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Effectiveness and Safety of Cimicifuga Racemosa and Blackberry Compared to Soy Isoflavone for the Treatment of Climacteric Symptoms: An Overview of Systematic Reviews

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Authors' contributions

This work was carried out in collaboration among all authors All authors read and approved the final manuscript.

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ABSTRACT

The female reproductive phase ends with climacteric syndrome, marked by hormonal variations (progesterone/estrogen). Cimicifuga racemosa (CR), Morus nigra (MN), and soy isoflavones (SI) have emerged as complementary treatments, potentially reducing symptoms. However, evidence

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gaps persist regarding the effectiveness and safety of CR and MN, necessitating a systematic review.
Objectives: To compare the effectiveness and safety of CR or MN with SI in managing climacteric syndrome.
Study design: A review of systematic reviews was conducted, structured using the PICO acronym. Searches were performed in March 2024 across Medline via PubMed, Web of Science, Cochrane, Embase, Lilacs, and grey literature. The study was registered in PROSPERO, adhering to PRISMA 2020 guidelines. Titles and abstracts were screened, followed by full-text reviews by two independent reviewers. Methodological quality was assessed with AMSTAR-2.
Results: Of 1,291 records, 27 studies underwent full-text review, but none were included. Variability in dosages, SI formulations, and the frequent use of placebo comparators precluded synthesis of safety and effectiveness for CR or MN versus SI.
Conclusion: Despite substantial scientific interest in herbal treatments for climacteric syndrome, comparative evidence on CR, MN, and SI remains unavailable. This gap limits evidence-based decision-making for managing climacteric symptoms.

Keywords: Cimicifuga racemosa; climacteric; complementary practices; phytotherapy; menopause; morus nigra; soy isoflavones.

1. INTRODUCTION

Starting at the age of 40, women experience physical and psychosocial changes, which, when combined with altered menstrual patterns, can indicate the diagnosis of climacteric syndrome (Cabral, et al., 2022). The climacteric is an important transitional period in a woman's life, encompassing premenopause, menopause, and post-menopause. Among these phases, menopause stands out, characterized by the absence of menstruation for twelve consecutive months due to a decline in ovarian hormones (estrogen and progesterone), typically occurring in women aged 45 to 55 years (Santos, et al., 2021, Ministério, 2004, Smail, et al., 2020).

According to the Brazilian Society of Endocrinology and Metabology (2017), the most common symptoms of climacteric syndrome include vasomotor instability, menstrual disorders, psychological symptoms, genitourinary atrophy, and, in the long term, osteoporosis and cardiovascular changes. This variety of signs and symptoms can strongly impact this stage of women-'s' health (Beltramini, et al., 2010). The presence and worsening of symptoms related to menopause, combined with poor sleep quality, may lead to the onset or intensification of other conditions such as anxiety and depression, in addition to vasomotor and sexual symptoms, potentially affecting autonomy and independence in daily activities, household tasks, and overall quality of life (Santos, et al., 2021). Weight gain is one of the common aspects in women during the climacteric and post-menopausal periods (Cabral, et al., 2022).

Women experiencing symptoms of climacteric syndrome and menopause often seek solutions for gynaecological disorders such as genitourinary atrophy, vaginal dryness, and decreased libido, with a preference for plant-based products and therapies. This is because hormone replacement therapies in menopause carry the risk of serious adverse events, such as breast cancer (Kenda, et al., 2021). Some herbal medicines, known as phytoestrogens, can mimic the effects of oestrogens, alleviating some climacteric symptoms and provid an accessible therapeutic alternative rooted in traditional knowledge (Welty, et al., 2007, Oliveira, et al., 2018). However, there are still gaps in the evidence regarding the effectiveness and safety of these treatments.

From the 1950s to the 1970s, clinical research on Cimicifuga racemosa (CR) followed the common practice of documenting and publishing clinical experiences. The German Medicines Act of 1976 mandated the requirement to provide proof of efficacy. From 1985 to 1987, the German Ministry of Health established standards for conducting clinical trials on medicinal products, leading to the first randomized, placebo-controlled clinical trial of any CR extract. Reports of liver toxicity during the use of CR products are rare; however, a causal relationship has not yet been confirmed (Henneicke, 1946).

The use of soy isoflavones (SI) to manage menopausal symptoms has been prioritized by researchers, as significant improvements have been observed in occurrences of hot flashes and

sweating. Regular consumption improves somatic and urogenital symptoms, enhancing quality of life during the peri- and post-menopausal periods (Vieira, et al., 2018). There is evidence that isoflavones reduce the intensity and frequency of vasomotor symptoms in women during the climacteric period. The ingestion of soy nuts was associated with a significant reduction in hot flashes and menopausal symptoms in postmenopausal women. A study using SI in a free-living state considered dietary soy a practical, safe, and inexpensive alternative to reducing menopausal symptoms, in addition to being associated with a significant improvement in quality of life (Welty, et al., 2007). Since soy and its products have a good safety profile (unless contraindicated for soy allergy or levothyroxine therapy), women suffering from hot flashes and night sweats may still try to alleviate them with soy supplements. Stanosz et al., conducted a clinical trial with 71 women in early menopause who received two doses of an ethanolic soy extract (corresponding to 52 mg and 104 mg of genistein equivalents) for 12 months. After 3 months, symptom relief occurred in the high-dose group and in the low-dose group after five months. Complete absence of hot flashes was reported in both groups after 12 months, both groups were compared to placebo with a 14% reduction. Another clinical study conducted by Faure et al., including 75 menopausal women who received 70 mg of standardized soy isoflavones per day for four months, observed a 61% reduction in hot flashes frequency compared to a 21% reduction in the placebo group (Kenda, et al., 2021).

The use of Morus nigra L. (MN, black mulberry) extract in tea form has been recommended for irritability during the premenstrual period and for treating some menopausal symptoms and disorders (Silva, 2019). Climacteric symptoms and quality of life appear to improve after administering black mulberry leaf powder for 60 days, similar to the effects of hormone therapy (Costa, et al., 2020). However, further studies on black mulberry, particularly more clinical trials evaluating the safety and efficacy of this plant, are needed (Oliveira, et al., 2018).

Considering the use of herbal medicine to relieve climacteric symptoms, this study aims to clarify the scientific gaps regarding the effectiveness and safety of these therapies compared to SI in alleviating the symptoms of climacteric syndrome and menopause.

2. MATERIALS AND METHODS

A review of systematic reviews was conducted to evaluate the comparative effectiveness and safety between CR/SI and MN/SI as herbal therapies for controlling climacteric syndrome symptoms. The research protocol was registered in PROSPERO under n. CDR 42024498124. The PRISMA 2020 guidelines were used to structure the article. Two independent reviewers assessed the eligibility of the studies. The reference manager ENDNOTE and the RAYYAN tool were used for study selection.

2.1 Search Strategies

The search strategies were developed by synthesizing the PICO acronym, used in the formulation of the research question. The primary search was conducted in five databases: Cochrane Library, Medline (via PubMed), Embase, Web of Science, and Lilacs, using DeCS/Mesh descriptors (Supplement 1). Subsequently, secondary searches were carried out in the grey literature, consultation with experts, and a review of the reference lists of the included articles. In the grey literature, the Mednar, World Wide Science, and Google Scholar databases were consulted by crossing the terms ("Cimicifuga" OR "Morus") AND "Isoflavones." The same terms were used in the Scopus database to identify the top ten researchers publishing on the topic. Emails were sent to these experts requesting information about the effectiveness and safety of the herbal medicines CR, SI, and MN. The titles and abstracts were read, followed by full-text reading of the selected articles, performed independently by two authors. Discrepancies were resolved by consensus with a third reviewer. The Kappa coefficient was calculated to measure the calibration of the researchers in their judgments based on the eligibility criteria. The agreement level among the researchers was considered acceptable if Kappa > 0.61 (substantial agreement) (Mchugh, 2012).

2.2 Inclusion Criteria

Systematic reviews of randomized clinical trials, without language or publication year restrictions, were included if they addressed the effectiveness and safety of CR or MN compared to SI for use during the climacteric period.

2.3 Data Extraction, Data Synthesis, and Quality Assessment

Two trained researchers, working independently to avoid biases, extracted the data. Information such as author, year of publication, country, dosage, administration and presentation, comparator, methodological quality, and factors that prevented analysis (e.g., unavailable full texts or conference proceedings) were recorded in Excel (Microsoft Corporation, Redmond, WA, USA).

These data, extracted from the included studies, were analysed through qualitative synthesis.

The A MeaSurement Tool to Assess Systematic Reviews (AMSTAR-2) (Shea, et al., 2017) was used to assess the methodological quality of the included studies and classify them into the following scores: critically low (more than one critical flaw), low (one critical flaw), moderate (more than one noncritical flaw), and high (no or one non-critical flaw).

3. RESULTS AND DISCUSSION

The calibration between the researchers, measured by the Kappa coefficient at the beginning of the selection process, resulted in an agreement of 0.775 (95 %). A total of 1,291 studies were identified, and 21 were selected for full-text reading. However, none met the defined eligibility criteria (Fig. 1). The reasons for exclusion are outlined in Table 1.

The use of CR and SI-based herbal medicines for the treatment of climacteric symptoms has been a topic of scientific interest. The hormonal toxicity of isoflavones, investigated by a systemic review with 400 included studies, conducted by Messina et al. showed that the evidence does not justify the criteria for classifying isoflavones as endocrine disruptors, in addition to the risk assessment of the European Food Safety Authority concluded that isoflavones do not exert side effects on the mammary gland,uterus and thyroid in peri- and postmenopausal women (Kenda, et al., 2021). No systematic reviews were found reporting clinical trials evaluating the action, safety and efficacy of NM compared to SI, those found had placebo as comparator, according to the searches developed in this review of reviews. However, the consumption of fruits and teas extracted from MN leaves has shown satisfactory results related to the pharmacological/therapeutic activities of diseases. This reinforces the importance of not only deepening research on MN but also conducting clinical trials on this and other plant species (Oliveira, et al., 2018). Furthermore, the current literature on medicinal plants and herbal formulations for climacteric symptoms is marked by inconsistent study designs, lack of standardized methods, and evidence quality (Portella, et al., 2024, Franciscis, et al., 2019, Dutra, et al., 2016).

Studies evaluating the action of herbal medicines describe effectiveness in reducing hot flashes, vaginal dryness, anxiety reduction, lipid index control, and vasomotor symptoms. These compounds exhibit a variety of pharmacological properties, such as estrogen-like, antioxidant, anti-inflammatory, and vasodilatory effects (Gomes, et al., 2023, Li, et al., 2021, Li, et al., 2023, Chen, et al., 2015). However, the long-term effects of using medicinal plants and herbal formulations to treat menopause symptoms are not fully understood and may result in unintended health effects (Franciscis, et al., 2019, Echeverria, et al., 2021, Teschke, et al., 2015). Although some studies have reported positive effects of plant-based interventions on menopausal symptoms, their results should be interpreted with caution due to methodological limitations and inconsistencies (Portella, et al., 2024).

Published studies on SI are divergent and difficult to interpret due to the heterogeneity of dosages and presentations used in clinical trials. Evidence suggesting a beneficial effect of soy foods and soy extracts on menopausal symptoms, as well as evidence opposing this claim, has been found (Kenda, et al., 2021). Based on high and moderate-quality studies analysed using the AMSTAR-2 assessment tool, it is evident that plant-based therapies are promising for treating menopausal symptoms. Several plant derivatives, such as SI and phytoestrogens, have proven effective in reducing hot flashes and serum levels of C-reactive protein and other inflammatory markers (Portella, et al., 2024). Available evidence does not support the use of soy and soy-derived products to relieve menopausal symptoms. This is mainly due to the low quality of conducted studies. However, it appears that the genistein content plays a crucial role in the effectiveness of soy-based supplements. Since soy and soyderived products have a good safety profile (except in cases of soy allergy or levothyroxine therapy), women suffering from hot flashes and night sweats may

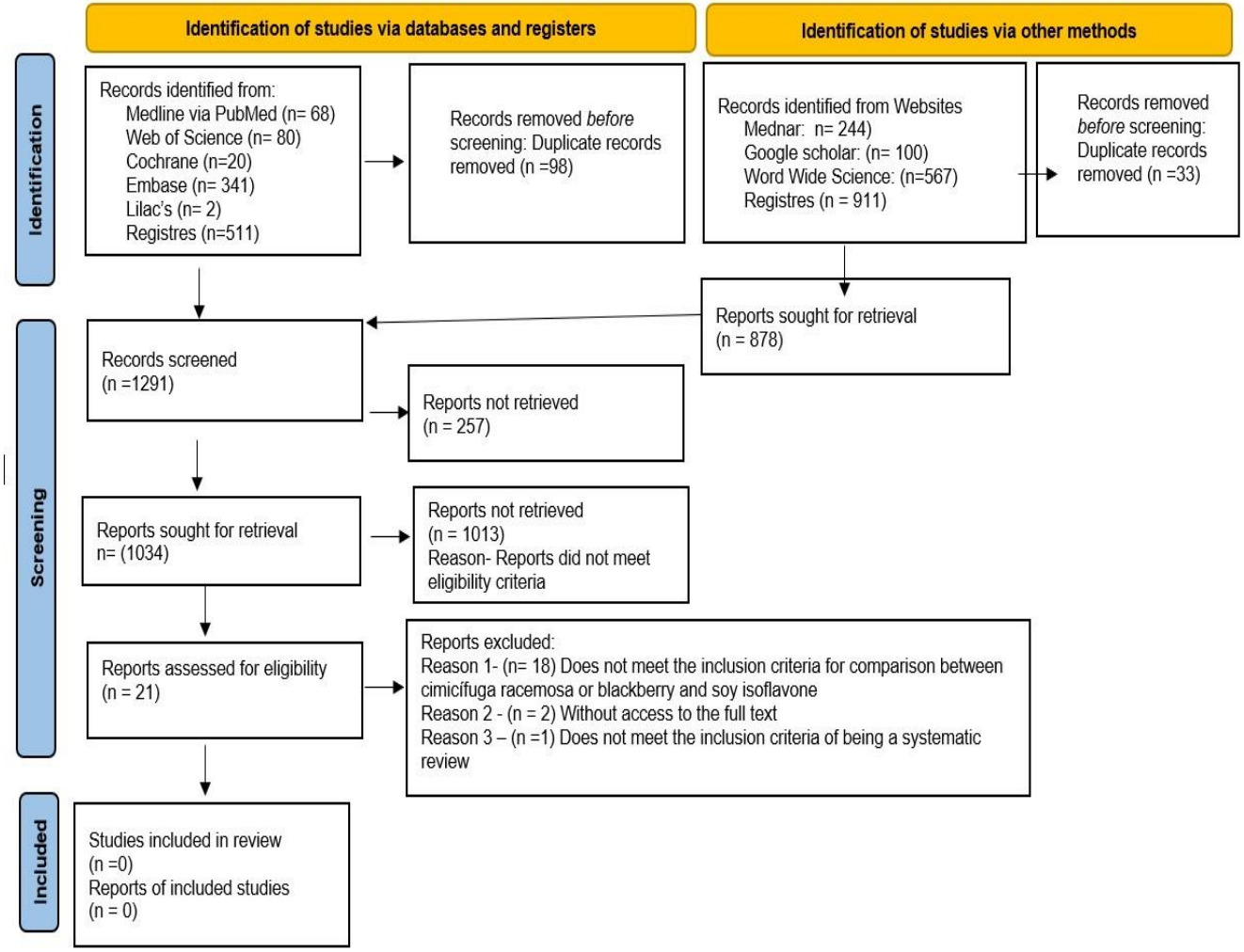

Fig. 1. PRISMA flowchart representing the study selection process

Table 1. Characterization of study exclusions

Author, year	Comparison between CR or MN with SI	Dosage/ presentation	Comparator	Methodological quality	Full text unavailable/ congress annals
Franco *et al.*,2016	Lack of exclusive comparison between CR/SI or MN/SI	Evaluation of SI in different forms of presentation, administration and dosage	Comparison to Placebo	High	
Jurgens *et al.,*2020	Lack of exclusive comparison between CR/SI or MN/SI	Evaluation of SI in different forms of presentation, administration and dosage	Comparison to Placebo	High	
Kargozar *et al.,* 2023					Full text of article not found
Maskarinec*.,* 2010	Lack of exclusive comparison between CR/SI or MN/SI		Comparison to Placebo	Low	
Oh *et al.*, 2024	Lack of exclusive comparison between CR/SI or MN/SI	Evaluation of SI in different forms of presentation, administration and dosage	Comparison to Placebo	High	
Pandozzi *et al.*, 2022					Full text of article not found
Taylor-Swanson *et al.*, 2014					Full text of article not found
Wood *et al.*, 2013					This was not a systematic review/ congress annals
Aarshageetha *et al.,* 2023	Lack of exclusive comparison between CR/SI or MN/SI	NR	NR	Low	
Batista *et al.,* 2023	Lack of exclusive comparison between CR/SI or MN/SI	NR	NR	Moderate	
Borrelli *et al.,* 2002	Lack of exclusive comparison between CR/SI or MN/IS	Different presentations and dosages	Comparison to Placebo	Moderate	
Borrelli *et al.,* 2008	Lack of exclusive	Different presentations and	Comparison to Placebo	Moderate	

	comparison between CR/SI or MN/SI	dosages		
Borrelli *et al.*,2008	Lack of exclusive comparison between CR/SI or MN/SI	Different presentations and dosages	Comparison to Placebo	Moderate
Chen *et al.,* 2014	Lack of exclusive comparison between CR/SI or MN/SI	Different presentations and dosages	Comparison to Placebo	High
Keshavarz *et al.,* 2018	Lack of exclusive comparison between CR/SI or MN/SI	Different presentations and dosages of SI and CR	Comparison to Placebo	Moderate
Abdi *et al.,* 2021	Lack of exclusive comparison between CR/SI or MN/SI	The included studies present different dosages, administrations	Comparison to Placebo/ conventional treatment	High
Aidelsburger *et al.,* 2012	Lack of exclusive comparison between CR/SI or MN/SI	Evaluation of SI in different forms of presentation, administration and dosage	Comparison to Placebo	Low
Karimi *et al.,* 2024	Lack of exclusive comparison between CR/SI or MN/SI	Evaluation of SI in different forms of presentation, administration and dosage	Comparison to Placebo	Moderate
Low Dog, 2005	Lack of exclusive comparison between CR/SI or MN/SI	The included studies present different dosages, administrations	Comparison to Placebo	Moderate
Shahmohammadi *et al.,* 2019	Lack of exclusive comparison between CR/SI or MN/SI	Evaluation of SI in different forms of presentation, administration and dosage	Comparison to Placebo	Moderate
Chen *et al.,* 2019	Lack of exclusive comparison between CR/SI or MN/SI	Evaluation of SI in different forms of presentation, administration and dosage	Comparison to Placebo	Low

** The reasons of exclusion of studies.*

still attempt to alleviate them with soy supplements (Kenda, et al., 2021).

However, the evidence found in systematic reviews presents results from heterogeneous sources, making it difficult to draw definitive conclusions about efficacy (Portella, et al., 2024). Laakmann et al. (2012) conducted a systematic review in which most studies comparing CR with placebo did not demonstrate a significant effect on climacteric symptoms supported by evidence. Additionally, (Shahmohammadi, et al., 2019) reported the possible positive effects of herbal medicines, such as CR, on anxiety and depression in peri-menopausal and post-menopausal women. It is important to note that the study conducted by Castelo-Branco et al. (2021) found that the isopropanol extract of Actaea racemosa was significantly more effective than a placebo in treating neurovegetative and psychological symptoms of menopause, with the treatment being well-tolerated, having a small number of mild adverse effects, and no impact on hormonal levels or estrogen-sensitive tissues.

The variety of dosages and presentations used in the studies makes it impossible to establish an effective comparison between SI and CR or MN, corroborating the questions raised in several studies. Among the potential methodological issues are the high rate of false-positive results in competitive inhibition assays, the detection of estrogenic activity despite the ability to bind to estrogen receptors, selective estrogen receptor modulating activity, or even additive or synergistic activity at those receptors (Overk, et al., 2008).

The heterogeneity between studies is recognized as a limitation of this study. Additionally, the lack of parameters for study eligibility and data analysis aligns with Portella et al. (2024) when considering the lack of standardization in studies on herbal medicines in clinical trials. The development of systematic study analyses on the use of herbal medicines in controlling climacteric symptoms, relating to the methodological diversities found in the studies, prevents the establishment of a precise conclusion (Portella, et al., 2024).

Dosages, forms of administration, and the lack of exclusive comparison between CR/SI and MN/SI represent another limitation of this study. These limitations align with those mentioned in Portella et al. (2024): “Variable dosages and types of soy supplementation, small or moderate sample sizes, and insufficient follow-up durations are some examples of these limitations" (Castelo-Branco et al., 2021).

Another questionable factor is the adverse reactions analysed through statistical data with different dosages and posologies compared to each other. Portella et al. (2024) essentially recommend considering how plant-based therapies may affect different populations differently based on factors such as race, ethnicity, age, and pre-existing medical conditions. Consequently, population-specific research could provide a basis for individualized studies.

Given this scientifically questionable context regarding the use of herbal medicines to control symptoms in climacteric syndrome, the present study suggests that posological and administrative standardizations for conducting clinical trials be rigorously implemented, aiming to evaluate the effectiveness and safety of these herbal medicines in future studies, establishing plausible statistical parameters for comparison between the different herbal medicines used, considering social, psychological, and environmental factors. It is suggested that the application of questionnaires gathering data on the economic and social conditions of individuals included in the studies could enhance the reliability of the samples, as these factors strongly interfere with analyses of hormonal variations.

4. CONCLUSION

No study was included due to the absence of scientific parameters allowing for an objective comparison between these herbal medicines. In contrast, this review reported the limitation of studies developed in the evaluation of herbal medicines for controlling climacteric syndrome due to inconsistency in the standardization of clinical trial conduct included in systematic reviews, which prevented the inclusion of studies that answered the research question.

This study calls for all established research groups familiar with randomized controlled trials to develop systematic studs to evaluate the effectiveness and safety of MN and CR to openly treat climacteric syndrome in premenopausal, menopausal, and postmenopausal women**.**

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Medline Searches - Via PubMed
Medline search list- Via Pub Med

#	Strategy	Results
1	("Climacteric" [Mesh]) OR (Climacterics) OR (Change of Life) OR (Life Change) OR (Life Changes) OR ("Menopause"[Mesh]) OR ("Perimenopause" [Mesh]) OR ("Postmenopause" [Mesh]) OR (Postmenopausal Period) OR (Post-Menopause) OR (Post Menopause) OR (PostMenopauses) OR (Post-menopausal Period) OR (Post menopausal Period) OR ("Premenopause" [Mesh]) OR (Premenopausal Period) OR (Premature Menopause) OR (Pre-Menopause) OR ("Menopause, Premature" [Mesh]) OR (Pre-menopausal Period) OR (Menopausal Symptoms) OR ("Estrogen Replacement Therapy" [Mesh]) OR (Estrogen Replacement Therapies) OR (Replacement Therapies, Estrogen) OR (Replacement Therapy, Estrogen) OR (Estrogen Replacement) OR (Estrogen Replacements) OR (Postmenopausal Hormone Replacement Therapy) OR (Hormone Replacement Therapy, Post-Menopausal) OR (Estrogen Progestin Replacement Therapy) OR (Estrogen Progestin Combination Therapy)	449,927
2	("Cimicifuga" [Mesh]) OR (Cimicifugas) OR (Cimicifuga racemosa) OR (Cimicifuga racemosas) OR (Black Bugbane) OR (Black Bugbanes) OR (Actaea racemosa) OR (Actaea racemosas) OR (Black Cohosh) OR (Black Cohoshs) OR ("black cohosh root extract" [Supplementary Concept]) OR (Actaea racemosa extract) OR (black cohosh extract) OR (cimicifugae rhizoma) OR (Actaea racemosa root) OR (rhizoma cimicifugae racemosae) OR (rhizoma cimicifugae) OR (Cimicifuga racemosa root) OR (Cimicifuga racemosa rhizome) OR ("Cimicifuga extract BNO 1055" [Supplementary Concept]) OR (CR extract BNO 1055) OR (BNO 1055) OR ("Morus" [Mesh]) OR (Mulberry) OR (Mulberries) OR ("Rubus" [Mesh]) OR (Rubus idaeus) OR (Raspberry Plant) OR (Raspberry Plants) OR (Rubus fruticosus) OR (Rubus glaucus) OR (Andean Blackberry) OR (Andean Blackberries) OR (Raspberries) OR (Raspberry) OR (Blackberry Plant) OR (Blackberry Plants) OR (Blackberries) OR (Blackberry) OR (Morus nigra) OR (Black mulberry)	10,726
3	("Isoflavones " [Mesh]) OR (Isoflavone Derivatives) OR (Isoflavone Derivative) OR(Isoflavone)OR (Homoisoflavones) OR (3-Benzylidene-4-Chromanone) OR (Homoisoflavone) OR (3-Benzylidene-4Chromanones) OR (3-Benzylchroman-4-Ones)	24,000
4	((#1) AND (#2)) AND (#3)	68

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