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Peganum harmala is a potential resource for novel treatments - a review

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ABSTRACT: For centuries, the seeds of *Peganum harmala*, a member of the Nitrariaceae family, have been utilized in traditional medicine to manage conditions like diabetes, neurological disorders, including Parkinson's disease, and psychiatric issues such as anxiety. Phytochemical studies reveal that this plant contains a diverse array of compounds, including various alkaloids, carbohydrates, lipids, proteins, and amino acids. Furthermore, its chemical profile comprises glycosides, phenolic compounds, anthocyanins, aglycone anthraquinones, flavonoids, coumarins, and anthracene derivatives. It is also a source of mono, sesqui, and diterpenes, saponins, both condensed and hydrolysable tannins, mucilage, as well as triterpenes and steroids. It possesses many pharmacological effects, including antioxidant, anticancer, antimicrobial, antiparasitic, cardiovascular, reproductive, protective, gastrointestinal, diuretic, anti-inflammatory, analgesic, neuropharmacological, antidiabetic, antitussive, expectorant and bronchodilating effects. As a traditional remedy in numerous cultures, *Peganum harmala* is the subject of this review, which offers a thorough analysis of its phytochemical makeup and pharmacological effects.
Keywords: phytochemical constituents; pharmacology; traditional medicine; toxicology.

Peganum harmala é um recurso potencial para novos tratamentos - Uma revisão

RESUMO: Durante séculos, as sementes de *Peganum harmala*, membro da família Nitrariaceae, têm sido utilizadas na medicina tradicional para o tratamento de doenças como diabetes, distúrbios neurológicos, incluindo a doença de Parkinson, e problemas psiquiátricos como a ansiedade. Estudos fitoquímicos revelam que esta planta contém uma gama diversificada de compostos, incluindo vários alcaloides, carboidratos, lipídios, proteínas e aminoácidos. Além disso, seu perfil químico compreende glicosídeos, compostos fenólicos, antocianinas, antraquinonas agliconas, flavonoides, cumarinas e derivados de antraceno. É também uma fonte de mono-, sesqui- e diterpenos, saponinas, taninos condensados e hidrolisáveis, mucilagem, bem como de triterpenos e esteroides. Possui diversos efeitos farmacológicos, incluindo ações antioxidante, anticancerígena, antimicrobiana, antiparasitária, cardiovascular, reprodutiva, protetora, gastrointestinal, diurética, anti-inflamatória, analgésica, neurofarmacológica, antidiabética, antitussígena, expectorante e broncodilatadora. Como remédio tradicional em diversas culturas, *Peganum harmala* é o tema desta revisão, que apresenta uma análise completa de sua composição fitoquímica e de seus efeitos farmacológicos.
Palavras-chave: constituintes fitoquímicos; farmacologia; medicina tradicional; toxicologia.

1. INTRODUCTION

A vast array of medicinal compounds is derived from the secondary metabolites produced by plants, which are biosynthesized from primary metabolic pathways (SALEHI et al., 2020). The significance of herbal medicine is underscored by World Health Organization data, indicating that roughly 80% of the global population, equating to four billion people, rely on medicinal plants for primary healthcare needs (AL-SNAFI et al., 2023; DAVIDSON-HUNT, 2000; JAFARI-SALES; HOSSEIN-NEZHAD, 2020; JAFARI-SALES et al., 2019; TALAB et al., 2025).

Ethnomedical studies have received significant attention in recent years because they have shed light on many unknown and under-recognized medicinal properties, particularly those of plant origin, which require phytochemical analysis, pharmacological screening, and clinical trials. This paper presents a detailed analysis of the phytochemical composition and pharmacological activities of *Peganum harmala*, a plant with a well-established history in diverse traditional medicine systems worldwide.

2. LITERATURE REVIEW

2.1. *Peganum harmala* Profile

2.1.1. Synonyms

Harmala multifida, Harmala peganum, Harmala syriaca, Peganum harmalum (FAYVUSH et al., 2017).

2.1.2. Taxonomic classification:

Kingdom: Plantae
Subkingdom: Viridiplantae,
Infrakingdom: Streptophyta,
Superdivision: Embryophyta,
Division: Tracheophyta,

Subdivision: Spermatophytina,
Class: Magnoliopsida,
Superorder: Rosanae,
Order: Sapindales,
Family: Nitrariaceae,
Genus: *Peganum*,
Species: *Peganum harmala* (LANSKY et al., 2017).

2.1.3. Common names

Arabic: Harmal;
China: Luo tuo peng,
English: African-rue, Syrian-rue, wild rue;
French: rue sauvage;
German: Harmalkraute, Steppenraute;
India: Harmel; Spanish: alharma, gamarza;
Swedish: harmelbuske (BENLARBI; CHAACHOUAY, 2025).

2.1.4. Distribution

It is distributed in **Africa** (Algeria, Egypt, Libya, Morocco, Tunisia, Mauritania), **Asia** (Kuwait, Saudi Arabia, Afghanistan, Iran, Iraq, Palestine, Jordan, Lebanon, Syri a, Turkey, Armenia, Azerbaijan, Georgia, Russian Federation, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmeni stan, Uzbekistan, Mongolia, China, Pakistan), **Europe** (Moldova, Russian Federation-European part, Ukraine, Bulgaria, Greece, Italy, Serbia, Spain), and naturalized and cultivated in wide areas (BENLARBI; CHAACHOUAY, 2025).

2.1.5. Description

This perennial herb reaches 30-70 cm in height, with an erect to spreading form and extensive branching from its base. Its smooth (glabrous) stems originate from roots up to 2 cm thick. The alternate leaves are ovate and dissected into 3-5 narrow, linear to lanceolate lobes, each measuring 1-3.5 mm long by 1.5-3 mm wide (Figure 1) (LANSKY et al., 2017).

Figure 1. *Peganum harmala* flower.
Figura 1. Flor de *Peganum harmala.*

2.1.6. Traditional uses

The seeds of *Peganum harmala* are used in traditional practices where their smoke, produced by placing them on burning charcoal, is used to fumigate rooms for several days following childbirth and during marriage ceremonies (HASSAN, 1967). Furthermore, a red dye derived from the seeds is commonly utilized in Turkey and Iran for coloring carpets (TURHAN, 1999). In ethnomedicine, the plant has been employed to manage diabetes, neurological disorders like Parkinson's disease, and psychiatric conditions, including anxiety (ASLAM et al., 2014).

2.1.7. Parts used medicinally

The seeds are the most extensively used and pharmacologically investigated part of *Peganum harmala* (DAVIDSON-HUNT, 2000).

2.1.8. Physico-chemical characteristics

The seed analysis yielded the following quantitative results (all % w w^{-1}): total ash 7.51 ± 1.16, acid-insoluble ash 1.56 ± 0.61, water-soluble ash 3.68 ± 0.83, alcohol-soluble extractives 7.94 ± 1.03, hydro-alcoholic soluble extractives 13.73 ± 1.85, water-soluble extractives 18.26 ± 2.17, foreign organic matter 0.62 ± 0.13, loss on drying 6.94 ± 1.05, with pH measurements of 6.52 ± 0.19 for a 1% aqueous solution and 5.67 ± 0.21 for a 10% aqueous solution (KASKOOS, 2014).

2.2. Chemical constituents

Initial phytochemical screening confirmed the presence of numerous bioactive compounds in *Peganum harmala* seeds. These include various alkaloids, carbohydrates, and lipids, alongside protein and amino acids. The analysis also identified glycosides, phenolic compounds, anthocyanins, and aglycone anthraquinones. Furthermore, the seeds were found to contain flavonoids, coumarins, anthracene derivatives, as well as mono-, sesqui-, and diterpenes. Additional constituents comprise saponins, both condensed and hydrolysable tannins, mucilage, triterpenes, and steroids (MOLOUDIZARGARI et al., 2013; KASKOOS, 2014; ARAUJO; AMARIZ et al., 2019).

Both the seeds and roots of *Peganum harmala* are characterized by the presence of a diverse range of β-carboline alkaloids and quinazoline derivatives. The primary β-carboline alkaloids identified include harmine, harmaline, harmol, harmalol, harman, peganine, isopeganine, dipeganine, and l-thioformyl-8-β-D-glucopyranoside-bis-2,3-dihydro-isopyridinopyrrol. The major quinazoline derivatives comprise vasicine, vasicinone, vasicinolone, (S)-vasicinone-1-O-β-d-glucopyranoside, (R)-vasicinone-1-O-β-d-glucopyranoside, (S)-vasicinone, vasicine, and deoxyvasicinone (KARTAL et al., 2003; ZAYED; WINK, 2005; FATHI et al., 2006; AZIZ et al., 2010; WANG et al., 2015) (Figures 2 and 3).

Phytochemical analyses reveal that *Peganum harmala* seeds contain a significant concentration (4% by weight) of beta-carboline alkaloids, primarily composed of harmaline (5.6%), harmine (4.3%), harmalol (0.6%), and tetrahydroharmine (0.1%). The plant's roots also contain substantial amounts of these compounds, specifically harmine (2.0%) and harmol (1.4%). Notably, the distribution of these alkaloids varies considerably across different plant parts; while seeds and roots show the highest concentrations, stems contain only trace levels, and flowers appear to be devoid of these compounds entirely (HERRAIZ et al., 2010). However, the alkaloid contents of *Peganum harmala* seed oil (μg g^{-1}) were: harmol 79-83, harmalol 8- 12, harmine 1714-6353 and harmaline 2314-7151 μg g^{-1} (HASSANI; EL HADEK, 1999).

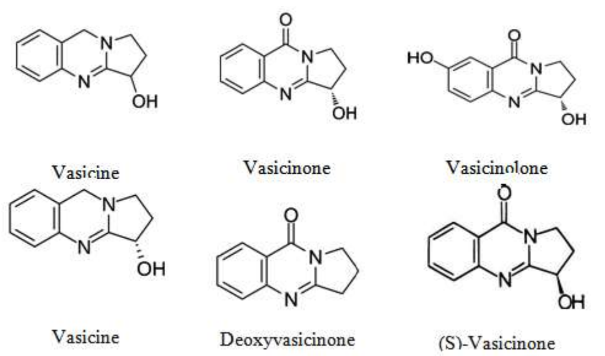

Figure 2. Quinazolin derivatives isolated from *Peganum harmala*.
Figura 2. Derivados de quinazolina isolados de *Peganum harmala*.

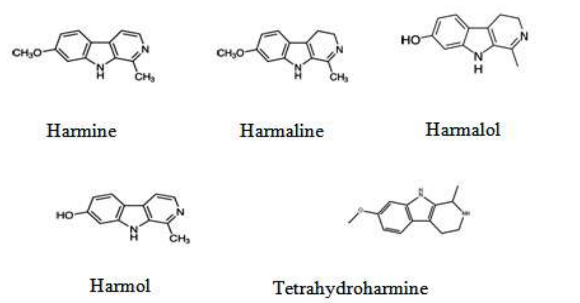

Figure 3. Beta-carboline alkaloids isolated from *Peganum harmala*.
Figura 3. Alcaloides beta-carbolínicos isolados de *Peganum harmala*.

Further phytochemical investigation of *Peganum harmala* has led to the isolation of additional alkaloid compounds beyond the primary β-carbolines and quinazolines. These include complex structures such as 1H-cyclopenta(b)quinoline, 2.3.5.6.7.8-hexahydro-9-amino-; vasicinone (also identified as 1H-Pyrrolo[2.1-b]quinazolin-9-one,3-hydroxy-2.3-dihydro); 2.2.6.6-tetramethyl-4-piperidone; quinoline, 2.3.4-trimethyl-; pyridine, 2-phenoxy-4-amino-; 4-(3-propynyloxy)-quinazoline; and 6.7.8.9-tetrahydro-pyrido[2.1-b]quinozolin-11-one(JAVZAN et al., 2011).

In a separate study, Fang *et al.* successfully isolated 14 distinct compounds from an ethanolic extract of *Peganum harmala* seeds. The identified compounds were: N-[3-(2-amino-4-methoxyphenyl)-3-oxopropyl]acetamide, dehydroharmalacidine, harmalacidine, harmine N-oxide, harmine, tetrahydroharmine, demethylharmalacidine, harmol, tetrahydroharmol, harmindol β-D-glucopyranoside, tryptophyl β-D-glucopyranoside, pegamine β-D-glucopyranoside, vasicol, and vasicinone (FANG et al., 2019).

The seed yield 10% oil, containing linoleic acid 54.6%, oleic acid 22.5%, palmitic acid 7.2%, linolenic acid 3.6%, stearic acid 3.4%, arachidonic acid 3.3%, arachidic acid 0 3.2%, palmitoleic acid 1.2% and myristic acid 0.58% (HASSANI; EL HADEK, 1999). In a distinct analytical investigation, Moussa and Almaghrabi characterized the fatty acid profile of *Peganum harmala* seed oil. Their findings indicated the presence of several saturated fatty acids, primarily hexadecanoic acid (48.13%) and octadecanoic acid (13.80%), alongside others, including tetradecanoic, pentadecanoic, tridecanoic, and heptadecanoic acids. The oil also contained saturated fatty acid derivatives such as 12-methyl tetradecanoic acid. Furthermore, the analysis identified four unsaturated fatty acids, with (Z,Z,Z)-9,12,15-octadecatrienoic acid (14.79%) and (Z,Z)-9,12-octadecadienoic acid (10.61%) being the most prevalent. Additionally, eight non-fatty acid compounds were detected, including 1-octadecene, 6,10,14-trimethyl-2-pentadecanone, and n-heneicosane, among others (MOUSSA; ALMAGHRABI, 2016).

Research on the methanolic extracts of *Peganum harmala* has identified several flavonoids and phenolic compounds in its leaves. The isolated flavonoids include acacetin 7-O-rhamnoside, 7-O-[6''-O-glucosyl-2''-O-(3'''-acetylrhamnosyl) glucoside], 7-O-(2'''-O-rhamnosyl-2''-O-glucosylglucoside), cynaroside (luteolin 7-glucoside), and the glycoflavone 2'''-O-rhamnosyl-2''-O-glucosylcytisoside. The phenolic compounds identified are hydrocaffeic acid, protocatechuic acid, caffeic acid, and rosmarinic acid SHARAF et al., 1997; MOAZENI et al., 2017; ELANSARY et al., 2020). A separate analysis of the seeds revealed the presence of catechin, rutin, p-coumaric acid, chlorogenic acid, and hesperetin (MOAZENI et al., 2017).

An analysis of *Peganum harmala* extracts using solvents of varying polarity revealed significant differences in phenolic compound concentrations. The total phenolic content, measured in gallic acid equivalents (GAE), ranged from 2.48 to 72.52 g kg^{-1} across petroleum ether, chloroform, ethyl acetate, ethanol, and water extracts. Tannin levels, expressed as catechin equivalents (CE), varied from 0 to 25.27 g kg^{-1}. Furthermore, anthocyanin concentrations were quantified between 0 and 20.56 mg cyanidin equivalent kg^{-1}, while flavonoid content ranged from 0 to 3.12 g quercetin equivalent kg^{-1} (CHABIR et al., 2015).

Three lupane-type triterpenoids, three oleanane-type triterpenoids, and ten pentacyclic triterpenoids were isolated from the seeds of *Peganum harmala* (LI et al., 2020).

2.3. Pharmacological effects

The different parts of the plants possessed different pharmacological activities (Figure 4), including:

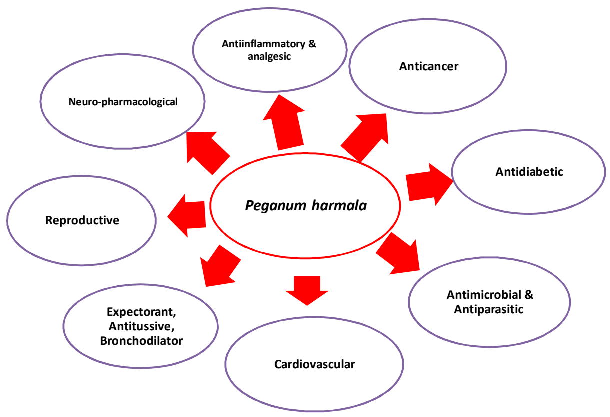

Figure 4. Pharmacological activities of *Peganum harmala*.
Figura 4. Atividades farmacológicas de *Peganum harmala*.

2.3.1. Antioxidant effect

The leaf extract of *Peganum harmala* demonstrates significant antioxidant activity. This property is primarily attributed to the rich polyphenolic profile of the leaves, which effectively reduces the accumulation of reactive oxygen species *(ROS)* (ELANSARY et al., 2020). The seed extract of *Peganum harmala* showed an IC_{50} value of 53.64 mg mL^{-1} in DPPH, 17.34 mg mL^{-1} in total antioxidant capacity and 84.75 mg mL^{-1} in reducing power tests (MAZANDARANI et al., 2012).

The antioxidant capacity of *Peganum harmala* seed extracts was evaluated using three distinct methodological approaches, yielding the following half-maximal inhibitory concentration (IC_{50}) values: 26.8 ± 2.9 μg mL^{-1} in the β-carotene bleaching assay, 1.5 ± 2.3 μg mL^{-1} in the DPPH radical scavenging assay, and 32.4 ± 3.5 μg mL^{-1} in the FRAP assay (ELANSARY et al., 2020). Ethanolic extract of the seeds possessed the highest activities against free radicals (IC_{50}=19.09±3.07 mg L^{-1}) (CHABIR et al., 2015). At a concentration of 1.0 mg mL^{-1}, the seed extracts of *Peganum harmala* demonstrated significant DPPH free radical scavenging activity, with the aqueous extract showing the highest inhibition at 86.37 ± 3.46%, followed by the hydroalcoholic extract at 78.98 ± 5.19%, and the ethanolic extract at 66.55 ± 4.29% (KASKOOS, 2014; DAVOODI et al., 2015). DPPH radical scavenging assay revealed that *Peganum harmala* seeds oil also possessed an important antioxidant activity of (62.50%) with an IC_{50} of 4.8 mg mL^{-1} (KHADHR et al., 2017).

Both the total extract of *Peganum harmala* and its two primary alkaloids, harmine and harmaline, demonstrated a protective effect by inhibiting $CuSO_4$-induced oxidation of low-density lipoprotein (LDL). Harmaline and harmine reduced the rate of vitamin E disappearance and exhibited a significant free radical scavenging capacity (DPPH). In comparative studies, harmaline demonstrated superior antioxidant efficacy to harmine. It exhibited a greater capacity for scavenging free radicals and provided more effective prevention against free radical-mediated damage. Furthermore, harmaline was more potent in inhibiting the oxidation-induced aggregation of the protein component of LDL (BERROUGUI et al., 2006).

The therapeutic potential of a 132 KD protein purified from *Peganum harmala* seeds was evaluated in a rat model of carbon tetrachloride (CCl_4)-induced oxidative stress. The isolated protein first demonstrated in vitro antioxidant capacity in a DPPH assay. In the animal study, CCl_4 administration caused significant hepatic damage, marked by elevated serum levels of aminotransferases, alkaline phosphatase, and lipid profile parameters, alongside increased hepatic malondialdehyde.

Conversely, it decreased serum total protein and reduced hepatic antioxidant enzymes (superoxide dismutase, catalase) and glutathione levels. Critically, treatment with the 132 KD protein following CCl_4 intoxication successfully mitigated these toxic effects, restoring the altered biochemical parameters and demonstrating significant curative action against the induced oxidative damage(SOLIMAN et al., 2013).

2.3.2. Anticancer effect

Research has demonstrated the anti-cancer potential of *Peganum harmala* extract, specifically against the MDA-MB-231 breast cancer cell line, by inhibiting proliferation and inducing programmed cell death (apoptosis). The mechanism involves a significant downregulation of the anti-apoptotic Bcl-2 gene and a marked upregulation of the pro-apoptotic genes Bax and Puma, indicating the activation of the intrinsic mitochondrial apoptosis pathway. Furthermore, the extrinsic pathway is also engaged, as evidenced by the overexpression of TRAIL, Caspase 8, and Bid genes (SHABANI et al., 2015). In a separate study, an ethanolic extract from the seeds showed potent activity against the MCF-7 human breast cancer cell line, exhibiting the highest efficacy among various tested extracts with an IC_{50} value of 32 mg L^{-1} (CHABIR et al., 2015).

Studies have demonstrated the selective cytotoxic effects of *Peganum harmala* seed extracts, which show toxicity to healthy human embryonic kidney (HEK-293) cells at concentrations exceeding 0.5 mg mL^{-1} (GOUDARZI; AZIMI, 2017), while simultaneously exhibiting dose- and time-dependent anti-leukemic activity at concentrations as low as 0.1 mg mL^{-1} after 48 and 72 hours of incubation (REZAEE; HAJIGHASEMI, 2019). The underlying mechanism for this cytotoxicity has been linked to the inhibition of the topoisomerase I enzyme, with the β-carboline alkaloid harmine identified as the most potent compound (IC_{50} = 13.5 ± 1.7 μg mL^{-1}), followed by harmane, harmaline, and the crude extract itself, as confirmed through DNA relaxation assays (SOBHANI et al., 2002).

The alkaloid fraction derived from the methanol extract of *Peganum harmala* seeds demonstrated significant anticancer activity against UCP-Med carcinoma, Med-mek carcinoma, and UCP-Med sarcoma cell lines. A substantial reduction in proliferation was observed across all tested concentrations (20-120 μg mL^{-1}) within the initial 24-hour exposure period. Subsequent to this, cell lysis commenced after 24 hours, progressively increasing and culminating in complete (100%) cell death within 48 to 72 hours (LAMCHOURI et al., 2000).

Since tumor progression is fundamentally reliant on angiogenesis, research has investigated the anti-angiogenic properties of a stable hydroalcoholic extract from *Peganum harmala* seeds. The study found that the extract significantly inhibited both the proliferation of endothelial cells (ECs) and the secretion of Vascular Endothelial Growth Factor (VEGF). Treatment with the extract across a range of concentrations led to a substantial reduction in angiogenesis, demonstrating an inhibitory dose 50 (ID_{50}) of approximately 85 μg/ml. Furthermore, VEGF secretion was notably suppressed at extract concentrations exceeding 10 μg mL^{-1} (YAVARI et al., 2015).

The cytotoxic activity of a total alkaloid extract from *Peganum harmala* seeds was evaluated on the MCF-7 breast cancer cell line. The extract demonstrated a dose-dependent reduction in cell viability, with the most potent effect observed at a concentration of 400 μg mL^{-1}, resulting in a viability reduction of 60.2% ± 2.8% (AL SAILY; OMRAN, 2020).

The antineoplastic potential of total alkaloid extracts from *Peganum harmala* seeds was comprehensively evaluated through both in vitro and in vivo models. In vitro testing against four tumor cell lines (Med-mek carcinoma, UCP-Med carcinoma, UCP-Med sarcoma, and Sp2/O-Ag14) demonstrated that all tested concentrations (10-120 μg mL^{-1}) significantly suppressed cellular proliferation within the first 24 hours, with a subsequent lytic effect leading to complete cell death within 48-72 hours. In a complementary in vivo study using BALB/c mice grafted with Sp2/O cells, oral administration of the active principle at 50 mg kg^{-1} for 40 days resulted in significant antitumor activity (LAMCHOURI et al., 1999).

Investigations into the cytotoxicity of *Peganum harmala* alkaloids against human leukemia cells identified harmalacidine as a particularly potent compound. It exhibited the highest cytotoxic effect against U-937 cells, with an IC_{50} value of 3.1 ± 0.2 μmol L^{-1}. The mechanism of action for this activity was found to involve the targeting of both mitochondrial function and the protein tyrosine kinase signaling pathways (PTKs-Ras/Raf/ERK) (WANG et al., 2015).

Both harmine and harmaline demonstrated dose- and time-dependent antiproliferative effects against HL60 leukemia cells, with higher concentrations exhibiting direct cytotoxic activity (ZAKER et al., 2007).

A comprehensive investigation into the cytotoxic and antiproliferative activities of *Peganum harmala* alkaloids revealed distinct potency profiles among the tested compounds. The cytotoxic screening against four tumor cell lines demonstrated that harmine was the most potent compound (IC_{50} = 2.43-18.39 µg mL^{-1}), followed by the total alkaloidal fraction (IC_{50} = 7.32-13.83 µg mL^{-1}), while peganine showed the weakest activity (IC_{50} = 50->100 µg mL^{-1}).

The Sp2/O-Ag14 cell line emerged as the most sensitive, whereas the UCP-med carcinoma was the least responsive. In parallel antiproliferative assays measuring the inhibition of ^{3}H-thymidine incorporation in Jurkat E6-1 cells, vasicinone (IC_{50} = 8.60 ± 0.023 µg mL^{-1}) and the total alkaloidal fraction (IC_{50} = 8.94 ± 0.017 µg mL^{-1}) exhibited superior potency, demonstrating significantly stronger effects than harmalacidine (IC_{50} = 27.10 ± 0.011 µg mL^{-1}) and harmine (IC_{50} = 46.57 ± 0.011 µg mL^{-1}). Peganine again showed minimal activity (IC_{50} >100 µg mL^{-1}), highlighting the structure-dependent bioactivity of these alkaloids (LAMCHOURI et al., 2013).

Research on the cytotoxic effects of harmaline and harmine against MDA-MB-231 and MCF-7 breast cancer cell lines demonstrated that a *Peganum harmala* extract reduced cell viability in a dose- and time-dependent manner. The extract exhibited an IC_{50} of 30 µg/ml against both cell lines, though their response kinetics differed: MDA-MB-231 cells showed increased motility after 24 hours at higher concentrations, while MCF-7 cells required longer exposure to achieve similar effects. Morphological analysis confirmed that cell death occurred primarily through apoptosis (TEHRANI et al., 2014).

An evaluation of seventeen quinazoline alkaloids and their derivatives isolated from *Peganum harmala* seeds revealed that eleven of these compounds exhibited moderate cytotoxic activity against PC-3 cancer cells, demonstrating a half-maximal inhibitory concentration (IC_{50}) of 15.41 µM (LI et al., 2018).

A screening of five quinazoline alkaloids from *Peganum harmala* seeds for antiproliferative effects on human gastric cancer cells (MCG-803) revealed that two of the compounds demonstrated moderate inhibitory activity (WANG et al., 2015).

An evaluation of triterpenoids isolated from *Peganum harmala* seeds demonstrated significant anti-proliferative effects against HeLa, HepG2, and SGC-7901 cancer cell lines. The majority of the tested triterpenoids exhibited potent cytotoxic activity, with only three compounds showing minimal effect. Furthermore, three specific compounds effectively suppressed HeLa cell proliferation in a dose-dependent manner, as confirmed through colony formation assays (LI et al., 2020).

Peganum harmala leaf extracts demonstrated selective cytotoxicity against various cancer cell lines, exhibiting IC_{50} values of 49.05 ± 3.2 µg mL^{-1} for Jurkat, 43.86 ± 2.7 µg mL^{-1} for MCF-7, 58.64 ± 4.2 µgmL^{-1} for HeLa, and 59.53 ± 4.2 µg mL^{-1} for HT-29 cells. In contrast, the extracts showed significantly lower toxicity toward normal HEK-293 cells, with an IC_{50} value exceeding 400 µg mL^{-1}, indicating a favorable therapeutic window (ELANSARY et al., 2020).

2.3.3. Antimicrobial effects

The essential oils derived from *Peganum harmala* were evaluated for their antimicrobial efficacy against *Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli*, and *Pseudomonas aeruginosa*, revealing varying degrees of growth inhibition across the tested bacterial strains (APOSTOLICO et al., 2016).

Research has consistently demonstrated the potent antimicrobial properties of *Peganum harmala* seed extracts against a broad spectrum of pathogens. Ethanol extracts exhibit significant antibacterial activity, particularly against resistant strains like *Staphylococcus aureus*, with a minimal inhibitory concentration (MIC) as low as 0.62 mg mL^{-1} and a MBC of 10 mg mL^{-1} (JAVADIAN et al., 2014). Effectiveness extends to methicillin-resistant *Staphylococcus aureus* (MRSA), with reported MIC_{50} and MIC_{90} values of 12.5 and 25 mg mL^{-1}, respectively (REZAEE; HAJIGHASEMI, 2019), and to *Streptococcus mutans* (MIC 1.83±0.6 mg mL^{-1}; MBC 4.3 ± 1.0 mg mL^{-1}) (MOTAMEDIFAR et al., 2016). Furthermore, methanol extracts show broad-spectrum inhibition against bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa*, as well as the fungus *Candida albicans* (AIT ABDERRAHIM et al., 2019). Beyond direct microbial killing, the extracts possess strong anti-biofilm capabilities, concentration-dependently inhibiting formation, reducing metabolic activity, and eradicating established biofilms, most notably against *Staphylococcus aureus* (90.28% inhibition) and *Streptococcus pneumoniae* (77.76% inhibition) (MOHSENIPOUR; HASSANSHAHIAN, 2016).

The methanolic extracts from various parts of *Peganum harmala*, including root, stem, leaf, flower, and seed, were evaluated for antimicrobial activity against several human pathogenic bacteria. The root and seed extracts demonstrated particularly strong and equivalent efficacy against MRSA, with both MIC and MBC values of 0.625 mg mL^{-1}. The seed extract showed the same potent level of activity (MIC/MBC = 0.625 mg mL^{-1}) against *Escherichia coli* and *Salmonella typhi* (DARABPOUR et al., 2011). The antimicrobial efficacy of the alkaloids harmine and harmaline, isolated from *Peganum harmala* seeds, was tested against a diverse panel of microorganisms. The results indicated a spectrum of susceptibility, with *Staphylococcus aureus*, *Saccharomyces cerevisiae*, and *Escherichia coli* identified as the most sensitive to the ethanol extract. In contrast, *Pseudomonas aeruginosa* and *Penicillium* sp. demonstrated resistance, while the remaining tested bacteria and fungi exhibited a moderate level of sensitivity (ARSHAD et al., 2008).

The antimicrobial activity of *Peganum harmala* was quantitatively assessed through both its seed alkaloids and smoke, revealing differential efficacy against standard and clinical isolates. The total alkaloid extract demonstrated potent activity against *Micrococcus luteus* (MIC 31.25±1.65 µg mL^{-1}) and *Candida albicans* (62.5±2 µg mL^{-1} for both strains), while showing lower potency against Gram-negative bacteria, particularly *Pseudomonas aeruginosa* (MIC 1500-2000 µg mL^{-1}). Notably, the smoke derivative exhibited significantly stronger antimicrobial effects across all tested organisms, with MIC values expressed in smoke-equivalent grams of seed ranging from 1.0 ± 0.04 to 8 ± 0.408. This enhanced activity was consistently observed against both standard strains and hospital isolates. However, clinical isolates of *Pseudomonas aeruginosa* and *Staphylococcus aureus* generally required higher concentrations for inhibition compared to their standard counterparts (IRANSHAHY et al., 2019).

Peganum harmala extract demonstrated significant antimycobacterial activity against all tested strains of *Mycobacterium tuberculosis*, producing an inhibition zone of 18.7±3.5 mm at a concentration of 200 mg mL^{-1}. Notably, the sensitivity between multidrug-resistant (MDR) and non-MDR strains showed no significant difference. In immunological studies using infected dU937 cells, infection with *Mycobacterium tuberculosis* substantially increased TNF-α production, which was significantly reduced following treatment with the extract. Both IL-6 and IL-10 production decreased to undetectable levels in *Mycobacterium tuberculosis*-infected dU937 cells, with this suppression maintained after extract treatment (DAVOODI et al., 2015).

The alcoholic extract of *Peganum harmala* exhibited potent fungicidal activity against various *Candida* species, with minimum fungicidal concentrations (MFC) ranging from 0.125 to 2.5 mg mL^{-1}. The extract demonstrated particularly strong efficacy against *Candida glabrata* (MFC: 0.62 mg mL^{-1}) and *Candida tropicalis* (MFC: 0.125 mg mL^{-1}), while showing comparatively lower activity against *Candida albicans* (MFC: 2.5 mg mL^{-1}). Additionally, the extract significantly suppressed both growth and sporulation in *Aspergillus* suspensions, although without achieving complete inhibition (DIBA et al., 2011).

Both the crude extract of *Peganum harmala* seeds and its total alkaloid fraction demonstrated inhibitory effects on influenza A virus replication in Madin-Darby canine kidney (MDCK) cells. The antiviral mechanism was found to involve the suppression of viral RNA replication and polymerase activity. However, the extract showed no effect on hemagglutination inhibition or direct virucidal activity (MORADI et al., 2017).

The ethanolic extract of *Peganum harmala* seeds demonstrated potent anti-influenza activity, exhibiting an IC_{50} value of 15.7 μg mL^{-1} in MDCK cells. In vivo studies using infected mouse models showed that oral administration of the extract at 200 mg kg^{-1} day^{-1} significantly improved survival rates, minimized body weight loss, and reduced lung viral titers, demonstrating comparable therapeutic efficacy to oseltamivir administered at 20 mg kg^{-1} day^{-1} (MORADI et al., 2017).

2.3.4. Antiparasitic effect

Research has demonstrated that *Peganum harmala* seed extracts possess notable antiplasmodial properties. Specifically, the ethanolic extract exhibited the most potent activity in vitro against a chloroquine-resistant strain of *Plasmodium falciparum*, with an IC_{50} value of 23 mg L^{-1} (FANG et al., 2019). Furthermore, the individual alkaloids harmine and harmaline also displayed moderate inhibitory effects against the malaria parasite (ASTULLA et al., 2008).

A study investigating the therapeutic efficacy of *Peganum harmala* alkaloids in lambs experimentally infected with *Theileria hirci* (the causative agent of ovine malignant theileriosis) reported a successful outcome. Following treatment, the clinical signs of the disease resolved and the parasites were cleared from the lymph node smears, resulting in the recovery of all infected animals. Pathological examination confirmed the treatment's effectiveness, as the characteristic lesions of theileriosis were observed in the untreated control group but were absent in the group that received the alkaloid extract (DERAKHSHANFAR; MIRZAEI, 2008).

In a field study evaluating the anti-theilerial properties of *Peganum harmala* extract, cattle naturally infected with *Theileria annulata* were treated with the extract at a dosage of 5 mg kg^{-1} per day for five days. The treatment resulted in the recovery of 39 animals, while 11 cattle did not respond to the therapy and died, yielding a recovery rate of 78% (MIRZAEI, 2007).

A clinical trial involving one hundred sheep naturally infected with *Theileria lestoquardi* was conducted using a chloroform extract of *Peganum harmala*. Administration of the extract at 5 mg kg^{-1} daily for five days resulted in the recovery of 65 sheep, while 35 animals did not survive. This outcome corresponds to a cure rate of 65% (MIRZAIEDEHAGHI, 2006).

The total alkaloid hydrochloride derived from *Peganum harmala* demonstrated high therapeutic efficacy in cattle naturally infected with various haemosporidian parasites. When administered at a dose of 0.5 mg kg^{-1} day^{-1}, the treatment achieved cure rates of 86% in 58 cases of *Theileria sergenti*, 85% in 13 cases of *Theileria annulata*, and 88% in 8 cases of *Babesia bigemina*. Additionally, a complete cure was observed in all three cases of *Anaplasma marginale*. The alkaloid preparation demonstrated superior potency to the standard drug diminazene, produced minimal side effects, and was found safe for administration to pregnant animals (HU et al., 1997).

Administration of the total alkaloid from *Peganum harmala* to cattle with experimentally induced parasitic infections yielded positive therapeutic outcomes. The treatment proved effective against *Babesia bigemina* infection, showed a substantial impact on the progression of *Theileria sergenti* infection, and demonstrated a moderate effect on mixed infections involving both parasites (FAN et al., 1997).

Peganine hydrochloride demonstrated significant antileishmanial properties, showing effectiveness against both extracellular promastigotes and intracellular amastigotes of *Leishmania donovani* within murine macrophages in laboratory conditions. Furthermore, in animal studies, the compound achieved 79.6 ± 8.07% efficacy against established visceral leishmaniasis in hamsters when administered at a dosage of 100 mg kg^{-1} (KHALIQ et al., 2009).

The crude alkaloid fraction from *Peganum harmala* seeds demonstrated potent in vitro activity against *Leishmania tropica* promastigotes, exhibiting an IC_{50} value of 50 μg/ml after 96 hours of exposure. The antileishmanial mechanism involved multi-target effects, including significant reduction of parasitic RNA, DNA, and protein content. Additionally, the alkaloids inhibited key metabolic enzymes, dihydrofolate reductase and thymidine phosphorylase and disrupted the parasite's energy metabolism (AL-HAMMOSHI, 2011).

The methanolic extracts of *Peganum harmala* seeds and roots, along with their purified alkaloid fractions, demonstrated significant, concentration-dependent inhibition of *Leishmania tropica* promastigote growth in vitro. The seed extract (IC_{50} = 18.61 ± 0.87 μg mL^{-1}) and root extract (IC_{50} = 16.41 ± 0.71 μg mL^{-1}) showed potent activity. Notably, the purified alkaloid fractions were substantially more effective, with the seed alkaloids (IC_{50} = 4.97 ± 0.43 μg mL^{-1}) exhibiting greater potency than the root alkaloids (IC_{50} = 9.23 ± 0.86 μg mL^{-1}) (MADAH et al., 2020).

In an in vivo study using a murine model, both aqueous and ethanol extracts of *Peganum harmala* were evaluated for anti-leishmanial activity. The ethanol extract demonstrated significant therapeutic efficacy, showing notable improvement in lesion treatment with statistically significant results ($p<0.05$) by the eighth week post-treatment. Furthermore, the ethanol extract produced a significant reduction in parasitic load ($p<0.05$) (KHOSHZABAN et al., 2014).

Peganum harmala seed extract demonstrated substantial antileishmanial efficacy in both laboratory and animal studies. In vitro testing revealed a concentration-dependent reduction in parasite numbers, with a half-maximal inhibitory concentration (IC_{50}) of 59.4 μg mL^{-1}. In vivo experiments confirmed these findings, showing statistically significant reductions in both lesion size and parasite burden in treated animals following administration of the extract (RAHIMI-MOGHADDAM et al., 2011).

The antileishmanial efficacy of harmine was significantly enhanced through nano-encapsulation technologies. When administered subcutaneously at 1.5 mg kg^{-1} over 15 days, the compound reduced spleen parasite burden by 40% in its free form, with substantial improvements observed in liposomal (60%), niosomal (70%), and nanoparticulate (80%) formulations. This demonstrated an inverse correlation between vesicle size and therapeutic effectiveness. The encapsulated forms also showed reduced hepatorenal toxicity, with toxicity profiles improving correspondingly with increased efficacy. Mechanistic studies indicated that harmine disrupts the cell division cycle in *Leishmania donovani* promastigotes without triggering apoptosis, suggesting that parasite death occurs primarily through necrotic processes resulting from non-specific membrane damage (LALA et al., 2004).

The alkaloid extract of *Peganum harmala* demonstrated potent antitrichomonal activity in both laboratory and animal studies. In vitro testing revealed a 24-hour MIC of 15 μg mL^{-1} for the total alkaloid extract, significantly lower than that of the standard drug metronidazole (50 μg mL^{-1}). Among the individual alkaloids, harmine showed greater potency (MIC 30 μg mL^{-1}) compared to harmaline (MIC 100 μg mL^{-1}). The therapeutic efficacy was confirmed in vivo, where treatment with the alkaloid extract resulted in complete recovery of infected pigeons within three days (TABARI et al., 2017).

The methanolic seed extract of *Peganum harmala* demonstrated potent ovicidal activity against *Fasciola hepatica* eggs in a time- and concentration-dependent manner. After 24 hours of exposure, the extract at concentrations of 1.0 and 3.0 mg mL^{-1} significantly suppressed miracidial formation to 5% and 2.2%, respectively. Following 48 hours of exposure, the inhibitory effect intensified, reducing miracidial formation to 0.5% at 1 mg mL^{-1} and completely preventing miracidial development at the higher concentration of 3 mg mL^{-1} (MOAZENI et al., 2017).

2.3.5. Cardiovascular effects

Peganum harmala extract demonstrated significant hypolipidemic effects in cholesterol-fed rats. Administration of the extract at doses of 100, 200, and 400 mg kg^{-1} resulted in reduced plasma cholesterol levels, while triglyceride reduction was observed at the 200 and 400 mg kg^{-1} doses. The treatment also significantly decreased very low-density lipoprotein (VLDL) and increased high-density lipoprotein (HDL) levels. The mechanism appears to involve regulation of hepatic cholesterol synthesis, as the extract counteracted the dietary cholesterol-induced increase in HMG-CoA reductase activity (KALHOR et al., 2015).

Harmine demonstrates anti-atherogenic properties by mitigating endothelial activation triggered by disturbed blood flow. This protective effect is mediated through the inhibition of protein tyrosine phosphatase PTPN14 and the downstream signaling molecule YAP (YANG et al., 2021).

The antiplatelet properties of six beta-carboline alkaloids were evaluated, revealing a selective inhibitory effect on collagen-mediated platelet activation. At 200 μM concentration, none of the compounds affected platelet aggregation induced by arachidonic acid, thrombin, or U46619. However, collagen-induced aggregation was inhibited with varying potency: harmane and harmine demonstrated the strongest inhibition, harmol showed moderate activity, while harmalol, norharmane, and harmaline exhibited weak, non-significant effects. Mechanistic studies revealed that harmane and harmine completely suppressed key collagen-mediated signaling pathways in a concentration-dependent manner, including phospholipase C gamma 2 activation, protein tyrosine phosphorylation, cytosolic calcium mobilization, and arachidonic acid liberation. The other tested compounds showed only partial or no effectiveness in disrupting these signaling events (IM et al., 2009).

The quinazoline alkaloid vasicinone, isolated from *Peganum harmala*, demonstrated significant vasorelaxant properties by effectively inhibiting phenylephrine-induced contractions in isolated rat aortic tissue (ASTULLA et al., 2008).

The alkaloids harmine and harmaline demonstrated complex vasorelaxant mechanisms in isolated rat aorta studies. Both compounds produced dose-dependent relaxation in aortic rings pre-contracted with noradrenaline or KCl, though through distinct pathways. Harmaline's activity was endothelium-dependent, involving nitric oxide synthase and cyclooxygenase pathways, while harmine's effects were largely endothelium-independent. Both alkaloids exhibited non-competitive antagonism at α1-adrenoreceptors and inhibition of L-type voltage-dependent Ca^{2+} channels. Additionally, they demonstrated phosphodiesterase inhibition and antioxidant properties, suggesting multiple cardiovascular protective mechanisms (BERROUGUI et al., 2002; BERROUGUI; MARTÍN-CORDERO; et al., 2006).

2.3.6. Reproductive effects

Peganum harmala administration demonstrated significant anti-fertility effects in male rats, characterized by substantial reductions in reproductive organ weight and impaired sperm parameters. Treatment resulted in decreased sperm motility and density in both the cauda epididymides and testicular ducts, accompanied by notable alterations in testicular histoarchitecture. The spermatogenic process was disrupted at both primary and secondary spermatocyte stages, while epididymides showed diminished spermatozoa counts, and vas deferentia lumens were largely devoid of sperm. The treatment also suppressed secretory activity in accessory reproductive glands, including the seminal vesicles and ventral prostate. Hormonal analyses revealed decreased testosterone and follicle-stimulating hormone (FSH) levels in treated animals. These physiological changes translated to functional reproductive impairment, evidenced by reduced pregnancy rates in females mated with treated males, along with decreased implantation sites and fewer viable fetuses (EL-DWAIRI; BANIHANI, 2007).

Administration of methanol and acetone extracts from the aerial parts of *Peganum harmala* to female rats at a dosage of 2.5 g kg^{-1} day^{-1} for 30 days resulted in a significant extension of the diestrus phase by one day. Furthermore, treatment with doses of 2.0, 2.5, and 3.5 kg^{-1} day^{-1} caused a significant, dose-dependent reduction in litter size. No alterations in the physical or nutritional status of the animals were observed, and the treatment did not produce any adverse toxicological effects (SHAPIRA et al., 1989).

A study examined the impact of a hydroalcoholic extract derived from *Peganum harmala* seeds on spontaneous rhythmic movements in the isolated uterus of rats. Compared to the solvent control, the extract significantly enhanced the spontaneous contractions of both the intact uterus and the stripped myometrium. The administration of atropine before the extract in both tissue preparations did not alter the response to cumulative doses of the extract. The removal of calcium from the solution resulted in reduced uterine contractions. In a calcium-free environment containing KCl, the extract induced a uterotonic effect at certain concentrations. This suggests that the extract could potentially enhance the influx of calcium via voltage-dependent calcium channels (FATHI et al., 2006).

2.3.7. The protective effects

An investigation was conducted on adult male rats to evaluate the protective potential of *Peganum harmala's* ethanol and chloroform extracts against pathologies induced by thiourea. The findings indicated that these extracts provided a defense against the carcinogenic impact of thiourea, as indicated by the return of neuron-specific enolase and thyroglobulin concentrations to standard levels. Additionally, the hepatocytotoxicity that manifested following thiourea administration was substantially mitigated (HAMDEN et al., 2007).

A study evaluated the hepatoprotective properties of an extract from *Peganum harmala* seeds in rats subjected to chronic ethanol administration. The extract was intraperitoneally co-administered with ethanol at a daily dosage of 10 mg kg^{-1} of body weight. While ethanol treatment induced significant disruptions to the antioxidant defense system, specifically affecting the activities of hepatic superoxide dismutase, catalase, and glutathione peroxidase, the concurrent administration of the extract effectively preserved liver function. This protective effect was demonstrated by the inhibition of lipid peroxidation and the restoration of antioxidant enzyme activities (BOUROGAA et al., 2015).

A study assessed the preventative and therapeutic properties of a 15 KD protein derived from *Peganum harmala* seeds against oxidative stress induced by CCl4 in rats. CCl4 administration resulted in elevated malondialdehyde and a reduction in both glutathione levels and glutathione-S-transferase activity within the brain, testes, and erythrocytes. Furthermore, CCl4 inhibited the activity of acetylcholinesterase (AchE) in the brain. Administration of the isolated 15 KD protein at doses of 4 and 8 mg kg^{-1}, whether given before or after CCl4 exposure, was effective in mitigating the induced oxidative stress in the brain, testes, and erythrocytes of the animals (SOLIMAN; FAHMY, 2011).

2.3.8. Gastrointestinal effects

Peganine demonstrated anti-ulcer efficacy in various induced ulcer models, showing inhibition rates of 50.0% for cold restraint, 58.5% for aspirin, 89.41% for alcohol, and 62.50% for pyloric ligation. The compound also led to a significant decrease in free acidity by 33.38% and total acidity by 38.09%, while boosting mucin secretion by 67.91%. Additionally, in vitro tests revealed that peganine acts as a potent inhibitor of H+ - K+ -ATPase activity, exhibiting an IC_{50} value of 73.47 µg mL^{-1}, which can be compared to the IC_{50} of omeprazole at 30.24 µg mL^{-1} (SINGH et al., 2013).

A study evaluated the impact of three principal alkaloids from *Peganum harmala* on contractions in rat ileum induced by acetylcholine, $BaCl_2$, and KCl. Harmalol and harmaline exhibited a concentration-dependent spasmolytic effect that was reversible upon washing the tissue. These two alkaloids suppressed contractions triggered by both acetylcholine and KCl. However, only harmalol was effective in inhibiting $BaCl_2$-induced contractions. In contrast, harmine demonstrated no significant inhibitory activity (SHATARAT et al., 2020).

2.3.9. Diuretic effect

The diuretic properties of a methanolic extract from *Peganum harmala* were assessed in dehydrated rats using doses of 150, 300, and 450 mg kg^{-1}, with furosemide (10 mg kg^{-1}) as a reference standard. Treatment with the extract resulted in a significant, dose-dependent increase in both urine volume and urinary electrolyte excretion relative to the control group ($p<0.05$). The potency of the extract's diuretic action was found to be similar to that produced by furosemide (AL-SAIKHAN; ANSARI, 2016).

2.3.10. Antiinflammatory and analgesic effects

An evaluation of the anti-inflammatory properties of *Peganum harmala* was conducted by measuring the inhibitory effects of its total alkaloid extracts and pure β-carboline compounds on myeloperoxidase (MPO). At a concentration of 20 µg mL^{-1}, the total alkaloids from the seeds and aerial parts potently suppressed MPO activity, with inhibition rates of 97 ± 5 % and 43 ± 4 %, respectively. In contrast, the root alkaloids at the same concentration exhibited minimal effect, with only 15 ± 6 % inhibition. The pure compounds harmine, harmaline, and harmane demonstrated significant MPO inhibition, with IC_{50} values of 0.26, 0.08, and 0.72 µM, respectively. A comparable inhibitory pattern was observed against MPO-induced LDL oxidation. The anti-inflammatory mechanism of *Peganum harmala* may therefore be attributed to this inhibition of MPO (BENSALEM et al., 2014).

A cream formulation incorporating 20% *Peganum harmala* seed oil demonstrated a significant anti-inflammatory effect. Five hours after the application of carrageenan, this formulation reduced inflammation by 60.4%, surpassing the 45.65% reduction achieved by a 1% diclofenac standard. Furthermore, in the plantar test, rats treated with the 20% cream exhibited a mild peripheral analgesic response (KHADHR et al., 2017).

The anti-arthritic and anti-inflammatory properties of a methanolic extract from *Peganum harmala* leaves were evaluated through both in vitro and in vivo models. In vitro assessments, which included the inhibition of egg albumin denaturation and the stabilization of human red blood cell membranes, yielded IC_{50} values of 77.54 and 23.90 mg mL^{-1}, respectively. An additional DPPH assay showed an IC_{50} of 58.09 μg/ml. In an in vivo model of Complete Freund's Adjuvant-induced polyarthritis, the extract produced a significant curative effect. It markedly reduced the severity of polyarthritis, paw edema, weight loss, and anemia. The treatment also normalized serum levels of C-reactive protein, rheumatoid factor, alanine transaminase, aspartate transaminase, and alkaline phosphatase. Furthermore, the extract reestablished the weight of immune organs and mitigated oxidative stress by restoring the levels of superoxide dismutase, reduced glutathione, catalase, and malondialdehyde. Serum concentrations of PG-E2 and TNF-α were also returned to normal in the treated polyarthritic rats (AKHTAR et al., 2022).

A double-blind, randomized, controlled clinical trial was conducted to assess the efficacy of a traditionally prepared *Peganum harmala* oil in treating knee osteoarthritis. Participants applied either the *P. harmala* oil or a control (olive oil) to the affected knee, using four drops three times daily over a four-week period. The Western Ontario and McMaster Universities Arthritis Index (WOMAC) and a Visual Analogue Scale (VAS) were administered at the study's outset and after four weeks. The findings indicated that the group receiving *P. harmala* oil experienced a significant reduction in pain and functional difficulty after four weeks. However, no statistically significant difference in stiffness was observed between the two groups (ABOLHASSANZADEH et al., 2015).

The analgesic and anti-inflammatory properties of various *Peganum harmala* seed extracts were assessed in experimental models. Administered orally at a dose of 200 mg kg^{-1}, the aqueous, alcoholic, chloroform, petroleum ether, and ethyl acetate extracts were tested against glacial acetic acid-induced writhing in mice and carrageenan-induced paw edema in rats. The results demonstrated that the ethyl acetate extract exhibited the most potent effects, followed by the alcoholic and chloroform extracts, in significantly reducing both pain response and inflammation (KUMAR et al., 2015).

The antinociceptive properties of an alkaloid extract from *Peganum harmala* were evaluated in mice using writhing, formalin, and hot plate tests. Administered at doses of 12.5 and 25 mg kg^{-1}, the extract produced a dose-dependent significant reduction in nociception induced by acetic acid. It also markedly suppressed the painful stimulus in both the early and late phases of the formalin test ($p<0.001$). Furthermore, a significant increase in reaction latency was observed in the hot plate test. Investigation into the mechanism of action suggested that the alkaloid extract exhibits both central and peripheral antinociceptive activities, potentially mediated through opioid receptors (FAROUK et al., 2008).

A study investigated the analgesic properties of a total alkaloid extract using the formalin-induced pain model in mice. The extract produced a significant, dose-dependent reduction in the pain response, with efficacy ranging from 28.63% to 100% compared to the control group. This inhibitory effect was observed in both the early and late phases of the test, with calculated ED_{50} values of 27.87 and 24.63 mg kg^{-1}, respectively (MONSEF et al., 2004).

The intraperitoneal injection of a *Peganum harmala* extract induced a significant and dose-dependent decrease in body temperature. This hypothermic effect was also replicated by its primary alkaloidal constituents, harmine and harmaline. An investigation into the mechanism, involving pretreatment with various receptor blockers, suggested that the alkaloids primarily achieve this hypothermia by stimulating endogenous 5-HT to act on the 5-HT1A receptor (ABDEL-FATTAH et al., 1995).

2.3.11. Neural effects

Research has indicated that β-carboline alkaloids derived from *Peganum harmala* exhibit antidepressant properties (BABAR; QURESHI, 1995; FARZIN; MANSOURI, 2006). An investigation into a series of these compounds assessed their capacity to inhibit monoamine oxidase (MAO) in homogenates from mouse brain and liver. The results demonstrated a more potent inhibition of MAO in the brain compared to the liver in vitro. Specifically, 6-Methoxy-1,2,3,4-tetrahydro-β-carboline showed stronger MAO inhibition when serotonin was used as the substrate versus β-phenylethylamine, both in laboratory and live animal studies. This suggests a relative selectivity of the compound for MAO type A inhibition (BUCKHOLTZ et al., 1997).

Research on *Peganum harmala* has demonstrated significant neuroactive properties. In a rat model of Parkinson's disease induced by 6-hydroxydopamine, an aqueous extract alleviated symptoms by markedly reducing muscle rigidity and unidirectional rotational behavior. The extract also conferred neuroprotection by significantly lowering levels of lipid and protein oxidation in the brain, inhibiting angiotensin-converting enzyme (ACE) activity, and preventing the degeneration of dopaminergic neurons (REZAEI et al., 2016).

Separately, a methanol extract exhibited a potent, irreversible inhibitory effect on acetylcholinesterase (AChE), with an IC_{50} value of 68 μg mL^{-1} (ALI et al., 2013).

An investigation was conducted into the mechanisms underlying tremors and the development of tremor tolerance in rats following repeated administration of total alkaloid extracts from *Peganum harmala* seeds. The tremor response elicited by high doses of the extract was found to be closely associated with the concentrations of serotonin (5-HT) and glycine (Gly) in cortical tissues. Furthermore, the observed tremor tolerance may be a consequence of degeneration in cerebellar Purkinje cells induced by the repeated alkaloid dosing (WANG et al., 2020).

An ethanolic extract derived from *Peganum harmala* seeds, administered orally at doses of 5, 2.5, and 1.25 mg kg^{-1}, demonstrated significant protection against sodium nitrite-induced memory deficits. This was evidenced by a reduced time to locate a water bottle in a spatial memory test. The extract dose-dependently improved both acquisition and retention of memory, reflected by a decrease in transverse latency and an increase in step-down latency. Biochemically, the treatment significantly inhibited acetylcholinesterase activity, elevated whole-brain glutathione (GSH) levels, and reduced thiobarbituric acid reactive substances (TBARS). Furthermore, it suppressed monoamine oxidase-A (MAO-A) activity, thereby delaying the metabolism of epinephrine, serotonin (5-HT), and other monoamines and indirectly enhancing their neurotransmitter action. At the 5.0 mg mL^{-1} dose, the extract also prevented DNA fragmentation in the frontotemporal cortex caused by sodium nitrite-induced hypoxia (BIRADAR et al., 2013; BIRADAR; JOSHI, 2014).

Research has demonstrated the neuroactive properties of *Peganum harmala* seed extracts. An ethanolic extract exhibited psychoactive effects by preventing motor impairment and increasing locomotor activity in mice, as measured by the rota-rod and actophotometer tests (BIRADAR; JOSHI, 2014).

In a separate study, the acetylcholinesterase (AChE) inhibitory potential of the crude extract, alkaloid fraction, and flavonoid fraction was evaluated. In normal mice, the extract (183, 550, 1650 mg kg^{-1}) and the alkaloid fraction (10, 30, 90 mg kg^{-1}) significantly reduced AChE activity and increased acetylcholine (ACh) levels in the cortex and hippocampus. Furthermore, in scopolamine-induced amnesic mice tested with the Morris water maze, the extract (550, 1650 mg kg^{-1}) and alkaloid fraction (30, 90 mg kg^{-1}) significantly reversed memory deficits by increasing swimming time in the target zone and platform crossings. This cognitive improvement was correlated with a significant decrease in AChE activity and protein expression, alongside an increase in ACh content in the cerebral cortex (LIU et al., 2017).

2.3.12. Antidiabetic effect

Multiple studies have confirmed the significant antidiabetic and antihyperlipidemic potential of *Peganum harmala* extracts. In streptozotocin (STZ)-induced diabetic rats, a hydroalcoholic extract administered orally at doses of 30, 60, and 120 mg kg^{-1} for four weeks produced a marked reduction in blood glucose, HbA1c, lipid profiles, malondialdehyde (MDA), and liver enzymes (ALT, AST, GGT), while increasing total antioxidant capacity (TAC) (PORBARKHORDARI et al., 2014; KOMEILI et al., 2016).

An ethanolic extract demonstrated potent efficacy, causing a maximum blood glucose reduction of 22.9% and 29.4% at 150 and 250 mg kg^{-1} in normal rats, and a more pronounced decrease of 30.3% and 48.4% in STZ-diabetic rats, with an effect comparable to metformin (SINGH et al., 2008).

Similarly, a methanolic extract at the same doses (150 and 250 mg kg^{-1}) in obese-diabetic rats significantly normalized blood glucose, cholesterol, triglycerides, LDL, MDA, glutathione, and superoxide dismutase levels, and restored the downregulated expression of PPARgamma (MAGDY et al., 2020).

The mechanism is partly attributed to its alkaloid constituent, harmine, which promotes adipogenesis and enhances insulin sensitivity by uniquely targeting the PPARgamma pathway without acting as a direct receptor ligand (WAKI et al., 2007).

2.3.13. Antitussive, expectorant and bronchodilating effects

A comprehensive investigation into the respiratory effects of a 50% ethanolic extract of *Peganum harmala* and its alkaloid and flavonoid fractions was conducted using various animal models. The study evaluated antitussive properties against coughing induced by ammonia liquor, capsaicin, and citric acid in mice and guinea pigs. Expectorant activity was assessed via the phenol red secretion method in mice, while bronchodilating effects were measured against bronchoconstriction triggered by acetylcholine chloride and histamine in guinea pigs. The results demonstrated that the extract and its fractions exhibited significant bronchodilating activity. In all antitussive tests, they markedly reduced cough frequency and prolonged the cough latent period. At the highest tested doses, 1650 mg kg^{-1} for the extract and 90 mg kg^{-1} for the fractions, the antitussive efficacy was comparable to the standard drug codeine phosphate (30 mg kg^{-1}). Furthermore, the extract and fractions dose-dependently enhanced phenol red secretion, a marker of expectorant action. The extract increased secretion by 0.64, 1.08, and 1.29-fold at doses of 183, 550, and 1650 mg kg^{-1}, respectively, while the fractions increased it by 0.63, 0.96, and 1.06-fold at doses of 10, 30, and 90 mg kg^{-1} (LIU et al., 2015).

2.3.14. Toxicity and side effects

The intramuscular administration of the extract in rats resulted in a median lethal dose (LD_{50}) of 420 mg kg^{-1}. Animals treated with high doses exhibited tremors and convulsions. A severe local inflammatory reaction was observed at the injection site, which was associated with a significant rise in leukocyte and neutrophil counts (MUHI-ELDEEN et al., 2008).

The acute oral toxicity of alkaloids derived from *Peganum harmala* was determined in Balb/c mice, with an LD_{50} value recorded at 1070 mg kg^{-1} (AL-HAMMOSHI, 2011).

In Wistar rats, the oral LD_{50} for harmaline was established at 2.70 $\pm$ 0.05 g kg^{-1}. A chronic toxicity study investigated a daily oral administration of an aqueous *Peganum harmala* extract, given six times per week for three months at doses of 1.0, 1.35, and 2.0 g kg^{-1}. The treatment resulted in elevated transaminase levels, while glucose and creatinine concentrations remained largely unchanged. Post-mortem examination revealed no major macroscopic alterations; however, histological analysis identified liver degeneration and spongiform changes in the central nervous system of rats receiving the 2 g/kg dose, effects not observed at the 1.0 g kg^{-1} therapeutic dose. Harmaline, a primary active alkaloid in the plant's seeds, and its related compounds are known to induce adverse effects, including visual disturbances, ataxia, agitation, delirium, and, at high concentrations, paralysis (LAMCHOURI et al., 2002).

An investigation into the impact of a boiled infusion of harmal seeds on pregnancy outcomes in mice revealed significant adverse effects. The infusion demonstrated both embryotoxic and teratogenic properties in the embryos of mothers administered doses of 1, 2, 4, and 6 g kg^{-1}. These effects were manifested as a reduction in litter size and the induction of teratogenic malformations affecting the head and tail regions (SASI et al., 2017).

An investigation into the acute and subacute toxicity of the total alkaloids from *Peganum harmala* seeds was conducted in female mice. In the acute study, an intraperitoneal dose of 118 mg kg^{-1} did not induce notable changes in general condition or mortality within 24 hours. However, it led to a significant increase in the relative weights of the heart and brain, without altering hematological or biochemical markers. When administered over five days, the same dose caused a significant reduction in kidney weight and an increase in brain weight, accompanied by changes in hematological indices (MCHC, MCV) and biochemical parameters (AST, ALP, Urea). In the subacute study, a dose of 18 mg kg^{-1} administered for 28 days resulted in no observable physical changes or fatalities. A significant increase in brain weight was recorded, along with elevated serum ALT and AST enzyme activities, while hematological parameters remained unchanged. Histopathological analysis revealed a ground-glass appearance in hepatocytes and vascular congestion (GUERGOUR et al., 2017).

A study on the acute toxicity of the total alkaloids from *Peganum harmala* seeds in female rats found that an oral dose of 60 mg kg^{-1} induced alterations in behavioral patterns and body weight, along with the appearance of clinical signs. The treatment also resulted in a significant decrease in relative liver mass and key serum biochemical parameters, including AST, ALT, alkaline phosphatase (ALP), direct bilirubin, and total bilirubin. Increases in red blood cell count, hemoglobin, and hematocrit were also observed. Despite these biochemical and hematological changes, histological examination indicated no remarkable toxic damage to the liver architecture in the treated animals (ALI et al., 2013; MAHDEB et al., 2020).

A clinical case report detailed the intoxication of a 24-year-old woman at 22 weeks of gestation following ingestion of *Peganum harmala* seeds. Upon admission, the patient presented with an altered state of consciousness, uterine contractions, and oliguria. Diagnostic tests identified concurrent renal failure and liver injury, necessitating treatment with hemodialysis. Her clinical course was complicated by a further decline in consciousness, requiring intubation, and was followed by a spontaneous abortion. Following extubation, the patient exhibited persistent neurological sequelae, including cerebellar ataxia and peripheral polyneuropathy (BERDAI et al., 2014).

A 31-year-old woman attempting to terminate an unwanted pregnancy consumed one glass of *Peganum harmala* seeds, resulting in intoxication. Her clinical presentation included severe nausea and vomiting, accompanied by mild abdominal pain, while her vital signs remained stable. Physical examination was otherwise normal, with the exception of leukocytosis. Medical management involved nasogastric tube insertion, gastric lavage, and the administration of activated charcoal. Although the patient discharged herself from the hospital against medical advice, subsequent follow-up confirmed that she had subsequently experienced a spontaneous abortion without further medical complications (VAHABZADEH et al., 2019).

An analysis of documented *Peganum harmala* poisoning cases in Morocco involving individuals over 24 years of age revealed a fatality rate of 6.2%. The clinical manifestations observed in these intoxications were primarily neurological (34.4%), gastrointestinal (31.9%), and cardiovascular (15.8%) (FRISON et al., 2008).

Patients experiencing intoxication from *Peganum harmala* may present with a range of symptoms, including low-grade fever, nausea, dizziness, vomiting, hypotension, bradycardia, headache, agitation, tremors, convulsions, visual hallucinations, euphoria, altered mental status, hypoacusia, paresthesia, and impaired cerebellar function(FRISON et al., 2008; HAMOUDA et al., 2000; YURUKTUMEN et al., 2008; MOSHIRI et al., 2013). In some less common presentations, the monoamine oxidase inhibitory property of harmaline can lead to a hypertensive crisis or tachycardia (YURUKTUMEN et al., 2008; BRENT et al., 2017).

3. CONCLUSIONS

Medicinal plants are the most important source of drug discovery all over the world. As raw materials, they continue to represent an important therapeutic method for alleviating human diseases in wide areas of the world. *Peganum harmala* is an important medicinal plant, with a wide range of pharmaceutical constituents and multiple pharmacological properties. This review describes the phytochemical and pharmacological properties of *Peganum harmala* to encourage further pharmacological studies and clinical trials to be introduced into medical practice as a treatment for several diseases.

4. REFERENCES

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