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Evaluating the pharmacokinetics and bioavailability of *Pterygota alata* inflorescence based on High-Resolution Mass Spectroscopy study to determine the reservoirs of Ayurvedic components with an emphasis on their potential therapeutic use for Diabetes mellitus

Research Article

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Abstract

Diabetes indeed requires a comprehensive approach, and dietary changes play a crucial role in managing the condition. While traditional methods like Ayurveda have been used for centuries to address various ailments, including diabetes. *Pterygota alata*, commonly known as the "winged seed" tree, has been explored for its potential antidiabetic properties in Ayurveda. Research into its efficacy and safety is ongoing, with some studies suggesting promising results. As with any herbal remedy, individuals with diabetes must consult healthcare professionals before incorporating them into their treatment regimen. While herbal products can complement conventional therapies, they should not replace them entirely. Additionally, potential interactions with other medications and individual variations in response should be carefully considered. Through UHPLC-Q-TOF-MS/MS system major antidiabetic component such as Agmatine, Migitol, Trigoneline, Betaine, Theophylline, Quercetin, Kaempferol, Isoliquiritigenin, Esculetin, Rutin, Ferulic acid, Eriodictyol, Naringenin, Luteolin, Salsonilon, Apigenin, Hesperitine, Carvone, Ursolic acid, Betulin, Lupeol, Eugenol.

Keywords: Diabetes, *Pterygota alata*, HRMS, Hyperglycemia, Pharmacokinetic, Bioavailability.

Introduction

Diabetes is an endocrine illness that is complex, rapidly expanding, chronic, non-communicable, and of worldwide importance. Patients with diabetes have a significant risk of acquiring complications related to their metabolism. Hyperglycemia, hyperlipidemia, and oxidative stress are characteristics of diabetes. These medical conditions can further result in chronic problems that impair the kidneys, eyes, blood vessels, nerves, and other body organs. The World Health Organisation (WHO) claims that It is a widespread illness with an increasing danger of morbidity as well as mortality (1).

Researchers have recently focused more on plant-based medications and functional diets to alter physiological characteristics and treat diabetes and its aftereffects. In simple terms, the illness is managed using a multifaceted, customized strategy that includes dietary changes, lifestyle modification, Panchakarma is one of the detoxifying and purifying Ayurvedic therapies. Other Ayurvedic medications include components derived from plants, animals, or minerals, either alone or in combination. Many of these medications are thought to function through both extrapancreatic and pancreatic actions (2).

Since Ayurveda aligns with patients' cultural and health beliefs, it is frequently used by them; hence, its acceptability, satisfaction, and reported relief are typically high, particularly among older, impoverished, rural, and Indigenous/minority communities (3). The Ayurvedic antidiabetic component of *Pterygota alata* inflorescence offers up-to-date estimations of safety and efficacy for all Ayurvedic medications for the treatment of type 2 diabetes mellitus. Approximately four billion people worldwide are directly or indirectly dependent on herbal products (4). In South Asia and Myanmar, P. alata (family Malvaceae) is widely dispersed. This plant's seeds are narcotic and are used in place of opium. The plants are used in medicine and seed are eaten by local people in India (5)

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Materials and Methods

Collection and authentication of *Pterygota alata* plant

Pterygota alata flowers from the Banaras Hindu University are Authenticated in the Department of Botany by Prof. N.K. Dubey (President of Indian Botanical Society) as *Pterygota alata (Roxb) R. Br*. and

the Voucher Specimen No. was Sterculia. 2023/01. Each flowers of collected inflorescences were separated and dried at room temperature in the shade. Dried flowers were ground into powder by a mixer grinder.

About Instrument

The High-Resolution Accurate Mass Spectrometry System instrument was used with the Model name Orbitrap Eclipse Tribrid Mass Spectrometer developed by Thermo Fischer Scientific. For small molecules Dionex UltiMate 3000 RSUHPLC System was used different solvent compound was used for phytochemical analysis.

Materials

Pterygota alata, methanol, distilled water, Whatman filter paper (100 mm pore size), Rotatory evaporator, Dry oven, Petri plate, and Measuring cylinder, The High-Resolution Accurate Mass Spectrometry System (HRMS) instrument was used with the Model name Orbitrap Eclipse Tribrid Mass Spectrometer developed by Thermo Fischer Scientific. For small molecules Dionex UltiMate 3000 RSUHPLC System was used different solvent compound was used for phytochemical analysis.

For grain extract

The unprocessed 500gm of *Pterygota alata* inflorescence have been made into coarse powder form for research analysis. The 40 gm of *Pterygota alata* inflorescence powder was taken and mixed with 400 ml of methanol in a conical flask, at every 10 min of the interval the flask was shaken, and the mixture solution was rested for 2 days. After 2- days the supernatant was filtered with Whatman filter paper (100 mm pore size) and collected in a beaker, 350 ml of methanolic extract grain solution was poured into a rota-evaporator, the Rota-evaporator set at a boiling temp is 45^0 C, and chiller temp 50^0 C, the extract solution was evaporated till 50 ml extract remains in the flask. The 50 ml grain extract was collected in a conical flask. Then 50 ml extract was put on a Petri plate and evaporated at 60^0 C in the oven. The dried extract was formed in Petri plates and stored for analysis.

For HRMS analysis

The dried sample was collected in an Eppendorf tube and 1 ml methanol was added to a tube. This methanol sample was passed from a syringe filter (0.02 mm) and collected in an Eppendorf tube. The sample collected in the Eppendorf tube was used for HRMS Analysis.

Solvent preparation of HPLC Column

Solvent A: 100% Water + 0.1% Formic Acid, Solvent B: 80% Acetonitrile + 0.1% Formic Acid, Solvent C: 100% Methanol + 0.1% Formic Acid. The Column Detail is the Hypersil GOLD™ C18 Selectivity HPLC Column, Particle size 1.9 µm with Diameter 2.1 mm, Length 100 mm. All the analyses were performed by the default parameters of "Compound discoverer 3.2.0.421" using online databases.

UHPLC-Q-TOF-MS/MS was used to examine the Pterygota alata grain metabolite profile. Thermo Compound Discoverer 3.3.2.31 was used for the analysis, with default settings and online databases—untargeted Metabolomics Workflow Using Molecular Networks, Online Databases, and mzLogic. The chemicals were identified based on fragment patterns produced by ChemSpider (formula or precise mass).

Results

Identified metabolites by UHPLC-MS

A list of antidiabetic compounds found in *Pterygota alata* inflorescence along with molecular formula, Molecular Weight, Retention Time, and Area (Max) is summarised in Table 1. The list of Antidiabetic compounds is Agmatine, Migitol, Trigoneline, Betaine, Theophylline, Quercetin, Kaempferol, Isoliquiritigenin, Esculetin, Rutin, Ferulic acid, Eriodictyol, Naringenin, Luteolin, Salsonilon, Apigenin, Hesperitine, Carvone, Ursolic acid, Betulin, Lupeol, Eugenol.

Table 1: Major Antidiabetics compounds identified by UHPLC-TOF-MS along with molecular formula, Molecular Weight, Retention Time, Area (Max)

S. No.	Compound name	Molecular formula	Molecular weight	Retention time	Area (Max)
1	Agmatine	$C_5H_{14}N_4$	130.122	0.718	11189178.62
2	Miglitol	$C_8H_{17}NO_5$	207.1108	0.767	14353716.67
3	Trigonelline	$C_7H_7NO_2$	137.0478	0.948	83716907.99
4	Betaine	$C_5H_{11}NO_2$	117.0792	0.96	2.29087.11
5	Theophylline	$C_7H_8N_4O_2$	180.0649	1.003	855316667.4
6	Quercetin	$C_{15}H_{10}O_7$	302.0428	1.145	334410324.7
7	Kaempferol	$C_{15}H_{10}O_6$	286.0478	1.168	591983036.6
8	Isoliquiritigenin	$C_{15}H_{12}O_4$	256.0736	1.217	23363744.53
9	Esculetin	$C_9H_6O_4$	178.0266	1.274	225959539.4
10	Rutin	$C_{27}H_{30}O_{16}$	610.1538	11.385	97351160.87
11	Ferulic acid	$C_{10}H_{10}O_4$	194.0572	11.744	270414412.4
12	Eriodictyol	$C_{15}H_{12}O_6$	288.0634	13.483	38689808.94
13	Naringenin	$C_{15}H_{12}O_5$	272.0684	15.085	12507389.09
14	Luteolin	$C_{15}H_{10}O_6$	286.0477	15.328	114643462
15	Salsonilon	$C_{10}H_{13}NO_2$	179.0938	15.482	38829556.66
16	Apigenin	$C_{15}H_{10}O_5$	270.0531	16.235	81745913.43
17	Hesperetin	$C_{16}H_{14}O_6$	302.0786	17.704	15735915.76
18	Carvone	$C_{10}H_{14}O$	150.1047	23.53	128446463.2
19	Ursolic acid	$C_{30}H_{48}O_3$	456.3604	24.573	61313129.73
20	Betulin	$C_{30}H_{50}O_2$	442.3811	26.333	182918900.2
21	Lupeol	$C_{30}H_{50}O$	426.386	27.404	29544868.35
22	Eugenol	$C_{10}H_{12}O_2$	164.0838	28.128	40655636.02

Literature reports have documented that these compounds show antidiabetic effects. Agmatine accelerates the insulin secretion from β-pancreatic cells to inhibit hyperglycemia and positively affects lipid metabolism disorders (6). Miglitol's anti-obesity effect contributes to developing effective drugs against obesity (7). By modulating insulin signing, Trigonelline has a beneficiary effect on insulin and lipid homeostasis (8). Betaine contains anti-inflammatory and antioxidant properties that enhance insulin sensitivity and improve blood glucose clearance (9). Theophylline is an α-amylase inhibitor containing acetyl conjugates (10). Quercetin has insulin-sensitizing activities and has a good role in glucose clearance (11). kaempferol separated from *C. sativus* is known for its α-amylase

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and α-glucosidase inhibition by lowering glucose levels (12). To manage diabetic neuropathy, Nrf2-directed antioxidant signalling was made possible through Isoliquiritigenin-mediated Sirtuin (SIRT1) activation (13). In STZ-induced diabetic rats, esculetin demonstrated anti-diabetes and anti-inflammatory properties by preventing the onset of detrimental processes of the sciatic nerve morphology, and internal cell functions (14). Rutin exhibits a preventive effect against nephropathy, neuropathy, liver damage, and cardiovascular diseases caused by hyperglycaemia and dyslipidaemia (15). Treatment with FA increases hepatic glycogenesis and insulin sensitivity in type 2 diabetic rats, but it also suppresses gluconeogenesis negatively regulators of normal glucose homeostasis and insulin signalling (16). One dietary flavonoid with antioxidant properties is eriodictyol (17). In high-glucose treated HepG2 cells, naringenin-induced phosphorylation of AMPK at Thr172 may improve glucose absorption independent of insulin stimulation (18). Luteolin's ability to prevent diabetes is mediated by preserving blood glucose levels and enhancing the body's cells' sensitivity to insulin (19). Salsolinol's hypoglycaemic action may be linked to AMPK activation and increased insulin secretion (20). Apigenin increases glycogen content in the muscles and liver while dramatically lowering blood sugar (21). Hesperetin induces glucose uptake in acute and chronic treatment (22). By enhancing important enzymes in the hepatic tissues of STZ-induced diabetic rats, carvone controls the metabolism of carbohydrates (23). 30 to 60 minutes after consuming maltose, the hypoglycemic effects of ursolic acid compounds were more noticeable (24). Protein tyrosine phosphatases (PTPs) PTPN1, PTPN9, and PTPN11 are inhibited by multi-targeting of linoleic acid, which may have anti-diabetic actions to prevent type 2 diabetes (25). Betulin activates AMPK similarly to metformin, so it may be a promising treatment drug for diabetes. Notably, in addition to exhibiting antidiabetic effects, BA also increased mouse endurance capacity, suggesting that it influences metabolic control (25). Lupeol modulates blood glucose levels and reduces oxidative stress (27). By activating the GLUT4-AMPK signaling pathway, eugenol promotes skeletal muscle glucose absorption and improves insulin sensitivity (28). Ursolic acid reduces oxidative stress in pancreatic tissue by the restoration of the free radical scavenging effect, the suppression of Traf-6, Mapk-8, and Traf-4 mRNA expression, and the regeneration of pancreatic insulin (29).

Pharmacokinetics

The pharmacokinetics study of compound reveal the absorption, digestion, metabolism, excretion (ADME) properties of Ayurveda component. The summarise details of all 22 compound are given in table 2. From 22 compound only 7 compound are not having good gastrointestinal absorption i.e. Miglitol, Betain, Rutin, Salsolinol, Ursolic acid, Betulin and Lupeol. Only 4 compound passed through blood brain barrier i.e. Isoliquiritigenin, Ferulic acid, Carvone and Eugenol. Pharmacokinetics detailed that oly 6 compound transfer through blood substrate binding i.e. Miglitol, Betaine, Rutine, Eriodictyol, Naringenin and Hesperetine

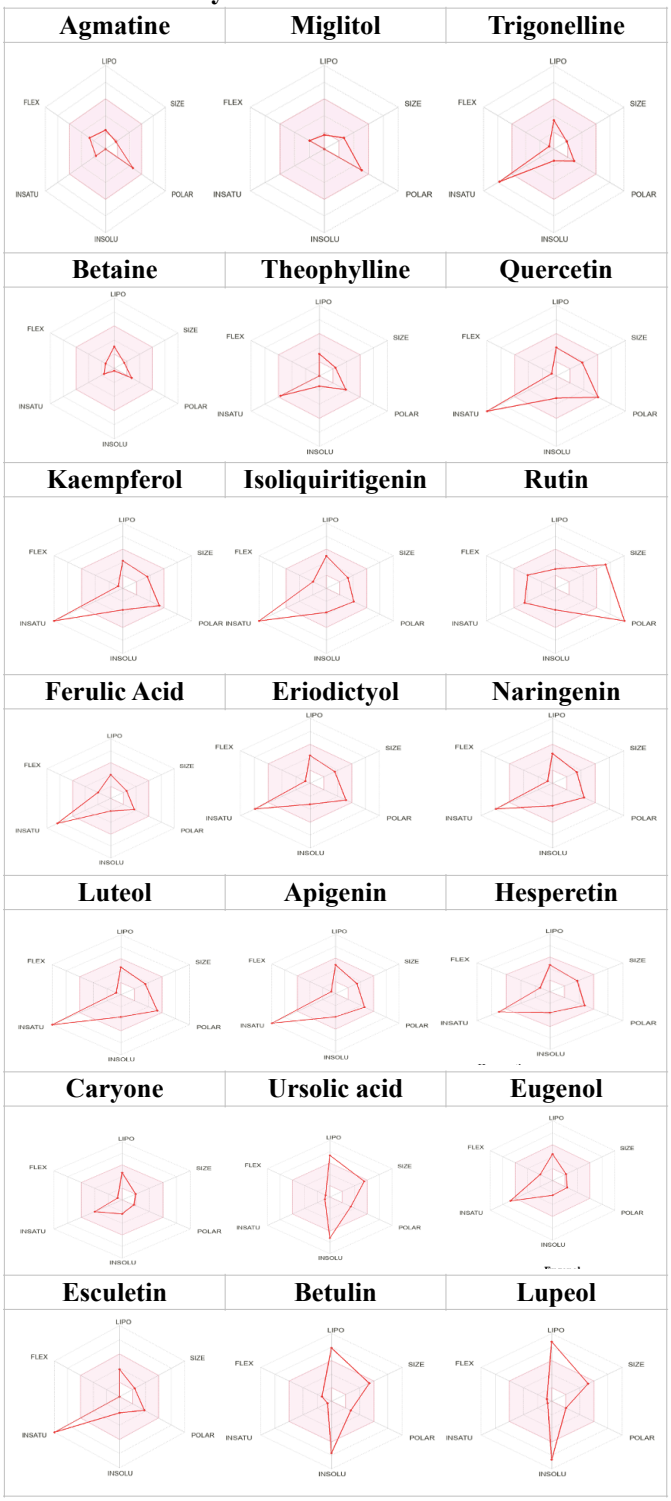
Table 2. The pharmacokinetics properties of all compounds based in gastrointestinal absorption (GI absorption), crossing to blood brain barrier (BBB permeant), transfer through blood substrate binding (P-gp substrate), and skin permeability (Log K_p (skin permeation)

S.No.	Compound name	GI absorption	BBB permeant	P-gp substrate	Log K_p (skin permeation)
1	Agmatine	High	No	No	-8.19 cm/s
2	Miglitol	Low	No	Yes	-9.39 cm/s
3	Trigonelline	High	No	No	-6.77 cm/s
4	Betaine	Low	No	Yes	-7.11 cm/s
5	Theophylline	High	No	No	-7.41 cm/s
6	Quercetin	High	No	No	-7.05 cm/s
7	Kaempferol	High	No	No	-6.70 cm/s
8	Isoliquiritigenin	High	Yes	No	-5.61 cm/s
9	Esculetin	High	No	No	-6.52 cm/s
10	Rutin	Low	No	Yes	-10.26 cm/s
11	Ferulic acid	High	Yes	No	-6.41 cm/s
12	Eriodictyol	High	No	Yes	-6.62 cm/s
13	Naringenin	High	No	Yes	-6.17 cm/s
14	Luteolin	High	No	No	-6.25 cm/s
15	Salsonilon	Low	No	No	-3.82 cm/s
16	Apigenin	High	No	No	-5.80 cm/s
17	Hesperetin	High	No	Yes	-6.30 cm/s
18	Carvone	High	Yes	No	-5.29 cm/s
19	Ursolic acid	Low	No	No	-3.87 cm/s
20	Betulin	Low	No	No	-3.12 cm/s
21	Lupeol	Low	No	No	-1.90 cm/s
22	Eugenol	High	Yes	No	-5.69 cm/s

Bioavailability for drug-likeness

The bioavailability radar, which offers a graphical snapshot of the drug-likeness properties of an oral bioactive medication, is exclusive to Swiss-ADME. The drug-likeness graph (Fig 1) is displayed as a hexagon, with each vertex denoting a characteristic that characterises a bioavailable medication. The compound which are oral bioavailability are shown in red colour zone. The lipophilic, flexibility, instauration, polarity and size are predicted by schematic bioavailability radar diagram. Agmatine, Miglitol, Betaine, Theophylline,Carvone, Eugenol are oral bioavailability nature it means they are suitable for drug-likeness formulation. . Trigonelline, quercetin, Kaempferol, Isoliquiritigenin, , Ferulic, Eriodictyol, Naringenin,Luteolin, Apigenin, Hesperetin, Esculetin show high insaturation they are not easily saturated. The Ursolic acid, Betulin, Lupeol are not good in water solubility as these compound shows high lipohilic properties. The Rutine has high molecular size showing hindrance in drug likeness formulation.

Fig 1:Schematic diagram of Bioavailability Radar for Drug likeness of a molecule (lipophilicity: XLOGP3 between-0.7 and+5.0, size: MW between 150 and 500 g/mol, polarity: TPSA between 20 and 130 A^0, solubility: log S not higher than 6, saturation: fraction of carbons in the sp3 hybridization not less than 0.25, and flexibility: no more than 9 rotatable bond



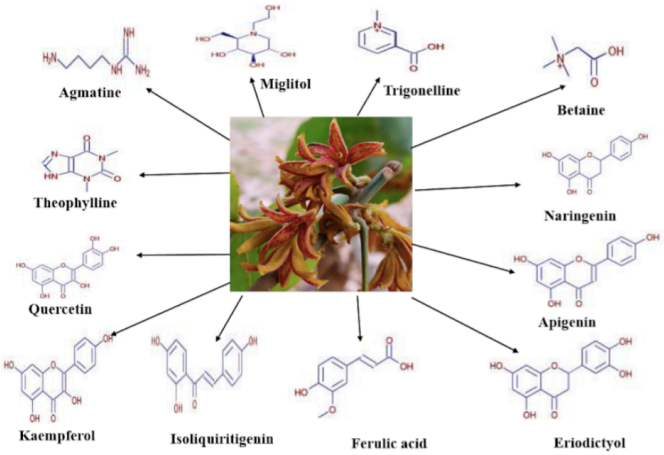
Discussion

The High-Resolution Accurate Mass Spectrometry System (HRMS) data of *Pterygota alata* inflorescence explored the 22 ayurvedic formulated antidiabetics components. The list of Antidiabetic compounds is Agmatine, Migitol, Trigoneline, Betaine, Theophylline, Quercetin, Kaempferol, Isoliquiritigenin, Esculetin, Rutin, Ferulic acid, Eriodictyol, Naringenin, Luteolin, Salsonilon, Apigenin, Hesperitine, Carvone, Ursolic acid, Betulin, Lupeol, Eugenol.

The lipophilic, flexibility, instauration, polarity and size are predicted by schematic bioavailability radar diagram Agmatine, Miglitol, Betaine, Theophylline, Carvone, Eugenol these compound which are oral bioavailability nature are shown in red colour zone it means they are suitable for drug-likeness formulation .These compound discovered from *Pterygota alata* inflorescence play important role in drug discovery against Diabetes mellitus. With everything taken into account, the discovery of these substances in Pterygota alata inflorescence highlights the potential of natural products as complementary treatments for diabetic malitus. More research into their medicinal qualities may result in the creation of safer, more easily accessible, and more reasonably priced therapy alternatives for people with diabetes mellitus.

Effective diabetes care ultimately revolves around individualised treatment programmes that include food changes, medication, exercise, and routine monitoring. To guarantee safety and maximise results, integrating conventional treatments like Pterygota alata inflorescence should be carried out under the supervision of licenced healthcare professionals. However, it's important to note that the scientific evidence supporting its use in managing type 2 diabetes mellitus may still be limited compared to conventional medications.

Figure 2: Chemical Structure of Antidiabetic compounds in *Pterygota alata* inflorescence



Conclusion

The identification of potential antidiabetic compounds in *Pterygota alata* inflorescence through advanced analytical techniques like UHPLC-Q-TOFMS/MS is an exciting development in the field of natural medicine. The compounds you've listed, such as Agmatine, Migitol, Trigoneline, Betaine, Theophylline, Quercetin, Kaempferol, Isoliquiritigenin, Esculetin, Rutin, Ferulic acid, Eriodictyol, Naringenin, Luteolin, Salsonilon, Apigenin, Hesperitine, Carvone, Ursolic acid, Betulin, Lupeol, Eugenol, have been studied for their various biological activities, including their potential role in managing diabetes mellitus. Overall,

the identification of these compounds in Pterygota alata inflorescence underscores the potential of natural products as adjunctive therapies in diabetes management. Further investigation into their therapeutic properties could lead to the development of safer, more affordable and accessible treatment options for individuals with diabetes mellitus.

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