYP2C19 inhibitor	No	No	No	No
CYP2C9 inhibitor	No	No	Yes	No
CYP2D6 inhibitor	Yes	Yes	Yes	No
CYP3A4 inhibitor	Yes	Yes	Yes	No
log Kp (cm/s)	-5.8	-7.05	-5.86	-10.26

Apigenin, quercetin, and cirsimaritin are bioactive compounds that share high rates of digestive absorption, which is an essential factor contributing to their potential effectiveness when consumed. However, rutin has a lower digestive absorption rate compared to these three compounds. This difference in digestive absorption limits its blood concentration. All of the studied compounds do not possess the ability to cross the blood-brain barrier, which is a protective mechanism that restricts the passage of certain substances from the bloodstream to the central nervous system. Consequently, their direct effects on the brain and central nervous system functions are limited. When it comes to their interaction with cytochrome enzymes, all three compounds, apigenin, quercetin, and cirsimaritin, inhibit the enzymes CYP2D6, CYP3A4, and CYP1A2. In addition, cirsimaritin also inhibits CYP2C9. These inhibitory effects can have significant implications, as they may interfere with the metabolism of various medications that rely on these enzymes for their proper functioning. Regarding skin absorption, apigenin (log Kp = 5.8 (cm/s)) and cirsimaritin (log Kp = 5.86 (cm/s)) exhibit very little skin penetration.

Discussion

Diabetes mellitus, a multifactorial disorder characterized by chronic hyperglycemia, has gained significant attention due to its increasing prevalence and associated complications. Current treatment objectives for type 2 diabetes focus on maintaining normal blood glucose levels. Lifestyle changes, such as diet and exercise, are the first approach, followed by pharma cological therapy. Several treatment strategies are available, including medications that improve insulin sensitivity, increase endogenous insulin, or decrease hepatic glucose production. However, these medications may have side effects or limitations, necessitating the search for new antidiabetic drugs.[13] Tp is a plant with a rich history of traditional use in treating various ailments, including diabetes. Phenolic compounds found in Tp extracts are of interest due to their potential antidiabetic effects. These compounds are metabolized quickly after ingestion, and their concentrations in the blood post-ingestion are not well-known. Therefore, it is crucial to evaluate the literature on Tp for treating type 2 diabetes and discuss the assessment strategies of studies examining key phenolic compounds in the aqueous Tp extract.[14]

The use of complementary and alternative medicine, including herbal remedies, as a response to the side effects of conventional diabetes treatments is increasing. Tp, a medicinal plant with reported antidiabetic properties, contains potential antidiabetic agents such as Apigenin, Quercetin, and Cirsimaritin. It also touches upon the importance of understanding the bioavailability and metabolic pathways of these flavonoids for their effective use in treating diabetes. Apigenin and quercetin are flavonoids found in Tp extracts and have been suggested to contribute to the plant's traditional use in treating diabetes. Both flavonoids have demonstrated antidiabetic properties in various experimental settings. The bioavailability of these flavonoids can be influenced by factors such as enzymatic hydrolysis, metabolic conjugation, and the formation of different metabolites in the gut and liver. Future studies should consider the final metabolites circulating in the body for a more accurate understanding of these flavonoids' effects.[14-17]

The potential use of three bioactive compounds, Apigenin, Quercetin, and Cirsimaritin, in managing diabetes found in various plants, especially in Tp, share some similarities in their molecular weights and basic structure, and they exhibit similar physicochemical properties. Cirsimaritin has high hydrophobicity, which allows it to penetrate biological membranes and maintain good solubility in physiological fluids. On the other hand, Apigenin has lower hydrophobicity due to the presence of hydroxyl and ketone functional groups on

its aromatic rings, resulting in higher solubility in physiological fluids. All three compounds inhibit CYP2D6, CYP3A4, and CYP1A2, which could potentially interfere with the metabolism of other medications that rely on these enzymes.

Conclusion

With the increasing prevalence of diabetes mellitus and the importance of effective management to prevent complications, it is crucial to explore alternative treatment options. Tp, a plant with a long history of traditional use, has shown potential in treating diabetes due to the presence of phenolic compounds like Apigenin, Quercetin, and Cirsimaritin. These compounds have demonstrated antidiabetic effects in various experimental settings by improving insulin sensitivity, increasing endogenous insulin, or decreasing hepatic glucose production.

Tp and its bioactive compounds, Apigenin, Quercetin, and Cirsimaritin, hold promise for managing type 2 diabetes. However, further research is needed to fully understand their bioavailability, metabolic pathways, and potential interactions with other medications. This understanding will be crucial for developing new antidiabetic drugs and integrating these natural compounds into complementary and alternative treatment strategies for diabetes patients.

Conflict of Interest

The author declares no conflicts of interest.

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