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Phytochemistry, pharmacology and toxicology of *Peganum harmala*

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Phytochemistry, pharmacology and toxicology of *Peganum harmala*

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Abstract

This systematic review focuses on the phytochemical, pharmacological and toxicological aspects of *P. harmala*, which aims to construct the scientific foundations of *P. harmala*-based drugs. Until now, over 390 secondary metabolites, including alkaloids, flavonoids, triterpenoids, phenolic acids, anthraquinones, fatty acids, and essential oils, had been identified from different parts of *P. harmala*. The plant and its important bioactive compounds demonstrated various pharmacological activities, mainly including anti-microbes, anti-cancer, anti-atherogenesis, anti-diabetes, anti-inflammation, neuropsychological, analgesic, hepatoprotective, bronchodilating, gastroprotective, diuretic, and hypothermic effects. However, excessive use of high doses of *P. harmala* extract could lead to serious hepatic, nephritic, and neuropathic toxicities. Current evidence validates the claimed effectiveness of traditional uses of *P. harmala* for many symptoms.

Introduction

Peganum harmala L., belonging to the family Zygophyllaceae, is a highly branched and perennial herbaceous plant with the special smell. The whole plant is 20 to 70 cm tall with short creeping roots. Its stem is scattered from the base, supine in the lower parts and oblique in the upper parts. The leaves are oval, born singly, and finely divided into long narrow segments 1 to 3.5 cm long and 1.5 to 3 mm width. The flowers, produced during summer, are pale yellow or white. Each bloom has five oblong elliptic petals as well as five narrow sepals of slightly longer length. Developed from the flower, the fruit of *P. harmala* stands erect on the stalk and is three-valve seed capsule with a diameter of 6 to 10 mm. Over 50 small black-brown triangular seeds, about 1.5 to 2 mm long, are implicit in one capsule matured in July or August (Asgarpanah and Ramezanloo, 2012; Niroumand et al., 2015).

P. harmala spontaneously generally grows in arid and semiarid regions, steppe areas, and sandy soils. The plant originated from central Asia but now is widely cultivated and distributed in large numbers of areas, including the Middle East (known as "Espand" or "Wild Syrian rue"), China (known as "Luo Tuo Peng"), north of Africa (known as "Harmel"), Mediterranean, Australia and America (known as "African rue," "Mexican rue" or "Turkish rue") (Asgarpanah and Ramezanloo, 2012). *P. harmala* is claimed as a holy plant in many beliefs. In areas of West Asia and Xinjiang (China), its dry plants are suspended in homes or cars and used as the amulet to prevent jealous forces or exorcise evil spirits. Shaman priests of Pakistan Hunzas believe that they can communicate with God by inhaling the smoke of *P. harmala*. In Iran, Afghanistan, Azerbaijan, and some Middle East countries, people pray for relief from "evil eyes" in the smoke produced by burning the dried *P. harmala* mixed with other ingredients. In addition, burning seeds of *P. harmala* is a common benediction in Persian weddings. In some countries of West Asia, the extracts of its fruits and seeds can be used as red and yellow dyes to stain

carpets and wool as well.

More importantly, various parts of *P. harmala*, including seeds, fruits, roots, and barks, have been used as herbs in many traditional medicine systems around the world for centuries. Accumulated evidence from laboratory research and clinical trials could construct the scientific foundations of its medicinal application stemming from those traditional uses, and even inspire the further development of *P. harmala*-based drugs. Therefore, this study aims to systematically review the traditional medicinal uses, research outcomes of phytochemistry and pharmacological aspects of *P. harmala*. Views regarding the toxicology and safety of this plant are discussed as well.

Materials and Methods

The authors searched several electronic databases, including PubMed, Scopus, Web of Science, Google-Scholar, and Science Direct up to the date on 31 July 2022. The following keywords were used as filters and were searched both alone and as combinations: "*Peganum harmala* L.", "Espand", "Wild rue", "Syrian rue", "Harmel", "African rue", "Mexican rue" and "Turkish rue". Searching was limited to articles in English only. Two reviewers extracted papers independently. The duplication articles were firstly deleted. The papers unrelated to phytochemistry and medicinal properties of *P. harmala* were then excluded. Patents, abstracts, case reports, and abstracts in symposium and congress were excluded as they didn't contain sufficient information for evaluation and comparison with other studies. The review articles were excluded as they did not contain the original data. Based on the criteria above, 187 articles were eligible to be evaluated.

Uses in Traditional Medicines

For centuries, *P. harmala* is used as a traditional herbal medicine to treat various ailments in different regions around the world. In Persian, it is used as an analgesic to relieve heart or colic pain in folk medicine (Abbas et al., 2021; Diba et al., 2011). The smoke from its seeds is traditionally used as a disinfectant agent in Iran (Darabpour et al., 2011) and as an antimicrobial appro-ach in India and North Africa (Iranshahy et al., 2019). Seeds and aerial parts of *P. harmala* are used in Algeria as anti-inflammatory remedies (Bensalem et al., 2014). In traditional Chinese medicine, *P. harmala* seeds are an important constituent of the related herbal formulae used in the treatment of cancer, cough, diabetes, asthma, rheumatism, jaundice, hypertension, colic, and lumbago (Wu et al., 2020). Aerial parts of *P. harmala* is used to treat amnesia in Uighur medicine (Deng et al., 2019). In Iran and Turkey, seeds, fruits, roots, and bark of *P. harmala* were traditionally used to treat coughs, rheumatism, hypertension, diabetes, and asthma as well (Moradi et al., 2017). The *P. harmala* seed was one of the most frequently used natural products in the traditional treatment of hypertension and diabetes in south-eastern Morocco (Tahraoui et al., 2007).

Generally, the seed is the most frequently used part of *P. harmala* for medicinal purpose. However, it should be applied in different forms for different conditions. The decoction is commonly used to control the symptoms involved in psychosis, kidney stones, laryngitis, rheumatism, jaundice, sciatica, and sexual impotency, while the powder and smoke can treat asthma, boils, pimples, and alimentary system issues. In addition, numbness, paralysis, joint pain, back pain, and coxalgia could be relieved using the seed poultice, but toothache and mosquitos bites need to be treated by the incense (Elansary et al., 2020; Sadaf et al., 2021).

Phytochemistry

The bioactive secondary metabolites are the basic functional units of herbal medicines. To date, multiple classes of phytochemicals, mainly including alkaloids, flavonoids, triterpenoids, phenolic acids, anthraquinones, and fatty acids, have been isolated directly from different parts of *P. harmala* (Table SI). Generally, alkaloid compounds are the most abundant constituents identified. In addition, a chemometric analysis indicated the significant differences in the metabolites within different parts of *P. harmala*. Compared to the other parts (stems, roots, flowers, and leaves), the seeds contained relatively higher amounts of bioactive alkaloids, mainly including harmaline, harmine, and vasicine. Moreover, the dominant amino acid proline and lysine, and sucrose contents were specified in the root parts (Li et al., 2018b).

Among the numerous secondary metabolites of *P. harmala*, harmine, harmaline, and vasicine are the representative compounds responsible for its various pharmacological effects. Harmine (7-methoxy-1-methyl-9H-pyrido[3,4-b]indole, $C_{13}H_{12}ON_2$) is a tricyclic β-carboline alkaloid widely spread throughout the animal, marine creature, plant, and insect species. It has fully aromatic α-β-carboline structures and can also be isolated from *Banisteria caapi* (Malpighaceae) (Huang et al., 2022), *Tribulus terrestris* (Zygophyllaceae) (Nikam et al., 2009), *Passiflor*a spp. (Passifloraceae) (Boeira et al., 2002). A wide range of its pharmacological properties have been reported as anti-cancer (Li et al., 2017), antimicrobial (Nenaah, 2010), anti-inflammatory (Niu et al., 2019), anti-oxidant (Ali et al., 2022), neuroprotective (Deng et al., 2019), antidiabetic (Waki et al., 2007), and vasorelaxant (Berrougui et al., 2006b) and central excitation (Herraiz and Guillén., 2018). Harmine can inhibit the growth of various types of cancer cells, such as gastric cancer (Li et al., 2017), lung cancer (Shen et

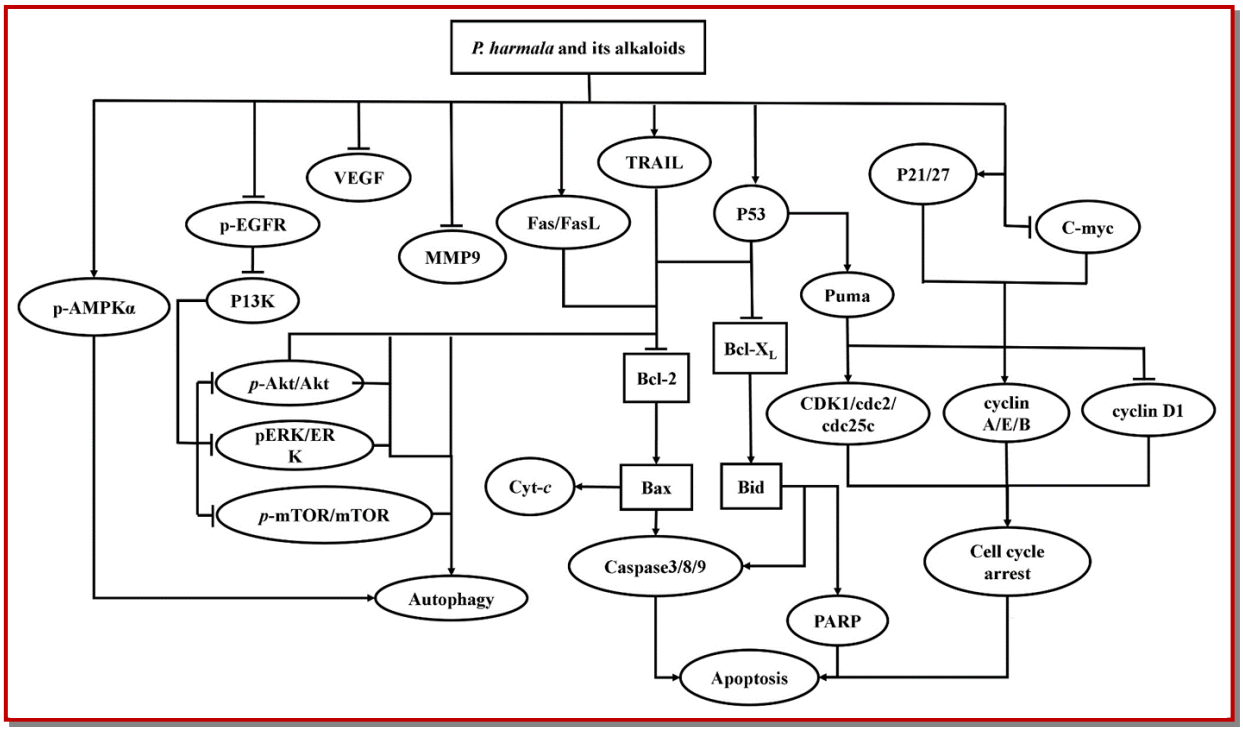

Figure 1: The reported anti-cancer mechanisms of *P. harmala* and its alkaloids

al., 2018), melanoma (Hamsa and Kuttan, 2011a & b), colon cancer (Liu et al., 2016), leukemia (Wang et al., 2015b) and cervical cancer cells (Ayoob et al., 2017). The anti-cancer mechanisms of harmine may contribute to the induced apoptotic and autophagic death of cancer cells through the reduced expression of both p-Akt/Akt and p-mTOR/mTOR and the enhanced phosphorylation of adenosine monophosphate-activated protein kinase (Li et al., 2017; Liu et al., 2016). Harmine exhibited its anti-inflammatory effects via the inhibition of the TLR4-NF-κB and NLRP3 inflammasome pathway (Niu et al., 2019). In addition, some bioactive molecules involved in the inflammatory process, including myeloperoxidase (Bensalem et al., 2014), TNF-α, IL-1β and IL-6 (Liu et al., 2017b), are considered to be targets of harmine. Regarding the neuropsychological mechanism, harmine can stimulate the central nervous system by inhibiting the metabolism of neurotransmitters, such as acetylcholine, 5-hydroxytryptamine, γ-aminobutyric acid, 5-hydroxy-indole-3-acetic acid, glutamic acid and monoamine oxidase (MAO-A), or by direct interaction with acetyl-cholinesterase (AChE) and butyrylcholinesterase (BChE) receptors (Deng et al., 2019; Herraiz and Guillén., 2018). In addition, harmine reduces cardiac hypertrophy and atherosclerosis through the regulation of NF-κB signaling pathway and endothelial activation (Huang et al., 2021; Yang et al., 2021).

Harmaline (7-methoxy-1-methyl-4,9-dihydro-3*H*-pyrido [3,4-b]indole, $C_{13}H_{14}N_2O$) is a β-carboline alkaloid which can also be isolated from *Grewia bicolor* (Malvaceae) (Jaspers et al., 1986), *Tribulus terrestis* (Zygophyllaceae) (Nikam et al., 2009) and *Passiflora incarnata* (Passifloraceae) (Lamounier et al., 2015). It can be transformed into harmine after oral administration through the dehydrogenation and oxidation metabolism by heme peroxidases (Wang et al., 2022), thus exerting multiple pharmacological effects including antimicrobial (Di Giorgio et al., 2004), anti-cancer (Rashidi et al., 2022), antiplatelet (Im et al., 2009), hypothermic (Wu et al., 2009) and vasorelaxant activity (Berrougui et al., 2006b). Due to its low toxicity towards human cells, harmaline is a suitable antileishmanial alkaloid as compared with its analogs harmine (Di Giorgio et al., 2004). It is also reported to exhibit inhibitory effects on breast and gastric cancer cells (Rashidi et al., 2022; Wang et al., 2015c). The underlying mechanisms may include the induced cell cycle arrest and apoptosis through inhibition of mTOR and regulation of p27 and Fas/ FasL (Wang et al., 2015c; Zhang et al., 2021). Moreover, harmaline behaves as tight-binding inhibitor of MAO-A, thus functioning as an antidepressant agent (Herraiz and Guillén., 2018). Vasorelaxant activities of harmaline are attributed to the enhanced NO release and the voltage-dependent Ca^{2+} channel blockage (Berrougui et al., 2006b; Shi et al., 2000). Vasicine ((3*S*)-1,2,3,9-tetra-hydropyrrolo[2,1-b] quinazolin-3-ol, $C_{11}H_{12}N_2O$) is a heterocyclic alkaloid which can also be obtained from *Adhatoda vasica* (Acanthaceae). It has been used to treat respiratory-tract ailments and Alzheimer's disease (Bhambhani et al., 2012; Liu et al., 2019). Vasicine possesses diverse pharmacological actions including antimicrobial, antioxidant, bronchodilator, and anti-allergic activity (Liu

et al., 2019). Vasicine can ameliorate amnesia by inhibiting AChE, activating choline acetyltransferase, regulating neurotransmitters, and reducing oxidative stress (Deng et al., 2019). In addi-tion, it also presents the bronchodilating effects and gastroprotective effects by inhibiting the H^+ K^+- ATPase activity in animal models (Liu et al., 2015a; Singh et al., 2013).

Besides those, as an aromatic plant, *P. harmala* contains large amounts of essential oils reported by several studies in the literature. Generally, the main components in essential oil are alcanfor, capillin, eugenol, α-pinene, monoterpene hydrocarbons, and propylic acid (Afzal et al., 2014; Apostolico et al., 2016; Faridi et al., 2013; Dastagir et al., 2014; Tahrouch et al., 1998). However, as shown in Table SII, the contents of essential oils are quite varied from those reported by different studies. It suggested that different factors, such as geographical features, climatic conditions, cultivation means, and extraction, and detection methods, could affect the oil composition.

Pharmacology

As an ethnomedicinal plant used worldwide in numerous clinical conditions, many relative pharmacological effects of *P. harmala* and its secondary metabolites have been evaluated using models of *in vitro*, *in vivo*, or clinical trials and reported in the literature. Herein, these effects, mainly including antimicrobial, anticancer, antiatherogenic, anti-diabetes, anti-inflammation, and neuropsychological effects, and their underlying mechanisms were comprehensively reviewed and elucidated as follows:

Antimicrobial activities

As shown in Table I, the extracts of *P. harmala* and its constituents have presented the inhibitory activities against various microbes, including bacteria, parasites, fungi, and virus. Generally, the extract from different parts of *P. harmala*, particularly seeds and roots, exhibited the broad-spectrum antibacterial effects. Most importantly, it could effectively control the growth of several drug-resistant strains, such as MRSA, MDR *P. aeruginosa* and ESBL-producing *E. coli* bacteria (Darabpour et al., 2011; Khadraoui et al., 2022; Saeidi et al., 2015). The β-carboline alkaloids harmane, harmine, harmaline and harmalol were found to be the main bioactive constituents contributing to its antibacterial effects (Nenaah, 2010).

The alcoholic extract of *P. harmala* presented the highest fungicidal effect with MFC at 0.625 mg/mL against *Candida glabrata* from clinical isolates of *Candida* species (Diba et al., 2011). In addition, a protein purified from *P. harmala* displayed the major antifungal activity to inhibit the mycelia growth of *Alternaria alternate*, *Penicillium degitatum*, *Rhizopus stuolonifer*, and *Magnaporthe grisea*. It also presented a maximum inhibition of 69.1% against HIV-1 reverse transcriptase (Ma et al., 2013). The methanol extract of *P. harmala* could inhibit the replication of the herpes simplex virus type 2 (HSV-2) over 5 hours after virus penetration. This action was exerted through the block of the specific recognition and binding between the virus envelope and the target cells (Benzekri et al., 2018). Oral administration of the *P. harmala* extract could effectively reduce the lung virus titer and thus increase the survival rate of BALB/c mice infected with mouse-adapted Influenza A virus (Moradi et al., 2017a). This effect was associated with the inhibition of viral RNA transcription (Moradi et al., 2017b). The anti-acanthamoeba activity of *P. harmala* was found to be correlated with the enhanced transcriptional expression of autophagy mRNA and cyst formation under the extract stress (Boonhok *et al.*, 2021). Compared with placebo and control animals, a significant decrease in the lesion size and parasite count was observed in *Leishmania major* infected mice under treatment of the *P. harmala* extract (Khoshzaban et al., 2014; Rahimi-Moghaddam et al., 2011). Besides those, the seed smoke of *P. harmala* could effectively reduce a load of fungi (up to 94.7%) and bacterial (up to 71.4%) bioaerosols in a closed space (60 m^3), which provided the scientific evidence for its traditional uses as a disinfectant in the Middle East (Filban et al., 2022).

Anti-cancer activities

Clinically, *P. harmala* is a critical ingredient of the herbal formula prescribed for the treatment of alimentary tract cancers in northwest China (Wang et al., 2016a). Theoretically, numerous studies have reported in the literature that the extracts of *P. harmala* and its compounds, especially β-carboline alkaloids, demonstrated significant cytotoxic activities against a broad of cancer cell lines *in vitro* (Table SIII).

As shown in Figure 1, the underlying mechanisms of those anti-cancer activities are composed of a complicated network that regulates the signaling associated with the progress of the cell cycle, autophagic and apoptotic death of cancer cells. The β-carboline alkaloids, including harmine, harmaline, harmalacidine and pegaharmine D, are the representative compounds reported to study the pharmacological mechanisms of anti-cancer effects of *P. harmala*. Generally, its total β-carboline alkaloids could reduce the protein and mRNAs expression of FAK, PI3K, AKT, mTOR in either *in vitro* or *in vivo* models of gastric cancer, thus initiating the apoptosis via the phosphatidylinositol 3-kinase/protein kinase B/mammalian target of the rapamycin (PI3K/Akt/mTOR) pathway (Fan et al., 2021). Concretely, harmine enhanced the phosphorylation of adenosine monophosphate-activated protein kinase (AMPK) to stimulate the autophagy through phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin pathway. Moreover, it reduced the expression of

Table I

Antimicrobial activities of *Peganum harmala*

Extracts/constituents	Types	Microbes	Activities (MIC)	References
Methanol extract	Parasite	*Leishmania tropica*	16.4-18.6 µg/mL (IC_{50})	Madah et al., 2020
		Acanthamoeba castellanii	100% trophozoites killed at 2 mg/mL	Shohaib et al., 2016
Ethanol extract		*Acanthamoeba triangularis*	225.1 µg/mL (IC_{50})	Boonhok et al., 2021
Water/ethyl acetate/ ethanol extract		*Leishmania major*	59.4 µg/mL (IC_{50})	Rahimi-Moghaddam et al., 2011
Water extract			40 µg/mL (IC_{50})	Yousefi et al., 2009
Total alkaloid		*Leishmania tropica*	5.0-9.2 µg/mL (IC_{50})	Madah et al., 2020
Harmine		*Plasmodium falciparum*	8.0 µg/mL (IC_{50})	Astulla et al., 2008
Harmaline			25.1 µg/mL (IC_{50})	
Methanol extract	Bacteria	*Bacillus subtilis*	50 µg/mL	Hadadi et al., 2020
		Staphylococcus aureus	1.6 µg/mL	
		Rathayibacter toxicus	12.5 µg/mL	
		Escherichia coli	1.6 µg/mL	
		Pseudomonas aeruginosa	25.0 µg/mL	
		Pseudomonas syringae	100 µg/mL	
		Pseudomonas viridifava	25 µg/mL	
		Xanthomonas campestris	25 µg/mL	
		Methicillin-resistant *Staphylococcus aureus* (MRSA)	0.625 mg/mL	Darabpour et al., 2011
		Bacillus anthracis	1.25-2.5 mg/mL	
		Escherichia coli	0.625 mg/mL	
		Salmonella typhi	0.625 mg/mL	
		Staphylococcus aureus	0.5 mg/mL	Abderrahim et al., 2019
		Escherichia coli	1.0 mg/mL	
		Pseudomonas aeruginosa	6.0 mg/mL	
		Escherichia coli	2.5 mg/mL	Hayet et al., 2010
		Klebsiella pneumoniae	5 mg/mL	
		Enterobacter cloacae	5 mg/mL	
		Serratia marcescens	5 mg/mL	
		Acinetobacter baumannii	5 mg/mL	
		Bacillus subtilus	2.5 mg/mL	
		Staphylococcus aureus	1.25 mg/mL	
		MRSA	0.512 mg/mL	
		Streptococcus pyogenes	0.512 mg/mL	
		Streptococcus agalactiae	0.256 mg/mL	
		Enterococcus faecalis	1.25 mg/mL	
		Enterococcus faecium	2.5 mg/mL	
		Corynebacterium spp	2.5 mg/mL	
Chloroform extract		*Bacillus subtilis*	50 µg/mL	Hadadi et al., 2020
		Staphylococcus aureus	50 µg/mL	
		Rathayibacter toxicus	50 µg/mL	
		Escherichia coli	50 µg/mL	
		Pseudomonas aeruginosa	1.56 µg/mL	
		Pseudomonas viridifava	12.5 µg/mL	
		Xanthomonas campestris	12.5 µg/mL	
n-Butanol extract		Multidrug-resistant (MDR) *Pseudomonas aeruginosa*	250 µg/mL	Khadraoui et al., 2022
		Escherichia coli	5 mg/mL	Hayet et al., 2010

Table I

Antimicrobial activities of *Peganum harmala* (Cont.)

Extracts/ constituents	Types	Microbes	Activities (MIC)	References
n-Butanol extract	Bacteria	*Klebsiella pneumoniae*	5 mg/mL	Hayet et al., 2010
		Enterobacter cloacae	5 mg/mL	
		Serratia marcescens	5 mg/mL	
		Acinetobacter baumannii	5 mg/mL	
		Bacillus subtilus	1.25 mg/mL	
		Staphylococcus aureus	5 mg/mL	
		MRSA	5 mg/mL	
		Streptococcus pyogenes	0.512 mg/mL	
		Streptococcus agalactiae	1.25 mg/mL	
		Enterococcus faecalis	5 mg/mL	
		Enterococcus faecium	5 mg/mL	
		Corynebacterium spp	5 mg/mL	
Ethyl acetate extract		*Escherichia coli*	5 mg/mL	Hayet et al., 2010
		Klebsiella pneumoniae	5 mg/mL	
		Enterobacter cloacae	5 mg/mL	
		Serratia marcescens	5 mg/mL	
		Acinetobacter baumannii	5 mg/mL	
		Bacillus subtilus	1.25 mg/mL	
		Staphylococcus aureus	5 mg/mL	
		MRSA	5 mg/mL	
		Streptococcus pyogenes	5 mg/mL	
		Streptococcus agalactiae	1.25 mg/mL	
		Enterococcus faecalis	5 mg/mL	
		Enterococcus faecium	1.25 mg/mL	
		Corynebacterium spp	5 mg/mL	
Chloroform extract		*Escherichia coli*	5 mg/mL	
		Klebsiella pneumoniae	5 mg/mL	
		Enterobacter cloacae	5 mg/mL	
		Serratia marcescens	5 mg/mL	
		Acinetobacter baumannii	5 mg/mL	
		Bacillus subtilus	0.256 mg/mL	
		Staphylococcus aureus	1.25 mg/mL	
		MRSA	0.512 mg/mL	
		Streptococcus pyogenes	0.512 mg/mL	
		Streptococcus agalactiae	0.256 mg/mL	
		Enterococcus faecalis	2 mg/mL	
		Enterococcus faecium	0.512 mg/mL	
		Corynebacterium spp	0.256 mg/mL	
Alcoholic extract		The extended-spectrum beta-lactamase-producing *Escherichia coli*	2.5 mg/mL	Saeidi et al., 2015
		Staphylococcus aureus	500 µg/mL	Jeppesen et al., 2012
		Bacillus subtilis	500 µg/mL	
		Escherichia coli	500 µg/mL	
		Acinetobacter sp.	0.19 mg/mL	Arshad et al., 2008
		Clostridium sp.	0.75 mg/mL	
		Escherichia coli	0.38-1.55 mg/mL	
		Pasteurella multocida	0.75 mg/mL	
		Staphylococci sp.	0.38 mg/mL	
		Streptococci sp.	0.75 mg/mL	
		Proteus sp.	1.55 mg/mL	
		Salmonella sp.	0.38-0.75 mg/mL	

Table I

Antimicrobial activities of *Peganum harmala* (Cont.)

Extracts/ constituents	Types	Microbes	Activities (MIC)	References
Total alka-loid	Bacteria	*Staphylococcus aureus*	125 µg/mL	Iranshahy et al., 2019
		Escherichia coli	500 µg/mL	
		Pseudomonas aeruginosa	1.5 mg/mL	
		Micrococcus luteus	31.25 µg/mL	
Harmane		*Escherichia coli*	0.5 mg/mL	Nenaah, 2010
		Proteus vulgaris	0.666 mg/mL	
		Staphyllococcus aureus	1.0 mg/mL	
		Bacillus subitilis	0.5 mg/mL	
		Asperagillus niger	0.75 mg/mL	Arshad et al., 2008
		Acinetobacter sp.	9 µg/mL	
		Clostridium sp.	35 µg/mL	
		Escherichia coli	20-155 µg/mL	
		Pasteurella multocida	75 µg/mL	
		Staphylococci sp.	18 µg/mL	
Harmane	Parasite	*Streptococci sp.*	155 µg/mL	
		Proteus sp.	310 µg/mL	
		Salmonella sp.	35-155 µg/mL	
Harmine	Parasite	*Escherichia coli*	0.75 mg/mL	Nenaah, 2010
		Proteus vulgaris	0.833 mg/mL	
		Staphyllococcus aureus	1.0 mg/mL	
		Bacillus subitilis	0.75 mg/mL	
		Asperagillus niger	0.666 mg/mL	
		Acinetobacter sp.	155 µg/mL	Arshad et al., 2008
		Clostridium sp.	625 µg/mL	
		Escherichia coli	310-1250 µg/mL	
		Pasteurella multocida	625 µg/mL	
		Staphylococci sp.	310 µg/mL	
		Streptococci sp.	625 µg/mL	
		Proteus sp.	625 µg/mL	
		Salmonella sp.	155-1250 µg/mL	
Harmaline	Parasite	*Escherichia coli*	1.0 mg/mL	Nenaah, 2010
		Proteus vulgaris	0.75 mg/mL	
		Staphyllococcus aureus	0.75 mg/mL	
		Bacillus subitilis	0.833 mg/mL	
		Asperagillus niger	1.0 mg/mL	
		Acinetobacter sp.	18 µg/mL	Arshad et al., 2008
		Escherichia coli	1.0 mg/mL	Nenaah, 2010
		Proteus vulgaris	0.75 mg/mL	
		Staphyllococcus aureus	0.75 mg/mL	
		Bacillus subitilis	0.833 mg/mL	
		Asperagillus niger	1.0 mg/mL	
		Acinetobacter sp.	18 µg/mL	Arshad et al., 2008
		Clostridium sp.	310 µg/mL	
		Escherichia coli	155-310 µg/mL	
		Pasteurella multocida	310 µg/mL	
		Staphylococci sp.	75 µg/mL	

Table I

Antimicrobial activities of *Peganum harmala* (Cont.)

Extracts/constituents	Types	Microbes	Activities (MIC)	References
Harmaline	Parasite	*Streptococci sp.*	310 µg/mL	Arshad et al., 2008
		Proteus sp.	625 µg/mL	
		Salmonella sp.	155-310 µg/mL	
Harmalol		*Escherichia coli*	0.833 mg/mL	Nenaah, 2010
		Proteus vulgaris	1.0 mg/mL	
		Staphyllococcus aureus	1.5 mg/mL	
		Bacillus subitiis	1.0 mg/mL	
		Asperagillus niger	1.5 mg/mL	
		Acinetobacter sp.	75 µg/mL	Arshad et al., 2008
		Clostridium sp.	625 µg/mL	
		Escherichia coli	310-625 µg/mL	
		Pasteurella multocida	1250 µg/mL	
		Staphylococci sp.	310 µg/mL	
		Streptococci sp.	625 µg/mL	
		Proteus sp.	1250 µg/mL	
		Salmonella sp.	625-1250 µg/mL	
Methanol extract	Fungi	*Candida albicans*	0.6 mg/mL	Abderrahim et al., 2019
		Candida glabrata	2.5 mg/mL	Hayet et al., 2010
		Candida albicans	2.5 mg/mL	
		Candida parapsilosis	2.5 mg/mL	
		Candida kreusei	2.5 mg/mL	
n-Butanol extract		*Candida glabrata*	2.5 mg/mL	
		Candida albicans	2.5 mg/mL	
		Candida parapsilosis	2.5 mg/mL	
		Candida kreusei	2.5 mg/mL	
Ethyl acetate extract		*Candida glabrata*	2.5 mg/mL	
		Candida albicans	2.5 mg/mL	
		Candida parapsilosis	2.5 mg/mL	
		Candida kreusei	2.5 mg/mL	
Chloroform extract		*Candida glabrata*	2.5 mg/mL	
		Candida albicans	2.5 mg/mL	
		Candida parapsilosis	2.5 mg/mL	
		Candida kreusei	2.5 mg/mL	
Alcohol extract		*Candida albicans*	1.25 mg/mL	Dabi et al., 2011
		Candida parapsilosis	0.625 mg/mL	
		Candida keiffir	0.625 mg/mL	
		Candida glabrata	0.312 mg/mL	
		Candida tropicalis	0.312 mg/mL	
		Candida dubliensis	0.625 mg/mL	
Total alkaloid		*Candida albicans*	62.5 µg/mL	Iranshahy et al., 2019
Harmane		*Candida albicans*	0.583 mg/mL	Nenaah, 2010
Harmine		*Candida albicans*	0.5 mg/mL	
Harmaline		*Candida albicans*	0.666 mg/mL	
Harmalol		*Candida albicans*	0.75 mg/mL	
Protein of *P. harmala*		*Alternaria alternate*	1.5 µM (IC_{50})	Ma et al., 2013
		Penicillium degitatum	37.5 µM (IC_{50})	
		Rhizopus stuolonifer	8.44 µM (IC_{50})	
		Magnaporthe grisea	12.19 µM (IC_{50})	

Table I

Antimicrobial activities of *Peganum harmala* (Cont.)

Extracts/constituents	Types	Microbes	Activities (MIC)	References
Methanol extract	Virus	Herpes simplex virus type 2	49 µg/mL ($IC_{50\ Vir}$); 43.36 (SI_{vir})	Benzekri et al., 2018 & 2020.
		Human cytomegalovirus	95% inhibition at 100 µg/mL	Hayet et al., 2010
		Coxsackie B virus type 3	52% inhibition at 100 µg/mL	
n-Butanol extract	Virus	Human cytomegalovirus	75% inhibition at 100 µg/mL	
		Coxsackie B virus type 3	31% inhibition at 100 µg/mL	
Ethyl acetate extract	Virus	Human cytomegalovirus	65% inhibition at 100 µg/mL	
		Coxsackie B virus type 3	24% inhibition at 100 µg/mL	
		Influenza A	15.7 µg/mL (IC_{50}); 8.87 (SI_{vir})	Moradi et al., 2017a
			9.87 µg/mL (IC_{50}); 12.45 (SI_{vir})	Moradi et al., 2017b
Chloroform extract	Virus	Human cytomegalovirus	51% inhibition at 100 µg/mL	Hayet et al., 2010
		coxsackie B virus type 3	16% inhibition at 100 µg/mL	
Total alkaloid	Virus	Influenza A	5.8 µg/mL (IC_{50}); 23.1 (SI_{vir})	Moradi et al., 2017b
Harmine	Virus		4.06 µM ($IC_{50\ Vir}$); 21.5 (SI_{vir})	Wu et al., 2020
Pegaharine B	Virus		25.22 µM ($IC_{50\ Vir}$); 3.0 (SI_{vir})	
Pegaharine C	Virus		31.82 µM ($IC_{50\ Vir}$); 3.1 (SI_{vir})	
Pegaharine D	Virus		2.12 µM ($IC_{50\ Vir}$); 35 (SI_{vir})	
Protein of *P. harmala*	Virus	HIV-1	1.26 µM (IC_{50})	Ma et al., 2013

both p-Akt/Akt and p-mTOR/mTOR to progress the apoptosis and autophagy through PI3K/Akt/ERK/mTOR pathway in cancer cells (Li et al., 2017; Liu et al., 2016). Additionally, a recent study further linked its anti-cancer mechanisms to the recovery of the malignant cell morphology by a series of processes involving the reorganization of the actin cytoskeleton, rescued cell-cell adhesion, inhibition of cell motility, and loss of anchorage-independent growth (Le Moigne et al., 2020). Meanwhile, using *in vitro* and *in vivo* models of B16F-10 melanoma and A549 non-small cell lung cancer (NSCLC), harmine was also found to exhibit anti-metastatic and anti-invasive effects by activating the reversion-inducing cysteine-rich protein with kazal motifs (RECK) signaling and down-regulating the pro-metastatic factors, such as AKT, extracellular regulated protein kinases (ERK), matrix metalloproteinase-9 (MMP-9) and vascular endothelial factors (VEGFs) (Hamsa and Kuttan, 2011b; Shen et al., 2018). Acting as a mTOR inhibitor and a regulator of CDK-Cyclin complex, harmaline could suppress the tumor growth of esophageal squamous cell carcinoma (50% volume reduction at 100 mg/kg p.o) and stomach adenocarcinoma (30% volume reduction at 15 mg/kg p.o) with minimal toxicity in patient-derived xenograft models (Wang et al., 2015c; Zhang et al., 2021).

Harmalacidine targeted and inactivated the mitochondrial and protein tyrosine kinase signaling pathways (PTKs-Ras/Raf/ERK) to inhibit the proliferation and then introduced apoptosis in leukemia cells (Wang et al., 2015b). Pegaharmine D, another β-carboline alkaloid of *P. harmala,* functioned as a G-quadruplex interactive ligand, thus playing an important regulatory role in c-MYC oncogene transcription and genome stability (Wang et al., 2016a).

Besides alkaloids, 3α-acetoxy-27-hydroxyolean-12-en-28-oic acid methyl ester, a triterpenoid isolated from *P. harmala*, especially presented an anti-non-small cell lung cancer (NSCLC) activity through inactivation of the epidermal growth factor receptor (EGFR) and its downstream signals, thus leading to the mitochondrial apoptosis of cancer cells (Wang et al., 2016b). Moreover, the hydroalcoholic extract of *P. harmala* presented an anti-angiogenic effect via down-regulation of vascular endothelial growth factor (VEGF), which could be a potential approach to inhibit tumor growth as well (Yavari et al., 2015).

Neuropsychological effects

The aerial part of *P. harmala* extracts is claimed to use as a traditional medicine to improve memory function and relieve neurodegenerative illnesses. The plant and its alkaloid ingredients have been reported to possess the effective acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibitory activities, which can improve the learning and memory impairment of animal models (Adhami et al., 2015; Ali et al., 2013; Liu et al., 2017a; Yang et al., 2015). In addition, harmine could effectively enhance the spatial cognition of scopolamine-induced mice and repair the impaired memory of transgenic Alzheimer's disease mice. The action was linked to the enhanced cholinergic neurotransmission through the AChE inhibitory activity as well (He et al., 2015). Deoxyvasicine, the main quinazoline alkaloid of *P. harmala*, could ameliorate the amnesia of scopolamine-induced mice via restoration of cholinergic

function (AChE inhibition and choline acetyltransferase activation), regulation of neurotransmitters (acetylcholine, 5-hydroxytryptamine, γ-aminobutyric acid, 5-hydroxyindole-3-acetic acid and glutamic acid), and attenuation of neuroinflammation (necrosis factor-α suppression) and oxidative stress (increased glutathione peroxidase) (Deng et al., 2019). A novel mechanism that *P. harmala* could enhance the hippocampal contents of glucagon-like peptide (GLP-1) and insulin, which could subsequentially promote the glucose transporter type (GLUT4) production to attenuate the insidious progression of Alzheimer's disease in the $AlCl_3$-induced pathology model (Saleh et al., 2021).

Besides Alzheimer's disease, another two neurodegenerative disorders, including Huntington's and Parkinson's diseases, were also reported to be sensitive to the *P. harmala* treatment. Using *Caenorhabditis elegans* as the model, the polysaccharides of *P. harmala* demonstrated an effect to reduce polyglutamine (polyQ) aggregation through the proteasome-mediated protein degradation pathway and then alleviating the associated neurotoxicity, thus providing a promising candidate against Huntington's disease (Guo et al., 2020). Aqueous extract of *P. harmala* could improve the symptoms by inhibiting AChE, and decreasing lipid peroxidation and protein oxidation in the brain of the Parkinson's rat model induced by 6-hydroxydopamine (Rezaei et al., 2016). Moreover, the seed and root extracts of *P. harmala* also showed a potent and selective inhibition of human monoamine oxidase (MAO-A), which could contribute to the antidepressant treatment (Herraiz et al., 2010; Herraiz and Guillén., 2018).

Anti-atherogenesis activities

According to the evidence-based studies reported previously, the extracts and beta-carboline alkaloids of *P. harmala* have been implicated as effective agents for the treatment of atherothrombotic diseases. The seed extracts, harmine, and harmaline all presented protective effects against human low-density lipoprotein oxidation which was the key event in the pathogenesis of atherosclerosis (Berrougui et al., 2006a). Harmane and harmine could prevent collagen-induced platelet aggregation by inhibiting PLCγ2 and protein tyrosine phosphorylation with sequential suppression of cytosolic calcium mobilization and arachidonic acid liberation (Im et al., 2009). Moreover, harmane also functioned as a lipid accumulation inhibitor by decreasing the expression of adipogenic and lipogenic factors, increasing adipocyte browning markers, and activating the liver kinase B1 (LKB1)- AMPK– sirtuin 1 pathway (Li et al., 2020c). Harmine could block the binding between protein tyrosine phosphatase non-receptor type 14 (PTPN14) and yes-associated protein (YAP) to reduce the oscillatory shear stress-induced endothelial activation, thus alleviating the atherosclerosis of mice models (Yang et al., 2021). In both spontaneously hypertensive rats and norepinephrine-induced hypertrophy of human embryonic stem cell-derived cardiomyocytes, harmine could reduce cardiac hypertrophy by modulating the activity of NF-κB signaling pathway (Huang et al., 2021). In addition, harmane, harmine, and harmaline all demonstrated vasorelaxant effects which were related to the enhanced NO release on the endothelial cells and the blockage of the voltage-dependent Ca^{2+} channel on vascular smooth muscle (Berrougui et al., 2006b; Shi et al., 2000).

Anti-diabetes effects

Ethanol extracts of *P. harmala* seeds have been reported to present hypoglycemic and antihyperlipidemic effects on streptozotocin-induced diabetic rats (Komeili et al., 2016; Singh et al., 2008). Moreover, one of its compounds, 4-hydroxypipecolic acid, could control hyperglycemia, hyperlipidemia and oxidative stress-mediated damage, thus relieving the characteristic symptoms of type 2 diabetes in the C57BL/KsJ-*db/db* mice (Singh et al., 2012). The anti-diabetes effects of *P. harmala* and its compound might be partially related to an enhanced glucose uptake caused by translocating insulin-sensitive glucose transporter-4 from the intracellular to the plasma membrane (Naresh et al., 2012).

Anti-inflammation effects

In both *in vitro* (heat-induced hemolysis) and *in vivo* (carrageenan-induced paw edema in rats) models, the *P. harmala* extract exhibited anti-inflammatory activities and inhibitory effects on egg albumin denaturation (Abbas et al., 2021; Edziri et al., 2018). Moreover, it could notably restore the level of C-reactive protein, rheumatoid factor, alkaline phosphatase, alanine transaminase, aspartate transaminase, prostaglandin-E2, and tumor necrosis factor-α in the serum of complete Freund's adjuvant-induced arthritis rat or cecal ligation and perforation-induced septic rat models (Akhtar et al., 2022; Özkanlar et al., 2015). The anti-inflammatory activities might be attributed to alkaloids, flavonoids, phenols, and polyunsaturated fatty acids (Akhtar et al., 2022; Khadhr et al., 2016). Among them, total alkaloids, especially harmine, harmaline, and harmane demonstrated significant inhibition of myeloperoxidase, a key enzyme in the inflammatory process (Bensalem et al., 2014). In acute lung injury mouse models, harmine could prevent the inflammatory damages accompanied by decreased levels of TNF-α, IL-1β and IL-6, which indicated its anti-inflammatory responses were via the inhibition of NF-κB signaling pathway (Liu et al., 2017b). In lipopolysaccharide-induced acute kidney injury mice, harmine reduced oxidative stress and inflammation responses by inhibiting the TLR4-NF-κB and NLRP3 inflammasome pathway (Niu et al., 2019).

Others

Besides the activities described above, *P. harmala* has also been reported many other pharmacological effects

including analgesic, hepatoprotective, bronchodilating, gastroprotective, diuretic, and hypothermic effects.

The total alkaloids of *P. harmala* presented both central and peripheral antinociceptive activities to release the nociception of writhing, formalin, or hot plate-induced pain response in mice models, which was mediated by opioid receptors (Farouk et al., 2008; Shoaib et al., 2016). Meanwhile, the extracts of *P. harmala* possessed a protective role against ethanol hepatoxicity via inhibition of lipid peroxidation by decreasing aminotransferase contents and increasing 17β-estradiol, superoxide dismutase, catalase and glutathione peroxidase activities (Bourogaa et al., 2015; Hamden et al., 2008; Hamden et al., 2009). The *P. harmala* extract, alkaloid fraction, and its quinazoline alkaloids vasicine and deoxyvasicine all presented the antitussive, expectorant, and bronchodilating activities in mice and guinea pig models (Liu et al., 2015a; Liu et al., 2015b). Furthermore, vasicine also could significant-ly reduce free acidity, total acidity and enhance mucin secretion by inhibiting the H^+K^+-ATPase activity, thus providing the gastroprotective effects against cold restraint, aspirin, alcohol, and pyloric ligation-induced gastric ulcer in rat models (Singh et al., 2013). Additionally, *P. harmala* was an effective diuretic that could significantly increase the urine output and urinary electrolyte excretion in experimental animals (Al-Saikhan and Ansari, 2016).

Toxicology

In addition to the therapeutic effects, cases of human intoxication caused by the application of *P. harmala* extracts or its products have been widely reported as well. Generally, intentional ingestion of *P. harmala* seed infusion could lead to toxic symptoms mainly in neurological, gastrointestinal, and cardiovascular systems, such as visual and auditory hallucinations, locomotor ataxia, nausea, tinnitus ringing, vomiting, agitation, disturbances of consciousness, hypertension, tachycardia, tachypnea, uterine contraction, and oliguria (Achour et al., 2012; Berdai et al., 2014; Frison et al., 2008; Sadr Mohammadi et al., 2016). Moreover, these intoxications might further cause anemia, thrombocytopenia, acute kidney disease, multiple areas of cerebral ischemia with subarachnoid hemorrhage, and interior hemorrhage of the uterus (Ghizlane et al., 2021; Yuruktumen et al., 2008). In addition, the aqueous extracts of *P. harmala* have also been found to exert adverse effects on somniferous tubules and the pituitary testicular axis, thus inhibiting the processes of spermatogenesis and fertility in the animal models (El-Dwairi and Banihani, 2007). However, there was no acute and subacute toxicity detected in rats when *P. harmala* extract was given at dose under 3 g/kg and 0.8 g/kg, respectively (Abbas et al., 2021). Subchronic toxicity was also not detected in rats under the treatment of total alkaloid extracts of *P. harmala* at dose as high as 45 mg/kg/day (Wang et al., 2019). Moreover, clinically no toxicity of either chloroform or aqueous extract of *P. harmala* was found in experimental rabbits (Ahmad et al., 2013).

The toxicology of *P. harmala* was mainly attributed to the β-carboline alkaloids through the regulation of amine neurotransmitters, inhibition of human monoamine oxidase, or direct interaction with related receptors for serotonin, dopamine and benzodiazepines in the central nervous system. The main toxicological compounds reported are harmaline, harmane, harmalol, harmol, and tetrahydroharmine (Frison et al., 2008; Herraiz et al., 2010; Nasehi et al., 2010). Moreover, the repeated dosing of the total alkaloids of *P. harmala* at a dose of 150 mg/kg/day could lead to the following tolerance after the initial tremor responses in rats. The tolerance was caused by the degeneration of cerebellar Purkinje cells resulting from the overexpression of c-*fos* and increased oxidative stress via multiple stimulations of *P. harmala* (Wang et al., 2020).

Taken together, the current data indicated that excessive use of high doses of *P. Harmala* could lead to serious damage to alimentary, urinary, neurological, and even reproductive systems, thus requiring great vigilance during their therapeutic uses.

Conclusion and Future Perspectives

Traditional records worldwide claim enormous health benefits and therapeutic effects of *P. Harmala*. In this review, we summarized the scientific research-based evidence of its phytochemical constituents, multiplex pharmacological and toxicological effects and associated mechanisms. Specifically, *P. Harmala* contains over 390 secondary metabolites, mainly including alkaloids, flavonoids, triterpenoids, phenolic acids, anthraquinones, fatty acids, and abundance essential oils. *P. Harmala* and its secondary metabolites, mainly β-carboline alkaloids, present many pharmacological activities, including antimicrobials (bacteria, parasites, fungi and virus), anti-cancer, anti-atherogenesis, anti-diabetes, antiinflammation, antioxidant, neuropsychological, analgesic, hepatoprotective, bronchodilating, gastroprotective, diuretic, and hypothermic effects. Concerning to the mechanistic aspects, *P. Harmala* exerts its antimicrobial effects by interfering the recognition of microorganisms and host cells, and regulating the genetic transcription. The anti-cancer actions of *P. harmala* and its β-carboline alkaloids are attributed to a complicated network which regulates the signals associated with the cell cycle arrest, and the autophagic and apoptotic death. In addition, numbers of molecules related to the neurotransmission, inflammation and oxidative stress, such as MAO-A, (GLUT) 4, PLCγ2, NF-κB, NLRP3, AChE and BChE receptors,

have been identified as targets of *P. harmala* and its alkaloids to exert neuroprotective, antiatherogenic, anti-diabetes, anti-inflammation and antioxidant effects. However, the higher doses and long periods of *P. harmala* exposure can cause serious hepatic, nephritic and neuropathic toxicities, thus need extra attentions.

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Conflict of Interest

Authors declare no conflict of interest

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