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A review study of therapeutic effects of *Peganum harmala*

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ABSTRACT

Peganum harmala. belongs to Asian Origin and grows in the Middle East and in part of South mainly in India and Pakistan, is a plant of the family Nitrariaceae. It is a perennial plant which can grow to about 0.8 m tall. The aim of this study is to overview its therapeutic effects than its nutritive and industrial effects. This review article was carried out by searching studies in PubMed, Medline, Web of Science, and Iran Medex databases up to 2016.totally, of 85 found articles, 40 articles were included. The search terms were "Peganum harmala.", "therapeutic", "pharmacological". Various studies have shown that Peganum harmala. possess Candidiasis ,Biological ,Anti- cholinesterase, Anti- tumor angiogenesis, Antiparasitic effect, Anti-inflammatory effect, Cerebroprotective effect, Cytotoxicity effect, Antioxidant effect ,Hepatoma cancer effect, AhR ligands-mediated effects, Hepatoprotective prevention effect, Hypoglycemic effect, Pesticide effect, Antibacterial effect, Theileriosis effect, Antimicrobial effect, Analgesic effect, Histo-functional effects, Antinociceptive effects ,Antitumor effect, Haemosporidian infections in cattle effect, Haemosporidian infections effect, Abortificient potential effect. Peganum has different properties and combinations and numerous medicinal properties of its extract, essential oils, its stems and leaves require more research about the other beneficial and unknown properties of this plant.

Keywords: *Peganum harmala*., "therapeutic", "pharmacological", "Pharmacognosy"

INTRODUCTION

It is proved that herbal medicine is effective in the treatment of many diseases [1-10]. *Peganum harmala*, belongs to Asian Origin and grows in the Middle East and in part of South Asia mainly in India and Pakistan, is a plant of the family Nitrariaceae. It is a perennial plant which can grow to about 0.8 m tall, the plant's seeds are especially noteworthy because they have seen continual use for thousands of years in the rites of many cultures.

The roots of the plant can reach a depth of up to 6.1 m, if the soil where it is growing is very dry. It blossoms between June and August in the Northern Hemisphere. The flowers are white and are about 2.5–3.8 cm in diameter. The round seed capsules measure about 1–1.5 cm in diameter, have three chambers and carry more than 50 seeds[4-8].

Peganum harmala has been used to treat pain and to treat skin inflammations, including skin cancers[11, 12]. *Peganum harmala* has been used as an emmenagogue and abortifacient agent. The "root is applied to kill lice" and when burned, the seeds kill insects and inhibit the reproduction of the *Tribolium castaneum* beetle. It is also used as an anthelmintic [to expel parasitic worms]. Reportedly, the ancient Greeks used the powdered seeds to get rid

of tapeworms and to treat recurring fevers [possibly malaria]. A red dye, "Turkey red", from the seeds [but usually obtained from madder] is often used in western Asia to dye carpets. It is also used to dye wool. When the seeds are extracted with water, a yellow fluorescent dye is obtained. If they are extracted with alcohol, a red dye is obtained. The stems, roots and seeds can be used to make inks, stains and tattoos[5-8].

In large quantities, it can reduce spermatogenesis and male fertility in rats. Harmine, a compound present in *Peganum harmala*, fluoresces under ultraviolet light .*Peganum harmala* has been shown to have antibacterial and anti-protozoal activity, including antibacterial activity against drug-resistant bacteria [7, 13]. One of the compounds found in *P. harmala*, *vasicine* [peganine], has been found to kill *Leishmania donovani*, a protozoan parasite that can cause potentially fatal visceral leishmaniasis.

Another alkaloid, harmine, found in *P. harmala*, has appreciable efficacy in destroying intracellular parasites in the vesicular forms[2,3]. A small study in sheep infected with the protozoal Theileriahirci found *Peganum harmala* extract to be an effective treatment. Peganum harmala for sale at a market in Kazakhstan.Seed extracts also show effectiveness against various tumor cell lines, both in vitro and in vivo. "The beta-carboline alkaloids present in medicinal plants, such as *Peganum harmala* and Eurycoma long if olio, have recently drawn attention due to their antitumor activities. Further mechanistic studies indicate that beta-carboline derivatives inhibit DNA topoisomerases and interfere with DNA synthesis." *Peganum harmala* has antioxidant and antimutagenic properties. Both the plant and the extract harmine exhibit cytotoxicity with regards to HL60 and K562 leukemiacelllines [7-9].

Candidiasis

The inhibitory effect of phenolic compounds and alkaloids of *Inonotus hispidus* and *Peganum harmala* on Candida rugosa lipase and their antioxidant activities was investigated. The results have shown that the phenolic and the alkaloid extracts are good inhibitors of C. rugosa lipase. Thus, the inhibitor molecules (harmaline and hispidin) have been isolated from *P. harmala* and *I. hispidus*. These isolated molecules could be used in the treatment of candidiasis [14].

Anti-inflammatory

Potential in vivo acute anti-inflammatory, analgesic activities, and in vitro antioxidative capacity of this plant was evaluated. Findings demonstrate that formulation cream of *P. harmala* seeds oil has an interesting anti-inflammatory activity with a slight peripheral analgesic effect due mainly to its richness on linoleic acid, γ-tocopherol, and polyphenols and to its important antioxidant capacity [15].

Anti- cholinesterase

Its inhibitory activities on acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) was evaluated. Bioassay-guided fractionation has led to the isolation of AChE and BChE inhibitors from the seeds of *P. harmala*. The results are in agreement with the traditional uses of the seeds of *P. harmala* [16].

Anti- tumor angiogenesis

The anti-angiogenic effects of heat and low pH stable hydroalcoholic extract of *P. harmala* seeds on endothelial cells (ECs) proliferation was investigated .result indicated that hydroalcoholic extract of *P. harmala* seeds contains a potent anti-angiogenic component, which exerts its inhibitory effect mainly through down-regulation of essential mediators such as VEGF (17).

Antiparasitic effect

The antiparasitic effect of a methanolic extract of *Peganum harmala* was explored. the results revealed that weight gain, feed intake, and feed conversion ratio (FCR) were depressed significantly in Ph-0 group with significant mortality percentage. Weight gain, total body weight, and FCR increased linearly with increasing dose of *P. harmala* with the exception of feed intake. The growth and feed efficiency of Ph-0/NC was better in Ph-0/NC compared to that in Ph-0/C and comparable to that in *P. harmala*-treated birds. [18].

Peganum harmala total alkaloids extracts and pure β-carboline compounds as an anti-inflammatory treatment by the inhibition of an enzyme key of inflammatory, myeloperoxidase (MPO) and HPLC quantification of the alkaloids from the different parts of plant was evaluated. The inhibition of MPO by *Peganum harmala* β-carboline alkaloids,

herein reported for the first time, may explain the anti-inflammatory effect traditionally attributed to its herbal medicine[19].

Cerebroprotective effect

The harmine alkaloids from the seeds of *Peganum harmala* (TAPH) and its cerebroprotective effect on cognitive deficit mice was isolated. The results showed that it reduces the metabolism of epinephrine, 5-HT and other monoamines and enhances the action of these neurotransmitters indirectly; this adrenergic system plays an important role in learning and memory. harmine alkaloids are potential enough to utilize in the management of Neurodegenerative disorders of the type Alzheimer's diseases[20].

Cytotoxicity

Components in P. harmala seed-extract responsible for the cytotoxic effects was examined. The harmala alkaloids inhibited the growth of four tumor cell lines, and proliferation of Jurkat cells with varying potencies. Harmine was the most potent in inhibiting cell growth, and vasicinone was most active as anti-proliferating substance. The TAF had significant cytotoxic as well as antiproliferating activity (21).

A novel triterpenoid and a phenolic glycoside were isolated and identified, as well as seven known compounds. OA showed the highest cytotoxicity against human lung cancer cells. OA had a potent anti-NSCLC cell activity by interfering with the epidermal growth factor receptor (EGFR) activation and its downstream signaling, and could exert an antiproliferative effect by inactivation of EGFR-driven antiapoptotic pathway followed by the release of mitochondrial cytochrome c, which might prove to be a promising leading compound for the development of an anti-lung cancer drug [22].

Antioxidant

The curative effect of the 132 KD protein isolated from the seeds of *Peganum harmala [P. harmala*] L. against carbon tetrachloride induced oxidative stress in rats was evaluated. The isolated protein possessed strong antioxidant activity comparable to that of BSA [negative control] and vitamin C [positive control] [23].

The effects of ethanol extracts of *P. harmala* seeds on the olive fruit fly, Bactroceraoleae [Rossi] [Diptera: Tephritidae], i.e., adult repellency, reproductive activity, and larval growth, as well as parasitism levels by Psyttaliaconcolor [Szépligeti] was investigated. There was a slightly prolonged developmental time from egg to adult. Parasitism of larval B. oleae by P. concolor was not affected by infested fruit treatment with 2% *P. harmala* extract. *P. harmala* extracts as a potential control for insect pest species are discussed [24].

Hepatomacancer

The effect of *P. harmala* extract on the expression of different cytochrome P450's [CYP] involved in drug metabolism was examined in human HepG2 cells. Results showed that *P. harmala* extract significantly increased the expression of CYP1A2, 2C19, and 3A4 whereas; CYP 2B6, 2D6 and 2E1 was significantly decreased. We concluded that care should be taken when *P. harmala* is co-administered with other drugs [25].

AhR ligands-mediated effects

The ability of the methanolic extract of *Peganum harmala L.* [Zygophyllaceae] fruiting tops to affect TCDD-activated AhR-mediated signal transduction in mouse hepatoma Hepa 1c1c7 cells was examined. Results showed that *Peganum harmala* extract significantly inhibited the TCDD-mediated induction of Cyp1a1 at mRNA, protein, and activity levels. Both of the active alkaloids showed an inhibitory effect on TCDD-induced Cyp1a1 activity level. We concluded that *Peganum harmala L.* can interfere with AhR ligands-mediated effects [26].

Hepatoprotective prevention

The putative protective effects of ethanol and chloroform extracts of *Peganum harmala* on thiourea-induced diseases in adult male rat was characterized. Result show that ethanol and chloroform extracts of *Peganum harmala* protected the animal against the carcinogenic effects induced by thiourea since neuron-specific enolase [NSE] and thyroglobulin [TG] levels were back to the normal range [27].

Hypoglycemic effect

The hypoglycemic activity of the ethanolic extract of this plant at two dose levels of 150 and 250mg/kg bw in sucrose challenged normal as well as in rats with streptozotocin induced diabetes was examined. The results show

that the ethanolic extract of *P. harmala* is as effective as metformin in reducing the blood glucose levels of normoglycemic and streptozotocin-induced diabetic rats [28].

Pesticide effect
The leaf extract and its fractions of *Peganum harmala L*. have shown pronounced mortal effect, decreased percent pupation and adult emergence of the cotton leaf worm, Spodopteralittoralis Boisd. The medicinal plant P. harmala could be carefully applied in integrated pest management due to its strong effect on cotton leaf worm pest [29].

Antibacterial effect
The antimicrobial potential of various extracts from 12 medicinal plants has been investigated in vitro on multiple antibiotic resistant pathogens and some selected protozoa isolated from poultry. It is concluded that *Peganum harmala* or its alkaloids could probably be used for the control of antibiotic resistant isolates of bacteria as well as protozoa[30].

Theileriosis
In an animal study, lambs were treated for internal and external parasite before commencement of the experiment. The lambs were experimentally infected with *T. hirci* by placing ticks Hyalommaanatolicumanatolicum infected with *T. hirci* on them. After treatment, the clinical signs and parasites in the lymph node smears of the animals in Group A disappeared and they all animals recovered. These parameters in the animals of Group B progressed until their death. Pathological studies showed the characteristic lesions of theileriosis in lambs in Group B, but not in Group A. The results indicate a therapeutic effect of the alkaloids of *P. harmala* for treatment of ovine malignant theileriosis [31].

Antimicrobial
Its efficacy on the course of colibacillosis and effects of long-term feeding on selected parameters of general health in chickens was investigated. It showed that the crude extract of *Peganum harmala* possesses limited antimicrobial activity against E. coli in vivo and long-term continuous feeding may induce undesired effects. Furthermore, the study underlines the value of in vivo experiments and the diverse picture that herbal products, in this case *Peganum harmala*, may deliver by testing them against specific pathogens [32].

Analgesic effect
The antinociceptive action was assayed in several experimental models in mice: writhing, formalin, and hot plate tests. These result showed that the alkaloid extract of Pgh contains active analgesic principles acting both centrally and peripherally. Furthermore, this antinociceptive effect has been avoided by naloxone at a dose of 1mg/kg in the first phase of formalin and hot plate tests indicating that this extract act partly through an opioid-mediated mechanism. In conclusion, the alkaloid extract of *Peganum harmala* seems to have both central and peripheral antinociceptive activities which may be mediated by opioid receptors [33].

Histo-functional effects
Effects of *Peganum harmala* on the reproductive system and fertility using adult male albino rats was examined. The aqueous extracts of *Peganum harmala* might have adverse effects on the processes of spermatogenesis due to direct or indirect effects on somniferous tubules and or the pituitary testicular axis[34].

Antinociceptive effects
The protective effect of *Peganum harmala*-extract [P-extract] and the two major alkaloids [harmine and harmaline] from the seeds of *P. harmala* against CuSO4-induced LDL oxidation was investigated. Harmaline had a markedly higher antioxidant capacity than harmine in scavenging or preventive capacity against free radicals as well as inhibiting the aggregation of the LDL protein moiety [apolipoprotein B] induced by oxidation. The results suggested that *P. harmala* compounds could be a major source of compounds that inhibit LDL oxidative modification induced by copper [35].

the effect of *Peganum harmala* [Syrian rue] a wild-growing flowering plant belonging to the family Zygophylaceae and found abundantly in Iran on formalin-induced pain response in mice was evaluated. Harmaline, the last step of extraction is the main effective antinociceptive agent of the *Peganum harmala* alkaloid extract [36].

Antitumor
Some aspects of the antineoplastic properties of the plant Peganum was investigated. Results obtained indicate that alkaloids of Peganum have a high cell toxicity in vitro. The active principle at a dose of 50 mg/kg given orally to mice for 40 days was found to have significant antitumoural activity. *Peganum harmala* alkaloids thus possess significant antitumour potential, which could prove useful as a novel anticancer therapy [12].

Haemosporidian infections in cattle
Cattle experimentally infected with Babesiabigemina or Theileriasergenti or mixed infestations of the two parasites were treated with Total Alkaloid of *Peganum harmala* L. The results showed that treatment was effective against B. bigemina infection, had a marked effect on the course of infection with *T. sergenti* and some effect on the course of the mixed infection [37].

Haemosporidia infections
Eighty two cattle naturally infected with haemosporidians were treated with total alkaloid hydrochloride of *Peganum harmale L.* The results suggested that the curative effect of total alkaloid of *P. harmale* was better than that of diminazeneaceturate and produced minimal side effects. The alkaloid could also be administered to pregnant animals. It was concluded that the total alkaloid of *P. harmale* showed a marked effect as a treatment for haemosporidican infections in cattle [38].

Treatment with *Peganum harmala* extract remarkably increased the mitotic index in Allium cepa root tips with increasing treatment duration at all exposure times used and with almost all concentrations. The extract caused a relatively high increase in the mitotic index after a long period of treatment with some low concentrations [39].

Abortifacient potential
The effect of methanol and acetone extracts of the epigeal parts of *Peganum harmala*, a common medicinal plant among Bedouins in Israel, was studied on several parameters of reproduction in female rats. The methanol extract at a dose of 2.5 g/kg/day, offered in food or in drinking suspension for 30 days, significantly prolonged diestrus by 1.0 day. The methanol extracts at doses of 2.0, 2.5 and 3.5 g/kg/day appeared to produce a dose-dependent significant decrease in litter size. No change in the physical and nutritional status of the animals and no adverse toxicological effects were observed [40].

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