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A COMPREHENSIVE REVIEW ON POTENTIAL THERAPEUTIC EFFECTS OF *PEGANUM HARMALA* IN MANAGING TYPE 2 DIABETES AND ITS RELATED COMPLICATIONS.

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Abstract:
Peganum harmala, also known as Syrian rue or Wild rue, is a medicinal plant that has been used for centuries in traditional medicine for various diseases. It contains several alkaloids, flavonoids, and other phytochemicals that have shown pharmacological activities such as anti-amicrobial, neuroprotective, antidiabetic, and antitumor effects.
This review summarizes the current evidence on the antidiabetic effects of P. harmala and its main alkaloid, harmine, in animal models and human studies. P. harmala extracts and harmine have been reported to lower blood glucose levels, increase insulin sensitivity, and protect against diabetic nephropathy and retinopathy. The mechanisms of action involve the activation of peroxisome proliferator-activated receptor gamma (PPAR-γ), the stimulation of beta-cell proliferation and regeneration, and the suppression of oxidative stress and inflammation. P. harmala and harmine may have potential therapeutic effects in managing type 2 diabetes and its related complications.

Key Words: Peganum harmala, Harmine, antidiabetic activity

1. INTRODUCTION :

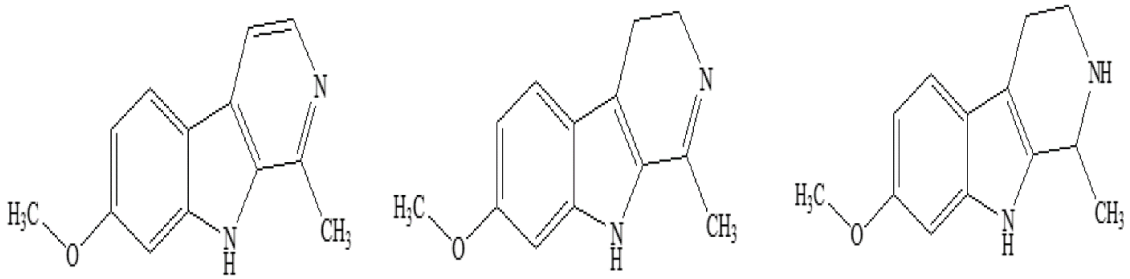
Diabetes is a chronic disease and is a group of metabolic disorders characterized by high levels of sugar in the blood.(1) Type 1 diabetes mellitus (T1DM) and type 2 diabetes Mellitus (T2DM) are both autoimmune diseases with a variety of risk factors. combination of environmental and genetic factors.(2,3)In developed countries, the prevalence of diabetes rose from 51 million to 72 million, reflecting a 42% increase. Subsequently, it further escalated from 84 million to 228 million, indicating a substantial 70% increase.(4).

The flowering plant Peganum harmala, also known as Syrian rue and Wild rue, is found widely in Central Asia, North Africa, and the Middle East.(5) (Figure 1) It belongs to the Zygophyllaceae family. Other than becoming widely distributed in North Africa, the Mediterranean, the Middle East, Pakistan, India, and southern Iran, Peganum species have also been imported to America and Australia.(6)

It was frequently used in traditional medicine in Egypt. Primarily in the Sinai Peninsula, where the smoke produced by the plant and its seeds were used as an analgesic for the treatment of headaches and CNS disorders from its burning leaves.(7) The effects mentioned come from β-carbolines, which are certain natural substances found in various plants. In the seeds of Peganum harmala, the main β-carbolines are harmine, harmaline, and tetrahydroharmine. (Figure 2)(8) These compounds exhibited significant activities like as gastrointestinal, osteogenic, antidiabetic, antimicrobial, and antitumor. (9).

In addition, harmine and harmaline When studied in a rat model using streptozotocin, showed antidiabetic activity. This result was attributed to the improvement of insulin sensitivity.[10,11]A broad-spectrum antibiotic STZ(streptozotocin) is produced by the bacteria Streptomyces achromogens. It has a glucose molecule attached to a highly reactive nitrosourea methyl-moiety, which is hypothesized to cause STZ's cytotoxic effects. while the glucose part helps target the chemical to the insulin-producing pancreatic β cells. STZ doesn't stay in the body for long because the liver rapidly breaks it down, and the kidneys eliminate it through urine. However, if someone has diabetes, the high blood sugar levels can harm the liver and kidneys even after STZ is gone.[12]

(Figure 1) P. harmala seeds and flower



(Figure 2) Chemical structure of β–carbolines: Harmine, Harmaline, and Tetrahydroharmine.

1.1 Harmine and its derivatives

Harmine is extracted from the seeds of Peganum harmala L., a medicinal plant that grows in desert regions like the Middle East and China.[13]Harmine (7-methoxy-1-methyl-9H pyrido[3,4-b]indole), A naturally occurring -carboline alkaloid[14] is known to have a wide range of biological & therapeutic activity suggested to treat cancer[15],anti-inflammatory[16],anti-oxidant[17],and anti-microbial[18], neuroprotective[19] and antidepressant activities.[20] Harmine is shown great potential in the treatment of diabetes in recent years. Harmine is one of two primary ingredients.[21] examined the metabolic characteristics of harmine in liver microsomes from eleven mammalian species(rat, mouse, pig, bull, sheep, camel, human, dog, monkey, guinea pig, and rabbit) The metabolization of harmine begins easily in rabbits, mice, and rats; mildly metabolized in Dogs and humans, as well as sheep with a slow metabolism.Dogs exhibited significant similarity with humans in the metabolic profiles and catalytic mechanisms of harmine.[22] Harmine is a competitive inhibitor of ATP binding to the kinase pocket of DYRK1A (dual-specificity tyrosine-(Y)-phosphorylation-regulated kinase 1A), but it also inhibits monoamine oxidases (MAOs), which are also members of the DYRK (Dual specificity tyrosine-phosphorylation-regulated kinase) family.[23] and has neuroprotective effects. Effectively

harmine ATP-competitive inhibition of DYPK1A activity-via interacting with the residues in the ATP-binding pocket and ATP is being displaced [24]. Also, harmineDYPK1A-catalyzed direct phosphorylation inhibited. tau protein and inhibited tyrosine auto-phosphorylation.[25-26] Harmine and its derivatives have been found to bind to DNA and inhibit topoisomerase activity. These compounds (6-, 8-, and 6,8-dichloroharmines) are effective photosensitizers.[27] Harmine derivatives showed spasmolytic activity[28] and inhibitory effects on Dengue virus[29] and haspin kinase.[30] harmine derivatives 7,9- or 2,7,9-substituted SerB2 activity(essential phosphoserine phosphatase that has been shown to be involved in Mycobacterium tuberculosis immune evasion mechanisms) might be inhibited by scaffolds of 7-oxy-1-methyl-b-carboline.an essential metabolic enzyme, and suspected virulence factor of Mycobacterium tuberculosis.[31]Harmine is showing protective benefits for cardiovascular diseases. Harmine inhibited the development of endothelial cells, which resulted in non-antiangiogenic with vasorelaxant effects and malignant effects.[32]

2. MATERIALS AND METHODS FOR EXTRACTION

2.1 Plant material: The seed of peganum harmala plant,were collected from Kashmir.The botany division of the institute verified the plant's identity and preserved a sample (voucher no.6375)and reference material in the centre Drug Research institute collection in Lucknow India. **[33]**

2.2 Preparation of the Ethanol Extract

They used 99.8% methanol and a Soxhlet extractor to get the extract from the P. harmala seeds. They crush the seeds first and then soak them for four days. After that, they will filtrate the liquid with Whatman No.1 filter paper and dry it with a rotary evaporator. They keep the dry extract in a cool place until they use it. [34]

3. Analytical methods

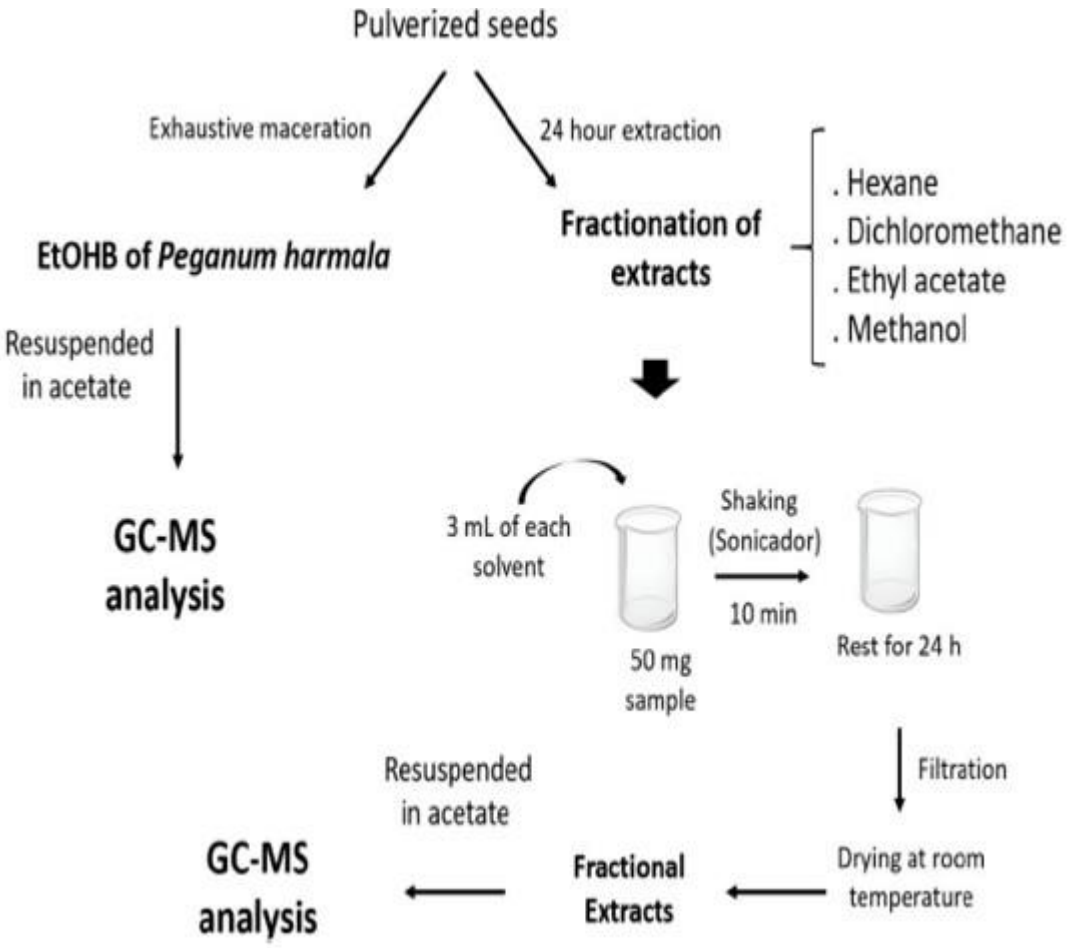
3.1 Gas chromatography coupled to mass spectrometry (GC-MS)

The analysis of the crude ethanolic extract of P. harmala (EtOHB of P.harmala)and the analysis of the fractionated extracts based on the increasing polarity of the solvents hexane, dichloromethane, ethyl acetate, and methanol, respectively—were used to evaluate the chemical profile of the plant species using gas chromatography coupled to mass spectrometry (GC-MS).

50 mg of seeds was taken and mixed with 3 ml of increasing polarity solvents. The mixture underwent 10 minutes of sonication, followed by a 24-hour rest. After filtering, the sample was transferred to the next solvent. The extract was air-dried at room temperature (25°C) and this process was repeated for each solvent in triplicate. The EtOHB of P. harmala was obtained using the same procedure as the extracts described above. For sample analysis, the extracts were mixed with ethyl acetate (HPLC-grade) to achieve a concentration of 10 mg/ml.

The analysis involved using a gas chromatograph connected to a Shimadzu® mass spectrometer (QP-2010) and a self-injector (AOC 20i). The chromatographic conditions included a RESTEK® RTX–5MS column (30.0 mm × 0.25 mm × 0.25 mm) with helium gas (99.99%) flowing constantly at 1.4 mL/min. A sample volume of 1.0 μL was injected in split mode with a 5:1 ratio (1 part injected, 4 parts discarded) and an injector temperature of 260°C. The ionization was achieved using electron impact mode at 70 eV, and the ion source was maintained at 250°C.

The oven temperature was set to start at 80°C (isothermal for 3 min). Then, it was raised at a rate of 5°C/min to 285°C (isothermal for 15 min). Afterward, the temperature was increased at a rate of 10°C/min to reach 320°C, where it was kept constant for 20 minutes. A hydrocarbon mixture (C9H20 to C40H82) was injected using the same parameters as the sample analysis. Compounds were identified by comparing their mass spectra with those stored in the SHIMADZU® database (GCMS Solution), specifically using the Wiley 7lib and NIST08lib libraries. A compound was marked as identified if its similarity index was 90% or higher (Figure 3). [35]



(figure 3) Peganum harmala extracts by using gas chromatography coupled to mass spectrometry (GC-MS).

3.2 Thin-layer chromatography:

TLC is a quick method for separating and analyzing chemicals in Peganum harmala. Harmaline and harmine, two compounds from P. harmala, were separated using a plate coated with silica gel G and a mixture of ethyl acetate, methanol, and ammonia water (at a ratio of 20:5:1). This helped identify these compounds in Peganum harmala Moreover, a TLC bioautographic assay was used to test the effects of vasicinone, vasicine, harmine, deoxyvasicinone, deoxyvasicine, harmaline, harmol, and harmane on acetylcholinesterase (AChE) inhibition. These compounds were separated on a special plate with silica gel, and the plates were analyzed with ethyl acetate-methanol-ammonia water (at a ratio of 10:1.5:0.5) under UV light and treated with Dragendorff's reagent and bioautographic assay. This technique was used to identify AChE inhibitors in Peganum harmala seeds and ensure their quality. A similar method was developed to find dipeptidyl peptidase IV (DPP IV) inhibitors from plant extracts. Out of nine medicinal herb extracts tested, P. harmala showed one active spot identified as harmine. Harmine was found to inhibit DPP-IV activity by 32.4% at 10 mM, compared to 54.8% at 50 µM for diprotin A, using a spectrophotometric method.[36]

4. Antidiabetic activity of Peganum harmala

P. harmala has been traditionally used to treat diabetes in folk medicine in elsewhere the world. The effect has been pharmacologically confirmed in several studies. The antidiabetic activity of the hydroalcoholic extract of P.harmala was verified in streptozotocin-induced diabetic rats at three doses of 30, 60, and 120 mg/kg.[37] Administration of the hydroalcoholic extract of P. harmala to diabetic rats resulted in a remarkable decrease in glucose, lipid profiles, malondialdehyde, alanine aminotransferase(ALT), aspartate aminotransferase(AST), gamma-glutamyl transferase, bilirubin, and glycosylated hemoglobin levels and increase in total antioxidant capacity relative to diabetic

group. The results indicated that the extract possessed antidiabetic and hypolipidemic activities and could be useful in the treatment of diabetes.[10] The oil of Peganum harmala seeds and drug were about 112.4 mg/dl and 119.8 mg/dl, respectively four weeks from the beginning of the experiment. Administration of Peganum harmala seeds oil to diabetic rats caused anti-diabetic and antioxidant activities by the diminution in plasmatic glucose levels.[38] The lack of β cells is closely associated with diabetes. The decrease in mature insulin-secreting β cells is one of the main causes of diabetes. Owing to the difficulty of self-proliferation of mature β cells, drug-induced β cell proliferation is a new area of interest in the treatment of diabetes.[39-40]Peroxisome proliferator-activated receptor(PPAR) and expression is regulated differently depending on the kind of cell. Harmin replicates the effects of PPAR and ligands on adipocyte gene expression and insulin sensitivity when administered to diabetic mice. However, harmine did not significantly increase weight loss in comparison to thiazolidinediones. gain or hepatic lipid build-up. According to molecular research, harmine regulated PPAR and expression by inhibiting the Wnt signaling pathway. This research established adipocyte phenotypic screening as a viable method for the discovery of bioactive small compounds and proposed that PPAR and expression regulators may act as a supplementary approach to PPAR ligands in the treatment of insulin resistance. [41] By testing on mice and human islets inside living systems, a comprehensive chemical test showed that when harmine is used to block dual-specificity tyrosine-regulated kinase-1a (DYRK1A), it boosts the growth and specialization of insulin-producing beta cells in the human pancreas. [21]

5. Anti-microbial activity

Harmine and its synthetic variations have been found to fight against various types of fungi, like Fusarium oxysporum and Colletotrichum gloeosporioides.[18] Harmine slowed down the growth of conidia when its concentration was between 0.5 to 1 mM. In a different research, harmine was effective in showing fungicidal activity in 60% of Physalospora piricola at a concentration of 50 mg/kg[42]

6. Gastrointestinal activity

P. harmala extract and powdered seeds have been utilized in traditional medicine across various regions globally to address colic in both humans and animals.[43] The plant's efficacy in colic treatment is attributed to its ability to act as an antispasmodic agent[44]. This effect is likely achieved by the plant's alkaloid content, particularly harmaline, which may block different types of calcium channels in the intestines. [45] Additionally, P. harmala is known to induce feelings of nausea and can act as an emetic.[46]

7. Anti-tumor activity

In several regions of the world, traditional healers have made a variety of remedies using P. harmala to cure tumors and cancer[47]. For example, P. harmala powdered seeds have been used often in Moroccan traditional medicine to treat skin and subcutaneous tumors[48]. Extracts containing P. harmala alkaloids could potentially serve as novel cytotoxic agents against chemotherapy-resistant cancer cells.[49] The ability to induce cell death and impede cell growth in breast cancer cell lines. Researchers have proposed that this herb might hold promise for deterring tumor development. [50]

8. Conclusion

Peganum harmala is a medicinal plant with a long history of use in traditional medicine for various diseases, especially diabetes. Recent studies have shown that Peganum harmala and its main alkaloids, such as harmine, have antidiabetic effects by stimulating insulin secretion, enhancing glucose uptake, inhibiting gluconeogenesis, and modulating lipid metabolism. Moreover, Peganum harmala and harmine have protective effects against diabetic complications, such as nephropathy, neuropathy, and retinopathy, by reducing oxidative stress, inflammation, and apoptosis. Therefore, Peganum harmala and its derivatives may have potential therapeutic value in managing type 2

diabetes and its related complications. However, further studies are needed to elucidate the exact mechanisms of action, pharmacokinetics, safety, and efficacy of Peganum harmala and its constituents in human trials.

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