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THERAPEUTIC ROLE OF VITEXAGNUS-CASTUS PCOS AND HORMONAL DYSREGULATION: A REVIEW

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(Chaste tree)

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ABSTRACT: Polycystic Ovary Syndrome (PCOS) is a prevalent endocrine disorder characterized by hormonal imbalance, ovarian dysfunction, and metabolic complications, significantly impacting women's reproductive health and quality of life. It is mainly characterized by hyperandrogenism, menstrual irregularities, and hormonal dysfunctions, which can lead to infertility and metabolic difficulties such as type 2 diabetes. Even though traditional pharmacological treatments such as oral contraceptives and insulin-sensitizing agents are effective, they are usually associated with side effects and long-term complications. Phytotherapeutics have emerged as promising adjuncts in PCOS management. *Vitex agnus-castus* (chaste tree), is a medicinal plant traditionally used to treat reproductive disorders. Its bioactive constituents, particularly diterpenes, influence prolactin secretion and restore luteinizing hormone balance, thereby improving ovulatory function and alleviating symptoms such as menstrual irregularities, acne, and infertility. Recent evidence highlights its role in enhancing progesterone levels and supporting follicular maturation, positioning *Vitex agnus-castus* as a natural therapeutic candidate in PCOS care. This manuscript explores the pharmacological mechanisms, formulation strategies, and clinical relevance of *Vitex agnus-castus* within the broader framework of lifestyle disorder management, underscoring its potential to complement modern pharmaceuticals in achieving patient-centric, sustainable outcomes.

INTRODUCTION: Polycystic Ovarian Syndrome (PCOS) is a multifaceted endocrine and metabolic disorder that predominantly affects women of reproductive age, with a global prevalence estimated between 6–20%. Clinically, PCOS is diagnosed by prolonged menstrual cycles exceeding 35 days and fewer than 10 cycles annually, accompanied by symptoms such as acne, obesity, alopecia, hypertension, and irregular menstruation.

The hormonal imbalances underlying PCOS particularly hyperandrogenism and disrupted gonadotropin secretion contribute to infertility and increase the risk of chronic metabolic conditions, including type 2 diabetes. Management of PCOS typically involves lifestyle interventions, pharmacological therapies, and, in some cases, surgical procedures.

Conventional medications such as metformin, clomiphene citrate, tamoxifen, and oral contraceptives remain widely used, though their long-term application is often limited by adverse effects. This has prompted growing interest in herbal therapeutics as adjunctive strategies, especially for mild presentations. Among these, *Vitex agnus-castus* (chaste tree berry) is notable as

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one of the oldest botanical remedies for female infertility and menstrual irregularities. Its phytoconstituents interact with dopamine, opioid, and estrogen receptors, lowering prolactin levels and modulating luteinizing hormone secretion, thereby restoring estrogen progesterone balance through regulation of the hypothalamic pituitary ovarian axis. Recent advances in reproductive endocrinology have highlighted kisspeptin, a hypothalamic neuropeptide that governs GnRH release and plays a pivotal role in puberty, ovulation, and lactation. Modulating kisspeptin signaling is emerging as a promising therapeutic approach for PCOS. Identifying the genetic and molecular targets influenced by *Vitex agnus-castus* could further refine treatment strategies and expand its clinical relevance. Despite its therapeutic potential, reported adverse effects including headache, nausea, gastrointestinal disturbances, acne, pruritus, and menstrual irregularities necessitate careful monitoring. Moreover, its ovarian-stimulating properties contraindicate use during pregnancy due to the risk of miscarriage. This review aims to critically examine the therapeutic role of *Vitex agnus-castus* in PCOS management, focusing on its phytoconstituent profile, mechanisms of hormonal regulation, preclinical and clinical evidence, and future prospects for integration into patient-centred treatment paradigms¹⁻⁵.

PCOS (Polycystic Ovary Syndrome) - Pathophysiology and Clinical Manifestation:

Polycystic Ovary Syndrome (PCOS) is a common multifactorial endocrine and metabolic disorder among reproductive-age female with a worldwide occurrence rate ranging between 4-21 per cent depending on the diagnostic criteria. PCOS exhibits hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology, most of the time, expressed by insulin resistance, metabolic abnormalities, and reproductive dysfunction⁶.

Pathophysiology and Hormonal Dysregulation:

The hormonal imbalance along the hypothalamic-pituitary-ovarian (HPO) axis is the feature of PCOS:

Neuroendocrine Change: GnRH pulse frequency increases in PCOS women, resulting in a subsequent surge of LH/FSH ratio and

subsequently exciting androgen production in the ovarian theca cells, and disrupting normal folliculogenesis.

Hyperandrogenism: Hyperandrogenism is the increased quantity of androgens, predominantly testosterone, due to intrinsic ovarian steroidogenic disequilibrium and gives rise to medical appearances such as hirsutism, acne, and alopecia⁷.

Insulin Resistance: A large proportion of PCOS women are insulin resistant, irrespective of obesity, which predisposes them to hyperandrogenism by dipping the formation of hepatic sex hormone-binding globulin (SHBG) and enhancing androgen availability.

The outcome of this complex interaction of endocrine processes is anovulation or oligo-ovulation, a disorderly menstrual cycle and, as a result, malfunction and infertility of reproductive processes⁸.

Clinical Manifestations:

Women with PCOS Normally Exhibit:

- ❖ Menstrual abnormalities and anovulation.
- ❖ Hyperandrogenic (e.g. hirsutism, acne)
- ❖ Metabolic, e.g. insulin resistance and dyslipidemia.
- ❖ Subfertility and infertility.
- ❖ Cardiometabolic long-term effects include type 2 diabetes and cardiovascular disease^{9, 10}.

***Vitex agnus-castus* (VAC) – Biology and Clinical**

Intervention: *Vitex agnus-castus* fruit having a high in dietary fiber, Sorbitol and arabinos were the major soluble sugars and the principal macro element is potassium and calcium and the micro element is iron and zinc it also 41 volatile compounds. If decoction was done then it has phenols, flavonoids, flavanols, tannins, diterpenoids, iridoids, volatile oils, essential fatty acids and Orthobenzidiol content^{11, 12}. It shows antioxidant activity, DNA protection power, antibacterial, antifungal^{13, 14}, analgesic, anti-inflammatory, diuretics and gastroprotective activity¹⁵. It has medicinal properties that help in the treatment of several diseases¹⁶.

Many medicinal belongs to the families like Rosaceae, Asteraceae, and Lamiaceae. And the best method to prepare the compound or substance used for medicinal purposes is decoction and infusion ¹⁷. VAC was used to treat several alignments and is still widely used. It belongs to the Lamiaceae family ¹⁸. It is generally safe, and thus this is a very popular choice for research. It is widely grown on the riverside of the Mediterranean, Central Asian and South European regions. Every part of this plant has medicinal properties ¹⁹. And the most widely used part is dried fruit, which is already ripe. According to various studies, it was observed

that VAC have several beneficial effects in disorders associated with females, such as menstrual pain and spasmodic dysmenorrhea ²⁰. It also has an effect on Eye Disease, Snake Bite, Scorpion String, rheumatoid, swelling, acne, and stomach-ache ²¹. Due to its antioxidant property, it shows a significant effect in the treatment of diabetes mellitus, cancer Neurodegenerative cardiovascular disorders. It is often associated with after effects like skin issues, Headaches, diarrhea, vertigo, and palpitations. But these effects are temporary, it disappears after stopping their use ²².



FIG. 1: ARIEAL VIEW OF VITEX AGNUS-CASTUS (CHASTE TREE)

Biological Activity of VAC: The pharmaceutical industry is working on various forms of extraction of the plant active metabolites to convert them into a drug *Vitex agnus-castus* L. fruits are conventionally used in consumption as food to

increase the volume of milk and to treat flatulence and diarrhea and cyclical mastalgia, menopause, acne, fertility issues, severe premenstrual syndrome and other menstrual disorders (amenia, dysmenorrhea) ^{23, 25}.

TABLE 1: MAJOR PHYTOCONSTITUENTS PRESENT IN VAC AND ITS PHARMACOLOGICAL ACTION

S. no.	Phytochemicals	Major Constituent	Parts of plants	Pharmacological action	Ref.
1.	Diterpenoids	Rotundifuran, Vitexilactone, Clerodadienol, clerodadienone	Fruits (berries)	Dopaminergic activity, reduces prolactin secretion and regulates the HPO axis	(24)
2.	Flavonoids	Casticin, Apigenin, Luteolin, Penduletin, isovitexin	Fruits and leaves	Antioxidant, anti- inflammatory and hormone modulating effects	(26)
3.	Iridoid glycosides	Agnuside, aucubin, Eurostoside	Fruits	Marker compounds used for extract standardization, anti-inflammatory, and hepatoprotective properties	(27)
4.	Phenolic Compounds	Chlorogenic acid, p- hydroxybenzoic acid	Fruits	Antioxidant activity and protection against oxidative stress	(28)
5.	Essential oils	1,8-Cineole, sabinene, Limonene, α-Pinene	Fruits	Aromatic compounds with mild antimicrobial and therapeutic effect	(29)
6.	Fatty Acids	Linolenic acid, Oleic acid, Palmitic acid	Seeds	Contribute to anti-inflammatory and metabolic regulatory activity.	(30)

TABLE 2: CLINICAL INTERVENTION FOR VITEX AGNUS-CASTUS

S. no.	Agent	MOA	NCT
1.	Agnucaston Tablets	A Clinical Trial to Evaluate the Efficacy and Safety of Agnucaston Tablets in the Treatment of Premenstrual Syndrome (PMS) (ACT-RCT-C 01)	NCT00672607 (31)
2.	<i>Vitex agnus-castus</i> BNO 1095 (20 mg)	Efficacy of <i>Vitex agnus-castus</i> BNO 1095 (20 mg) in Women with Primary Dysmenorrhea	NCT06211049 (32, 33)
3.	<i>Vitex agnus-castus</i> Extract	Possibilities of Phytomedicine in Monotherapy of Benign Breast Diseases	NCT05717894 (34)

Mechanism of action of *Vitex agnus-castus*:

Vitex has the ability to influence the discharge of different hormones in the body. The level of the hormone was tested in animals based on the treatment with *vitex*, which confirmed its role. It influences the activity of the hypothalamic kisspeptin, adrenocorticotrophic hormone of the pituitary, TSH, prolactin, FSH, LH and other peripheral hormones and is accompanying with a broad range of physiological processes such as metabolism, immunity, etc³⁵.

Research indicates that *vitex* suppresses the discharge of pituitary hormones such as prolactin, gonadotropin and testosterone by interacting with the dopamine-2 receptors, and thereafter its down-regulation begins in the pituitary gland.

Vitex is also analgesic, and it can be achieved by stimulating endogenous opioids, muscarinic and acetyl cholinergic nerve system receptors. The phytoconstituents that mediate the analgesic activity include apigenin, 3-methylkaempferol, luteolin and casticin that interact with delta and mu opioid receptors²⁶.

In *in-vitro* experiments, the actions of *vitex* flavonoids, casticin, quercetagenin and isovitexin on the oestrogen beta receptor have been demonstrated and consequently prevent age-related osteoporosis, neurodegenerative diseases, and stroke.

It also possesses anti-inflammatory properties, and this is the reason why it has anti-cancer³⁶. Isoflavone such as casticin also prevents inflammation by suppressing the transcription factors NFkB, Akt and mitogen-activated protein kinase (MAPK) pathways, lymphocytes proliferation and expression of inflammation protein cytokines³⁷. It has been observed *in-vivo* and *in-vitro* that it possesses anti-oxidant properties in the inhibition of the oxygen enzyme (lipoxygenase) and proinflammatory transcription

factor NFkB induced by the reactive oxygen species. And based on this, it is suggested that it is useful in treating obesity, liver steatosis, lung injuries and other inflammation. It further induces oxidative enzymes, Heme oxygenase-1 and NADPH oxidase, to cause oxidative stress to cultured cancer cells.

This implies that it has the cancer cell apoptosis and death property. It also enhances nuclear apoptosis that is related to DNA fragmentation, and accumulation of promoters of cytoplasmic/mitochondrial apoptotic protein, and reduces the level of anti-apoptotic protein, as it was proved by additional *in vitro* experiments on cancer³⁸.

Vitex molecules have the ability to hinder the progress of cancer cells through the blocking of the G2 to the M stage of mitosis. This mitotic arrest might be facilitated by the alteration of intracellular ATP and p38 MAP kinase pathway, the increase in mitosis-inhibitory PI3/Akt pathway and the decrease in cyclin B, the master regulator of mitosis³.

This reveals its overall impact in the body and its response to various forms of disease or disorder, or its involvement in other diseases.

Mechanism of Action on the Female Reproductive System:

Estrogenic and Dopaminergic Action: *Vitex* constituents combine with dopamine D2 receptors and may influence the prolactin release, but some phytochemicals possess low affinity as estrogens and may be used as a factor in reinstating hormonal balance in endocrine reproductive disorders.

Effect on Gonadotropins and Prolactin: *Vitex* may cause reduced prolactin and alter patterns of gonadotropin release, which may enhance menstrual regularity, both in preclinical and clinical studies³⁹.

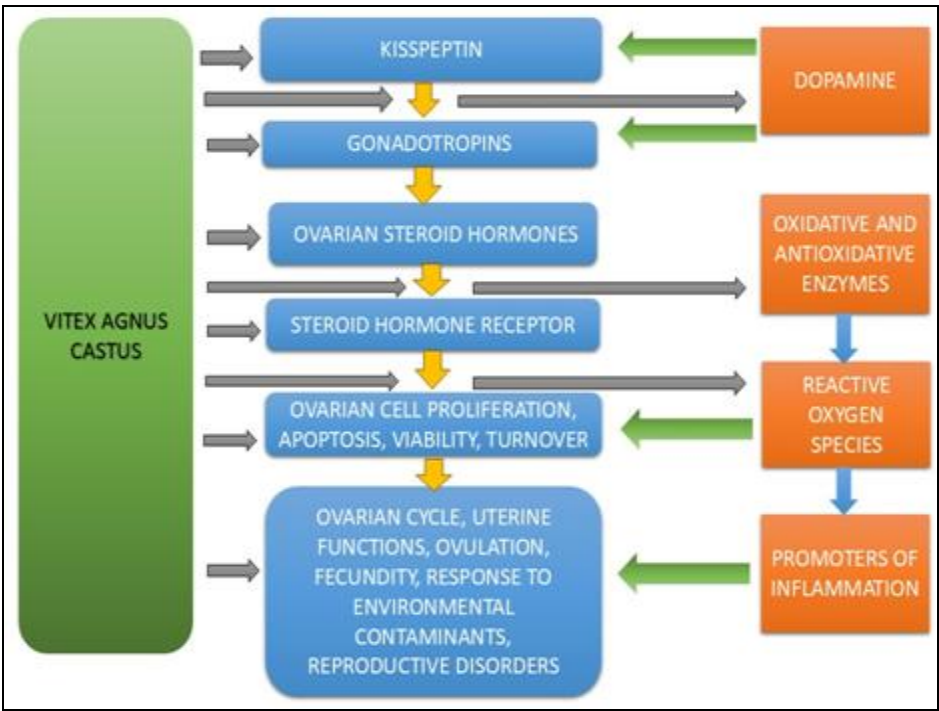


FIG. 2: TARGET SITE OF VITEX AGNUS-CASTUS³

Vitex agnus-castus in PCOS: *Vitex agnus-castus* (chaste tree or chasteberry) is a conventional botanical agent which is gaining interest in the modulatory action on hormonal pathways implicated in PCOS: HPO Axis Modulation: The existence of experimental models of PCOS has indicated that *Vitex* extract can regulate the expression of the hypothalamic kisspeptin (KISS-1) gene, and thereby potentially induce a normalization of GnRH, FSH and progesterone

elevation and LH and testosterone decrease. *Vitex* constituents combine with dopamine D2 receptors and may influence the prolactin release, but some phytochemicals possess low affinity as estrogens and may be used as a factor in reinstating hormonal balance in endocrine reproductive disorders. *Vitex* may cause reduced prolactin and alter patterns of gonadotropin release, which may enhance menstrual regularity, both in preclinical and clinical studies⁴.

TABLE 3: VITEX AGNUS- CASTUS ON HORMONAL IMBALANCE

Sr. no.	Target	Species	Character of influence	Ref.
1.	Fecundity	Mice, Women	Stimulation	(9,40-42)
2.	Uterine growth	Rat, Mice	Stimulation	(40)
3.	Sexual behaviour	Women	Stimulation	(43)
4.	Release of progesterone and estradiol	Pig, women	Simulation and Inhibition	(9, 44-47)
5.	Release of kisspeptin	Women	Stimulation	(9, 41)
6.	Release of FSH and LH	Women	Stimulation	(9, 41)
7.	Proliferation of ovarian cells	Pig	Stimulation	(47)
8.	Apoptosis of ovarian cells	Pig	Stimulation	(46)
9.	Viability of ovarian cells	Pig	Stimulation	(46)

Safety, Dosage and Toxicology: *Vitex agnus-castus* has been reported extensively as a well-tolerated herbal medicine in situations where it has been administered through recommended therapeutic doses. Regulatory assessments and clinical studies show that the most frequently stated adverse effects are minor and transient like gastrointestinal discomfort, headache, pruritus, dizziness, acne and mild skin effects such as

urticaria, rash, and swelling of the face. The adverse effects are of a mild nature and no serious organ toxicity is to be seen in clinical application⁴⁸. The data of non-clinical studies indicate that VAC activates the hypothalamus and pituitary gland and then interacts with the dopaminergic receptor of the anterior pituitary gland and causes the destruction of prolactin secretion *in-vivo* and *in-vitro*. Appropriate non clinical research on VAC is

not done yet. As far as little data on the toxicology was available, it was discovered that VAC leads to liver toxicity in two repeated-dose toxicity studies in an animal model. It was also found that the VAC fruit extract could influence lactation⁴⁹.

Typical dosage Standardized *Vitex agnus-castus* extracts are usually used in a dose of 20-40mg of dried fruit extract per day depending on the formulation and indication. Extract standardization is closely associated with clinical efficacy and safety, especially with regard to active diterpenes that cause dopaminergic activity. *Vitex agnus-castus* can be used with such drugs since its dopamine-mediated inhibition of prolactin can be affected by dopamine agonists, antagonists, and by some hormonal drugs. The patients under antipsychotic medications, hormonal contraceptives, or hormone replacement therapy should therefore be taken with caution. It is also considered not to be safe during pregnancy and lactation as there is a lack of safety data on its use⁵⁰. Observational studies and clinical information over a long period have indicated that *Vitex agnus-castus* is safely administered during multiple menstrual cycles, and its use is well-tolerated by patients and is associated with few side effects. Nevertheless, the importance of the long-term clinical trials developed properly, especially in the population of PCOS, has been repeatedly reiterated in recent articles^{51, 52}.

Comparison with Conventional Therapies: The current management of polycystic ovary syndrome (PCOS) involves combined oral contraceptives (COCs), insulin sensitizing drugs (metformin) and anti-androgens, ovulation agents (clomiphene citrate or letrozole), and dopamine agonists when hyperprolactinemia occurs. Although these pharmacological treatments are useful in management of symptoms, they may have some adverse effects, metabolic issues and be intolerated by the patient after some period of use. In this regard, *Vitex agnus-castus* has been considered as Phyto therapeutic alternative or adjunct because of its neuroendocrine-modulating and favourable safety profile.

Comparison with Dopamine Agonists: Bromocryptine and cabergoline are dopamine agonists that are commonly used to treat

hyperprolactinemia, which can be one of the causes of menstrual abnormalities and ovulatory dysfunction in PCOS. Recent mechanistic and clinical data demonstrates that *Vitex agnus-castus* has a dopaminergic effect through interaction with the dopamine D2 receptors in the anterior pituitary, and leads to diminished prolactin secretion. Recent clinical reviews also confirm that *Vitex agnus-castus* has a clinical role to play in mild hyperprolactinemia and functional luteal phase defects^{3, 37}.

Vitex preparations are usually linked to less severe and less frequent adverse effects in contrast to synthetic dopamine agonists, which could cause nausea, dizziness, hypotension, and gastrointestinal disorders. Though no head-to-head randomized trials that are large in scale and directly compare *Vitex* to dopamine agonists are present, the existing evidence indicates that *Vitex* can be used as a milder option in patients with mild prolactin elevation or intolerance to traditional dopamine agonists^{3, 26}.

Comparison with Combined Oral Contraceptives; Combined oral contraceptives should continue to be brought in as the first-line action in the regulation of the menstrual cycle and decrease hyperandrogenic symptoms in PCOS. They do so by inhibiting ovulation and reducing ovarian androgen. Nevertheless, there are concerns about the risk of thromboembolism, changes in metabolism, mood fluctuation and the long-term hormonal inhibition^{3, 37}. Conversely, *Vitex* without agnus-castus does not suppress the ovulation but seems to regulate the hypothalamic-pituitary-ovarian (HPO) axis by attenuating the effect of dopaminergic and endocrine-regulating pathways by action and applicability on ovulation prevention is not possible in those cases when COCs are needed. In its place, it can be regarded in women who want to have control over their cycle without suppressed hormones^{49, 51}.

Comparison with Insulin-Sensitizing Agents: Metformin is also commonly employed as a form of PCOS management of insulin resistance and metabolic dysfunction. Its action is mainly directed at glucose metabolism and the insulin sensitivity instead of direct neuroendocrine control. Conversely, *Vitex agnus-castus* has a major

consequence on the secretion of pituitary prolactin and gonadotropin balance through the action of the dopaminergic systems. Presently, there are no strong comparative studies done between Vitex and metformin. Thus, Vitex can be more suitable as an adjunctive treatment in women when their major concerns are irregular menstruation, luteal insufficiency, or minor endocrine disproportions, and not severe metabolic dysfunctions^{3, 15, 37}.

Comparison with Ovulation Induction Agents: Clomiphene citrate and letrozole are still considered as first-line treatments of ovulation induction in infertile PCOS patients. These drugs directly induce the development of the follicles by the modulation of oestrogen receptors, or by inhibition of aromatase. In comparison, *Vitex agnus-castus* could indirectly promote ovulatory, by regulating the amount of prolactin and enhancing the sufficiency of luteal phases. Although there is mechanistic plausibility, there is no existing evidence to replace the conventional protocols of ovulation induction with Vitex in

infertile patients with anovulatory infertility. Rather, Vitex can complement women with mild cases of ovulatory dysfunction or the luteal phase abnormalities^{3, 26}.

Advantages and Limitations Compared with Conventional Therapies: *Vitex agnus-castus* has favorable tolerability profile compared to conventional pharmacotherapy, with most adverse effects reported as mild gastrointestinal effects, headache, acne or temporary menstrual effects. Its natural source of plants and endocrine-controlling effect might render it to be used in the long term in a few patients who are in search of non-synthetic forms of therapy. Nevertheless, the limitations exist even with the good mechanistic and clinical evidence. They consist of heterogeneity of extract standardization, inconsistency in study design, relatively small sample size, and limited large-scale randomized controlled trials that directly compare *Vitex agnus-castus* to standard first-line PCOS therapies until more impregnable comparative evidence is provided^{3, 15, 51}.

TABLE 4: COMPARISON OF VITEX AGNUS-CASTUS WITH CONVENTIONAL THERAPIES IN PCOS AND HORMONAL DYSREGULATION

Parameter	VAC	Dopamine agonist	Combined Oral Contraceptive (COCs)	Metformin	Ovulation-Induced Agents	Ref.
Primary mechanism	Dopamine D2 receptor modulation, decreased prolactin, HPO axis regulation	Direct dopamine agonism D2	Suppresses ovulation, decreases ovarian androgen production	Improve insulin sensitivity, decrease hepatic glucose production	Oestrogen receptor modulation or aromatase inhibition	(3, 37)
Target Level	Pituitary HPO axis	Pituitary	Ovarian hypothalamic feedback	Peripheral metabolic pathways	Ovarian follicular stimulation	(3, 37)
Effect on prolactin	Mild moderate reduction	Strong reduction	No direct effect	No direct effect	No direct effect	(3, 26)
Effect on menstrual regulation	Improves cycle regularity in mild dysfunction	Effective if prolactin related	Highly effective cycle control	Indirect improvement	Induces ovulation	(3, 37, 51)
Effect on androgen	Indirect modulation	Minimal	Significant reduction	Modest reduction	Minimal direct effect	(3, 26)
Ovulation	Supports physiologic ovulation	Restores if prolactin mediated	Suppressed	May improve	Direct induction	(3, 26)
Metabolic benefit	Limited evidence	None	May worsen metabolic profile in some cases	Strong metabolic benefit	None	(3, 37)
Common adverse effects	Mild GI upset, headache, acne	Nausea, dizziness, hypotension	Weight gain, thromboembolic risk	GI disturbance, B12 deficiency	Hot flashes, ovarian hyperstimulation	(37, 39)
Contraceptive effect	No	No	Yes	No	No	(49)
Best	Mild hormonal	hyperprolact	Menstrual control and	Insulin resistance	Anovulatory	(3,

clinical use	imbalance, luteal defects, preference for phytotherapy	inemia	androgen suppression	infertility	37, 49, 51)
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CONCLUSION: *Vitex agnus-castus* has appeared as a promising herbal agent in the management of polycystic ovary syndrome (PCOS) and hormonal dysregulation. Its principal mode of action is dopaminergic modulation at anterior pituitary level, which leads to reduced prolactin secretion and following regularization of the hypothalamic–pituitary–ovarian (HPO) axis. And this leads to improved menstrual cycle, increased luteal phase function, and maintained ovulation. Clinical evidence suggests its beneficial properties in women. Plant-based interventions often suggest an alternative and tolerable option when compared with traditional pharmacotherapies such as dopamine agonists, combined oral contraceptives, metformin, and ovulation-inducing agents. However, it is usually appropriate for mild to moderate endocrine disturbances rather than severe metabolic or infertility-driven PCOS cases.

The current evidence is still limited and lacks large-scale randomized controlled trials that directly establish *Vitex* as first-line therapy. Future research should focus on establishing well-designed multicenter trials, standardized dosing regimens, and long-term safety profile to evaluate its definitive clinical positioning. Research should also focus on the other mechanism of action expect dopaminergic such as insulin resistance, inflammatory etc. Long term safety study should also be taken in consideration, drug- drug interaction, combination therapies or maybe in combination with conventional therapies. In conclusion, *Vitex agnus-castus* represents a potentially valuable adjunct or complementary therapy in the integrative management of PCOS and hormonal imbalance. While it should not replace evidence-based traditional treatments in complex or severe cases, it offers a biologically plausible and generally well-tolerated option within personalized and patient-centered reproductive care strategies.

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