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Menopause in Latin America: Symptoms, Attitudes, Treatments and Future Directions in Costa Rica

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Abstract

Similar to their US counterparts, Costa Rican women enter menopause at ~50 years of age, have similar symptoms, including hot flashes and night sweats, as well as an overall negative attitude toward the menopausal transition. One study of rural women in Monteverde reported that women knew little about the menopausal transition, as the subject was not discussed. Similar to other Latin American women, the use of hormone therapy by Costa Rican women is low and instead they use alternative therapies, including massage, dietary changes and herbal medicines. A wide variety of herbal therapies are used, and some of these herbs have estrogenic activities in vitro. However, clinical data on the safety and efficacy of any of these treatments is lacking. Recently, a disturbing increase in the incidence of human papilloma virus infections in menopausal women has been reported, due in part to more sexual freedom after menopause. Fortunately, the strain of HPV infecting these women is not associated with cervical cancer. Overall, there is a significant lack of scientific and medical research on menopausal women in Costa Rica. Considering the

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Contributors

TDL did the literature research and prepared Table 1, and edited the manuscript.
BJD wrote and edited the manuscript.
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GBM wrote and edited the manuscript.

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aging population, the high use of herbal medicines by menopausal women and the lack of clinical studies on these treatments, future research should focus on gaining a better understanding of menopause in this population. Furthermore, new educational programs for these women and the health professionals who serve them are necessary, as well as investigations of the safety and efficacy of the herbal supplements women use to manage their menopausal symptoms.

Keywords

estrogen; ethnically diverse; herbal; HPV; menopause

2.0 Introduction

Located on the Central American isthmus, Costa Rica (CR) is bordered by Nicaragua to the north, Panama to the south, the Caribbean Sea to the east and the Pacific Ocean to the west [1]. Geographically, Costa Rica is renown for its active volcanoes, verdant cloud forests, waterfalls, stunning river valleys, and upwards of 300 beaches along both the Pacific and Caribbean coasts. While its land mass is only 51,100 sq. km. (0.03% of the earth's surface), CR is considered to be one of the 20 countries with the greatest biodiversity in the world [1]. Including its 589,000 sq. km. of territorial waters, the country is home to over 500,000 species, representing nearly 4% of the estimated total number of species worldwide [1]. As compared with the United States, CR has almost 70 times the number of plant species per unit area [2].

In addition to its biodiversity, CR is also an ethnically and culturally diverse country. There are three main groups, Europeans, Afro-descendants, and indigenous peoples, but as is common in most of Central America, the intermixing of different races has led to a large part of the population being of mixed races, such as mestizos and mulattoes [3]. Approximately 83.6% are white or mestizo 83.6%, mulato 6.7%, indigenous 2.4%, black of African descent 1.1%, 1% are ethnic Chinese, and <1% of the population are from the Middle East (mainly of Lebanese descent but also Palestinians) [4]. There are eight indigenous populations reported in Costa Rica including the Bribri, Brunca/Boruca, Cabécar, Chorotega, Huetar, Maleku/Guatuso, Ngöbe/Guaymí, and Teribe/Térraba [3]. Because of the attractiveness of CR for retirement, there are communities of North American retirees from the United States and Canada, Europe and Australia [3–5]. There remains a small indigenous population numbering about 60,000 (1% of the population) with some Miskito and Garifuna (a population of mixed black African and Carib Indian descent) living in the coastal regions. The median age in CR is 30.9 years, with women generally living to 81.4 years of age. By 2025, more than 20% of the population of CR will be over the age of 60 years, resulting in an increased demand for health services and a smaller share of income contributions [3–6].

Historically, CR has been a model for Central America in that it is politically stable and has a relatively high standard of living as compared with other countries [1, 3]. It is an unusual developing country in that only 1% of its population are indigenous, it has a very high literacy rate (95.3%) due to the availability of education for all, and there has been a concerted effort focused on improving healthcare [3]. Although CR ranks 50th in relative

health care expenditures to GDP, it ranks 37th in overall healthcare quality in the world, while the United States, which is ranked 1st in expenditure relative to GDP, ranks 38th in health care, falls just below CR [6]. Over the past 10 years, CR has implemented health care programs to improve women's health, particularly in the field of reproductive health (e.g., high coverage of institutional deliveries and prenatal care). However, like most other countries, it faces key challenges associated with rapid changes in age demographics and epidemiologic transition, such as cardiovascular disease, control and treatment of cervical cancer, breast cancer, poor nutrition, mental health, and other problems associated with menopause [3, 6]. Numerous women's groups and physician's associations in CR have been organizing for over 15 years due to the recognition that changing age demographics, and the understanding of the chronic sequelae associated with menopause, including cardiovascular disease, osteoporosis and cognition, will be a problem in the near future [3, 7–10]. Fortunately, CR has a universal healthcare system, one of the few in Central America that actually offers almost complete, universal coverage, both financial and geographical [11].

3.0 Menopause in Costa Rica

Interestingly, women in CR enter menopause around the same age as their U.S. counterparts (between 45–55 years of age, average ~50 years), and suffer from similar menopausal symptoms [10, 12–14]. Currently, there is very limited information concerning the attitudes, symptoms and understanding of menopause in CR. One small study assessed these issues in women living in the Monteverde, a small rural town in the mountains of Puntarenas province in northwestern CR, renowned for its beautiful cloud forests [13]. This study found that for women living in this rural area of CR, the menopausal transition was a confusing time and, similar to our study of menopausal women from the rural Livingston area of Guatemala, menopause in Monteverde was a topic that was taboo to discuss [13, 15]. For most women, there was little information available about menopause, and their first introduction to menopause is when they begin to the experience symptoms. Most women felt that they could not adequately discuss the issues of menopause until they underwent the transition. Generally, women from rural Monteverde, below the age of 39 years expressed little knowledge of the subject, however these women had novel ways to deal with their menopausal symptoms, such as trying to be healthier with diet, enjoying personal time and seeking natural remedies [13]. A second study involving 176 subjects, 108 CR women and 68 CR men, between the ages of 35 to 65 looked at menopause and andropause in Costa Rica [14]. In terms of the knowledge of the concept of menopause, only 64% were familiar, while the concept was not familiar to 36%. Of the persons familiar with the concept of menopause, only 48% could state that it was the period of transition between the reproductive life and the loss of reproduction [14]. In terms of symptoms, the majority of women stated a sense of shame, insomnia, a decrease of the sexual desire, emotional changes, increased perspiration, as well as reduction in vaginal lubrication, and chills [14]. While women looked to family members or their physicians for answers about menopause, overall, education was limited and this study recommended the development of education programs from menopausal women and the healthcare professionals that serve them [14].

3.1 Attitudes toward menopause

Unlike rural Guatemala where older women openly welcomed the menopausal transition, as it marks an end to the reproductive years and allows for more sexual freedom [14, 15], women from Monteverde viewed menopause as a time of uncertainty, with new social roles and lifestyle changes [13]. Interviews of middle-aged women between the ages of 55 to 65 years of age, reported that they expressed unhappiness about aging, while women over the age of 65 believed that aging was a normal process, but added that it is "*un tiempo de experiencia y un tiempo de preocupaciones*" (a time of more experiences and more worries)" [13]. Physical and emotional responses included reduced quality of life issues including an increase in generalized illness, aches and pains, wrinkles, reduced appetite, inability to work hard and a reduced sexual desire. In terms of menopause, some women defined it by the associated symptoms such as "*calores*" (hot flashes), "*frios*" (chills), irregular heavy menses, bleeding, aches and pains and generalized illness. Similar attitudes and symptoms were reported in another study of menopausal women in CR by Diaz et al., [14]. Thus, unlike Guatemala, but similar to the USA, women from rural CR have a negative attitude toward menopause and see a reduced quality of life due to symptoms and an increase in generalized illness during this time [9, 10, 13–14].

3.2 Symptoms of menopause in Costa Rica

There are few studies that describe menopausal symptoms of women in Central America, particularly indigenous women [9, 10, 13–14]. In a study by Lopez et al., [13], menopausal symptoms reported by women from rural Monteverde were similar, and sometimes the incidence was higher than symptoms reported by women from the USA. Costa Rican women reported shortness of breath (36.4%), hot flashes (45.4%), headache (90.9%), backache (54.4%); dizziness (27.3%); lack of energy (72.7%), irritability (27.3%), chills, stress, irregular periods, depression (54.5%), lack of sex drive and "pain in the ovaries" [13]. Thus, women from the rural Monteverde region in CR appear to have a similar level of hot flashes, but much higher levels of headache, pain and fatigue than menopausal women in the U.S. and other Western countries. This may be due to the heavy manual workload and other lifestyle issues that are common in women in the rural villages. Other more serious symptoms described by these women included hemorrhages and heavy menstrual flow (menorrhagia) occurring during the menopausal transition, when menstruation was irregular [13]. Women also described emotional symptoms [13–14], such as feeling blue, crying and boredom. Since no drug therapy was available, the women often alleviate symptoms by walking, sleeping, or just waiting until these feelings passed. The study also suggested that younger women (< 50 years of age) have a very limited knowledge or understanding of menopause in general, including specific menopausal symptoms or treatments [13]. Older women, who had experienced menopause were more knowledgeable about symptoms, and described personal techniques used for alleviating symptoms [13]. Interestingly, the study by Diaz et al., [14], noted similar lack of knowledge and misconceptions about menopause and made a series of recommendations to improve this situation in Costa Rica, including educational programs.

4.0 Treatment of Menopause in Costa Rica

Although CR women suffer from similar menopausal symptoms as their U.S. counterparts, their overall use of hormone therapy (HT) is low [9, 10, 12, 16–18]. Interestingly, a study recently published in Maturitas in 2016 showed that although prescribing HRT was popular among Latin American gynecologists, its use among women in these countries remains very low among women aged 45–59 being only 12.5% in large cities, and much lower in smaller towns and rural areas [16]. While the lower use of HT was associated with lower economic status [17], and the lack of a medical prescription [16], our research, and that of others, suggests that Latino women in general, and CR women specifically, prefer more natural therapies to manage their menopausal symptoms and use a wide range of natural methods including herbal medicines to improve the quality of life in the peri- and postmenopausal periods [7–10, 13, 16– 20]. A study published by DeSantis et al., [19] also reported that HT use among Hispanic women in the U.S. was low, ranging from ~9–10%. Rural CR women used other lifestyle changes to manage their menopausal symptoms such as taking natural herbal supplements, for example teas like chamomile, eating more vegetables and fruits, soaking feet in hot water, walking and additional exercising, joining women's groups and starting new hobbies have been reported [13]. Interestingly, women also used foods to reduce specific menopausal symptoms. For example, women ate avocados to reduce hot flashes and nigh sweats, bananas for fatigue (perhaps due to the potassium content), soy and bee pollen for hot flashes, flaxseed (omega -3-fatty acids) to reduce joint pain, and ate spinach, salmon and milk products including yogurt and cheese to reduce bone loss (osteoporosis). They also reported using evening primrose oil (*Oenothera biennis* L., a good source of omega-3-fatty acids) to reduce symptoms of depression and fatigue [13].

4.1 Herbal Therapies for Menopause

In 2002, we began working in Costa Rica as part of an international collaboration with our colleagues at CIPRONA, University of Costa Rica under a Memorandum of Agreement. This work was funded by the National Center for Complementary and Alternative Medicine at the National Institutes of Health from 2004–2008, and other sources from 2008–2017. As part of the WHO Collaborating Centre for Traditional Medicine, our interest was to investigate the traditional plant-based (herbal) medicines used by CR women to treat menopause and other reproductive disorders. Costa Rican women use a wide variety of herbal medicines to manage their menopausal symptoms, and many of these plants were readily available in markets [7–10, 20–21]. We visited the *Mercado Central* located in San Jose, where herbs are sold in *tiendas* (stands where herbs are sold) and found 8 plant species that were ingredients in herbal remedies for menopause. At the *tiendas*, signs advertising specific herbs and herbal combinations for the treatment of menopause (*Menopausia*) were displayed [7]. Twelve additional plants were identified from a review of the scientific literature as being used by CR women for menopause [7–10, 20–21]. Plants described as abortifacients and emmenagogues were excluded. Twenty plant species (Table 1) were collected in bulk and were identified and authenticated at the University of Costa Rica. The plants were extracted, and extracts were tested for biological activity relevant to menopause, such as binding to estrogen and progesterone receptors, cyclo-oxygenase 2 inhibition, and modulation of gene expression in breast cancer cells [7–10, 20–24]. Many of these herbal

extracts bound to the ERα and ERβ receptors, suggesting potential estrogenic effects (Table 1; 7, 20–24). Similar effects were found for the herbal extracts in functionalized cell-based reporter gene assays, such as the ER®-CALUX® reporter gene assay in the human osteoblastic osteosarcoma cell line U2-OS, and an ERE-regulated reporter gene assay in stably transfected MCF-7 breast cancer cells, which detects the extract's ability to induce transcription of an estrogen responsive reporter gene [7, 20, 22]. In addition, many of the tested herbal extracts also induced endogenous expression of the estrogen-responsive genes pS2, the progesterone receptor (PR) and PTGES in MCF-7 cells. We also tested the possible estrogen agonist and antagonist effects of the herbal extracts in MCF-7 cells in combination with estradiol (E2) treatments. Five of the extracts demonstrated synergistic effects with E2 in pS2 expression. However, treatment of the MCF-7 cells with E2 and *P. dioica* or *S. domingensis* resulted in a statistically lowered expression of PTGES and PR mRNA, suggesting a potential estrogen antagonist effect [20]. Because of the novelty of *P. dioica* leaf extract being an estrogen agonist and antagonist, and its ability to down-regulate the expression of E2-induced PTGES expression (a marker for cancer), *P. dioica* was followed up for further testing [20, 22]. The effect of *P. dioica* on endogenous PTGES in MCF-7 breast cancer cells is very interesting as the anti-tumor effects of cyclooxygenases are mediated by the inhibition of Prostaglandin E2 (PGE2), *P. dioica* may be of potential use in the prevention of breast cancer chemoprevention [20]. In this regard we further tested the effects of *P. dioica* extracts and fractions in MCF-7 cells and SKBr3 cells to determine the potential anticancer effects [22, 23]. Bioassay-guided fractionation led to the isolation of four compounds including the major constituent quercitrin and three new C-methylated flavonoids. A new 2-phenoxychromone, namely 2-(p-hydroxyphenoxy)-6,8-dimethyl-5,7-dihydroxychromone and quercitrin bound to the ERβ with an IC_{50} of 0.39 mM which equates to a binding affinity of 1.28×10^{-5} relative to estradiol [22]. In addition, one of the newly identified compounds inhibited the growth of MCF-7 cells and induced apoptosis in these cells by activating caspase 8 and increasing the expression of Bax, thereby increasing the Bax/Bcl-2 ratio, indicating a mitochondrial mechanism of apoptosis [22]. In SKBr3 breast cancer cells, the extract of *P. dioica* and two identified compounds inhibited cell viability and reduced the mRNA expression and tyrosine kinase activity of HER2 [24]. Other researchers have also reported that an aqueous extract of berries of *P. dioica* reduced the viability of BrCa breast cancer cells in vitro and in vivo with limited toxicity in non-tumorigenic, quiescent cells [25].

The results from the testing of herbal extracts used in CR for the management of menopausal symptoms suggests that many of the herbal supplements have estrogenic agonist/antagonist and perhaps progesterone agonist effects. There is also some indication that some herbals may have chemopreventative activities. However, there has been little research done in vivo, so the safety and efficacy of these herbs remains unknown. Considering that many women in CR use herbal medicines to treat their menopausal symptoms, assessment of these herbs in vivo should be a specific focus for future studies.

5.0 Other issues associated with menopause in Costa Rica: HPV and cervical cancer

Population-based cohort studies of age-specific human papilloma virus (HPV) prevalence in Guanacaste, CR have reported a spike in the prevalence of HPV in post-menopausal women [46, 47]. Historically, HPV peaked in Guanacaste women between the ages of 18 and 25 (36.9%), then it declined in other age groups to ~ 20%. However, a 2010 study showed a second spike in HPV in menopausal women after the age of 55 (31.4% prevalence among women ≥65 years) [47]. The HPV prevalence among older women was observed for both oncogenic and non-oncogenic HPV types, with a more pronounced effect observed for non-oncogenic HPV. This spike in HPV prevalence was associated with a reduced immune response [46].

A second nested case–control cohort study involving 10,049 women living in Guanacaste was performed to determine other possible causative factors of the HPV spike [46]. The analyses of the sexual behavior of women and their partners appeared to be the best predictors of the HPV prevalence, and among women who reported no sexual activity during the period when HPV appearance was documented, a weakened immunologic response was the only significant predictor of HPV [46]. Overall, the study suggest that 21% of HPV infections detected in older CR women were attributable to sexual behavior around the time of acquisition, while 12% of infections were attributable to a weakened immune response [47]. Fortunately, most of the HPV infections were non-oncogenic, and none of the women in the study were reported to have cervical pre-cancer or cancer. The authors concluded that although HPV infections are common among older women in Costa Rica, they may not necessarily be associated with risk of cancer development, and this should be considered when evaluating the benefit of HPV vaccination among older women [47].

6.0 Conclusions and Future Perspectives

Menopause is a universal female experience that marks the end of the reproductive years, and is associated with vasomotor symptoms, insomnia, pain, and anxiety, all of which can reduce the quality of life [9, 10]. Women in CR enter menopause at approximately the same age as women in the U.S., and appear to have similar problems with symptoms, as well as have a negative attitude toward menopause. Numerous women’s groups and physician’s associations in CR have been organized due to the recognition of changing age demographics and the fact that the chronic sequelae of menopause will be a challenge in CR in the near future. In general, CR women expressed a desire for more information before, during, and after menopause to better prepare for, and deal with symptoms. As more women live longer, the management of the menopause and the post-reproductive years will become critically important for CR and other Latin American countries. Thus, healthcare professionals need to be adequately educated and trained to deal with these patients and the management of menopause. Hormone therapy is generally not well accepted by Latin American women, and herbal remedies and other complementary and alternative therapies tend to be their first choice for the management of menopausal symptoms. In rural areas of the country herbal and other alternative therapies may be the only treatments available.

However, the majority of these herbal therapies used by menopausal women in CR have not been scientifically tested in vivo, and thus their safety and efficacy overall is not known. Many herbs from CR used to manage menopause have some estrogen-like effects in vitro, thus suggesting potential safety issues. Thus, future research should focus on large scale studies of menopausal women in CR and the rest of Central America, the training of healthcare professionals, educational programs for women, as well as assessing the safety and efficacy of these herbal medicines, especially in vivo or human studies. Rising levels of HPV infections in menopausal CR women is also alarming, and educational programs to help deal with sexuality and the spread of HPV would be very helpful for these women.

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Highlights

- Women in Costa Rica have menopausal symptoms similar to those of women in the USA.
- The use of hormone therapy by Costa Rican women to manage menopausal symptoms is low.
- Costa Rican women rely on alternative therapies, such as herbal medicines, which are sold in many of the markets, to manage their menopausal symptoms.
- Some of the herbal medicines have estrogenic or progestagenic effects in vitro but have not been tested in vivo or in human studies for safety or efficacy.
- General information about the menopausal transition is lacking in Costa Rica and educational and training programs for women and healthcare professionals to deal with the physical and emotional symptoms are urgently needed.

TABLE 1

Methods:

Searched Pubmed, Medline and SCOPUS using plant name plus search terms: gynecology; menopause, hot flashes, hot flushes, menopausal symptoms, premenstrual syndrome, menstruation, dysmenorrhea, amenorrhea; menstrual complaints, female complaints, women's health. All plant names were confirmed through theplantlist.org database

Plant Species	Family	Common Name	Parts used	Use/experimental data	References
Artemisia absinthium L.	Compositae/Asteraceae	Wormwood; absinthe; Ajenjo	Whole plant; leaves; stems	Menopause, menstrual colic; regulating menstrual cycle. Extracts bound to the estrogen receptors in MCF-7 cells. Stimulated reporter gene expression in the ERβ-CALUX® assay and modulated expression of E2-dependent genes in MCF-7 cells	20, 26–28
Brosimum alicastrum Sw.	Moraceae	Ramon nut, Maya nut, Ujushte, corn tree, breadnut	Fruit, nuts	Menopause. Hormone-like effects. Extracts bound to estrogen receptors (ERα and ERβ and induced a SEAP reporter gene in transiently transfected MCF-7 cells, which was inhibited by the ER antagonist ICI 182,780 indicating estrogenic effects were mediated through the ER.	15, 20, 23, 29
Buddleja sessiliflora Kunth. (syn. *Buddleja verticillata*)	Buddlejaceae		Leaves	Extracts bound to estrogen receptors (ERα and ERβ).	20, 30–31.
Citrus aurantium L.	Rutaceae	Bitter orange,	Leaves	Anxiety, menorrhagia, hot flashes and night sweats. Extracts did not significantly bind to estrogen receptors (ERα and ERβ).	20, 30–31
Dioscorea villosa L.	Dioscoreaceae		Root	Menopausal symptoms and Hormonal effects. Estrogenic in female rats. Extracts bound to estrogen receptors (ERα and ERβ).	20, 31
Euphorbia lancifolia Schltdl.	Euphorbiaceae	Ixbut, corona de Cristo, hierba lechera, sapillo, tiriciaxihuit, jeguite para la tiricia, hierba de la tristeza	Leaves	Galactogogue, aphrodisiac, menopause. Extracts did not significantly bind to estrogen receptors (ERα and ERβ).	20, 32
Equisetum bogotense Kunth	Equisetaceae	Cola de caballo	Leaves	Menopause. Extracts did not significantly bind to estrogen receptors (ERα and ERβ).	20
Hamelia patens Jacq.	Rubiaceae	Chichipin; hierba de cancer	Leaves	Menopause, headaches. Extracts weakly bind to estrogen receptors (ERα and ERβ).	20, 31
Hisbiscus sabdarrifa L.	Malvaceae	Sorrel; roselle; Rosa de Jamaica, sarril; karkade, rose tea	calices	Cramps and inflammation of uterus, menopause. Extracts bound to estrogen receptors (ERα and ERβ and induced a SEAP reporter gene in transiently transfected MCF-7 cells, which was inhibited by the ER antagonist ICI 182,780 indicating estrogenic effects were mediated through the ER. Estrogenic effects in immature rats.	20, 31, 33–34
Hibiscus rosa-sinensis L.	Malvaceae	hibiscus	Flowers and leaves	Amenorrhea; Female complaints; heavy flow during menstruation; nervous conditions.	14, 26,35

Plant Species	Family	Common Name	Parts used	Use/experimental data	References
Justicia pectoralis Jacq.	Acanthaceae	Tilo, carpenter's bush	Leaves	Menopausal symptoms, cooling, anxiety. Extracts bound to both ERα and ERβ; induced estrogen- dependent transcription in the ERβ-CALUX; and bound to the progesterone receptor. The extract also modulated the expression of endogenous estrogen responsive genes pS2, PR, and PTGES in MCF-7 cells. Activation of a 2 ERE-construct in transiently transfected MCF-7 cells by the extract was inhibited by the estrogen receptor antagonist ICI 182,780, indicating that the effects were mediated through the estrogen receptor. Estrogenic in rodent models.	21, 34, 36
Pimenta dioica (L.) Merr.	Myrtaceae	All spice, Bay Rum, Jamaica pepper, pimento	Leaves	Dysmenorrhea and menopause. Extracts bound to estrogen receptors (ERα and ERβ) and induced a SEAP reporter gene in transiently transfected MCF-7 cells, which was inhibited by the ER antagonist ICI 182,780 indicating estrogenic effects were mediated through the ER. Stimulated reporter gene expression in the ERβ-CALUX® assay and modulated expression of E2-dependent genes in MCF-7 cells.	20, 37
Phlebodium aureum (L.) J. Sm.	Polypodiaceae	Blue star fern; goldfoot fern, golden polyplody, kalakwal	Rhizomes	Menopause, menorrhagia. Extracts did not bind to the estrogen receptor.	20, 31
Plantago major L.	Plantaginaceae	Common plantain; Llatén	Leaves; juice	Menstrual disorders, hot flashes, menorrhagia, menopause. Extracts bound to the estrogen receptors. Stimulated reporter gene expression in the ERβ-CALUX® assay and modulated expression of E2-dependent genes in MCF-7 cells.	15, 20, 29–31, 38–39
Punica granatum L.	Punicaceae	Pomegrante	Seeds	Menorrhagia, menopause. Extracts weakly bound to the estrogen receptors. Showed estrogenic effects in ovarectomized rodents. Also showed antiosteoportic effects.	20, 31, 40
Smilax domingensis Willd	Smiliaceae	Zarzaparrilla; cuculmeca; bejuco de canasta, chiquihuite; palo de la vida, corona de Cristo, tietie, China-root	Rhizomes	Night sweats. Extracts bound to estrogen receptors (ERα and ERβ) and induced a SEAP reporter gene in transiently transfected MCF-7 cells, which was inhibited by the ER antagonist ICI 182,780 indicating estrogenic effects were mediated through the ER.	15, 20, 41
Tanacetum parthenium (L.) Sch. Bip.	Compositae/Asteraceae	Feverfew; Altamisa; wild chamomile	Flowers; leave	Regulate menstrual cycle; to treat cramps; Induce menstrual bleeding; to treat problems with menstruation; promote menstruation; uterine cramps; dysmenorrhea; amenorrhea. Extracts bound to estrogen receptors (ERα and ERβ and induced a SEAP reporter gene in transiently transfected MCF-7 cells, which was inhibited by the ER antagonist ICI 182,780 indicating estrogenic effects were mediated through the ER. Stimulated reporter gene expression in the ERβ-CALUX® assay and modulated expression of E2- dependent genes in MCF-7 cells.	20, 42–43
Zingiber officinale L.	Zingiberaceae	ginger	Rhizomes	Menopause, hot flashes, fibroids. Extracts weakly bound to estrogen receptor (ERα). Docking studies show binding to the ER and weakly estrogenic in rodents. However, contrary to this study, another study showed no in vivo	20, 44, 45

Plant Species	Family	Common Name	Parts used	Use/experimental data	References
				effect on classic estrogen target organs, such as uterus or bone.	