



# *Vitex agnus castus* and Some Female Disorders: A Review

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## ABSTRACT

*Vitex agnus castus* L., is a deciduous tree which has been utilized in ancient Greece, Iran, Egypt and Rome for over 2500 years for a large variety of female reproductive system health difficulties. In Saudi Arabia, many women have menstrual cycle disturbances and menopausal dysfunction and many have polycystic ovary syndrome at young age. Using Vitex is not in Saudi tradition like other Arab countries. Recently, just few people used this herb for treating some infertility problems. A variety of beneficial effects of this curative herb have been reported in clinical studies, including antioxidant, anti-inflammatory, hypolipidemic, anti-diabetic, hormonal modulatory, anti-nociceptive and opioidergic activities, preventing oxidative stress and nonalcoholic fat liver disease. Adverse effects of the plant are mild and reversible. The advantages of this herb as natural medicine attract the people and make it one of best choose and utilize widely in women disorders specially that related with menopause. Its constituents could interact with dopaminergic antagonists and exhibited progestogenic and estrogenic activities. This brief review introduces this plant to Saudi society and others to expand its usage and discusses the potential effect of the plant to cure some of the women disorders displaying its main ingredients and the side effects.

**Key words:** Amenorrhea, Medicinal plant, Menopause, *Vitex agnus-castus*.

Natural sources and plants frame the promise of today's advanced pharmaceutical and contribute to a large scope to the commercial medicate productions fabricated nowadays. Almost 25% of drugs endorsed around the world are inferred from plants. Herbs still frequently used instead of drug in health cares (Wachtel-Galor *et al.*, 2011). Over the past three decades, the use of herbal medicine has augmented significantly and at least 80% of people around the world depend on them for some part of primary healthcare (Ekor, 2014). Herbal remedies have also been widely used in many developed countries and becoming mainstream in the UK and the rest of Europe, as well as in North America and Australia (Anquez-Traxler, 2011). Based on the long history of using herbal perpetration on clinical issues of various indigenous societies, the success rate of creating new drug from natural herbal sources must be higher than that from chemical perpetration (Pan *et al.*, 2013).

*Vitex agnus castus* (VAC) is one of the herbs used as a medicinal plant. It is considered a traditional herbal remedy, primarily used in Anglo-American and European practice for a variety of female reproductive dysfunction (Van Die *et al.*, 2013). It is derived from dried fruit of chastisea trees and since ancient Greece used as female boitincal health (Wuttke *et al.*, 2003). In Morocco, vitex agnus is regularly utilized in conventional medication for treatment of many medical situations such as diabetes, rheumatism, respiratory, stomach related tract, dermatological, genitourinary and glands disorders (Berrani *et al.*, 2018).

Vitex is often used to relieve the symptoms associated with female hormonal in-balances such as the depression, cramps, mood swings, water retention and weight gain. In European Medical practice and Herbalism, the Vitex recommended for uterine fibroid cysts and to assist alleviating the obnoxious side effects of menopause (Hobbs

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1991). VAC has historically been utilized in recovering several female dysfunctions encompassing premenstrual syndrome, menstrual disorders (dysmenorrhea, amenorrhea), corpus luteum insufficiency, infertility, hyper-prolactinemia, disrupted lactation, acne and menopause (Daniele *et al.*, 2005).

*Vitex agnus castus* L. is a little deciduous chaste tree that has been employed in ancient Egypt, Iran, Greece and Rome for various gynecological issues over 2500 years (Niroumand *et al.*, 2018). A variety of plant phytochemical including flavonoids and linoleic acid which may be responsible for the biological activities have been isolated from chasteberry (Chen *et al.*, 2011; Webster *et al.*, 2011).

In Saudi Arabia, many women have menstrual cycle disturbances and menopausal dysfunction and many have polycystic ovary syndrome at young age. Guraya, (2013). reported that many Saudi women have reproductive system problems such as PCOS in young age, delay in pregnancy, menstrual irregularity. Using Vitex is not common in Saudi tradition like other Arab countries. Recently, just few people used this herb for treating some infertility problems. So, this brief review to expand the use this herb and discuss the

different usages, beneficials effects of this medicinal plant and touching on the side effects.

The literature published from (1990-2019) was reviewed using the database google, scholar, PubMed, research gate and Academia. The research was carried out using various terms such as *Vitex agnus castus*, polycystic ovarian syndrome (PCOS), hormonal anomalies in female, menopause, the management of PCOS and management of menopause. All recovered articles were wisely evaluated and data were gotten.

### Characteristics of plants

*Vitex agnus-castus* is a small tree that included in the family of Verbenaceae (Ono *et al.*, 2011; Rani and Sharma., 2013; Rashed., 2013). The plant *Vitex agnus castus* is a deciduous shrub that reaches a height of up to 5 m (Berrani *et al.*, 2018). The leaves appear like fingers with 5-7 finger-like leaflets and 7.5-10 cm in diameter (Fig 1) (Niroumand *et al.*, 2018). The leaves are arranged in opposite, with a lengthened petiole. The green leaflets are linear, lanceolate, toothed and dark on the top and grey below (Ono *et al.*, 2011). The flowers are fragrant with lilac, blue, pink, or white color (Berrani *et al.*, 2018). Fruits are berries which contains four seeds resemble to black pepper (Niroumand *et al.*, 2018). The skin of the fruits is hard and has a purple to a black color, yellowish inside and half covered by their green sage-calyces. It has aromatic and spicy scent and the flavor is warm and singular after maturation (Berrani *et al.*, 2018). This plant is viewed as one of a medicinal herbs because both the fruit berry and the dried leaves have been utilized in many therapeutic issues (Mancho and Edwards., 2005; Niroumand *et al.*, 2018).

### Botany and Natural Occurrence

*Vitex agnus castus* is affiliated to Verbenaceae family, commonly known as chaste tree and monk's pepper (Ono *et al.*, 2011; Rani and Sharma., 2013). This tree grows in all Mediterranean regions, in tropical and subtropical regions (Rashed, 2013) and in temperate zone (Duymuş *et al.*, 2014). VAC distributed not only the Mediterranean Region and Central Asia, but it also can be found in Southern Europe

and cultivated in the various regions including the United States (Ono *et al.*, 2011; Li *et al.*, 2013; Rani and Sharma., 2013).

The plant often found growing next to streams and it loves water, but it could be seen growing in dry, rocky spots on the Greek islands. (Hobbs., 1991). VAC is growing in areas where the Mediterranean climate is dominant, rather rocky places, wetlands such as stream banks and valleys. VAC can also be found on limestone slopes, in sunny and warm areas (Rajić *et al.*, 2016).

### Phytochemical compounds

There are different reports on the Phytochemical continents of VAC. Fruits, flowers and leaves of VAC are reported to contain different bioactive compounds (Rajić *et al.*, 2016). It includes Vitexlactam C, Vitexlactam B (Li *et al.*, 2013), essential fatty acids, volatile oil, alkaloid, progestins, flavonoids, iridoid glycosides (Arokiyaraj *et al.*, 2009), iridoids (Rajić *et al.*, 2016), two simple phenols (Li *et al.*, 2013), diterpenoids and phytosteroids which have antihistaminic, antioxidant anti-inflammatory, hepato-protective properties (El-Nawasany., 2019).

Iridoid glycosides are mainly two (agnuside, aucubin) (Li *et al.*, 2013; Rajić *et al.*, 2016). Flavonoids named as Casticin, luteolin 7-methyl ether and luteolin 7-O-glucopyranoside (Aissaoui *et al.*, 2016), vitexin, kaempferol, quercetagenin (Rajić *et al.*, 2016), 5-hydroxy-3,6,7,42 -tetramethoxyflavone and artemetin (Li *et al.*, 2013). Progestins includes progesterone, hydroxy progesterone and androstenedione (Rajić *et al.*, 2016). Alkaloids such as viticin; volatile oil includes 1,8-cineol, limes,  $\alpha$ -pinenes,  $\beta$ -pinenes. Essential fatty acids such as palmitic acid, oleic acid and stearic acid (Rajić *et al.*, 2016). The two simple phenolic are p-hydroxybenzoic acid and p-hydroxybenzoic acid glucose ester (Li *et al.*, 2013).

The main Chemical compounds of this plant include vitexin, casticin, agnuside, p- hydroxybenzoic acid, alkaloids, diterpenoids. Flavonoids, terpenoids, neolignans, one glyceride and phenolic compounds are found in its fruits (Rafieian-Kopaei and Movahedi, 2017).

### Traditional uses

The use of VAC in medicine has a long history. Hippocrates (460-370 BC), The ophrastors (371-287 BC) and Pedanius Dioscorides (90-40 BC) already reported it on the preparation. It was used to inhibit libido, diseases of the uterus, promote wound healing and in the Middle Ages to preserve the vow of chastity so it was called chastity mud and chaste tree (Anwendung, 2009).

Since more than 2500 years, Vitex fruits have been linked to a number of gynecological issues in ancient Egypt, Greece, Iran and Rome. It was also used for its suspected libido suppression (Roemheld Hamm, 2005). It has long tradition in outdated medicine, as a medicinal plant. It has been commonly used since 17th century as a popular folk treatment for female reproductive dysfunction encompassing corpus luteum insufficiency, premenstrual syndrome (PMS), menopausal symptoms and inadequate milk production

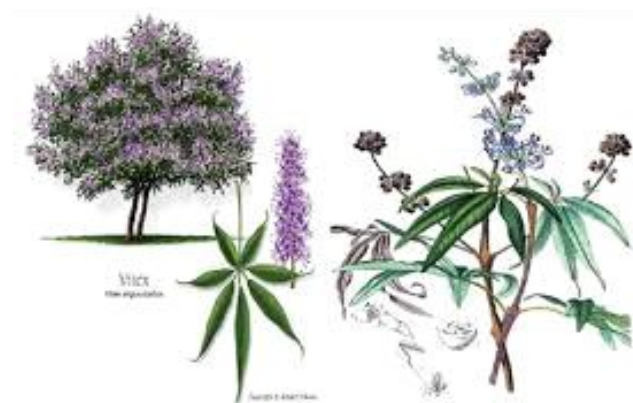


Fig 1: A graphic of *Vitex agnus Castus* tre (Niroumand *et al.*, 2018).

(Duymuş *et al.*, 2014). It is used as diuretic, digestive antifungal, against anxiety and stomachache in Anatolian folk medicine (Kuruuzum\_Uz *et al.*, 2003). It has been utilized for reproductive disorders in female since Greek and Roman times. In 4<sup>th</sup> century B.C., Hipocrates suggested the plant for treating injuries, inflammation and swelling of spleen. (Daniele *et al.*, 2005).

During the past 50, years, chasteberry in Europe has been commonly used in premenstrual syndrome (PMS), menstrual bleeding, menstrual disorders and uterine dysfunction. The German commission E accepts the application of VAC by family doctors and gynecologists for menstrual cycle disorders, cyclic breast pain and PMS (Roemheld-Hamm, 2005).

Vitex fruits and leaves are ideal candidate as flavor and spice to be used in food and the berries as pepper alternative in Persian traditional medicine (Li *et al.*, 2013). The fruits have been suggested as hormone-like medication to improve menstrual disorders and as antiepileptic, carminative, energizer, anticonvulsant, tranquilizer agents and to recover the digestive dysfunction (Ghannadi *et al.*, 2012). According to ethnomedicine of various nations, this shrub is utilized to relieve menstrual pain, spasmodic dysmenorrhea, insufficient lactation, treatment of acne and eyes disease, stomach pain, snake and scorpion bites and as antispasmodic, aphrodisiac and as emmenagogue agents (Niroumand *et al.*, 2018). In folk medicine, it has been commonly used for treating insufficiency of ovaries, uterine bleeding, premenstrual syndrome, fibroid cysts, infertility and acne of teenagers. It has also historically been used to promote digestion, sedation and anti-infection (Arokiyaraj *et al.*, 2009).

The fruits of Vitex are called Manjingzi in Chines Pharmacopoeia. Manjingzi is a Chines traditional medicine used to recover ophthalmodynia, migraines and headaches. The leaves of Vitex are used in treating asthma, phlegm and coughs (Yao *et al.*, 2016). Several parts of Vitex including seeds, roots and leaves are commonly used as anti-inflammatory, anti-rheumatism, analgesic and insecticide agents (Zheng *et al.*, 2015).

In Arabic countries, the dried seed is taken orally as a lactogenic agent and emmenagogue. The hot water extract is used as a contraceptive and the entire plant is inhaled, by fumigation, as an emmenagogue (Razzack, 1980). In Morocco, the seed and leaf powder used externally or fumigation to treat burn, cold and headache (Saadi *et al.*, 2013).

### Alternative and complementary medicine uses

Nowadays, VAC is widely used in USA in complementary and alternative medicines as a medicinal plant to treat premenstrual syndrome (PMS) (Weis and Kaapen, 2009, Niroumand *et al.*, 2018). It has fewer side effects so it used as effective alternative herbal medicine to treat symptom related to PMS (Röhl *et al.*, 2017). Fruits traditionally used to treat minor symptoms of PMS such as monthly pain, mood disorders and swelling (Dickerson, 2003; Röhl *et al.*, 2017). In Europe, the fruits extract used as effective alternative

agent instead the chemical drugs to treat PSM (Berger *et al.*, 2000). The agency of European medicines and Health authorities in Germany have confirmed the positive effects of the VAC on menstrual cycle management and the PMS and Mastalgia care (Girman *et al.*, 2003 and Mari *et al.*, 2015). It well known in North America and in Europe as an effective substitute instead of the pharmaceutical drugs in treating other different disorders such digestive complaints, Acne, infertilities and lactation supports (Niroumand *et al.*, 2018).

Vitex has been included in numbers of herbal perpetrations which used in clinical treatment. Clinical evidence indicates that the extract of VAC dried fruits is effective for the recovery of premenstrual syndrome, menstrual abnormality, amenorrhea, mastodynia and hyperprolactinemia which all due to elevated the level of prolactin (Azarnia *et al.*, 2007). Both fluid extract or dried leaves extract in pill form were used in clinical trials at various doses (Azarnia *et al.*, 2007; Carmichael and Can, 2008; Dugoua *et al.*, 2008). A routine consumption of 30-40 mg of dried herb in capsules or liquid preparation is recommended by German commission E monograph. This is normally taken once in the morning sequentially with liquid for several months. For premenstrual syndrome or heavy period, the herb can be consumed for 4-6 months on a regular basis. Infertile women with amenorrhea can consume the *V. agnus castus* for 12-18 months unless they are pregnant during treatment (Healthnotes Resource, 2006).

### Clinical application

Chaste tree has dopaminergic, estrogenic, cytotoxic and probably antibiotic properties. Clinical studies have shown that it can be used to cure galactorrhea, mastodynia, hyperprolactinemia and premenstrual syndrome. Sub-fertile women suffering from hormonal problems which resulted from hyperprolactinemia with consecutive luteal phase insufficiency, using chaste tree preparation can be very helpful (Anwendung, 2009).

### Female reproductive system hormonal disorders

The, development and the function of the female reproductive system depends upon hormone concentrations and balance. Endocrine dysfunctions may lead to many abnormalities *e.g.*, menstrual cycle irregularities impaired fertilities endometriosis and polycystic ovarian syndrome (PCOS). These abnormalities may results from modulation of the concentration of estrogens thecal androgens and thyroid hormones (Nicolopoulou-Stamati and Pitsos, 2001). Irregular or absent menstrual periods due to ovulation problem which account for subfertility in 20-25% of couples It can be, substantiated through measurement of reproductive hormones (Bretveld *et al.*, 2006).

Vitex modulates the rise or reduction in sex hormones by physiological and pharmacological activities (Liu *et al.*, 2004). Studies by Jelodar and Askari (2012) demonstrated that the vitex extract rise the progesterone concentration and reduce the testosterone concentration but Vitex doesn't change the level of de-hydro-epi-androstenedione

and estrogen in animal with polycystic ovary syndrome (PCOS). Ibrahim *et al.* (2008) found that *Vitex* rises the level of progesterone and estrogen hormone and decrease the level of LH without affecting FSH hormone in ovariectomized rats.

*Vitex* secretes substantial amount of androgen that converted to estrogen (Ibrahim *et al.*, 2008). Apigenin is the main active phytoestrogen in *vitex*, can bind to the estrogen receptors (Jarry *et al.*, 2003). Linoleic acid which considered one of estrogenic substance in *Vitex*, can binding to estrogen receptors and stimulate certain estrogen inducible genes (Liu *et al.*, 2004). *Vitex* modulates the Luteal phase disorders in female and rises the progesterone level, thereby the chance of conception is improved (Ahangarpour *et al.*, 2016). Lu *et al.* (2011) reported that *Vitex* probably elevates the progesterone concentration which leads to regulate luteal phase dysfunction.

Earlier research showed that VAC fruit extract controls the imbalance of sex hormone levels like progesterone hormone in PSM (Milewicz *et al.*, 1993). Xu *et al.* (2014) revealed that *Vitex* returned the regular function of the abnormal estrous cycle in D-galactose and aging group female mice, *Vitex*, also lightly rise the weight of ovaries and uterus and ovaries and uterus weight / body weight percentage in D-galactose and aging group mice.

#### Primary dysmenorrhea

Many women monthly suffer from menstrual cramps which sever enough to impact their quality life and work productivity (Ju *et al.*, 2014). In primary dysmenorrhea, a condition related to PMS, intense uterine contractions are thought to trigger moderate to intense pain and mediated by the release of prostaglandins, leukotrienes and infiltration of leukocytes that normally accompany the breakdown of endometrial lining (Röhl *et al.*, 2017). Primary dysmenorrhea identified by hyper-production of uterine prostaglandins, especially PGF<sub>2a</sub> and PGF<sub>2</sub> resulting in increased uterine tone and high-amplitude contractions (Iacovides *et al.*, 2015; Bernardi *et al.*, 2017). Prostaglandin production is controlled by progesterone and progesterone level drops immediately prior to menstruation and prostaglandin level increase (Bernardi *et al.*, 2017). It was found that *Vitex* extract modulate a number of potential mechanism responsible for dysmenorrhea. The studies on *Vitex* extract showed it is potent anti-inflammatory as it has ability to suppress leukotriene synthesis, cytokines release and reactive oxygen species (ROS) production from isolated leukocytes which prevent spasmodic action and support beneficial effects of extract (Röhl *et al.*, 2017).

#### Menopausal symptoms

Menopause is transition natural period occurs in women life (Norzi *et al.*, 2010). Menopausal symptoms have significant undesirable effects on women quality life (Naseri *et al.*, 2019). During menopause the activities of estrogen and progesterone dramatically reduced (Tanira *et al.*, 2009). Taking VAC extract as a phytoestrogenic therapy can relieve menopausal symptoms in women (Naseri *et al.*, 2019).

Conducting numerous alternative or complementary therapy to alleviate the unpleasant effects of menopause is commonly acceptable today. Amongst, phytoestrogens are conducted as hormonal remedies in menopausal women; which have less possible side effects due to their herbal source (Jing *et al.*, 2009).

*Vitex agnus-castus* has phytoestrogenic activities (Ahangarpour *et al.*, 2016) and used to cure irregular menstruation, menopausal complication and menstrual pain (Naseri *et al.*, 2019). The dopaminergic activities of VAC are documented in pharmacological research, intimacy to opioid receptors and capability to rise melatonin secretion support the *Vitex* activities to reduce the menopausal symptoms (Van Die *et al.*, 2009).

Furthermore *Vitex agnus-castus* has antiaging, antioxidant effects with high level of phytoestrogen. It was established that the *Vitex* decreases many aging problems in female mice reproductive system. It can be useful for some aging events such as oxidative stress, deficiency women's sex hormones and an atrophic endometrium (Ahangarpour *et al.*, 2016).

#### Adverse effects

The safety of VAC was studied and the adverse effects have been found to be mild and reversible (Bornhorst, 1996; dugoua *et al.*, 2008; Ho Sh *et al.*, 2011; Rani and Sharma 2013; Niroumand *et al.*, 2018). The most common ones emphasize: Nausea, headache, mild gastrointestinal complaints, fatigue, Menorrhagia, dry mouth, acne, pruritus and erythematous rash (Rani and Sharma 2013; Daniele *et al.*, 2005).

Randomized controlled trials conducted in a woman with PSM, luteal phase defects or premenstrual dysphoric disorder. Some of these studies did not mention any adverse effects and showed few adverse effects which included acne, multiple abscesses, inter-menstrual bleeding, urticarial and each event was reported once only and resolved without discontinuation. Non-randomized clinical trials conducted in women and men treated with VAC at least for 3 months, no mention of adverse events was made (Claudia *et al.*, 2005).

#### CONCLUSION

*Vitex agnus castus* has long history as therapeutically herb and considered one of the most beneficial medicinal herbs, especially for women. It reduces symptoms of premenstrual syndrome, decreases prolactin hormone and helps to regulate reproductive hormones in women. It also relieves menopausal symptoms, improves the bad impact of menopause and improves fertility in women. Side effects are mild and reversible, so many studies have proven its safety and the usefulness of this plant.

#### REFERENCES

- Ahangarpour, A., Najimi, S.A. and Farbood, Y. (2016). Effects of *Vitex agnus-castus* fruit on sex hormones and antioxidant indices in a d-galactose-induced aging female mouse model. *Journal of the Chinese Medical Association*. 79(11): 589-596.



- Aissaoui, H., Algabr, M. and Mezhoud, S. (2016). Chemical constituents of *Vitex agnus-castus* (Verbenaceae). *Pharma Chemica*. 8: 491-4.
- Anquez-Traxler, C. (2011). The legal and regulatory framework of herbal medicinal products in the European Union: a focus on the traditional herbal medicines category. *Drug Inf. J.* 45: 15-23.
- Anwendung, K. (2009). *Vitex agnus castus*. *Gynäkologische Endokrinologie*. 7: 33-38 DOI 10.1007/s10304-008-0285-2.
- Arokiyaraj, S., Perinbam, K., Agastian, P. and Kumar, R.M. (2009). Phytochemical analysis and antibacterial activity of *Vitex agnus-castus*. *International Journal of Green Pharmacy (IJGP)*. 3(2): 162-164.
- Azarnia, M., Ejtemaei-Mehr, S., Shakoor, A. and Ansari, A. (2007). Effects of *Vitex agnus-castus* on mice fetus development. *Acta Med Iran*. 45: 264-70.
- Berger, D., Schaffner, W., Schrader, E., Meier, B. and Brattstrom, A. (2000). Efficacy of *Vitex agnus castus* L. extract Ze 440 in patients with pre-menstrual syndrome (PMS). *Arch Gynecol. Obstet*. 264(3): 150-3.
- Bernardi, M., Lazzeri, L., Perelli, F., Reis, F.M. and Petraglia, F. (2017). Dysmenorrhea and related disorders. *F1000Research*. 6: 1645. <https://doi.org/10.12688/f1000research.11682.1>.
- Berrani, A., Lrhorfi, L.A., Larbi, O.M., El Hessni, A., Zouarhi, M., Erahali, D. and Bengueddour, R. (2018). Hypoglycemic effect of *Vitex agnus castus* extract in diabetic rats induced by streptozotocin. *Phytothérapie*. 16(S1): S40-S47.
- Bornhorst, H.L. (1996). Growing native Hawaiian plants: A how-to guide for the gardener. Honolulu: The Bess Press. 26-27.
- Bretveld, R.W., Thomas, C.M., Scheepers, P.T., Zielhuis, G.A. and Roeleveld, N. (2006). Pesticide exposure: The hormonal function of the female reproductive system disrupted? *Reproductive Biology and Endocrinology*. 4(1): 30.
- Carmichael, A.R. (2008). Can *Vitex agnus castus* be used for the treatment of mastalgia? What is the current evidence? *Evid Based Complement Alternat. Med*. 5: 247-50.
- Chen, S.N., Friesen, J.B., Webster, D., Nikolic, D., van Breemen, R.B., Wang, Z.J., Fong, H.H., Farnsworth, N.R. and Pauli, G.F. (2011). Phytoconstituents from *Vitex agnus-castus* fruits. *Fitoterapia*. 82: 528-533.
- Claudia, D., Coon, T. and Max, P.H. (2005). *Vitex agnus castus*: A Systematic Review of Adverse Events. *Drug Safety*. 28: 319-32.
- Daniele, C., Coon, J.T., Pittler, M.H. and Ernst, E. (2005). *Vitex agnus castus*. *Drug safety*. 28(4): 319-332.
- Dickerson, L.M., Mazyck, P.J. and Hunter, M.H. (2003). Premenstrual syndrome. *Am. Fam. Physician*. 67(8): 1743-52.
- Dugoua, J.J., Seely, D., Perri, D., Koren, G. and Mills, E. (2008). Safety and efficacy of chastetree (*Vitex agnus-castus*) during pregnancy and lactation. *Can. J. Clin. Pharmacol*. 15: e74-9.
- Duymuş, H.G., Çiftçi, G.A., Yıldırım, Ş.U., Demirci, B. and Kırimer, N. (2014). The cytotoxic activity of *Vitex agnus castus* L. essential oils and their biochemical mechanisms. *Industrial Crops and Products*. 55: 33-42.
- Ekor, M. (2014). The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. *Frontiers in Pharmacology*. 4: 177.
- El-Nawasany, L.I. (2019). The use of *Vitex Agnus-Castus* to produce functional stirred yoghurt. *J. of Food and Dairy Sci., Mansoura Univ*. 10(9): 297-301.
- Ghannadi, A., Bagherinejad, M., Abedi, D., Jalali, M., Absalan, B. and Sadeghi, N. (2012). Antibacterial activity and composition of essential oils from *Pelargonium graveolens* L'her and *Vitex agnus-castus* L. *Iran J. Microbiol*. 4: 171 6.
- Girman, A., Lee, R. and Kligler, B. (2003). An integrative medicine approach to premenstrual syndrome. *Am J. Obstet. Gynecol*. 188: S56 65.
- Guraya, S.S. (2013). Prevalence and ultrasound features of polycystic ovaries in young unmarried Saudi females. *Journal of Microscopy and Ultrastructure*. 1(1-2): 30-34. <http://www.healthnotes.com>.
- Healthnotes Resource Page. *Vitex agnus-castus*. (2006). [Last accessed 2008 May 10]. Available from: <http://www.healthnotes.com>.
- Ho, S.H., Singh, M., Holloway, A.C. and Crankshaw, D.J. (2011). The effects of commercial preparations of herbal supplements commonly used by women on the biotransformation of fluorogenic substrates by human cytochromes P450. *Phytother Res*. 25: 983 9.
- Hobbs, C. (1991). The Chaste Tree: *Vitex agnus castus*. *Pharmacy in History*. 33(1): 19-24.
- Iacovides, S., Avidon, I. and Baker, F.C. (2015). What we know about primary dysmenorrhea today: a critical review. *Human Reproduction Update*. 21(6): 762-778.
- Ibrahim, N., Shalaby, A., Farag, R., Elbaroty, G., Nofal, S. and Hassan, E. (2008). Gynecological efficacy and chemical investigation of *Vitex agnus-castus* L. fruits growing in Egypt. *Nat. Prod. Res*. 2: 537e46.
- Jarry, H., Spengler, B., Porzel, A., Schmidt, J., Wuttke, W. and Christoffel, V. (2003) Evidence for estrogen receptor beta-selective activity of *Vitex agnus-castus* and isolated flavones. *Planta Medica*. 69: 945e7.
- Jelodar, G. and Askari, K. (2012). Effect of *Vitex agnus-castus* fruits hydroalcoholic extract on sex hormones in rat with induced polycystic ovary syndrome (PCOS). *Physiology and Pharmacology*. 16: 62e9.
- Jing, Z., Yang, X., Ismail, K.M., Chen, X. and Wu T. (2009). Chinese herbal medicine for premenstrual syndrome. *Cochrane Database Syst. Rev*. 21 (1): CD006414.
- Ju, H., Jones, M. and Mishra, G. (2014). The prevalence and risk factors of dysmenorrhea. *Epidemiologic Reviews*. 36(1): 104-113.
- Kuruuzum-Uz, A., Stroch, K., Demirezer, O. and Zeeck, A. (2003). Glucosides from *vitex agnus castus*. *Phytochemistry*. 63: 959-964.
- Li, S., Qiu, S., Yao, P., Sun, H., Fong, H.H. and Zhang, H. (2013). Compounds from the fruits of the popular European medicinal plant *Vitex agnus-castus* in chemoprevention via NADP (H): Quinone oxidoreductase type 1 induction. *Evidence Based Complementary and Alternative Medicine*. 2013: 432829, 7.
- Liu, J., Burdette, J., Sun, Y., Deng, S., Schlecht, S., et al. (2004). Isolation of linoleic acid as an estrogenic compound from the fruits of *Vitex agnus castus* L. (chaste-berry). *Phytomedicine*. 11: 18e23.

- Lu, A., Beehner, J.C., Czekala, N.M., Koenig, A., Larney, E. and Borries, C. (2011). Phytochemicals and reproductive function in wild female Phayre's leaf monkeys (*Trachypithecus phayrei crepusculus*). *Hormones and Behavior*. 59: 28e36.
- Mancho, P. and Edwards, Q.T. (2005). Chaste tree for premenstrual syndrome. An evolving therapy in the United States. *Advance for Nurse Practitioners*. 13: 43-4, 46.
- Mari, A., Montoro, P., D'Urso, G., Macchia, M., Pizza, C. and Piacente, S. (2015) Metabolic profiling of *Vitex agnus castus* leaves, fruits and sprouts: Analysis by LC/ESI/ (QqQ) MS and (HR) LC/ESI/ (Orbitrap)/MS n. *Journal of Pharmaceutical and Biomedical Analysis*. 102: 215-21.
- Milewicz, A., Gejdel, E., Sworen, H., Sienkiewicz, K., Jedrzejak, J., Teucher, T. and Schmitz, H. (1993). *Vitex agnus castus* extract in the treatment of luteal phase defects due to latent hyperprolactinemia. Results of a randomized placebo-controlled double-blind study. *Arzneimittelforschung*. 43: 752e6.
- Naseri, R., Farnia, V., Yazdchi, K., Alikhani, M., Basanj, B. and Salemi, S. (2019). Comparison of *Vitex agnus-castus* extracts with placebo in reducing menopausal symptoms: A randomized double-blind study. *Korean Journal of Family Medicine*. 40(6): 362-367. <https://doi.org/10.4082/kjfm.18.0067>.
- Nicolopoulou-Stamati, P. and Pitsos, M.A. (2001). The impact of endocrine disrupters on the female reproductive system. *Human, Reproduction, Update*. 7(3): 323-330.
- Niroumand, M.C., Heydarpour, F. and Farzaei, M.H. (2018). Pharmacological and therapeutic effects of *Vitex agnus-castus* L.: A review. *Pharmacognosy Reviews*. 12: 103-14.
- Norozi, A., Kasiri, N. and Aslami, A. (2010). Attitudes and perceptions of women 45 years of menopause. *Journal of Health Systems Research*. 7:14.
- Ono, M., Eguchi, K., Konoshita, M., Furusawa, C., Sakamoto, J., Yasuda, S., Ikeda, T., Okawa, M., Kinjo, J., Yoshimitsu, H. and Nohara, T. (2011). A new diterpenoid glucoside and two new diterpenoids from the fruit of *Vitex agnus-castus*. *Chemical Pharmaceutical Buletin* (Tokyo). 59: 392-6.
- Pan, S.Y., Zhou, S.F., Gao, S.H., Yu, Z.L., Zhang, S.F., Tang, M.K., Sun, J., Ma, D., Han, Y., Fong, W. and Ko, K. (2013). New perspectives on how to discover drugs from herbal medicines: CAM's outstanding contribution to modern therapeutics. *Evidence-Based Complementary and Alternative Medicine*. 2013: 25.
- Rafieian-Kopaei, M. and Movahedi, M. (2017). Systematic review of premenstrual, postmenstrual and infertility disorders of *Vitex agnus castus*. *Electronic Physician*. 9(1): 3685.
- Rajić, M., Molnar, M., Bilić, M. and Jokić, S. (2016). The impact of extraction methods on isolation of pharmacologically active compounds from *Vitex agnus-castus*-a review. *International Journal of Pharmaceutical Research and Allied Sciences*. 5(4): 15-21.
- Rani, A. and Sharma, A. (2013). The genus *Vitex*: A review. *Pharmacognosy Reviews*. 7(14):188.
- Rashed, K.N. (2013). Antioxidant activity of different extracts of *Vitex agnus-castus* (L.) and phytochemical profile. *Research in Pharmacy*. 3(6): 01-05.
- Razzack, H.M.A. (1980). The concept of birth control in Unani medical literature. Unpublished Manuscript of the Author, 64 pp.
- Roemheld Hamm, B. (2005). Chasteberry. *American Family Physician*. 72: 821-4.
- Röhl, J., Werz, O., Ammendola, A. and Künstle, G. (2017). *Vitex agnus-castus* dry extract BNO 1095 (Agnucaston®) inhibits uterine hyper-contractions and inflammation in experimental models for primary dysmenorrhea. *Clinical Phytoscience*. 2(1): 1-12.
- Saadi, B., Msanda, F. and Boubaker, H. (2013). Contributions of folk medicine knowledge in Southwestern Morocco: the case of rural communities of Imouzzer Ida Outanane Region. *International Journal of Medicinal Plant Research*. 2(1): 135-145.
- Tanira, S., Wazed, F., Sultana, A., Amin, R., Sultana, K. and Ahmad S. (2009). Knowledge, attitude and experience of menopause an urban based study in Bangladesh. *Journal of Dhaka Medical College*. 18: 33-6.
- van Die, M.D., Burger, H.G., Teede, H.J. and Bone, K.M. (2009). *Vitex agnus-castus* (Chaste-Tree/Berry) in the treatment of menopause-related complaints. *The Journal of Alternative and Complementary Medicine*. 15(8): 853-862.
- van Die, M.D., Burger, H.G., Teede, H.J. and Bone, K.M. (2013). *Vitex agnus-castus* extracts for female reproductive disorders: a systematic review of clinical trials. *Planta Medica*. 79(07): 562-575.
- Wachtel-Galor, S. and Benzie I.F.F. (2011). Herbal Medicine: An Introduction to Its History, Usage, Regulation, Current Trends and Research Needs. In: *Herbal Medicine: Biomolecular and Clinical Aspects*. [Benzie I.F.F., Wachtel-Galor S., (editors)]. 2<sup>nd</sup> edition. Boca Raton (FL): CRC Press/Taylor and Francis, Chapter 1. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK92773/>.
- Webster, D.E., He, Y., Chen, S.N., Pauli, G.F., Farnsworth, N.R. and Wang, Z.J. (2011). Opioidergic mechanisms underlying the actions of *Vitex agnus-castus* L. *Biochemical Pharmacology*. 81(1): 170-177.
- Weisz, G. and Knaapen, L. (2009). Diagnosing and treating premenstrual syndrome in five Western Nations. *Social Science and Medicine*. 68: 1498-505.
- Wuttke, W., Jarry, H., Christoffel, V., Spengler, B. and Seidlová-Wuttke, D. (2003) Chaste tree (*Vitex agnus-castus*): pharmacology and clinical indications. *Phytomedicine*. 10: 348-357.
- Xu, Y., Ding, J., Ma, X.P., Ma, Y.H., Liu, Z.Q. and Lin, N. (2014). Treatment with Panax ginseng antagonizes the estrogen decline in ovariectomized mice. *International Journal of Molecular Sciences*. 15: 7827e40.
- Yao, J. L., Fang, S. M., Liu, R., Oppong, M. B., Liu, E. W., Fan, G. W. and Zhang, H. (2016). A Review on the Terpenes from Genus *Vitex*. *Molecules* (Basel, Switzerland). 21(9): 1179. <https://doi.org/10.3390/molecules21091179>.
- Zheng, C. J., Li, H. Q., Ren, S. C., Xu, C. L., Rahman, K., Qin, L. P. and Sun, Y. H. (2015). Phytochemical and pharmacological profile of *Vitex negundo*. *Phytotherapy Research*. 29(5): 633-647.