REVIEW ARTICLE

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Narrative review of Vitex agnus-castus in symptoms in Gynecology

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INTRODUCTION

Since ancient times, it is said that women can look different than usual, especially in the phase that precedes menstruation. Hippocratic texts mention tremors, fatigue, and pressure in the head. Romans cite torpor, nausea, and loss of appetite. The name "premenstrual tension" was given by Frank in 1931, based on the set of physical, psychological, and behavioral changes that appear in the period before menstruation and regress with it. In 1953, Greene and Dalton advised using the term "syndrome" instead of tension, as the condition is usually represented by a set of symptoms, with multiple variables and different aspects, depending on the affected people[1].

In 1987, the American Psychiatric Association defined "late luteal phase dysphoric disorder" as a mental disorder[1,2]. This inclusion led to a great deal of discussion, along with several objections, as it represents the evident potential risk of using this diagnosis in criminal charges, in addition to promoting prejudice against the female sex. However, the diagnosis remains recorded in the manuals. At present, this disorder is considered a diagnosis only in very serious cases in which impairment of socialization and usual activity is evident.

Premenstrual syndrome is defined as a set of disorders with somatic, affective, cognitive, and behavioral manifestations that occur in the luteal phase of the menstrual cycle and disappear after menstruation, cyclic, recurrent, and sometimes disabling. One study found that only 3–15% of women have severe symptoms[2].

Due to the day-to-day implications, there is great interest in treating affected women, providing them with greater well-being and friendly coexistence. One of the treatment alternatives is to use the extracts of Vitex agnus-castus.

HISTORIC

In ancient Greece, about two millennia ago, Dioscorides describes Vitex agnus-castus as a medicinal plant. It is also called monk's pepper, chaste tree (or chasteberry in English), northern rosemary, and so on. Its name Vitex agnus–castus was derived from the Latin "chaste lamb". Owing to its ability to reduce sexual desire, the monks used this plant to maintain their vow of chastity[3].

This plant has been traditionally used for centuries to treat various female problems, such as cyclical breast tenderness, menstrual irregularities, and premenstrual tension[4].

CHEMICAL COMPOSITION

Most of the studies were carried out with tinctures or extracts obtained from the fruits containing essential oils, iridoid glycosides, diterpenes, and flavonoids. Essential oils contain limonene, cineole, pinene, and sabinene; primary flavonoids include casticine (Figure 1), orientin, kaempferol, quercetagetin, and isovitexin; diterpenes consist of vitexilactone, rotondifuran, and 7-beta-diacetoxy-13-hydroxy-labda-8,14-diene; and iridoid glycosides include agnosidium (Figure 2) and aucubin (Figure 3). The agnoside is used as a quality marker of extracts. There is no accurate information on the presence of progesterone, 17-hydroxyprogesterone, testosterone, and epitestosterone[4,5].

PHARMACOLOGY

Vitex extract promotes a reduction in prolactinemia. This action results from the binding of components with dopaminergic properties to protein receptors[6]. There is evidence that shows binding to dopamine receptors in the hypothalamus and anterior

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pituitary and inhibiting the release of prolactin. There also seem to be other endocrine effects, such as increased progesterone secretion and induction of corpus luteum formation[4].

The estrogenic activity of the ethanol extract was demonstrated in ovariectomized rats by promoting an increase in uterine volume, increasing the dosage of progesterone and estrogens, and also inducing a reduction in LH and prolactin[7].

CLINICAL TRIALS

Premenstrual syndrome

A multicenter study with 1634 patients, observed during three menstrual cycles, using Vitex extract, answered a questionnaire about their psychic symptoms, and attributed to water retention; 93% of the patients reported symptomatic improvement, without significant adverse effects[8].

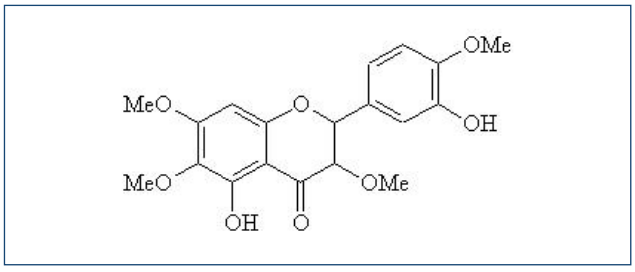

Figure 1. Chemical structure of Casticine[5].

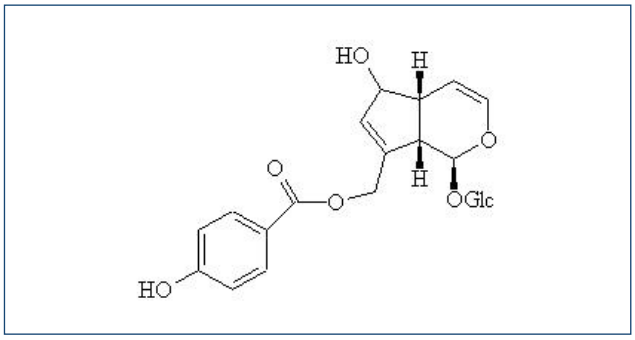

Figure 2. Chemical Structure of Agnosidium[5].

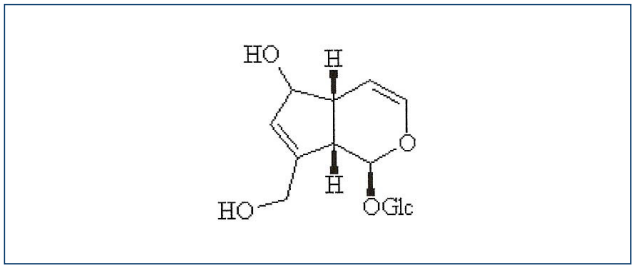

Figure 3. Chemical structure of Aucubin[5].

A study on 170 patients (84 of them with the herbal medicine) during three menstrual cycles compared the efficacy of Vitex agnus-castus with placebo and found an important superiority of the herbal medicine ($p<0.001$), with adverse events without seriousness but similar to the placebo group[9] (Table 1).

With regard to therapeutic options (especially fluoxetine, sertraline, and Vitex), and the above findings, Carr considered the option of using agnus chaste very promising[10].

Comparing the herbal medicine with fluoxetine, a study with 24 patients, during two cycles, did not observe a significant difference between treatments with fluoxetine and monk's pepper, although both improved the psychological and physical symptoms[11].

In a prospective, multicenter study conducted in China, compared with placebo, 202 patients completed 3 months of observation (101 using the extract). The symptom score was significantly lower in patients who used the active drug, leading to the conclusion that this treatment was effective, well-tolerated, and safe[12] (Table 2).

OTHER CLINICAL SITUATIONS

In a review of several studies, the reduction of breast tenderness by reducing prolactinemia is considered an excellent therapeutic option[12].

The immunomodulatory activity of casticin, a flavonoid from Vitex agnus-castus, has been demonstrated in vitro[13].

The effect of a hydrophilic plant extract has also been described in rats to reduce epileptic seizures[14].

The action in fertility regulation has been described for some time. A case of ovarian hyperstimulation attributed to

Table 1. Reduction of symptoms in two therapeutic groups.

Symptoms	Reduction of symptoms (%)	
	Vitex agnus-castus (n=86)	Placebo (n=84)
Headache	-17.8	-5.9
Irritability	-28.9	-18.2
Mood changes	-28.7	-17.6
Changes in breasts	-18.6	-9.4

Significance at $p<0.001$.

Table 2. Therapeutic group scores for moderate-to-severe premenstrual syndrome in Chinese patients.

	Vitex agnus-castus (n=101)	Placebo (n=101)
Previous score	26.17	27.10
Final score	9.92	10.69

Significance at $p<0.01$.

the use of Vitex has been described in a patient undergoing in vitro fertilization treatment[15]. In other circumstances, it was considered an alternative option to assist infertile couples[16]. A double-blind study comparing placebo and nutritional products with various components, including agno chaste, green tea, vitamins, and minerals, demonstrated a very significant increase in progesterone and elevation of basal temperature, regularization of menstrual cycles, and increase in the number of fertilization (p=0.01), without significant adverse effects[17].

In a culture of human neoplastic cells of various types, the extract exerted a cytotoxic action, attributed to the intracellular oxidation activity of the treatment with the extract[18]. Its ability on the biology of prostate cells was also studied, concluding that the extracts may be useful in the treatment of not only prostate cancer but also benign hyperplasia[19]. In colon carcinoma, also in cell culture, treatment with this plant induced apoptosis, suggesting a mechanism of gene activation and proving to be a useful aid in the treatment of this type of cancer[20].

Its possible use in the treatment of problems linked to menopause may be of special interest nowadays. A study in cell culture demonstrates that phytoestrogens contained in the stratum of Vitex agnus-castus can exert actions mediated by estrogen receptors, and apigenin seems to be the most active of these compounds, such as vitexin and penduletin[21]. In vitro studies have also shown that linoleic acid from the fruits of this plant can bind to estrogen receptors and interfere with gene induction, with a protective effect on breast and endometrial cancer, which is desirable in the treatment of climacteric[22]. In rabbits, the action of flavonoids from agnus castus extract in the healing of bone fractures was demonstrated, a fact that may have implications for the treatment of osteoporotic women with fractures[23]. Using a product with extracts from six plants, including Vitex, or placebo, for 3 months (50 patients between 44 and 55 years old), a progressive and marked improvement in climacteric symptoms was observed (47% with the product, 19% with placebo)[24]. Another study in which 93 climacteric women ended 16 weeks using a product combining extracts of Hypericum perforatum and Vitex agnus-castus, or placebo, however, did not show a different effect between the groups, although no important adverse effects were found and tolerability was good[25].

Toxicology

Vitex agnus-castus is quite safe and has no significant toxic effects. The adverse effects cited are mild and reversible. As it is used in the treatment of women with premenstrual syndrome, as well as in the treatment of infertility, that is, women of childbearing age and possibly ovulatory, its use is likely to occur after fertilization. And no harm to the pregnancy or fetus is reported. Its use during lactation to increase milk production has been reported in herbal medicine textbooks, but there are also reports of decreased lactation due to the suppressive action of prolactin. Although there are reports of progesteronic, emmenagogue, and abortion-preventive activity, it is not clear whether or not its use during pregnancy is harmful since the scientific evidence is poor. . Therefore, caution is recommended regarding its use in pregnant or lactating women[4].

Drug interactions

Agno casto should not be used in conjunction with drugs with dopaminergic action, such as bromocriptine and metoclopramide, or any other dopamine agonist. Also, it should not be associated with antipsychotic drugs. Caution is suggested when using hormonal contraceptives or during climacteric hormonal treatment[4].

Adverse reactions

The adverse effects mentioned in the different studies with the plant are of low intensity and reversible. Erythematous rashes, acne, itching, headache, nausea, mild gastrointestinal complaints, fatigue, dry mouth, and menstrual disorders are the most common complaints. Nocturnal seizures occurred in a patient using a combination of herbs, including monk's pepper; however, this effect does not seem to be due to the use of plant[4].

Contraindications

Due to its hypersensitivity reaction, Vitex agnus-castus is also contraindicated in pregnancy and breastfeeding women. Although there is no clinical evidence or reports of hormone interaction, based on theoretical grounds, caution is recommended when using Vitex agnus-castus with hormone therapy.

Indications

The main indications are irregularities of the menstrual cycle such as irregular bleeding, absence of menstruation, and decreased menstrual flow and premenstrual tension, especially if there are symptoms such as breast pain and fluid retention. Other indications include hyperprolactinemia, infertility due to low progesterone levels, or corpus luteum failure. In men, it is useful in cases of sexual frigidity and impotence[5].

Posology

Based on the recommendations of the German Commission E, the recommended daily dose is 40 mg of Vitex agnus-castus, once a day, on an empty stomach.

Overdose

We found no references about overdose.

Prescription information

In cases of infertility, treatment is recommended for 5–7 months[5].

In the case of premenstrual syndrome, the treatment must be carried out for at least 3 months, continuing even after the symptoms are relieved[5].

AUTHORS' CONTRIBUTIONS

CM: Project administration, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **AMF:** Project administration, Data curation, Formal Analysis, Writing – review & editing. **MSA:** Project administration, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **LHCMB:** Project administration, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **ECAV:** Writing – original draft, Writing – review & editing. **ICES:** Writing – original draft, Writing – review & editing. **ECB:** Writing – original draft, Writing – review & editing. **JMSJ:** Project administration, Data curation, Formal Analysis, Writing – review & editing.

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