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TITLE: Review Article: Alkaloidal content, medicinal, properties of *Peganum harmala* L. (*P. harmala*)

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Structured Abstract:

Background: This review article analyzes the medicinal properties of *Peganum harmala* L. [Nitrariaceae] also known as *P. harmala*, Syrian rue, wild rue, harmal seeds, and Esfand. The *P. harmala* is a medicinal plant and its seeds have been known to alleviate symptoms of diabetes mellitus, depression, and liver damage; seed extracts also have antioxidant and disinfectant properties. Burning *P. harmala* seeds releases disinfectant properties and is also believed to ward off the "evil eye" in Iranian culture.

Objective: The central focus of this review article is to review the positive influence of *P. harmala* (methanolic, alkaloidal, and dry seed extracts) as a remedial agent for diabetes mellitus, cancer, depression, and liver damage, in various *in vitro* and *in vivo* studies.

Methods: Content for this review article was gathered searching for "*P. harmala*;" "*Peganum harmala* L.;" "Esfand;" "rue;" "*P. harmala* remedies;" "alkaloids and *P. harmala*;" and "harmala seeds" through electronic articles such as PubMed, Science direct, Elsevier and Google Scholar. Journals included Journal of Traditional Chinese Medicine, African Journal of Pharmacy and Pharmacology, and Phytomedicine.

Results: Fifty-eight review research/articles were reviewed to better understand the remedial properties of *P. harmala*. Studies were focused on the therapeutic components of *P. harmala* and:

- Diabetes mellitus
- Cancer
- Depression
- Liver damage
- Antioxidant properties
- Disinfectant properties

The multifunctional capabilities of *P. harmala* are a result of the alkaloidal content. The alkaloidal content of *P. harmala* is a strong candidate for anticancer therapies, as alkaloidal activity was found to delay cell growth in rats with induced UCP-Med carcinoma, Med-mek carcinoma, and UCP-Med sarcoma [8]. Other *in vitro* studies in animals have found *P. harmala* to improve liver damage. The antihyperglycemic components in the alcoholic extract of *P. harmala* position the plant to be a candidate for treating insulin resistance and type 2 diabetes mellitus [1]. Tests on β-carboline alkaloids in *P. harmala* have also helped determine the positive and negative influence of monoamine oxidase (MAO) enzyme inhibition [Figure 1].

Conclusion: Phytotherapy is an important candidate for alternative medicine as plant-based medicines have low probability for addiction, are naturally abundant compared to commercial drugs, and have less side effects and harmful symptoms compared to commercial drugs [3]. To better understand the possibility of the β-carboline alkaloids as disease-curing agents, additional testing, especially on human metabolism and chemical compounds of

extracted seeds, is encouraged [4]. With additional research, *P. harmala* may be a leading candidate for phytotherapy.

Keywords: Cancer, depression, diabetes mellitus, liver damage, disinfectant properties, Esfand, *P. harmala*

1. INTRODUCTION

Peganum harmala L. *(P. harmala)* [Nitrariaceae] is also known as African rue, Syrian rue, harmal and harmal seeds [7]. In Iran, *P. harmala* is known as esphand. *P. harmala* grows in dry environments and is predominant in the Middle East and North Africa, near the Mediterranean [7]. The succulent plant grows in predesertic and semiarid terrains [8], and is predominant in dry areas throughout the Mediterranean, north India, eastern Iran, North Africa, China, parts of the western United States, and the Middle East [18].

P. harmala is a bright-green rootstock with branches that grow up to four feet [4]. The plant blooms white flowers with oblong petals between June and August [4]. The blooms have the ability to harvest fruit, contained in a shell that ranges between three to eight inches in diameter on the plant stalk [4]. Over fifty *P. harmala* seeds are found inside the shell, usually dark brown and angular [4].

P. harmala is a medicinal plant and its seeds have been known to alleviate symptoms of diabetes mellitus, depression, and liver damage; seed extracts also have antioxidant and disinfectant properties [Figure 2]. *P. harmala* seeds and extracts assist with hypothermia and have been used medicinally as narcotics and sedatives. Seeds and extracts have also been cited to reduce fever, malaria, arthritis, asthma and syphilis [20-26]. *P. harmala* seeds, in combination with other seeds and ingredients, are burned and used as a protectant against the "evil eye" in Iran [36]. *P. harmala* is also significant because of its antimicrobial [9-11], hallucinogenic [14-17] and hypothermic properties [12-13].

Due to increased resistance of antibiotics and alternatives to antibiotics, alternative approaches must be considered to reduce microbial infection and disease. In many plant studies, it is often undetected if pharmacological reactions are caused by or correlated with other compounds and the activities of harmala alkaloids [7].

2. Traditional Medicine

P. harmala has been used in traditional medicine to alleviate anxiety and similar psychological symptoms [40], alleviate pain [41], and symptoms of the nervous system. [38] [39]. *P. harmala* works with nervous system receptors via beta-carbolines. Beta-carbolines communicate with imidazoline receptors [43], opioid [41], benzodiazepine, GABA (Gamma-Aminobutyric acid) [42], and 5-hydroxytryptamine [38]. *P. harmala* alkaloids have improved various cardiovascular effects, including lowering blood pressure and assisting with bradycardia [38].

In traditional Iranian medicine, *P. harmala* is also known as esfand, espand, and harmal [44] [46]. *P. harmala* is significant in traditional Iranian medicine because it serves as a disinfectant when seeds are burned and seed smoke is disseminated via heat; burning seeds is also believed to protect against the "evil eye [45] [46]." In traditional Moroccan medicine, extracts of *P. harmala* seeds are turned into a powder and can be used to remedy skin tumors

and cancer treatment [3] [8]. In traditional forms of cancer therapy in Iran, *P. harmala* extracts are incorporated in ethnobotanical preparations used for cancer treatment [37].

When *P. harmala* extracts were tested *in vitro* and *in vivo* on leukemic cell lines, leukemic cell lines were reduced and metastases of melanoma cells were blocked [46-52]. Extracts have also been documented to relieve symptoms of pain, including toothache, chronic headache, and joint pain [46].

3. Chemical Compounds and activity

Significant beta-carboline alkaloids in extracts of *P. harmala* include harmine, harmaline, harmalol, harmol, and tetrahydroharmine [4]. Alkaloids, flavonoids, and anthraquinones are the phytochemical mechanisms in *P. harmala*. Approximately 2 to 5% of *P. harmala* is composed of alkaloids [4]. The following flavonoids glycosides are located in the aerial region of *P. harmala* plant: acacetin rhamnoside, glucosyl glucoside, glucosylglucoside, glycoflavone. [53].

Studies have explored the anticancerous [8] [54], vasorelaxant [62-63], antinociceptive and analgesic effects [56] [23], and hypothermic mechanisms [57-58] of crude extracts and β-carbolines [61]. Additionally, the monoamine oxidase inhibitors of β-carbolines position *P. harmala* as a possible therapeutic drug for Parkinson's disease [59-61]. In various *in vitro* and *in vivo* studies, chemical compounds of *P. harmala* are extracted, or combined with commercial drugs, to assist with diabetes mellitus, cancer, depression, and liver damage [Figure 1].

Harmful side effects of *P. harmala* include agitated mood, confusion, vomiting and nausea, visual and auditory hallucinations, and motor-function paralysis [36]. These side effects stem from β-carbolines [36].

3.1 Phenology

When *P. harmala* extracts from Tunisia were tested for antiviral activity, the highest total phenolic content was with methanolic and butanolic extracts [4]. The lowest was ethyl acetate extract [4].

4. Toxicity

The seeds of *P. harmala* contain toxic alkaloid compounds harmine and harmaline, of which harmaline is more intense in toxicity. Harmaline is known for its ability to cause convulsions as it suppresses the central nervous system when taken without precaution. Harmine is less dangerous, although it resembles pharmacological components and functions similar to harmaline [4]. Symptoms of *P. harmala* overdose include hallucinations, nausea and vomiting, and decreased sensory activity relating to the nervous system [4]. High doses of *P. harmala* is known to cause spontaneous abortion.

5. Diabetes mellitus

Naresh et al. determined 4-hydroxypipecolic acid (4-HPA), isolated from *P. harmala* seeds, as having antihyperglycemic properties. The antihyperglycemic components in the alcoholic extract of the *P. harmala* position the plant to be a candidate for treating insulin resistance Type 2 diabetes mellitus [1]. In an effort to discover new drugs that treat hyperglycemia in relation to Type 2 diabetes mellitus, Naresh et al. tested 4-HPA on glucose

absorption and the variation of glucose transporter-4 (GLUT4) in the skeletal muscle of rat cells [1]. 4-HPA is an amino acid similar to insulin-tropic and insulin trigger known as 4-hydroxyisoleucine and fagomine [1-2]. As reported by Naresh et al., 4-hydroxypipecoic acid (4-HPA) carries antihyperglycemic components.

GLUT4 transports glucose from peripheral tissue (internal membrane) to the plasma membrane to assist with glucose uptake [1] [66]. GLUT4, with the assistance of other receptor substrates, helps bind insulin and trigger a series of activities that allows glucose in the cell [1]. Insulin resistance inhibits the function of GLUT4, and handicaps the glucose triggered by insulin [1].

When 4-HPA glucose levels were tested on L6-GLUT4*myc* myotubes with varying levels of 4-HPA for 16 hours, glucose absorption occurred at a level of 5 µM (p <0.5) and at a level of 25 µM (1.25 times the control, p <0.01) [1]. The positive control in this study was insulin [1]. To determine the possible correlation between 4-HPA increase and GLUT4 movement from intercellular regions to the plasma membrane, Naresh et al. recorded the surface level of GLUT4*myc* via an antibody-coupled assay [1] [64]. GLUT4 increased at the surface level at 10 µM (p <0.05). Levels reached the highest at 25 µM (130%, p<0.01).

To determine if 4-HPA triggers GLUT4 movement and activity to the cell surface, the influence of insulin activity of cells separate from the hormone was observed [1]. Insulin increased GLUT4 activity and movement in L6-GLUT4*myc* myotubes over basal state [1].

PI-1-K was observed to better understand if 4-HPA triggered GLUT4 movement in a similar fashion to insulin. Wortmannin (WRT), a PI-3-kinase blocker that prohibits insulin signaling, was investigated with GLUT4 and 4-HPA [1] [65]. WRT (50 nM) returned insulin activity and movement of GLUT4 at the cell surface to standard levels [1]. In 4-HPA treatment, WRT stopped the increase of 4-HPA in GLUT4 movement and activity of cells to the cell surface [1]. PI-3-kinase triggers the variation of GLUT4, postulating similar activity of 4-HPA on the same pathway [1].

P. harmala extracts were proven to be as successful in lowering blood glucose concentration as commercial drug metformin, in diabetic rats induced with streptozotocin post sucrose-challenge, as reported by Singh et al. [4-5]. In rats induced with streptozotocin (STZ), ethanolic extracts of *P. harmala* proved to be as remedial as metformin [5]. Blood glucose level decreased in non-diabetic and diabetic rats with controlled doses of *P. harmala* at doses of 150 and 250 mg/kg, according to body weight [5].

6. Cancer

Lamchouri et al. investigated the alkaloidal activity and function of *P. harmala* on carcinoma and sarcoma cells to find that dry seeds have various cytotoxic effects on rats with induced UCP-Med carcinoma, Med-mek carcinoma, and UCP-Med sarcoma [8].

The alkaloidal fraction of *P. harmala* was mixed with dimethyl sulfide (DMSO) [8]. In UCP-Med carcinoma cells, the first 24 hours of alkaloidal fraction in culture revealed delayed growth and cell lysis started at hours 24-72,

according to treatment [8]. Delayed cell growth occurred when treated with 20 µg/ml with UCP-Med sarcoma in the first 24 hours [8]. After 24 hours of exposure to dosage 60-100 µg/ml, cell life reached 100% [8].

Compared to UCP-Med carcinoma cell lines and UCP-Med sarcoma cell lines, Med-mek carcinoma cell lines showed slower cell growth, evident almost as soon as cells were exposed to alkaloid treatment, and most evident at doses of 80 and 100 µg/ml [8]. Cell growth rate was not as evident in lower doses. There were no living cells after 48 hours [8].

Lamchouri et al. found that cytotoxicity was correlated to *P. harmala* dose and vulnerability to alkaloids. After 24 hours of exposure, the median growth inhibitory level for UCP-Med carcinoma was 33.67 µg/ml; Med-mek carcinoma was 18.42 µg/ml; UCP-Med sarcoma was 23.14 µg/ml, accordingly [8].

An additional study by Lamchouri et al. determined *P. harmala* seeds as cytotoxic on tumor cell lines. Alkaloids harmine, harmalicidine, peganine (vasicine), and vasicinone were tested on Med-mek carcinoma, UCP-med sarcoma, Med-mek carcinoma, and SP2/O-Ag14. Alkaloidal activity, cytotoxic impact, and total alkaloidal fraction (TAF) of tumor cell lines were determined [3]. Similar to findings from other studies, Lamchouri et al. determined the extracted alkaloids of *P. harmala* seeds as exhibiting cytotoxic activity on the four cancer cell lines [3].

In a study by Zaker et al. and Douer et al., extracts of *P. harmala* that consist of harmine, harmaline, harmalol, and harman, have antitumor function in mice with tumors [18-19] [88]. *In vitro* studies found apoptotic activity of alkaloids to stop tumor cell growth [18] [3]. On human promyelocytic cell lines, harmaline decreased the development of new cells at a dose of 6-10 µg/mL and cytotoxicity was evident at a dose of 15-30 µg/mL [18].

Harmine and harmaline are two alkaloids that provide cytostatic effects and stop cell growth on the human promyelocytic cell line (HL60 cells) [4]. In cell lines, including breast cancer, melanoma, ovarian cancer, fibrosarcoma, and hepatocarcinoma, harmaline was most effective [4]. Further studies on the activity and function of alkaloids will help establish *P. harmala* as a candidate for antitumor growth.

7. Depression

Herratz et al. investigated the presence of β-carboline alkaloids in *P. harmala* while also determining the positive and negative influence of monoamine oxidase (MAO) enzyme inhibition, a mitochondrial enzyme that sparks the oxidation of monoamines [26]. Harmine and harmaline act as reversible inhibitors of MAO-A enzymes [36].

Special attention was given to β-carboline because of its psychopharmacological capabilities, caused by MAO blocking and unique binding to opiate receptors, serotonin, benzodiazepine, and imidazoline [26]. Existing as MAO-A and MAO-B, these inhibitors are significant because of their function in the central nervous system and peripheral organs [26-28]. MAO-A inhibitors can be useful antidepressants while MAO-B inhibitors serve as neuroprotectants [26] [28-30] [33-35]. MAO inhibitors, by way of β-carboline alkaloids, have antidepressant components [26] [31-32].

Different parts of *P. harmala* were studied to better understand β-carboline alkaloid activity and function. MAO blocking and biological activity was also studied [67]. The study found *P. harmala* as having MAO-A in seed and root extracts, β-carboline in seeds (harmine and harmaline) and roots (harmine) at a high concentration [67], and assisting MAO-A blocking. The following is in order of highest extraction found by Herraiz et al.: harmine and harmaline, followed by harmalol and harmol [67]. Each part of the plant varied in β-carboline amounts.

8. Liver damage

A study by Soliman et al. found extracts of *P. harmala* as having an antioxidant protein that improves liver function in rats with induced liver damage [83]. Soliman et al. compared isolated protein 132 KD extracted from *P. harmala* seeds to carbon tetrachloride oxidative stress (CCI_4) in rats [83]. Rats were administered oral doses of CCI_4 in olive oil and injected with 132 KD isolated protein and vitamin C for 7 days, followed by oral administration of CCI_4 in olive oil. Oral administration was observed for 2 days [83].

Rats were administered with controlled doses of 132 KD at 4 and 8 mg/kg according to body weight; bovine serum albumin (BSA) at 8 mg/kg according to body weight; and vitamin C at a dose of 250 mg/kg per body weight [83]. The control group was given olive oil for 2 days followed by doses of distilled water for 7 days. The negative control group was given an intraperitoneal injection of BSA at a dose of 8 mg/kg by body weight. Results showed that the antioxidant in the isolated protein is comparable to antioxidant function of vitamin C and BSA [83].

Hamden et al. investigated the role of *P. harmala* ethanol and chloroform extracts as the antithesis of cancer-causing agents via thiourea, a drug that assists with carcinogens and its impact on liver damage [82]. In cultured cancer cell lines, *P. harmala* extracts protected against liver damage caused by thiourea, and decreased the tumor parameters of the neuroendocrine system (NSE) and thyroid (TG) amounts [82]. The negative control rat group was administered with water and thiourea, and the remaining two groups were given thiourea and *P. harmala* extracts in their food. Extracts were air-dried, ground, and modified in a laboratory. Samples were extracted and mixed with food [82]. *P. harmala* extracts assisted in lowering neuron-specific enolase (NSE) and thyroglobulin (TG) to a normal level [82]. Hamden et al. proposed the beta-carbolines of *P. harmala* as the main inhibiting agent in cell cultures [82].

9. Antioxidant properties

Antioxidant activity and function is very important in shielding the human body from diseases caused by reactive free radicals that appear in diseases, including Parkinson's and Alzheimer's, ischemic heart disease, and atherosclerosis [4]. Using the ammonium thiocyanate method, Asgarpanah et al. determined the antioxidative levels of *P. harmala* leaves. Linoleic acid oxidation blocked by methanol extract of the plant leaves was 75.9 ± 0.3 after 5 days of incubation [4]. Activity was compared to tocopherol at a dose of 80.12 ± 0.4 [6]. According to Asgarpanah et al., the antioxidant activity may be caused by the phenolic compounds, including flavonoids and tannis, which do not exist in the methanolic extract [4]. The compounds in *P. harmala* may be comprehensive in providing antioxidant activity [4].

10. Disinfectant properties

To better understand the *P. harmala* seed smoke as an antimicrobial agent, Shahverdi et al. tested the cytotoxicity of *P. harmala* extract [Esphand] smoke on the surface culture of the following microorganisms:

A. fumigates (PLM 112)

A. niger (PLM 16404)

C. neoformans (PLM 589)

E. coli (ATCC 25922)

P. aeruginosa (ATCC 27853)

S. aureus (ATCC 25923)

S. epidermidis (ATCC 12228)

P. harmala seeds were dried, crushed, and deduced via maceration in methanol at room temperature for approximately 24 hours [84]. The seeds were burned to produce [Esphand] smoke. The [Esphand] smoke was exposed to cultured plates for 15 minutes. Monoculture plates that were not exposed to seed smoke served as the control group [84]. Cultured plates were Balb/C 3T3 fibroblast cells that survived in a mixture of 90% Dulbecco's modified Eagle's medium, 100 IU/ml penicillin, 100 µg/ml streptomycin, 5% fetal calf serum, 5% newborn calf serum, and 2 mM glutamine [84].

Shahverdi et al. determined the dose-dependent relationship as the causation of cytotoxicity. Lower doses (10, 20 µg/ml) had no impact on cytotoxicity on the tested cell lines while higher levels of smoke condensate acted as a block for cell growth [84]. Cell growth was blocked 50% when smoke condensate was at a level of 4 µg/ml [84]. Cell growth was blocked over 95% when [Esphand] smoke condensate was at a level of 8 µg/ml [84]. [Esphand] smoke condensate was captured via a condensing tower and stored in dichloromethane. Cytotoxicity experiments were performed with a combination of the evaporated methanol extracts and [Esphand] smoke condensate [84].

In an earlier study by Shahverdi et al., harmine was identified as the compound with the strongest anti-bacterial capacity. Over thirty-five compounds were also present. Using a GC/MS analysis, 93% of the revealed compounds were dichloromethane and *n*-hexane extracts [85].

11. Results

Eight of the nine glioma patients in the study by Pathak et al. saw a reversal in their brain cancer with treatment of combined Ruta 6 and $Ca_3(PO_4)_2$ [86]. Two patients, one with pituitary tumors, and the other with craniopharyngioma, saw tumor suppression; the patient with neurinoma experienced tumor suppression for an extended amount of time [86]. *In vitro* tests determined the effect of Ruta 6 and $Ca_3(PO_4)_2$ and whether the combination sparked cell death in human cancer cells (HL-60 and MGR1 glioma) and murine cancer cells (K 1735

clone X-21), and whether the combination harmed telomeric DNA in normal human PBLS and B-lymphoid cells [86]. On MGR1 glioma cancer and normal β-lymphoid cells, Ruta 6 reduced telomeric DNA and had a strong impact on brain cancer cells. No impact was found on β-lymphoid cells [86].

When methanolic extracts of dried *P. harmala* seeds were tested for MAO inhibition, human MAO-A and β-carbolines, including harmalol, harmine, and harmaline, were found in the seed extracts [67]. These β-carbolines were able to inhibit MAO-A with approximately 87% of inhibition from harmine and harmaline [67]. Roots also exhibited a high volume of β-carbolines harmine and harmol. When roots were diluted for MAO-A inhibition, β-carboline yielded MAO-A inhibition [67]. Compared to root and seed extracts, the stem and leaf extracts of *P. harmala* had a lower concentration of MAO-A inhibitors and was in accordance with the low harmine level [67].

In the additional study by Lamchouri et al., Sp2/O-Ag14 had the most cell growth with IC_{50} concentrations between 2.43 µg/mL and 19.20 µg/mL [3]. The cell line with the least activity was UCP-med carcinoma with an IC_{50} range of 13.83 µg/mL to 59.97 µg/mL [3]. Lamchouri et al. found harmine to have most functional compounds with a range of 2.43 µg/ml and 18.39 µg/mL in IC_{50} for the four tumor cell lines [3]. TAF had the most activity next to UCP-med carcinoma with an IC_{50} range of 7.32 µg/mL to 13.83 µg/mL [3]. The least active compound was peganine with an IC_{50} range of 50 µg/mL to > 100 µg/ml, accordingly [3].

Harraiz et al. reported that the flowers had low level of β-carboline; stems had little concentration of harmol and harmine; and leaves had a distinct amount of harmine [67]. Dried seeds and roots had the highest concentrations of alkaloids, namely seeds with harmaline and harmine at 5.6% and 4.3% (w/w) respectively [67], tetrahydroharmine at 0.11% (w/w) [67], and harmalol at 0.6% (w/w) [67]. In roots, harmine and harmol were evident as the most significant alkaloids and had levels of 2.1% and 1.4% (w/w) with a lower level of harmalol [67]. Harmine and harmol were found in various sections of *P. harmala*, while harmol was mostly present in the roots [67].

In the study by Soliman et al., CCI_4 lowered serum aminotransferases (AST, ALT), catalase (CAT), lipid profile parameters and liver malondialdehyde (MDA), and alkaline phosphatase (ALP). The overall amount of liver superoxide dismutase (SOD) and CAT was also lowered, and the total protein serum and glutathione (GSH) concentrations also decreased [83]. Results also showed that rats treated with protein extract *P. harmala* seven days after $CC1_4$ saw a lowered level of ALT and AST serum activities.

12. Discussion

β-carboline alkaloids harmaline and harmine are responsible for the pharmacological and toxicological components of *P. harmala*. High levels of harmaline and harmine exist in the seeds and roots at upwards of 10% (w/w) [67]. Harmine is most present in seeds, while harmaline exists in roots and stems, respectively [67]. Herraiz et al. note that the differences in β-carboline levels may be a result of plant processing and geographical origin of the plant [67].

The study of β-carboline levels and activity is important because β-carboline attaches to human body and brain receptors, including imidazoline, serotonin, benzodiazepine, and opioid. β-carbolines also communicate with a

number of enzymes, including MAO. MAO serves as an ingredient in prescription antidepressants [67]. β-carbolines vary the application and absorption of neurotransmitters that effect platelet anti-aggregation, convulsion, body temperature, and antidepressant activity [67-81]. These effects, including antidepressant activity, are moderated by MAO enzymes [67].

The β-carbolines have the ability to block MAO-A, positioning *P. harmala* as a promising candidate for antidepressant drugs [67]. When Harraiz et al. studied MAO-inhibition, it was found that MAO-A inhibition was present via β-carbolines harmaline and harmine. Harmaline and harmine were present in seeds and harmine was present in roots. Seed extracts contained six times the amount of harmaline and harmine concentration compared to root content [67].

P. harmala extracts also lowered the risk of other diseases caused by thiourea [82].

Nenaah determined a level of "synergism" between β-carboline alkaloids against bacterial and fungal strains [7]. "Synergism" between chemicals is found in places where toxicity, therapeutic or other fitness impacts one compound and increases the activity of other compounds [7]. The "synergis[tic]" properties of harmala alkaloids may be an effective medication for microbial diseases when paired with other compounds and therapeutic drugs. Perhaps trial studies and advanced research will provide more information about the limitations and side effects of paired compounds and new treatments [7].

13. Conclusion

Phytotherapy is an important candidate for alternative medicine as plant-based medicines have low probability for addiction, are naturally abundant compared to commercial drugs, and have less side effects and harmful symptoms compared to commercial drugs [3]. It is important to test crude drug material to better understand plant materials and pharmacological capacity, especially for commercial use. Authentic material will guarantee the source of the material and provide authentic creation of pharmaceutical drugs, especially if mixed with other ingredients [87].
To better understand the possibility of the β-carboline alkaloids as disease-curing agents, more tests and chemical experiments, especially on human metabolism, is encouraged [4].

Abbreviations

Alkaline phosphatase: ALP; bovine serum albumin: BSA; carbon tetrachloride oxidative stress: CTOS; catalase: CAT; GABA: Gamma-Aminobutyric acid; glutathione: GSH; glutamic oxaloacetic transaminase: GOT; glutamic Pyruvic transaminase: GPT; liver malondialdehyde: MDA; monoamine oxidase enzyme: MAO; neuron-specific enolase: NSE; serum aminotransferases: AST, ALT; streptozotocin: STZ; superoxide dismutase: SOD; thyroid/thyroglobulin: TG; wortmannin: WRT

Conflict of Interest

Authors declare no conflict of interest.

Supportive/Supplementary Material

[Figure 1] The significant chemical compounds and compounds used for studies reviewed in this article, including methods of extraction. As described in this review article, *P. harmala* compounds were mixed with drugs and other compounds to test remedial and medicinal capabilities as related to various diseases.

[Figure 2] The alkaloidal components of *P. harmala* seeds and extracts assist with the listed diseases. *P. harmala* extracts also have strong antioxidant and antimicrobial properties.

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[Figure 1] The significant chemical compounds and compounds used for studies reviewed in this article, including methods of extraction. As described in this review article, *P. harmala* compounds were mixed with drugs and other compounds to test remedial and medicinal capabilities as related to various diseases.

Figure 1: Flow Diagram Process

This Flow Diagram Process explains the significant chemical compounds and compounds used for studies reviewed in this article, including methods of extraction. As described in this review article, *P. harmala* compounds were mixed with drugs and other compounds to test remedial and medicinal capabilities as related to various diseases.