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Review Article

Antiviral Properties of Peganum Harmala (Espand) as a Medicinal Plant: A Literature Review

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Abstract

Labeled Objective: Peganum Harmala is a traditional multipurpose medicinal plant in Iran, China and other countries of Asia and Africa. This review study intends to identify and report its antiviral properties. To carry out this review article, the articles published by Scopus, PubMed, EMBASE, ScienceDirect, Google Scholar, SID, and Magiran from 2010 to 2020 were searched. The key words included Peganum harmala, viral, and virus. 32 articles were found eligible after screening titles and abstracts. After excluding the articles that met the exclusion criteria, eight studies remained. In these studies, the effects of Peganum harmala on some viruses such as the human immunodeficiency virus, influenza A virus, herpes simplex virus type 2, enterovirus 71, herpes simplex virus type 1, and coxsackie B virus type 3 has been investigated. In all of the studies under review, P. harmala smoke or extract has been introduced as an effective antiviral even compared to other disinfectants. According to these findings, it is recommended to pay attention to the Peganum Harmala in processes of viral infections treatments and environmental viral disinfection.

Keywords: Peganum harmala, Human immunodeficiency virus, Influenza A virus, Herpes simplex virus, Enterovirus 71, Coxsackie B virus

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Introduction

Peganum harmala (PH), locally called Espand in Iran, belongs to the Zygophyllaceae family. The popular organs of this plant are its seeds (1). Peganum harmala has a long history of use in a Chinese traditional medicine in the treatment of diabetes, hypertension, cough, asthma and many other illnesses. It has become progressively famous in Asia, Iran, Northwest India, and North Africa (2).

Chemical Components of PH

Phytochemical investigations have indicated the existence of a number of active alkaloids in P. harmala, especially beta-carbolines such as harmalol, harmaline, and harmine (3). Methanol extract of P. harmala seed has a high phenolic content and high antioxidant activity (4). Its psychopharmacological and toxicological properties are attributed to quinazoline and β-carboline alkaloids. Quinazoline alkaloids are able to have bronchodilator and abortifacient actions, and could contribute to the impacts reported in P. harmala

(5). The β-Carboline alkaloids have an expansive pharmacological range of antimicrobial (6-9) and antiviral (10) agents. The harmane and flazinamide in βC have anti-HIV activity (11, 12). Moreover, several derivatives of 1,3-disubstituted βC that have a substituted carbohydrazide group at C-3 were active against vaccinal poliovirus and HSV-1 (13). Furthermore, 9-methylharmine inhibited dengue virus 2 in vitro (10). Also, a study conducted on the antiviral activity of harmine, a photoactive β-carboline alkaloid, revealed that harmine + UVA was able to inactivate protein and RNA synthesis and DNA replication in cytomegalovirus (14).

The Antimicrobial Activity of Smoke and Extract of P. Harmala Seeds

It has been indicated that herbal medicinal smokes have remarkable antimicrobial and antioxidant activities (15), including the smoke of P. harmala seeds which is traditionally used in Iran and other countries as a disinfectant agent (16, 17). P. harmala smoke has antibiotic properties and its extract of water, ethanol and smoke affect Candida albicans (18). Moreover, P. harmala smoke could be as an efficient disinfectant as hydrogen peroxide (19). α-Pinene in P. harmala smoke is an anti-inflammatory agent via PGE1, with 60% human pulmonary uptake and with quick metabolism or redistribution (20) and seems to be an antimicrobial agent (21). α-pinene has anti-IBV (Infectious Bronchitis Virus) properties, and so is a potential source of anti-IBV components for medicinal production. Infectious bronchitis virus is classified in the Coronaviridae family (22). P. harmala smoke is effective on the gram-negative bacilli, and it could be as an efficient disinfectant as hydrogen peroxide, so it could be used as an auxiliary disinfectant in therapeutic wards (19). Furthermore, smoking with Espand could remarkably reduce the building's ambient air fungi burden (23). The P. harmala extract with its antibacterial activity can reduce the Enterococcus faecalis biofilm at the root of the teeth like sodium hypochlorite (24). Moreover, P. harmala could be utilized as an air disinfectant, an anti-bacterial and anti-parasite agent and a pain reliever. The Harmin, Harmaline and Vazikinoun content of alkaloid compounds in the seeds of P. harmala showed antifungal anti-parasitic and anti-bacterial properties (25). Anti-bacterial (16, 26-30) and anti-fungi (16, 23, 31) properties of P. harmala have been proven in other studies.

Other Properties of PH

P. harmala is also capable of inhibiting the proliferation of carcinoma (31). Several pharmacological activities have been reported for this plant. These activities include carminative, galactagogue, diuretic, emmenagogue, antithrombotic, analgesic, cholinesterase, monoamine oxidase inhibitory activities, antitumor, insecticidal, antiparasitic, anti-leishmaniasis and antioxidant activities. Also, it has many medicinal impacts such as cardiovascular, neurologic, antineoplastic, and gastrointestinal effects. However its use is contraindicated for pregnant women (2, 32). P. harmala is a multipurpose medicinal plant with anti-inflammatory, anti-cancerous, hypothermic and hallucinogenic activities (3). Its seed smoke is recommended for toothache (33). Hence, the isolation and characterization of the P. harmala active compounds and examination of the fundamental mechanisms of its antiviral action are highly recommended (34).

Viral infections have been quickly spreading in recent years. The use of medications available for the treatment of viral infections has occasionally resulted in failure due to certain reasons including drug resistance, virus mutations and recurrent infections. Therefore, new antiviral mixtures are being increasingly sought out (35). Due to the recent high prevalence of viral diseases worldwide, there is a need for more affordable substances and methods with fewer side effects for treatment and prevention. One of these substances is “Peganum Harmala” (PH), which is a traditional herbal medicine known in Asian and African countries for its antimicrobial and antiviral properties. Hence, based on the above introductory explanations concerning the function of Peganum Harmala, this study was conducted to identify and report its antiviral properties. This information highlights the significance of traditional herbal resources for pharmacological and therapeutic activities and affords baseline evidence for future researches.

Main Body

In this review article, Scopus, PubMed, EMBASE, ScienceDirect, Google Scholar, SID, and Magiran

Table 1: Characteristics of the reviewed studies related to antiviral properties of Peganum Harmala

Ref.	Author(s) (year)	Title	Virus type	Main findings
(31)	Ma X. et.al (2013)	Purification and characterization of a novel antifungal protein with antiproliferation and anti-HIV-1 reverse transcriptase activities from Peganum harmala seeds. (Full text)	Human Immunodeficiency Virus (HIV-1)	PHP inhibited HIV-1 reverse transcriptase (RT) with an IC(50) of 1.26 μM. A novel protein with antiproliferation and anti-HIV-1 RT activities was obtained from P. harmala seeds.
(36)	Moradi MT. et.al (2017)	In vitro antiviral effects of Peganum harmala seed extract and its total alkaloids against Influenza virus. (Full text)	Influenza A/Puerto Rico/8/34 (H1N1; PR8) virus	In vitro antiviral activity of P. harmala seed extract against influenza virus is most probably associated with inhibiting viral RNA transcription. This extract and its total alkaloid should be further characterized to be developed as anti-influenza A virus agent.
(37)	Benzekri R. et.al (2018)	Anti HSV-2 activity of Peganum harmala (L.) and isolation of the active compound. (Abstract)	Herpes Simplex Virus type 2 (HSV-2)	P. harmala extract exerts a virucidal action both during the entry of viruses and the release of the newly formed virions. Harmine could be associated to ACV to improve the treatment of genital herpes essentially for the immunocompromised patients.
(38)	Chen D. et.al (2018)	A small molecule derived from natural sources inhibits enterovirus 71 replication by targeting NF-κB pathway. (Abstract)	Enterovirus 71 (EV71) cause of neurological disease	Harmine inhibited EV71 replication by its ability to diminish plaque formation induced by EV71 and to reduce the level of viral RNA and protein. Harmine may present as a candidate antiviral drug for the treatment of EV71 infection.
(39)	Kiani S. et.al (2007)	Peganum harmala seed extract can prevent HSV-1 replication in vitro. (Full text)	Herpes Simplex Virus type 1 (HSV-1)	The replication of HSV-1 was inhibited, indicating that the P.harmala L. extract contains an anti-HSV-1 substance.
(40)	Faridi P. et.al (2013)	Chemical composition of Peganum harmala smoke and volatile oil. (Full text)	---	The major component of P. harmala smoke was α-pinene (60.4 %). Styrene and some other components with potential antimicrobial and immunomodulatory activities were found in the smoke

(34)	Moradi MT. et.al (2017)	In vitro and in vivo effects of Peganum harmala L. seeds extract against influenza A virus. (Full text)	Influenza A Virus	***P. harmala*** seeds extract can inhibit influenza A virus replication ***in vitro*** and ***in vivo***.
(41)	Edziri H. et.al (2010)	Antibacterial, antiviral and antioxidant activities of aerial part extracts of Peganum harmala L. grown in Tunisia. Toxicological & Environmental Chemistry. (Abstract)	Human Cytomegalovirus (HCMV) strain AD-169 (ATCC Ref. VR 538) and Coxsackie B virus type 3 (CoxB-3)	The methanol extract showed significant antiviral activity against CoxB-3 virus.

were searched with the keywords Peganum harmala, viral, and virus in March and April 2020, and related studies of the past ten years (2010-2020) were found. Duplicate, irrelevant, non-English articles and the articles that did not deal with research on viruses were excluded from analysis. No human or animal sample was used in this study. Ethical standards of publishing and citation have been observed.

The electronic search identified 100 related articles. 32 articles were eligible after screening titles and abstracts. After excluding the articles that met the exclusion criteria, eight studies remained. All of them were carried out in the laboratory fields. In a study by Ma *et al*., a novel protein with anti-proliferation and anti-human immunodeficiency virus-1 RT activities was obtained from P. harmala seeds. They pointed to the P. harmala seed extract properties in the inhibition of HIV-1 reverse transcriptase (31). Due to their findings about the in vitro antiviral activity of P. harmala seed extract against influenza virus, Moradi *et al*. recommended developing further studies on the use of P. harmala extract and its total alkaloid as an anti-influenza A virus agent (36). Benzekri *et al.* recommended the application of Harmin, an effective substance in P. harmala extract, with acyclovir to achieve a synergic effect in order to improve the treatment of genital herpes for immunocompromised patients. With regard to the virucidal action of Harmin, both during the entry of viruses and the release of the newly formed virions, no cell protection effect was detected (37). Chen *et al.* defined a small molecule derived from P. harmala called Harmin that can inhibit Enterovirus 71 replication by targeting NF-κB signaling pathway at their laboratory. Harmin is capable of diminishing plaque formation induced by EV71 and decrease the level of viral RNA and protein. Harmine could be a potential antiviral drug for the treatment of EV71 infection (38). Moreover, Kiani *et al.* investigated and confirmed the inhibitory properties of P. harmala seed extract on the replication of herpes simplex virus Type 1. They indicated that p.H extract contains an anti-HSV-1 substance (39). Faridi *et al*. analyzed the smoke of P. harmala seed and found out that the major component of P. harmala smoke was α-pinene (60.4 %) (40). α-pinene has antiviral properties (22). Edziri *et al*. conducted a study on the use of a cytopathic effect (CPE) reduction assay. They found an antiviral activity of the methanol extract of P. harmala against CoxB-3 virus (41).

Peganum harmala is a famous plant in Iran. Distinct parts of this plant such as seeds, leaf, and root have been utilized as traditional medicine. Recent researches have identified some pharmacological and healing properties of P. harmala and its alkaloids, particularly harmine and harmaline (42). Asgarpanah *et al*. introduced P. harmala pharmacology properties. They noted the inhibition of herpes simplex virus (HSV) yield and indicated that treating the cells with the extract of P.H one hour after infection could remarkably decrease virus titer in the first phase and totally inhibit virus production in the third phase (43). Kiani *et al.* evaluated HSV-1 protein expression in infected cells using immune-fluorescence assay. They showed that the extract of P. harmala was able to prevent viral gene expression in the transcription or translation level (39). Also, Hayet *et al*. examined different extracts of P. harmala leaves and showed that P. harmala had anti-human cytomegalovirus (HCMV) activity in different concentrations. They emphasized that the most active extract was methanol extract which also manifested moderate antiviral activity against HCMV (44). Other studies demonstrated the antiviral activity of methanolic extract (probably due to the high phenolic content) and identified the existence of flavonoids and tannins whose antiviral activity has been acknowledged (45-48). The result of our review study is consistent with the results of these studies.

Conclusion

In the reviewed studies, effects of Peganum Harmala on some viruses such as human immunodeficiency virus (HIV), influenza A (H1N1) virus, herpes simplex virus type 2 (HSV-2), enterovirus 71 (EV71), herpes simplex virus type 1 (HSV-1), and coxsackie B virus type 3 (Coxb-3) were studied. Some studies have investigated the smoke from burning P. harmala, and in others, P. harmala seed extract was used. However, P. harmala with antimicrobial properties has been introduced as an effective antiviral in all of the studies. In some studies, its antiviral properties have been compared with other disinfectants and their results

reported that the efficacy of P. harmala in eliminating viruses seems to be the same as the disinfectants or P. harmala. According to the findings of this review study, P. harmala is one of the medicinal plants, which is effective on viral infections. Thus, plant is able to disinfect the environment from viruses. Hence, the use of Peganum harmala in the treatment of viral infections and environmental viral disinfection is highly recommended.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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