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Review Article

Possible therapeutic effects of *Plantago major* in women with high menstrual bleeding: A systematic review of randomized clinical trials

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Abstract

Objective: High menstrual bleeding (HMB) is a common issue affecting women's health, often leading to significant physical and psychological distress. While several medical treatments are available, many women face treatment failures or undesirable side effects, prompting interest in natural remedies. This systematic review aims to evaluate the therapeutic effects of *Plantago major* on women with high menstrual bleeding, focusing on randomized clinical trials.

Materials and Methods: A comprehensive literature search was conducted in various databases such as, PubMed, ScienceDirect, Cochrane Library, and Google Scholar to identify relevant randomized clinical trials assessing the efficacy of *Plantago major* in reducing menstrual bleeding until July 2024. Various preparations of *P. major* were utilized in the included studies.

Results: Administration of *P. major* leaf and seed extract significantly reduced both the duration and severity of bleeding. These extracts also led to a decrease in hemoglobin (Hb) and hematocrit (HTC) levels in the intervention group compared to the control group. The rectal suppository of *P. major* seed extract significantly decreased bleeding during the first 4 hours postpartum compared to the control group. Additionally, vaginal suppositories of *P. major* leaf extract notably reduced the mean in the pictorial blood loss assessment chart (PBAC) and improved the duration of bleeding in the intervention group.

Conclusion: The extracts of *P. major* seeds and leaves may enhance hematological parameters and reduce both the mean and severity of menstrual bleeding; however, the clinical significance of these findings necessitates further assessment in future trials.

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Introduction

Menorrhagia is defined as unusually heavy or prolonged menstrual bleeding and can be classified as abnormal uterine bleeding (AUB). It is a common issue that leads many women to seek clinical referral (Livingstone and Fraser 2002). AUB or heavy menstrual bleeding (HMB), is a gynecological disorder that significantly impacts the quality of life, particularly

among young women. HMB is characterized by menstrual blood loss exceeding 80 ml per cycle or lasting more than seven days, with no identifiable pathological causes (Magon et al. 2013).

The incidence of HMB is estimated to be between 11% and 13% in the general population, increasing to 24% among women aged 36–40 years. However, the prevalence varies across different populations (Marret et al. 2010). AUB of endometrial origin (AUB-E) is a disorder common among women of reproductive age, adversely affecting their quality of life, daily activities, and social engagements (Cihangir et al. 2013). It has been reported that up to 18 million women of reproductive age in the United States suffer from anemia due to AUB-E (Heliövaara-Peippo et al. 2013).

Various management strategies for AUB-E have been suggested, including treatment with nonsteroidal nonsteroidal anti-inflammatory drugs (NSAIDs), anti-fibrinolytics, oral progestins, oral contraceptives, and the levonorgestrel-releasing intrauterine system (Bahamondes and Ali 2015; Lukes et al. 2010). Although these medications may effectively reduce the severity of AUB-E, they often come with undesirable side effects. Consequently, there has been a growing trend toward using complementary herbal medicine for treatment (Lukes et al. 2010).

Recently, there has been a shift toward herbal medications for treating various disorders worldwide (Cheng et al. 2012; Khazdair et al. 2021; Mortazavi Moghaddam et al. 2020). Herbal medicine is generally considered to be better tolerated than synthetic drugs, based on critical assessments of clinical data (Izzo et al. 2016; Khazdair et al. 2020). Several medicinal plants are used to address gynecological issues in women, including infertility, AUB-E, and irregular menstrual cycles (Steenkamp 2003; van Andel et al. 2014).

Plantago major (*P.major*), a member of the Plantaginaceae family, has been utilized for nearly 4000 years, particularly in Asia, Europe, and America. Furthermore, *P. major* is widely grown and traditionally used in many regions of Iran (Mozaffarian 2013). According to Persian Traditional Medicine, *P. major* is employed to treat various ailments including coughs, wounds, infections, bleeding, fever, and inflammation (Najafian et al. 2018).

Various pharmacological properties including antidiabetic, anti-diarrhea, anti-inflammatory, anti-nociceptive, antibacterial, and antiviral as well as anti-ulcerative and wound healing effects for *P. major* were reported (Adom et al. 2017). The hydroalcoholic extracts of *P. major* leaves showed great antibacterial activity against both Gram-positive and Gram-negative bacteria (Zhakipbekov et al. 2023). Therapeutic effect of the *P. major* extract on the healing of second-degree burn wounds was reported. Subjects with second-degree burn received *P. major* and silver sulfadiazine ointment (10% and 1%, respectively). The complete healing duration in the *P. major* was 11.73 *vs.* 13 days in control group, and on the seventh day, all bacterial cultures were negative (Keshavarzi et al. 2022).

P. major extract contains a wide range of chemicals such as polysaccharides, phenols, lipids, amino acids, flavonoids, caffeic acid, iridoid glycosides and terpenoids which have the potential to exert different biological effects (Kizi 2022). The results of a clinical study indicated that the topical application of phenytoin cream (1%) combined with a formulation containing *P. major* has a synergistic effect for improving pressure ulcers without side effects (Ghiasian et al. 2021). Another randomized clinical trial demonstrated that topical Plantavera gel (a mixture of *Aloe vera* and *P. major*) combined with routine care significantly decreased total ulcer scores and ulcer surface area compared to the control group receiving only routine care (Najafian et al. 2019).

These findings support the traditional use of *P. major* in wound healing. Based

on the Persian traditional medicine, preclinical and clinical research, *P. major* has demonstrated wound healing properties. Therefore, the present study aims to review the effectiveness of *P. major* in treating heavy menstrual bleeding (HMB).

Materials and Methods

Eligibility criteria

The inclusion criteria were assessed based on the PICOS (Population, Intervention, Compare, Outcome, and Study Design) criteria (Table 1). Eligible clinical trials involved women treated with *P. major* for abnormal uterine bleeding (AUB) or heavy menstrual bleeding (HMB, also known as menorrhagia) resulting from endometrial dysfunction. Studies on women with HMB associated with conditions such as ovarian cysts, fibroids, and endometriosis, as well as those involving experimental interventions, were excluded. Furthermore, there were no restrictions regarding the formulation or route of administration for *P. major*, allowing for various methods of preparation, including suppositories, capsules, syrups, or extract.

Table 1. The PICOS criteria

PICO	Inclusion criteria	Exclusion criteria
Population	Women with abnormal Uterine bleeding	Basic studies
Intervention	Examining the effect of *Plantago major* on uterine hemorrhage	Effect of *P. major* on other hemorrhage
Compare	Control group	Other study types (case reports or series)
Outcome	The mean of bleeding duration The mean of bleeding severity The mean levels of HB and HTC	
Study Design	Randomized clinical trial	Other study types
Others	Publication in English being a research paper. Access to full texts of papers	Repeated studies, systematic or narrative review articles, reports and lecture notes, and letter to editor and clinical studies

Search strategy

(((((((dysfunctional uterine bleeding[Title/Abstract]) OR (abnormal uterine bleeding[Title/Abstract])) OR (dysfunctional uterine hemorrhage[Title/Abstract])) OR (intermenstrual hemorrhage[Title/Abstract])) OR (heavy menstrual bleeding[Title/Abstract])) AND (Plantago major[Title/Abstract])) OR (Plantago[Title/Abstract])) OR (Plantain[Title/Abstract]) in PubMed

Cochrane Reviews, matching Menorrhagia in (Title Abstract Keyword) OR Abnormal Uterine Bleeding in (Title Abstract Keyword) OR Dysfunctional Uterine Bleeding in (Title Abstract Keyword) OR Dysfunctional Uterine Hemorrhage in (Title Abstract Keyword) AND *Plantago major* in (Title Abstract Keyword.

(Abnormal Uterine Bleeding [Search Terms]) OR Dysfunctional Uterine Bleeding) OR Heavy Menstrual Bleeding) OR Intermenstrual Hemorrhage) AND *Plantago major*) in ScienceDirect.

In this systematic review, all clinical studies examining the effect of *P. major* specifically related to uterine hemorrhage were included. Basic studies (*in vitro* or *in vivo*) unrelated to clinical outcomes, Review articles, Letters to the editor and Clinical studies investigating *P. major* effects on uterine hemorrhage that did not include a control group were excluded from this systematic review.

Study selection

Initially, a total of 281 articles were extracted from the databases. Two reviewers independently assessed the suitability of primary studies based on their titles and abstracts (MK, and MRK). Following the removal of unrelated articles, including duplicates, basic studies, review articles, letters to the editor, and clinical studies lacking a control group, a total of 6 randomized clinical trial articles were identified for further evaluation. This selection process was conducted after a thorough review of the titles and abstracts of the extracted studies, as illustrated in Figure 1.

Study design

This systematic review aimed to evaluate randomized clinical trials (RCTs) that explored the use of *Plantago major* (*P. major*) seeds or leaves in the treatment of idiopathic abnormal uterine bleeding (AUB). The PRISMA reporting guideline (Page et al. 2021) was used for the reporting of the current systematic review (Table 2).

Databases utilized in this review included PubMed, ScienceDirect, Google Scholar, and the Cochrane Central Register of Controlled Trials. The search strategy was focused on various keywords relevant to the topic, including "dysfunctional uterine bleeding," OR "abnormal uterine bleeding," OR "dysfunctional uterine hemorrhage," OR "intermenstrual hemorrhage," OR "heavy menstrual bleeding," AND "Plantago major." The search was conducted to find studies published in English until July 8, 2024, ensuring a comprehensive collection of clinical studies that met the inclusion criteria for this systematic review.

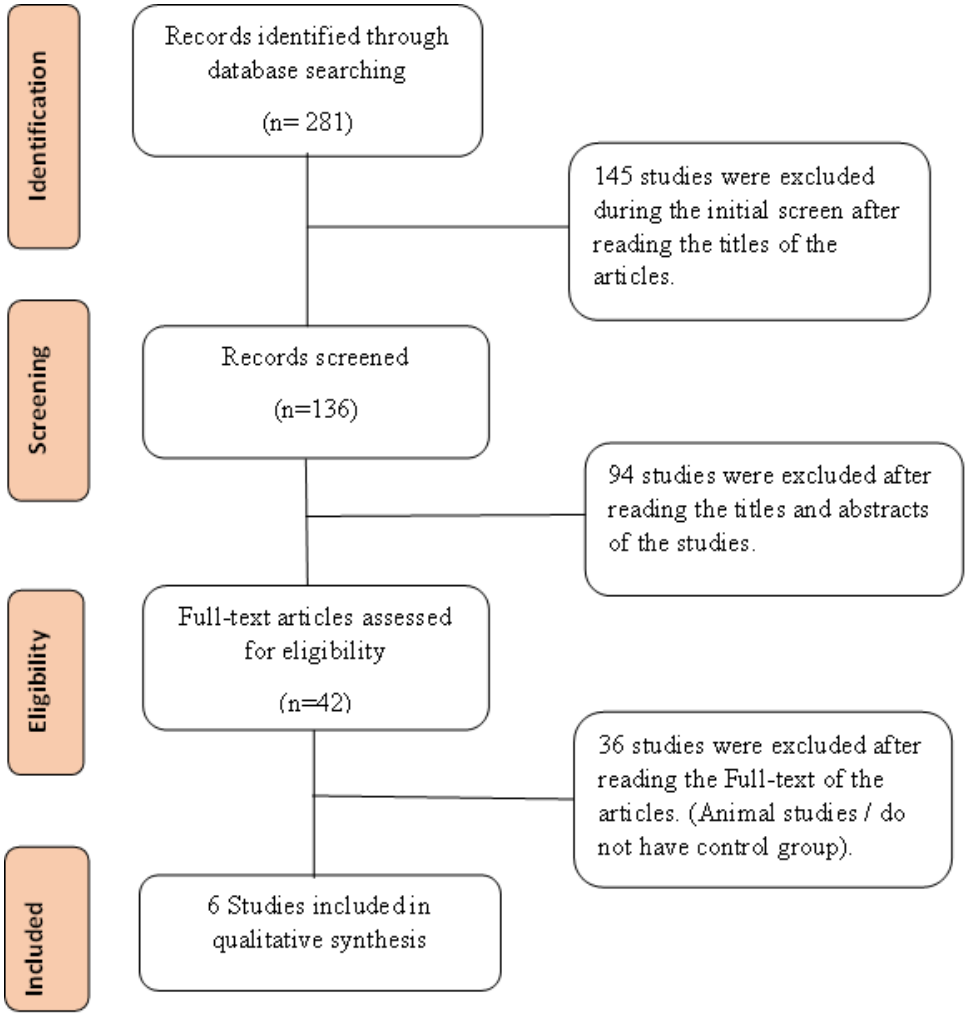

Figure 1. Flowchart of the search and the selection of relevant studies.

Table 2. Characteristics of the included studies based on PICOS

Author/Year	Study design	Samples/ aged	Intervention	Duration of follow up	Primary outcome	Secondary outcome
Navaei et al. 2020	Double -blind randomized, clinical trial	60 women with uterine leiomyoma and heavy menstrual bleeding (HMB) / 18 to 50 years	*P. major* leaf extract vaginal suppositories (*p. major* supp) + mefenamic acid capsule every 8 hours in the first 3 days of menstruation	3 menstruation cycles	Decreased the mean of pictorial blood loss assessment chart (PBAC) in the intervention group, while increased in control group in third month. A trend of improvement was significantly changes between two group. The mean of bleeding duration improved in patients of the intervention group.	The complications was similar between two groups, only 1 subject in each group complained of abdominal vaginal and pain.
Khodabakhsh et al. 2020	Triple blinded randomized clinical trial	68 women with HMB, bleeding volume more than 80 cc per menstruation and/or bleeding duration more than 7 days/ 36–45 years	*P. major* leaves extract syrup + placebo capsule in the first 5 days of menstruation	3 menstruation cycles	The bleeding duration and severity diminished in both groups of treatment. Duration of bleeding in control group was reduced significantly in comparison with intervention group.	The laboratory indices including; (FSH-TSH-PTT-BUN-CR-SGPT-SGOT-HB-LH-PT) was no significant difference between the two groups.
Khojastehfard et al. 2019	Single-blind randomized clinical trial	70 high-risk pregnant women that had a chance of Postpartum hemorrhage (PPH) with a score equal to or greater than 10/ 15–50 years	Both groups received infusion of 30 units oxytocin after delivery. Test group: the first dose of *P. major* seed extract rectal suppository, followed by 5 doses every 30 min interval.	4 hr after labor	The mean of bleeding 4 h after delivery was significantly lower than control group.	There was no observe any side effects (Nausea, vomiting and dizziness) between two groups.
Nejati et al. 2018	Double-blind, randomized, clinical trial	100 women with normal vaginal delivery with less than 3 time pregnancy / 20–35 years	Immediately after placental expulsion, Intervention group: infusion of 20 units of oxytocin and 100 cc of *P. major* syrup 20%	6 hr postpartum	The levels of HB and HTC dropping in the intervention group was significantly lower that control group after intervention. The mean levels of HB and HTC were not significant between two groups before the intervention	The vital signs such as, heart rate, systolic and diastolic pressure were not significant between two groups.
Khojastehfard et al. 2022	Triple blinded randomized clinical trial	105 pregnant with risk of PH divided randomly into three groups	Control group *P. major* rectal supp. (120 mg) and Dill rectal supp. (290 mg) received immediately after removal of the placenta, and then the next doses were placed every 30 minutes to 5 doses.	4 hr after labor	The mean of bleeding at the first 4 h after delivery significantly decreased in *P. major* and Dill groups compared to control group.	*P. major* rectal suppository can more effectively reduce PH.
Ghasempour et al. 2024	Double-blind, randomized, clinical trial	65 women who had referred to the gynecology clinic / 35 to 50 years	*P. major* seeds extract syrup + placebo syrups from the first day of menstruation and continue for a menstrual cycle	One menstruation cycles	Significantly reduced menstrual blood loss and menstrual duration compared to the beginning of the study.	The levels of Hb and Hct in treatment group was significantly increased

FSH; Follicle-stimulating Hormone, Supp: suppository, TSH: *thyroid stimulating hormone*, PTT; partial thromboplastin time, BUN; Blood Urea Nitrogen, CR; creatine, AST/SGOT; Aspartate Aminotransferase, ALT/SGPT; Alanine Aminotransferase, HB; Hemoglobin, HTC; hematocrit, LH; Luteinizing Hormone, PT; prothrombin time, PH; Postpartum hemorrhage.

Data extraction

The following information were extracted: The authors' names and publication dates, study design, age of subjects, details regarding interventions (including supplementation and placebo types), duration of follow-up, and both primary and secondary outcomes.

Risk of bias (Robs) and quality assessment

The Robs in the six eligible studies was evaluated using the Cochrane Collaboration RoB tools (Higgins 2011). Key domains assessed included sequence generation, allocation concealment, blinding, and other potential biases. The assessment of potential bias was based on scores obtained through these domains, which were stratified into three categories: "no" (high risk of bias), "yes" (low risk of bias), and "unclear" (uncertain risk of bias). A summary of the risk of bias assessment can be found in Table 3 and Figure 2.

Table 1. Quality assessment of studies selected for analysis.

Study	Navaei et al., 2020	Khodabakhsh et al., 2020	Khojastehfard et al., 2019	Nejati et al., 2018	Khojastehfard et al., 2022	Ghasempour et al., 2024
Random sequence generation	Yes	Yes	Yes	Yes	Yes	Yes
Allocation concealment	Yes	Yes	Yes	Yes	Yes	Yes
Blinding of participants and personnel	Yes	Yes	Yes	Yes	Yes	Yes
Blinding of outcome assessment	Unclear	Yes	Unclear	Unclear	Unclear	Unclear
Incomplete outcome data	Yes	Yes	Yes	NO	Unclear	Yes
Selective reporting	Yes	Yes	Yes	Unclear	Unclear	Unclear
Other source of bias	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Yes: low risk of bias, No: high risk of bias, Unclear: unclear risk of bias.

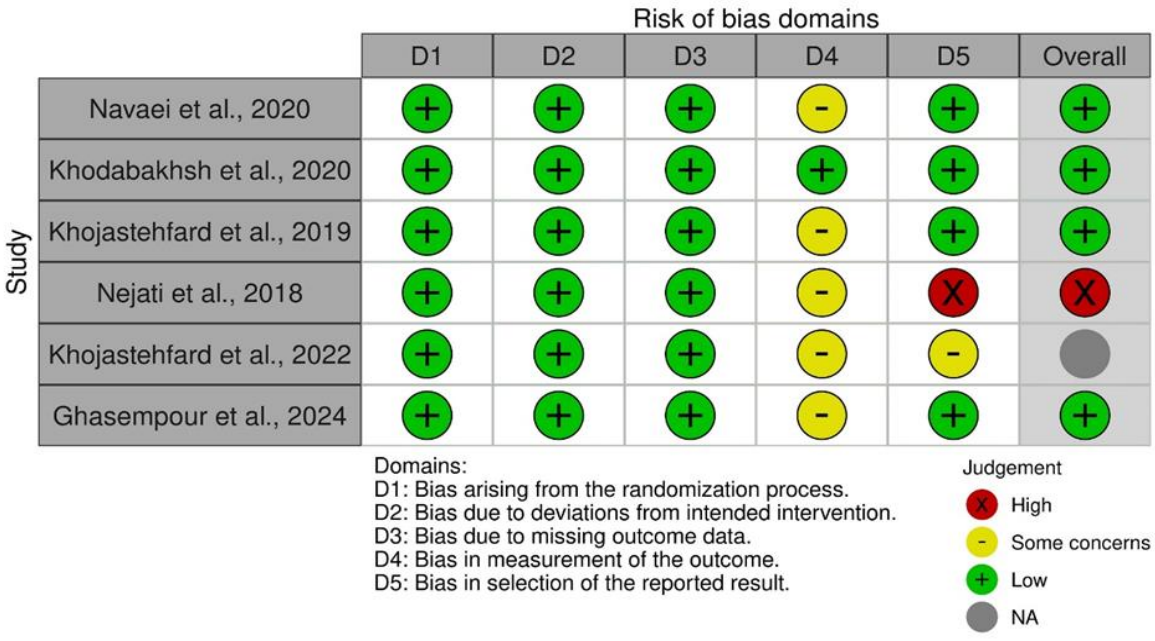

Figure 2. Risk of bias assessment by Cochrane risk of bias tool

Results

Following the initial electronic search using the specified keywords across the databases, a total of 281 articles were identified (as shown in Figure 1). Upon preliminary review, 145 articles were eliminated as they were either non-relevant or duplicates. Further screening of titles and abstracts led to the exclusion of 94 additional studies. After reading the full text of the remaining articles, 36 studies were excluded for not meeting the inclusion criteria. Ultimately, six articles were included in this systematic review.

The demographic characteristics of the included studies, which are all randomized clinical trials (RCTs), are summarized in Table 2. The total sample size across the studies amounted to 463 participants, with publication dates ranging from 2018 to 2024.

All included studies were clinical trials featuring single to triple blinding randomization, conducted on women of varying ages. With regard to the form of supplement prescription, one study received vaginal suppositories of *P. major* leaf extract (Navaei et al. 2020), two studies have used placebo capsule along with *P. major* leaves extract syrup (5 ml) every 8 hr (Ghasempour et al. 2024a; Khodabakhsh et al. 2020), one study administered 100 ml of *P. major seed* extract 20% and infusion of 20 U of oxytocin (Nejati et al. 2018), and in two studies, the intervention subjects received rectal suppository of *P. major* (Khojastehfard et al. 2019; Zahra et al. 2022). This variation in formulation and method of administration highlights the diverse approaches taken in evaluating the therapeutic effects of *P. major* on AUB.

Effects of *P. major* on bleeding duration and severity

Administration of *P. major* leaves extract syrup (12%) 5 ml every 8 hr to 68 women with HMB at first five days of menstruation for three menstruation cycles (MCs) in a randomized clinical trial showed significant reduction in bleeding duration and severity. The severity of bleeding was not significantly different between the intervention (*P. major* syrup + placebo capsule) and control (Mefenamic acid capsule (250 mg) + placebo syrup) groups. Duration of bleeding in the control group significantly reduced compared to the intervention group. The mean hemoglobin (Hb) changes in the control group significantly changes between before and after treatment, but there were no significant changes between the two groups after the intervention (Khodabakhsh et al. 2020). In the other similar study, administration of *P. major* syrup (5 ml every 8 hr) to 65 women with menorrhagia with mean age 41.33 ± 3.97 years old, significantly reduced menstrual blood loss and menstrual duration compared to the beginning of the study. Furthermore, the levels of Hb and hematocrit (Hct) in treatment group were significantly increased (Ghasempour et al. 2024a).

In another RCT, the effect of *P. major* seeds extract syrup on women with normal vaginal delivery was studied. One hundred subjects were divided to intervention (infusion of 20 units of oxytocin and 100 ml of *P. major* syrup 20%) and control (infusion of 20 units of oxytocin and 100 ml of placebo syrup) groups immediately after placental expulsion and Hb and Hct levels were measured in subjects 6 hr postpartum. The levels of Hb dropping in the intervention group (1.17±0.4) were significantly lower that control group (2.19±0.6) after intervention. Furthermore, the levels of Hct dropping in the intervention group (2.81±3.4) were also significantly lower than the control group (7.22±2.4) (Nejati et al. 2018).

In a study administration of *P. major* leaf extract as vaginal suppository on HMB in women with uterine leiomyoma (UL) was investigated. Subjects with UL (n=60) and HMB were assigned randomly to the treatment (*P. major* vaginal sup.) + capsule of mefenamic acid and control group (placebo sup.) + capsule of mefenamic acid every 8 hr at first

three days of menstruation for three MCs. The mean of pictorial blood losses assessment charts (PBAC) was remarkably decreased in the intervention group while increased in control group after 3 months. Also, the mean of bleeding duration was significantly improved in intervention patients (Navaei et al. 2020).

The effect of *P. major* seed extract administered as rectal suppositories on the rate of postpartum hemorrhage (PPH) in women was investigated. A total of 70 eligible pregnant women at high risk for PPH, with a risk score of ≥ 10, were randomly assigned to either the control group or the intervention group. In both groups, oxytocin (30 units) was infused in 1000 ml of crystalloid solution after delivery, in accordance with routine clinical practice. Intervention group received the first dose of *P. major* rectal suppository (120 mg), followed by 5 doses with intervals of 30 min closely after the removal of the placenta and fetal membranes and uterine massages. Average bleeding rate 4 hr after delivery significantly decreased in the intervention group (253.3±14.23 ml) compared to the control group (306.2±11.21 ml) without any adverse effects (Khojastehfard et al. 2019). In the other similar trials, effects of rectal suppository of *P. major* and *Anethum graveolens* (Dill) on the PH were investigated. The eligible pregnant women (n=105) for vaginal delivery were randomly divided into 3 groups (n=35 in each group) including *P. major* rectal suppository (120 mg), Dill rectal suppository (290 mg) and control groups. All participant received infused oxytocin (30 units) after delivery. The treatment groups received the first dose of rectal suppository of *P. major* and Dill, followed every 30 min to five doses after removal of the placenta and fetal membranes. The mean of bleeding at the first 4 hr after delivery significantly decreased in *P. major* (253.5 ± 14.2 ml) and Dill (282.4 ± 9.6 ml) groups compared to the control group (306.2 ± 11.2 ml) (Zahra et al. 2022).

Discussion

Heavy menstrual bleeding (HMB) can be challenging to manage, as numerous medical treatment options exist; however, many women experience treatment failure or hormonal side effects, which may lead them to opt for surgical interventions (Maybin and Critchley 2016). In recent years, there has been growing interest in natural products and herbal medicines due to their low cost, ease of availability, and minimal or absent side effects (Parasuraman 2018).

The results from six included studies suggest that extracts from the leaves or seeds of *P. major* may improve HMB and alleviate complications associated with postpartum anemia. These studies have documented the efficacy of *P. major* in controlling bleeding (Ghasempour et al. 2024b; Keshavarzi et al. 2022; Khodabakhsh et al. 2020; Khojastehfard et al. 2019; NAVAEI et al. 2020; Zahra et al. 2022).

In comparison, conventional treatments for HMB, such as hormonal therapies (e.g. oral contraceptives), non-steroidal anti-inflammatory drugs (NSAIDs) (Davies and Kadir 2017), and procedural interventions like dilation and curettage or endometrial ablation (Lethaby et al. 2013), show varied efficacy. While hormonal options can be effective for many women, they are often accompanied by side effects such as mood changes, weight gain, and an increased risk of thromboembolism. NSAIDs may reduce menstrual bleeding but often cause gastrointestinal discomfort and other complications. Surgical options offer definitive solutions but are invasive and carry inherent risks of complications.

As a well-known medicinal herb, *P. major* contains a variety of bioactive constituents, including alkaloids, flavonoids, terpenoids, phenolic compounds, fatty acids, vitamins, and polysaccharides, found in nearly all parts of the plant, including the leaves, flowers, seeds, and roots. The herb exhibits a range of pharmacological effects that are useful

for managing various conditions, including viral and bacterial infections, diarrhea, ulcers, pain, cancer, and inflammation (Adom et al. 2017).

An *in vitro* study demonstrated that the ethanolic extract of broadleaf *P. major* seeds significantly reduced activated partial thromboplastin time in the blood, indicating a coagulation effect (Mazinani et al. 2020).

Additionally, the efficacy of the whole *P. major* plant was investigated for its potential to reduce plaque and gingivitis. The results showed that a 5% extract of *P. major* significantly decreased all clinical parameters, including the gingival index, plaque index, and bleeding on probing, when compared to control subjects (Reddy et al. 2018).

A case described the experience of a 35-year-old man with chronic pancolitis, who presented with significant symptoms including bloody defecation and inflammation. After receiving a decoction of *P. major* (5 g in 250 ml of hot water) twice daily, the patient reported improvement within a few days. A subsequent clinical investigation, including colonoscopy and pathology tests, indicated that he remained clinically stable during a two-year follow-up (Tafazoli et al. 2022).

These findings collectively suggest that *P. major* possesses anti-inflammatory and hemostatic effects, supporting its potential therapeutic applications.

One clinical study evaluated the effects of *P. major* extract on the healing of diabetic foot ulcers (DFU) and pressure ulcers (PU). The results indicated that a 10% topical gel of *P. major* leaf extract significantly reduced wound size by the end of the first and second weeks when compared to the control group (Ghanadian et al. 2022).

Additionally, a combination gel of *Aloe vera* and *P. major* (referred to as Plantavera gel) was applied twice daily for four weeks to DFU patients (n=40), significantly decreasing both total ulcer score and ulcer surface area compared to the control group, with no reported side effects among the subjects treated (Najafian et al. 2019). Several studies have indicated that the expression of E series prostaglandin receptors and cyclooxygenase-2 (COX-2) enzymes is elevated in women with HMB (Jabbour et al. 2009; Smith et al. 2007).

Prostaglandin E2 may contribute to excessive bleeding by increasing vasodilation of the spiral arteries, altering endothelial cell function, and enhancing fibrinolysis. Moreover, inflammatory cytokines, including endometrial mediators and matrix metalloproteinases (MMPs), have been implicated in HMB (Archer 2012).

Notably, the level of tumor necrosis factor-alpha (TNF-α), a pro-inflammatory cytokine, was found to be significantly elevated in women experiencing HMB compared to those with normal bleeding (Malik et al. 2006). Therefore, inhibiting prostaglandin synthesis may represent an effective approach for the treatment of HMB. The anti-inflammatory effects of water and ethanol extracts of *P. major* leaves (0.01, 0.1, and 1 mg/ml) were evaluated in oral epithelial cells (H400) using the nuclear factor kappa beta (NF-kB) assay, yielding significant results (Zubair et al. 2019). Another *in vitro* study assessed the phenolic content, antioxidant properties, and anti-inflammatory activity of various *Plantago* species. The results indicated notable phenolic content and pronounced antioxidant and anti-inflammatory effects, including the inhibition of COX-1 and 12-lipoxygenase across four cell lines (Beara et al. 2012).

Moreover, the anti-inflammatory effects of *P. major* leaf and seed extracts were investigated in a rat model of ulcerative colitis (UC) induced by acetic acid. The study found that intraperitoneal (i.p.) administration of *P. major* leaf and seed extracts (400 and 700 mg/kg, respectively) for seven consecutive days significantly reduced histopathological damage and the ulcer index. Additionally, the plant extracts lowered levels of

interleukin-6 (IL-6), TNF-α, prostaglandin E2 (PGE2), IL-1β, myeloperoxidase (MPO), and malondialdehyde (MDA) compared to the control group (Farid et al. 2022).

Combination treatment involving four plant leaves, including *P. major*, *Dammul Akhwain*, *Punica granatum*, and *Red Ochre*, demonstrated significant effectiveness in reducing menstrual bleeding. A 10-day treatment over three consecutive menstrual cycles resulted in a notable reduction in both the volume and duration of bleeding in the treatment group compared to the control group (Bano 2007).

In a separate study, the uterotonic activity of an aqueous extract of *Ficus deltoidea* leaves was evaluated during the diethylstilbestrol-induced estrous phase in female rats, identifying saponins, tannins, and flavonoids as key chemical constituents responsible for stimulating uterine smooth muscle contractions and estrogen receptor activity (Amiera et al. 2014).

One notable advantages of *P. major* is its safety profile, as suggested by traditional Persian medicine (Najafian et al. 2018). The results of various studies indicate minimal or absent side effects associated with its use, making it an attractive alternative in clinical trials (Ghasempour et al. 2024b; NAVAEI et al. 2020). The cost of medications of HMB, such as tranexamic acid (250 mg) , NSAIDs like mefenamic acid (200 mg), or medroxyprogesterone (5 mg), ranges from USD 0.10 to 1 per tablet, with recommended dosages of 1-2 tablets taken three times per day throughout the menstrual period. . The monthly expense of oral medications averages USD 10 to 30 . Additionally,, levonorgestrel-releasing intrauterine system (LNG-IUS) costs between USD 100 and 200 per set, while gonadotropin-releasing hormone (GnRH) agonists are the most expensive at USD 150 per month (Chen et al. 2015). Integrating *P. major* into current treatment guidelines for HMB presents a significant opportunity to enhance patient care. Its widespread availability and low cost make it an accessible option for women seeking effective relief, particularly in resource-limited settings (Saggar et al. 2022). As policymakers and practitioners increasingly prioritize patient-centered care, the inclusion of *P. major* as a complementary therapy alongside conventional treatments could improve adherence while minimizing side effects.

However, the limited number of randomized controlled trials and heterogeneity of interventions involving *P. major*, including the use of syrups or suppositories, highlight the need for more robust methodologies, including improved blinding techniques and more transparent reporting practices to minimize bias in outcome assessment. These findings suggest that *P. major* extracts, due to their constituents (such as flavonoids, terpenoids, and phenolic compounds), may exert beneficial effects in managing HMB. While further studies with larger sample sizes and diverse populations are needed to evaluate the effects of *P. major* on menstrual health, establishing research priorities such as investigating optimal dosages, long-term effects, or specific patient populations would provide a more actionable roadmap for future work.

The findings from the reviewed studies indicate that *P. major* may enhance the management of HMB by potentially reducing the duration and severity of bleeding, as well as improving hemoglobin levels. Its anti-inflammatory, antioxidant, and uterotonic properties, along with its bioactive compounds, signal promise in alleviating symptoms associated with menorrhagia, although the current evidence base is limited.

To substantiate these claims further, additional randomized clinical trials involving larger participant cohorts are necessary to generate more robust scientific data. Future research should prioritize multicenter RCTs with larger sample sizes and longer follow-up periods, as well as explore optimal dosages, assess effects

across diverse patient populations, and evaluate the long-term safety and efficacy of P. major to establish comprehensive treatment guidelines in clinical practice.

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Conflicts of interest

The authors declare no competing interests.

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