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A review of *Parthenium* management: Transforming a troubling weed into a therapeutic medicinal plant

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Abstract

Parthenium hysterophorus L., an invasive plant species, has proliferated globally beyond its native distribution, exacerbating ecological challenges. Traditionally, plants have been an integral part of medicinal practices, particularly in less industrialized countries, where herbal remedies are cost-effective alternatives to modern pharmaceuticals. The management of invasive weeds like *P. hysterophorus* involves various methods; however, its medicinal potential, particularly for addressing diabetes, could also be explored. Contrary to conventional intervention methods such as physical, chemical, or biological controls, this review advocates exploring *Parthenium*'s medicinal applications. Phytochemical and medicinal assessments reveal the plant's efficacy against a spectrum of health concerns, including antimicrobial, anti-anemic, antipyretic, anticancer, antioxidant, lipoprotective, hypoglycemic and hepatoprotective properties. Diabetes mellitus, impacting approximately 1.5% of the global population, remains a pervasive and enduring metabolic condition, posing a substantial global health challenge. In India, in regions like Maharashtra and Gujarat, *P. hysterophorus* weeds are being used to treat diabetes mellitus. The plant's extensive medicinal uses suggest its potential in preventive measures against various diseases, positioning it as a valuable asset in the development of future medications. This review underscores the importance of shifting from conventional weed management strategies to exploring the untapped medicinal potential of invasive species like *P. hysterophorus*, offering a dual benefit of environmental conservation and medical advancements.

Keywords

active compounds; β-sitosterol; hypoglycemic effect; pharmacological uses

Introduction

The World Health Organization states that herbal remedies are utilized by 80% of people for the treatment of various illnesses caused by diverse factors (1). *Parthenium hysterophorus* L., an invasive plant species of the Asteraceae family is found extensively across the globe, beyond its original distribution in North and South America and the West Indies (2-4). This invasive plant is regarded as one of the most challenging weeds currently recognized in the farming system (5). Its global impact on human and animal health includes causing dermatitis, asthma and bronchitis, while also causing significant agricultural losses and posing a significant threat to biodiversity (6–10).

The prevailing notion suggests that the seeds of this weed found their way into India through grains imported from the USA under the US PL 480 initiative, also known as "Food for Peace" (11). In India, Professor Paranjape first identified this weed in Poona (Maharashtra) in 1951, noting it as stray plants on refuse heaps. Later, it was reported as a new species in India (12). However, the species has a historical presence in India, with its earliest documentation dating back to 1814 by Roxburgh (13). Subsequently, the weed proliferated extensively, spreading like wildfire across nearly all states in India and establishing itself as a naturalized plant.

Numerous studies have indicated that various plant extracts and their secondary metabolites exhibit potential anti-diabetic effects, notably by inhibiting α-amylase or α-glucosidase enzymes (14, 15). Owing to their limited adverse side effects and widespread availability, there is an increasing interest in exploring medicinal plant extracts or their derived secondary metabolites as viable adjunctive natural therapy for managing diabetes (16, 17).

in *P. hysterophorus* is hymenin, which also encompasses hysterin and dihydroisoparthenin. Parthenin, identified as the chief allergen in *P. hysterophorus*, belongs to the pseudoguinolides class of SLs (24). It, along with its derivatives, is virtually insoluble in water but soluble in alcohol, chloroform, ether, acetone and ethyl acetate (25).

The roots, leaves and stems of *P. hysterophorus* boast a wealth of diversified organic acids, comprising anicic acid, fumaric acid, ferulic acid, vanicillic acid and chlorogenic acid. Furthermore, the aerial components of *P. hysterophorus*, notably its leaves and stems, house an assortment of flavonoids. These include apigenin, luteolin, syringaresinol, santin, saponins and aglycone, recognized for their multifaceted biological effects and potential therapeutic properties (26). Additionally, it has been observed that the boiling points of all components present in the *P. hysterophorus* extract fall within the range of 329 °F to 428 °F, whereas the boiling point of methanol is 148.46 °F. Notably, these constituents do not form an azeotropic mixture, allowing for their separation through conventional distillation methods. This extracted material shows the promising effect of pesticides or insecticides (25). The key chemical composition is systematically delineated in Table 1 (27, 28).

Table 1. Different bio compounds in *P. hysterophorus*

Chemical class	Constituents
Amino acids	Abundance of proline and glycine, coupled with moderate quantities of alanine and lysine.
Amino sugars	Acetylglucosamine and N-acetylgalactosamine are both present.
Terpenoids	Sesquiterpene lactones, exemplified by germacranolides (such as parthenolide, artemorin and chrysanthemonin), guaianolides (chrysartemin A, partholide and chrysanthemolide) and eudesmanolides (including santamarin, reynosin and magnolialide), also encompass parthenin, cornopolin, artecanin and balchan.
Volatile oils	Multiple monoterpenes and sesquiterpenes, including camphor (56.9%), camphene (12.7%), ρ--cymene (5.2%), bornyl acetate (4.6%), tricyclene, α--thujene, α--pinene, β-pinene, γ--terpinene and related esters, are part of the composition.
Flavonoids	Compounds including luteolin, apigenin, quercetin, chrysoeriol, santin, jaceidin and centaureidin are identified in luteol. Further compounds found in luteol consist of 6-hydroxy kaempferol 3,6-dimethyl ether, 3,6,4′-trimethyl ether (tanetin), quercetagetin 3,6-dimethyl ether, 3,6,3′-trimethyl ether and centaure.
Others	Charminarone, 8-acetoxyhysterone C, 8-acetoxymethylacrylyloxyambrosin, 8-acetoxymethylacrylyloxy-11, 13-dihydroparthenin, 8-acetoxymethylacrylyloxyparthenin, 2-acetoxycoronopilin, hysterone (A, B, C, D), 1, 2, 4 and 12-olide, pyrethrin, as well as tannins (of an unknown type), melatonin, potassium chloride and protein are present.

Phytochemistry of P. hysterophorus

Phytochemicals, recognized as secondary plant metabolites, exhibit various pharmacological and biochemical impacts on organisms (18). Analysis of *P. hysterophorus* revealed a wide array of compounds, including alkaloids, proteins, saponins, tannins, carbohydrates, glycosides, terpenoids, steroids, volatile oils, amino acids, amino sugars, lignans, phenolic compounds, flavonoids, metallic elements, organic acids and others (19–22). Phytochemical screening of the aerial parts of *P. hysterophorus* revealed the presence of various compounds such as flavonoids like 6-hydroxykaempferol-3,7-dimethyl ether, parthenin and stigmasterol (19). Additionally, the leaves produce essential oils, flavonoids, parthenin, acids, campesterol and stigmasterol. Ambrosanoli is present in the flowers (19, 23).

Most *P. hysterophorus* plants contain primary sesquiterpene lactones (SLs), specifically parthenin or hymenin, alongside lesser amounts of ambrosin, coronopilin, tetraneurin A and hysterophorin. The principal SL present

Distinctive biofunctionalities of active compounds extracted from P. hysterophorus

Historically, *P. hysterophorus* has been utilized to address fevers, migraine headaches, rheumatoid arthritis, stomach aches, toothaches, insect bites, infertility and challenges associated with menstruation and childbirth labor (29, 30). Abounding in essential bioactive compounds, such as sesquiterpene lactones, flavonoid glycosides and pinenes, the plant showcases a diverse array of pharmacologic properties, including anticancer, anti-inflammatory, cardiotonic, antispasmodic, emmenagogue and vermifuge effects (31). Traditionally, the bioactive compounds are being utilized for alleviating itching, skin ailments, rheumatic pain, eczema, heart issues and reproductive difficulties (32). A formulation incorporating ginger has demonstrated effectiveness in the treatment of migraines, particularly during the early stages of pain (33). Furthermore, women's vaginal and urinary issues have occasionally been treated with tea made from *P. hysterophorus* leaves and roots (34).

Parthenin

Parthenin, the primary compound in the invasive tropical weed *P. hysterophorus* , is a pseudoguaianolide sesquiterpene lactone (STL) (35). It is predominantly accumulated in the capitate-sessile trichomes distributed across different regions of *P. hysterophorus*, with the highest concentration in the foliage (36). The production of parthenin experiences a 49% surge under 400 ppm CO_2, surpassing levels observed at 350 ppm, a correlation that has recently been established with increased concentrations of carbon dioxide (37). The ongoing production of parthenin in plants is most pronounced during reproductive stages. This compound is either emitted from decomposed tissues or naturally leached from the plant through trichomes and root exudates (36). Parthenin exhibited significant effectiveness against a drug-resistant strain of *Plasmodium falciparum*, which was resistant to multiple medications and bore no structural resemblance to the newly developed antimalarial drug qinghaosu (36). In the case of artemisinin resistance, parthenin's activity against *P. falciparum* was potent enough to potentially replace artemisinin-based medications (38). A docking study of parthenin analogs against lactate dehydrogenase proteins revealed the identification of ligands with exceptional binding affinities for both *P. vivax* and *P. falciparum*. This discovery suggests the potential use of these compounds as effective medications for malaria (39). Fig. 1a illustrates the structure of parthenin (28).

Parthenolide

Parthenolide, a prominent sesquiterpene lactone (SL) extensively found in medicinal plants, particularly feverfew, is prevalent. Its epoxide group and methylene lactone ring exhibit nucleophilic traits, enabling rapid interactions with biological targets. These interactions have been associated with parthenolide's capability to induce oxidative stress (OS) and its diverse anticancer and pro-apoptotic properties (40). Furthermore, it is predicted that parthenolide provokes a pro-apoptotic response, activating p53 and enhancing the production of reactive oxygen species (ROS). It is noteworthy that non-cancerous cells typically lack pro-apoptotic activity, which is primarily observed in cancer cells with heightened ROS levels. The intracellular redox state plays a pivotal role in influencing both cell survival and programmed cell death. Parthenolide demonstrates two principal effects: inhibiting NF-κB and inducing OS (41). The structure of parthenolide is outlined in Fig. 1b (28).

Ferulic acid

The category of phenolic acids, housing ferulic acid, is abundantly present in *P. hysterophorus* (42). Ferulic acid stands out as the most prevalent cinnamic acid derivative, alongside vanillin, caffeic, p-coumaric, synapse and syryte acids. Foods rich in ferulic acid, such as whole parsley, grapes, grains, spinach, rhubarb and cereal seeds, particularly those derived from wheat, oats, rye and barley, consistently feature these compounds. The noteworthy role of phenolic acids, especially those stemming from cinnamic acid, is their antioxidant activity, making it one of their most crucial function (43). Ferulic acid exhibits enhanced absorption and a prolonged presence in the body compared to other phenolic acids. It is recognized for its potential as a robust antioxidant (44). Fig. 1c displays the structural framework of ferulic acid (28).

Caffeic acid

Caffeic acid finds extensive use as an antioxidant due to its predominant physiological activity. In addition to its antioxidant properties, numerous studies have explored its therapeutic advantages in treating microbial infections. It is well-documented for its recognized effects, including

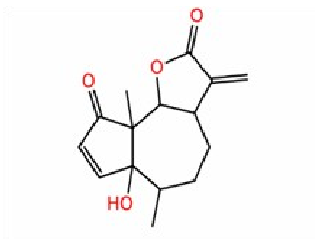

Fig. 1a. Structure of parthenin

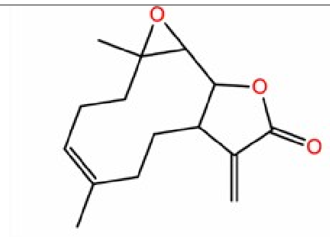

Fig. 1b. Structure of Parthenolide

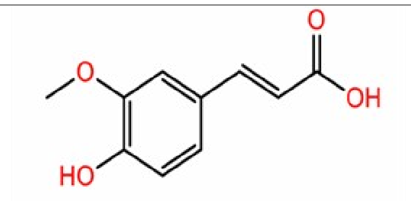

Fig. 1c. Structure of Ferulic acid

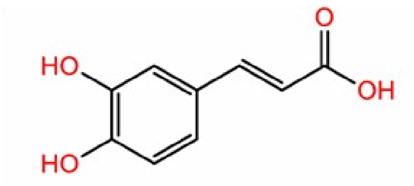

Fig. 1d. Structure of Caffeic acid

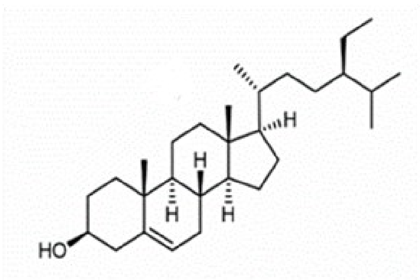

Fig. 1e. Structure of beta-sitosterol

Fig. 1 (**a**). Structure of parthenin, (**b**). Structure of parthenolide, (**c**). Structure of ferulic acid, (**d**). Structure of caffeic acid and (**e**). Structure of β-sitosterol.

antithrombotic, antihypertensive, antidiabetic, anticancer and anti-inflammatory properties. The antibacterial and antifungal efficacy of caffeic acid arise from its ability to inhibit enzyme activity, alter membrane permeability, disrupt protein structure and damage the DNA of human pathogenic fungi (45). Additionally, caffeic acid shows potential as an antiviral agent, particularly against viruses such as influenza, thrombocytopenia syndrome and herpes simplex viruses (46). The structure of caffeic acid is depicted in Fig. 1d (28).

β-sitosterol

The previous study provided compelling evidence regarding the efficacy of β-sitosterol, extracted from the leaves of *P. hysterophorus*, as a formidable inhibitor of amylase (47). This inhibition mechanism proved to be instrumental in achieving substantial reductions in blood glucose levels. The findings underscore the potential of β-sitosterol as a promising therapeutic agent for managing diabetes, offering a novel approach to glycemic control through the modulation of amylase activity. The structure of β-sitosterol is presented in Fig. 1e (48).

Pharmacological potentials of P. hysterophorus

Anti-inflammatory property

Inflammation, the biological response to potentially harmful stimuli such as bacteria, allergens, or immune reactions, is a well-known phenomenon (28). Recent studies have shown that administering *P. hysterophorus* treated with acetic acid orally to mice with carrageenan-induced paw edema effectively mitigates their symptoms, such as swelling or edema in the mice paw, by inhibiting the cellular phospholipases function (49). Interestingly, further investigation into various dosages of parthenolide (ranging from 10, 20, 30 and 40 mg kg^{-1}) consistently yielded positive results, maintaining normal sleep patterns and locomotor activity in the mice. Moreover, this treatment had no discernible impact on body temperature in rats and did not disrupt the normal life cycle of the mice (50). The anti-inflammatory property could result from the inhibition of cellular phospholipases, thereby impeding the release of arachidonic acid when triggered by appropriate physiological signals (18).

Antifungal activity

P. hysterophorus exhibits strong antifungal properties that can be harnessed for treating fungal infections in both humans and animals (45). The sesquiterpene lactones (SLs) identified in *P. hysterophorus* demonstrate sensitivity to fungi associated with dermatitis, suggesting their potential application in addressing various skin disorders (51, 52).

Anti-HIV activity

The leaf extract of *P. hysterophorus* exhibits antiviral properties by targeting the HIV reverse transcriptase enzyme. A reverse transcriptase inhibition kit was employed in the experiment to assess efficacy at concentrations of 0.6 and 6.0 g/mL, revealing varying degrees of inhibitory potential. This implies the presence of active compounds meriting further research and purification to elucidate their role in reverse transcriptase inhibition (53, 54).

Anticancer activity

Parthenolide, extracted from feverfew herb leaves, is currently garnering significant attention for its potential in combating cancer (55). *In vitro* studies have demonstrated its efficacy as a growth inhibitor across various cancer cell lines, including mouse fibrosarcoma (MN-11), human lymphoma (TK6), human lung carcinoma (A549), human medulloblastoma (TE671), human colon adenocarcinoma (HT -29) and human umbilical vein endothelial cells (18). Investigation revealed that the methanolic extract of *P. hysterophorus* possesses anticancer properties in mice hosting transplantable lymphocytic leukemia. Administration of *P. hysterophorus* extract to mice afflicted with cancer cells resulted in either complete remission or prolonged their lifespan (56).

Antidiabetic activity

The consumption of an aqueous extract of *P. hysterophorus* (100 mg kg^{-1} body weight) significantly lowered serum glucose levels in both normal and alloxan-induced diabetic rats, although to a lesser degree than glibenclamide (57, 58). β-sitosterol not only restores pancreatic tissue but also plays a crucial role in regulating blood glucose levels (59).

Antimicrobial activity

In vitro studies indicate that the hydroalcoholic extract of *P. hysterophorus* exhibits effectiveness against *P. falciparum* (60). Under controlled laboratory conditions, this plant exhibited antiamebic properties against both polygenic and axenic cultures of *Entamoeba histolytica*, the causative agent of amebiasis, comparable to the efficacy of metronidazole (61). Notably, its aqueous, methanol and n-hexane extracts demonstrated strong activity against Fusarium wilt, a significant fungal disease affecting potatoes caused by *Fusarium solani* (62). Additionally, its potential application extends to hepatic amebiasis (32). Furthermore, it displays antibacterial, antifungal and antiviral activities against *Pseudomonas aeruginosa*, *Escherichia coli* and *Candida albicans*, respectively (61).

Hypoglycemic effects of P. hysterophorus

The flavonoids, glycosides, alkaloids, tannins and phenolics from *P. hysterophorus* contribute to the plant's ability to induce hypoglycemia (22). Regular administration of the methanolic extract from *P. hysterophorus* has been observed to significantly reduce blood glucose levels. Experimental rabbits treated with 100 mg kg^{-1} of the methanolic extract of *P. hysterophorus* (MEPH) displayed enhanced tissue restoration, surpassing the effects observed with Glucophage (standard drug), which effectively lowered blood sugar levels but did not facilitate tissue repair (59). The decline in blood glucose levels may be attributed to increased insulin secretion, reduced conversion of dietary carbohydrates into glucose, inhibition of gluconeogenesis and glycogenolysis, as well as the healing of pancreatic tissue (63). MEPH's phenols and flavonoids exhibit the potential to inhibit α-glucosidase, leading to a decrease in glucose synthesis from dietary carbohydrates and its absorption into the bloodstream (64). Specific phenolic compounds, like chlorogenic acid found in MEPH, demonstrate hypoglycemic potential by inhibiting glucose-6-phosphate translocase, which transports glucose-6-phosphate into the endoplasmic reticulum for hydrolysis into glucose (65). β-sitosterol derived from *P. hysterophorus* leaves acts as a potent inhibitor of amylase, significantly lowering blood glucose levels (47).

A way forward trajectory in human

Impacting roughly 1.5% of the overall population, diabetes mellitus remains an enduring and widespread chronic metabolic condition, posing a considerable ongoing global health dilemma (64). As of 2023, diabetes mellitus represents a substantial global health challenge, impacting over half a billion individuals. Approximately 422 million people worldwide are diagnosed with diabetes, with the majority residing in low- and middle-income regions and the disease is responsible for 1.5 million deaths annually (66). Beyond its impact on life quality and expectancy, diabetes mellitus is primary cause of numerous microvascular and macrovascular complications, leading to outcomes such as blindness, renal failure, myocardial infarction, stroke and the need for limb amputation (67). The aqueous extract of *P. hysterophorus* exhibited robust hypoglycemic effects (32). Within the territories of Maharashtra and Gujarat in India, some people utilize *P. hysterophorus* weed for treatment of diabetes mellitus. Despite this, there is a notable dearth of scientific data elucidating the impact of *P. hysterophorus* on blood glucose levels (64).

Comparison with conventional treatments

In addition to conventional therapeutic options, various traditional medicines have been advocated for the diabetes treatment. Globally, traditional plant remedies are utilized to address a wide range of diabetic symptoms (48). Achieving complete remission of diabetes using insulin and oral hypoglycemic agents without adverse effects has proven to be difficult (68). In the field of diabetes therapy, there is an active promotion of several traditional medicines alongside existing therapeutic options. Traditional plant medicines employed worldwide effectively manage a diverse array of diabetic symptoms. The acknowledged benefits of plant remedies include their lower incidence of adverse effects and cost-effectiveness, which influence both public perception and healthcare practices (69). Herbal drugs emerge as crucial anti-diabetic agents, addressing the limitations of synthetic medications in combating hyperglycemia (59).

Positive approaches for the control of P. hysterophorus

The *P. hysterophorus* plant is predominantly associated with its influence on natural ecology and its negative implications for human and animal health. Numerous techniques have been employed for weed control, with the most promising method involving managing the weed through proper utilization (70). *P. hysterophorus* is reputed for its capacity to treat fever, malaria, diarrhea, dysentery and neurologic disorders (71). Instead of relying on conventional techniques like physical, chemical or biological interventions for *P. hysterophorus* weed management, positive approaches involve exploring its medicinal applications for combating diabetes. Phytochemical and medicinal assessment of the entire plant has unveiled its efficacy in addressing antimicrobial, anti-anemic, antipyretic, anticancer, antioxidant, lipo-protective, hypoglycemic, hepatoprotective and anti-cancer concerns (59). The methanolic infusion of *P. hysterophorus*, administered at dosages of 50 mg kg^{-1} and 100 mg kg^{-1}, exhibits noteworthy anti-diabetic properties. Remarkably, the 100 mg kg^{-1} dosage showcases impressive restorative effects on damaged pancreatic tissue, attesting to MEPH's inherent tissue-healing capabilities (59). Moreover, numerous advantageous facets of parthenium exist, presenting opportunities for its utilization as a raw material or additive in various applications. These include serving as feedstock (72), forage (73), herbicide (74–76), pesticide (77), insecticide (78, 79), ethanol (80, 81), compost (82–85), green manure (86), synthesis of nanoparticles (87, 88), feed additive for silkworm (89) and decolorizing agent (90), exemplifying its diverse range of applications.

Conclusion

P. hystreophorus is a notified weed, exhibiting both adverse and advantageous impacts on crops, humans and livestock. Combating the spread of this weed demands a multifaceted approach. Tackling this issue involves the development of public awareness and the adoption of participatory strategies to control invasive weeds. Encouraging research on the potential applications of this weed and evaluating its efficacy through field trials is imperative. An effective approach to weed control involves utilizing it appropriately and this can be accomplished through collaborative efforts by researchers, farmers, governmental and non-governmental agencies. Uncovering the diverse applications of this weed may serve as a pathway to its indirect eradication. Currently, despite being categorized as a weed, *P. hysterophorus* is gaining prominence for its newfound applications. The necessity arises to devise a cost-effective and straightforward method to eliminate harmful allelopathic chemicals, facilitating the productive utilization of *P. hysterophorus*. Possessing an extensive range of medicinal uses, *P. hysterophorus* has the potential to offer preventive measures against various diseases and could be a valuable asset in the development of future medications.

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Authors' contributions

TA collected the literatures and drafted the manuscript. KT, RK, GP, RS, PD, VS, PP, SA and VS read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest: The authors state that they have no conflicts of interest.

Ethical issues: None

AI Declaration

During the preparation of this work the authors used grammarly in order to check and improve the grammer and readability. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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