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HERBAL CARE FOR WOMEN: A GUIDE TO PHYTOTHERAPEUTIC AGENTS IN GYNAECOLOGY AND REPRODUCTIVE HEALTH

CHAPTER 2: PHYTOCHEMISTRY AND MECHANISMS OF ACTION OF MEDICINAL PLANTS IN WOMEN'S HEALTH

Mr. Utkarsh Ravindra Mandage^{1*}, Miss. Jagruti Ravindra Patil²

¹Lecturer, Department of Pharmacognosy, Ravindra Vidya Prasarak Mandal Institute of Pharmacy, Dwarka, Nashik, Maharashtra, India.

²Lecturer, Department of Pharmaceutics, Ravindra Vidya Prasarak Mandal Institute of Pharmacy, Dwarka, Nashik, Maharashtra, India.

***Corresponding author:** Mr. Utkarsh Ravindra Mandage

Email: rxutkarshmandage@gmail.com

ABSTRACT

Medicinal plants used in gynaecology and reproductive health act through defined chemical constituents, and their clinical value can be judged only when the constituent, its molecular target and its fate in the body are known. This chapter classifies the phytochemicals of greatest relevance to women's health and relates each class to its principal mechanisms. Phytoestrogens (isoflavones, lignans, coumestans and prenylflavonoids) bind oestrogen receptors with a preference for the β subtype and behave as partial agonists or antagonists depending on tissue and endogenous hormone levels. Terpenoids and saponins, including the clerodane diterpenes of *Vitex agnus-castus* and the triterpene glycosides of *Actaea racemosa*, act largely through neuroendocrine pathways: dopamine D2 agonism that lowers prolactin, and serotonergic and opioidergic signalling in thermoregulatory and mood circuits. Alkaloids such as berberine activate AMP-activated protein kinase and improve insulin sensitivity, a mechanism of direct interest in polycystic ovary syndrome. Gingerols and curcuminoids inhibit cyclo-oxygenase, lipoxygenase and nuclear factor- κ B, which explains their use in dysmenorrhoea and inflammatory gynaecological disease. Enzyme-level actions, including aromatase inhibition by





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flavones and suppression of ovarian androgen synthesis by glycyrrhetic acid, add a further layer. The pharmacokinetic dimension is treated in equal detail, since glycoside hydrolysis, gut microbial conversion (for example daidzein to equol), conjugation and enterohepatic cycling determine whether a constituent reaches its target at an active concentration. The chapter closes with the multi-target and synergistic behaviour of whole extracts, the network-pharmacology approach used to describe it, and the methodological limits of mechanism claims drawn from in vitro work at supraphysiological concentrations. The aim is a mechanistic framework on which the disorder-specific chapters of this book can build.

Keywords: Phytoestrogens; Oestrogen receptor β ; Dopaminergic diterpenes; Equol; Berberine; Network pharmacology

2.1 Introduction

A medicinal plant is a mixture of several hundred compounds, of which a small number account for most of its pharmacological effect. Phytochemistry identifies those compounds, and pharmacology describes what they do at receptors, enzymes and signalling pathways. For women's health the two disciplines meet at a particular point: many of the conditions treated with herbs (premenstrual syndrome, polycystic ovary syndrome, dysmenorrhoea, infertility and the menopausal transition) are disorders of hormonal signalling, and plant constituents interact with that signalling at several levels.

Three levels of action can be distinguished. The first is the receptor, where a constituent mimics or opposes an endogenous hormone, as isoflavones do at oestrogen receptors. The second is the neuroendocrine axis, where a constituent alters the release of a pituitary or hypothalamic hormone, as the diterpenes of chaste tree do for prolactin. The third is the tissue, where inflammatory, metabolic or oxidative pathways are modulated without any direct hormonal effect, as with ginger in dysmenorrhoea or berberine in insulin resistance. A single plant frequently acts at more than one level, and that property distinguishes most herbal medicines from single-target synthetic drugs.

2.2 Classification of Bioactive Phytochemicals Relevant to Gynaecology

Phytochemicals of gynaecological relevance are classified here by chemical class, since chemical structure predicts both receptor affinity and pharmacokinetic behaviour. Table 2.1 summarises the classes, representative compounds and principal targets.





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Table 2.1. Major phytochemical classes used in women's health, with representative constituents and principal mechanisms

Chemical class	Representative constituents (source)	Principal target or mechanism	Gynaecological relevance
Isoflavones	Genistein, daidzein, formononetin, biochanin A (<i>Glycine max</i> , <i>Trifolium pratense</i>)	ER β -preferring partial agonism; tyrosine kinase inhibition	Vasomotor symptoms, bone loss
Lignans	Secoisolariciresinol diglucoside, converted to enterodiol and enterolactone (<i>Linum usitatissimum</i>)	Weak ER binding; aromatase modulation	Menopause, hormone-sensitive tissue
Coumestans	Coumestrol (<i>Medicago sativa</i> , clover)	ER agonism	Largely experimental
Prenylflavonoids	8-Prenylnaringenin (<i>Humulus lupulus</i>)	Potent ER α agonism	Vasomotor symptoms
Diterpenes and iridoids	Rotundifuran and other clerodanes; agnuside; casticin (<i>Vitex agnus-castus</i>)	Dopamine D2 agonism; μ -opioid binding	Premenstrual syndrome, cyclical mastalgia, latent hyperprolactinaemia
Triterpene glycosides	Actein, 23-epi-26-deoxyactein (<i>Actaea racemosa</i>)	Serotonergic and opioidergic activity; no clear ER binding	Vasomotor and mood symptoms
Steroidal saponins	Diosgenin (<i>Dioscorea</i> spp.), shatavarins (<i>Asparagus racemosus</i>), protodioscin (<i>Tribulus terrestris</i>)	Varied; not converted to human steroid hormones	Traditional reproductive tonics
Withanolides	Withaferin A, withanolide D (<i>Withania somnifera</i>)	HPA-axis modulation; GABAergic activity	Stress-related menstrual and menopausal symptoms
Alkaloids	Berberine (<i>Berberis aristata</i> , <i>Coptis chinensis</i>)	AMPK activation; insulin sensitisation	Polycystic ovary syndrome
Phenolic ketones and curcuminoids	6-Gingerol, 6-shogaol (<i>Zingiber officinale</i>); curcumin (<i>Curcuma longa</i>)	COX and 5-LOX inhibition; NF- κ B suppression	Dysmenorrhoea, endometriosis
Triterpenoid saponin (sweet)	Glycyrrhizin, glycyrrhetinic acid (<i>Glycyrrhiza glabra</i>)	17 β -HSD and 11 β -HSD2 inhibition	Hyperandrogenism in PCOS





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Chemical class	Representative constituents (source)	Principal target or mechanism	Gynaecological relevance
Phenylpropanoids	trans-Anethole (<i>Foeniculum vulgare</i>)	Weak oestrogenic and spasmolytic action	Dysmenorrhoea, lactation

ER, oestrogen receptor; *AMPK*, AMP-activated protein kinase; *COX*, cyclo-oxygenase; *5-LOX*, 5-lipoxygenase; *NF-κB*, nuclear factor-κB; *HSD*, hydroxysteroid dehydrogenase; *HPA*, hypothalamic–pituitary–adrenal.

2.2.1 Phytoestrogens

A phytoestrogen is a plant-derived compound that binds the oestrogen receptor and produces an oestrogenic or anti-oestrogenic response. The shared structural feature is a phenolic ring with a second hydroxyl group placed roughly 11 Å away, a geometry that mimics the 3- and 17β-hydroxyl groups of oestradiol [1]. Four subclasses matter clinically. Isoflavones occur in legumes, chiefly soy and red clover, where they are stored as glycosides (genistin, daidzin) or as methylated precursors (biochanin A, formononetin). Lignans are diphenolic compounds concentrated in flaxseed; the parent secoisolariciresinol diglucoside has little activity until colonic bacteria convert it to the mammalian lignans enterodiol and enterolactone. Coumestans, of which coumestrol is the example, are potent in vitro but minor in the human diet. The prenylflavonoid 8-prenylnaringenin from hops is the most potent phytoestrogen identified to date, with activity exceeding that of the soy isoflavones by more than an order of magnitude [2].

2.2.2 Terpenoids and saponins

Terpenoids are built from isoprene units and include monoterpenes, diterpenes, triterpenes and their glycosides. Chaste tree fruit contains labdane and clerodane diterpenes (rotundifuran among them), the iridoid glycosides agnuside and aucubin, and the flavonoid casticin; the diterpene fraction carries the dopaminergic activity [3]. The rhizome of black cohosh (*Actaea racemosa*, syn. *Cimicifuga racemosa*) is characterised by cycloartane triterpene glycosides such as actein and 23-epi-26-deoxyactein, which serve as the usual standardisation markers, together with phenolic acids and small amounts of N^o-methylserotonin [4].

Steroidal saponins require a specific caution. Diosgenin from *Dioscorea* species was the starting material for the industrial semisynthesis of progesterone and corticosteroids, and this history underlies the marketing of “wild yam” creams as natural progesterone. The human body





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has no enzyme pathway to perform that conversion. A controlled trial of topical wild yam extract found no change in serum progesterone, oestradiol or menopausal symptoms [5]. The shatavarins of *Asparagus racemosus* and the withanolides of *Withania somnifera* are also steroidal in skeleton, and their actions are adaptogenic and neuroendocrine rather than hormone-replacing.

2.2.3 Alkaloids, phenolics and other classes

Berberine, a protoberberine isoquinoline alkaloid, is the best characterised alkaloid in reproductive endocrinology. The gingerols and shogaols of ginger rhizome are phenolic ketones; shogaols form from gingerols by dehydration during drying and heating, so the ratio between them varies with processing. Curcumin is a diarylheptanoid. Glycyrrhizin, the sweet triterpenoid saponin of liquorice, is hydrolysed in the gut to glycyrrhetic acid, which is the active aglycone. The phenylpropanoid trans-anethole gives fennel and anise their oestrogen-like reputation, a property recognised in the pharmacological literature for more than four decades [6].

2.2.4 Chemical variability and its mechanistic consequences

The chemical form in which a constituent is present alters both the dose delivered and the mechanism that follows. Soy isoflavones occur as aglycones, β -glycosides, and 6''-O-malonyl and acetyl glycosides, and their proportions change with processing: fermentation (as in miso and tempeh) raises the aglycone fraction, whereas heating converts malonyl to acetyl forms. Because the sugar adds mass without activity, doses are expressed as aglycone equivalents. The molecular mass of genistin (432 g/mol) is about 1.6 times that of genistein (270 g/mol), so 100 mg of genistin supplies only about 62 mg of genistein. Trials that report “isoflavone content” without this correction are not directly comparable.

Processing changes composition in other plants too. Drying and heating dehydrate gingerols to shogaols, which are more pungent and, in several assays, more potent inhibitors of inflammatory mediators, so dried ginger powder and fresh rhizome are not chemically equivalent. Extraction solvent determines which constituents are recovered: an ethanolic extract of *Vitex agnus-castus* fruit contains the lipophilic diterpenes that carry dopaminergic activity, whereas an aqueous infusion extracts mainly iridoid glycosides and flavonoids. The same logic applies to black cohosh, where isopropanolic and ethanolic extracts differ in triterpene glycoside profile. Mechanistic conclusions drawn from one preparation therefore apply to that preparation, a point developed further in Chapter 9.





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2.3 Mechanisms of Action

2.3.1 Oestrogen receptor modulation

Oestradiol acts through two nuclear receptors, ER α and ER β , which differ in tissue distribution. ER α predominates in the endometrium, breast stroma and liver; ER β is prominent in the ovary (granulosa cells), vascular endothelium, bone, and parts of the brain. On relative binding affinity, genistein binds ER β roughly twenty times more strongly than ER α , and daidzein shows the same preference to a smaller degree [7]. The consequence is a selective oestrogen receptor modulator (SERM)-like profile: an isoflavone can support bone and vascular tissue while exerting little proliferative stimulus on the endometrium.

Two further points govern the net effect. First, phytoestrogens are partial agonists. In a low-oestrogen state, such as after the menopause, they add a weak oestrogenic signal; in a high-oestrogen state, such as the late follicular phase, they compete with oestradiol for the receptor and can act as functional antagonists. Second, the response is concentration dependent. Genistein stimulates proliferation of oestrogen-responsive breast cancer cells at low micromolar concentrations and inhibits it at higher concentrations, a biphasic pattern that complicates extrapolation from cell culture to patients [1]. The common error is to treat “oestrogenic” as a fixed property of a plant. It is a property of a constituent, a dose, a receptor subtype and a hormonal background taken together.

8-Prenylnaringenin differs from the isoflavones in favouring ER α , and it is for this reason that hop extracts are studied separately and standardised to their 8-prenylnaringenin content [2].

Several phytoestrogens also act outside the classical receptor. Genistein inhibits tyrosine-specific protein kinases, including the epidermal growth factor receptor kinase, at micromolar concentrations [8], and it binds the G protein-coupled oestrogen receptor (GPER). These non-genomic actions are relevant to its antiproliferative effects but occur at concentrations that dietary intake rarely reaches.

2.3.2 Neuroendocrine modulation

The best-documented neuroendocrine mechanism is the dopaminergic action of *Vitex agnus-castus*. Diterpenes from the fruit bind dopamine D2 receptors on pituitary lactotrophs and inhibit prolactin release, in the same direction as bromocriptine though far more weakly [3]. Latent (stress-induced or nocturnal) hyperprolactinaemia shortens the luteal phase and is associated with cyclical mastalgia, and its correction offers a rational basis for the use of chaste





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tree in premenstrual syndrome. A randomised placebo-controlled trial of a standardised fruit extract (Ze 440) reported a responder rate of 52% against 24% for placebo on a composite premenstrual symptom score [9]. Chaste tree extracts also bind μ -opioid receptors, and certain flavonoid fractions show opioid agonist activity, which may account for part of the effect on mood and pain [10]. The dopaminergic mechanism carries a practical implication: concurrent use with dopamine agonists or antagonists (bromocriptine, cabergoline, antipsychotics, metoclopramide) is pharmacologically unsound.

Black cohosh illustrates how a mechanistic explanation can change as evidence accumulates. Early work attributed its effect on hot flushes to oestrogenic activity, but standardised extracts do not bind oestrogen receptors or stimulate the endometrium in most studies. Extracts bind the serotonin 5-HT₇ receptor and act as mixed competitive ligands and partial agonists there [11], and N^ω-methylserotonin has been proposed as one active constituent [4]. Because the thermoregulatory centre in the preoptic hypothalamus is modulated by serotonergic and noradrenergic inputs, this mechanism is consistent with the observed efficacy of selective serotonin reuptake inhibitors in vasomotor symptoms. Opioid receptor activity has also been reported.

Withania somnifera acts on the hypothalamic–pituitary–adrenal axis. A randomised trial of a high-concentration root extract in chronically stressed adults found a reduction in serum cortisol of about 28% and improvement in stress and anxiety scales [12]. Because psychological stress suppresses gonadotrophin-releasing hormone pulsatility and aggravates menstrual and menopausal complaints, an HPA-axis effect is a plausible indirect route to reproductive benefit, although direct gynaecological trials remain few.

2.3.3 Modulation of steroidogenic enzymes

Plant constituents can alter the amount of hormone synthesised rather than the response to it. Flavones such as chrysin and apigenin, and to a lesser extent isoflavones, inhibit aromatase (CYP19A1), the enzyme that converts androgens to oestrogens; site-directed mutagenesis has located the binding of these compounds within the enzyme's active site [13]. Mammalian lignans also inhibit aromatase in vitro and raise sex hormone-binding globulin, which lowers the free fraction of circulating sex steroids.

Liquorice provides an example relevant to polycystic ovary syndrome (PCOS). Glycyrrhetic acid inhibits 17 β -hydroxysteroid dehydrogenase, the enzyme converting androstenedione to testosterone. In healthy women, 3.5 g of liquorice daily for two menstrual cycles reduced total





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serum testosterone [14]. The same aglycone inhibits renal 11β -hydroxysteroid dehydrogenase type 2, allowing cortisol to occupy the mineralocorticoid receptor; this produces the hypertension and hypokalaemia of liquorice excess and limits the dose and duration that can be recommended.

2.3.4 Anti-inflammatory and spasmolytic mechanisms

Primary dysmenorrhoea results from excessive endometrial synthesis of prostaglandin $F_{2\alpha}$ and E_2 at menstruation, producing uterine hypercontractility and ischaemic pain. Gingerols and shogaols inhibit both cyclo-oxygenase and 5-lipoxygenase and suppress the induction of inflammatory genes [15]. Their action therefore reaches the same target as non-steroidal anti-inflammatory drugs, with an additional effect on leukotriene formation. A meta-analysis of randomised trials concluded that ginger reduced pain intensity in primary dysmenorrhoea compared with placebo [16].

Curcumin inhibits the activation of nuclear factor- κ B, lowers the expression of cyclo-oxygenase-2, matrix metalloproteinases and vascular endothelial growth factor, and in rodent models reduces the growth of endometriotic implants. These data support its investigation in endometriosis. They must be read against a well-documented difficulty: curcumin is chemically unstable, reacts non-specifically in many assay systems, and has repeatedly failed to translate from in vitro activity to clinical benefit [17]. Anethole and the essential oil of fennel relax uterine smooth muscle and reduce oxytocin- and prostaglandin-induced contractions, which provides a spasmolytic mechanism for its traditional use in painful menstruation.

2.3.5 Metabolic and insulin-sensitising mechanisms

Insulin resistance and compensatory hyperinsulinaemia drive ovarian androgen production in a large proportion of women with PCOS, since insulin acts synergistically with luteinising hormone on theca cells. Berberine activates AMP-activated protein kinase (AMPK), increases glucose uptake, reduces hepatic gluconeogenesis and lowers lipid synthesis [18]. The mechanism overlaps with that of metformin. In a three-month randomised study in women with PCOS, all of whom also received cyproterone acetate with ethinylestradiol, berberine improved insulin resistance to a degree comparable with metformin and produced greater reductions in waist-to-hip ratio and in total cholesterol and triglycerides [19]. Cinnamon procyanidins and the polyphenols of fenugreek act on insulin signalling by related pathways and are covered with clinical data in the chapter on PCOS.





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2.3.6 Anti-androgenic mechanisms

Hirsutism, acne and androgenic alopecia in PCOS reflect both excess ovarian androgen production and increased peripheral conversion of testosterone to dihydrotestosterone by 5 α -reductase. Plant constituents act on both steps. Glycyrrhetic acid lowers testosterone synthesis, as described above. Spearmint (*Mentha spicata*) tea, taken twice daily for one month by women with hirsutism and PCOS, reduced free and total testosterone and raised luteinising and follicle-stimulating hormone in a small randomised trial, and patients' self-rated hirsutism improved, although the objective Ferriman–Gallwey score did not change over that short period [20]. The lag in the objective score is expected, since a hair follicle cycle lasts several months. Fatty acid and sterol fractions of saw palmetto (*Serenoa repens*) inhibit 5 α -reductase and are used for androgenic alopecia, but clinical evidence in women is limited to small uncontrolled series. Any anti-androgen carries a theoretical risk to a male fetus, and these agents are not appropriate when pregnancy is planned.

Table 2.2 relates the principal gynaecological indications of this book to their mechanistic basis.

Table 2.2. Mechanistic rationale for herbal use in common gynaecological conditions

Condition	Dominant pathophysiology	Mechanism targeted	Example agents
Premenstrual syndrome, cyclical mastalgia	Latent hyperprolactinaemia; altered serotonergic sensitivity	Dopamine D2 agonism; opioid modulation	<i>Vitex agnus-castus</i>
Primary dysmenorrhoea	Excess endometrial prostaglandin F _{2α} and E ₂	COX/5-LOX inhibition; uterine spasmolysis	Ginger, fennel
Polycystic ovary syndrome	Insulin resistance; ovarian hyperandrogenism	AMPK activation; 17 β -HSD inhibition; anti-androgen activity	Berberine, cinnamon, liquorice, spearmint
Endometriosis	Oestrogen-dependent chronic inflammation	NF- κ B suppression; aromatase inhibition	Curcumin, flavones (experimental)
Menopausal vasomotor symptoms	Oestrogen withdrawal; narrowed thermoneutral zone	ER β -preferring agonism; serotonergic modulation	Soy and red clover isoflavones, hops, black cohosh
Stress-related cycle disturbance	HPA-axis activation suppressing GnRH pulsatility	Cortisol reduction; adaptogenic activity	<i>Withania somnifera</i> , <i>Asparagus racemosus</i>

GnRH, gonadotrophin-releasing hormone; other abbreviations as in Table 2.1.





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2.3.7 Antioxidant, epigenetic and other mechanisms

Oxidative stress affects oocyte quality, sperm function and endometrial receptivity, and most plant polyphenols scavenge reactive oxygen species in vitro. This property is so widespread that it discriminates poorly between plants and seldom explains a specific clinical effect; the antioxidant capacity measured in a test tube does not predict the redox state achieved in the ovary. Epigenetic effects are better defined for individual compounds. Genistein inhibits DNA methyltransferase activity and alters histone acetylation in cell models, and in rodent studies neonatal exposure to genistein changes reproductive tract development [1]. Such findings are relevant to the safety of high-dose isoflavone exposure in infancy and pregnancy rather than to therapy.

2.4 Pharmacokinetic Determinants of Activity

A constituent that is active in vitro is not necessarily active in vivo. For many phytochemicals the pharmacokinetic step determines the outcome, and three processes dominate.

Deglycosylation. Most flavonoids and lignans occur as glycosides that are too polar to cross the intestinal epithelium. Lactase-phlorizin hydrolase on the brush border and β -glucosidases of the colonic microbiota release the aglycones, which are then absorbed [21].

Microbial biotransformation. Colonic bacteria convert daidzein to equol and secoisolariciresinol to enterodiol and enterolactone. Equol has greater oestrogenic potency and antioxidant activity than daidzein and a longer half-life. Only an estimated 30–50% of adults carry a microbiota capable of producing equol, and the proportion is higher in Asian populations with long-standing soy consumption [21]. Equol-producer status has been proposed as one explanation for the inconsistent results of soy isoflavone trials, and it has led to the development of S-equol as a supplement in its own right.

Conjugation and enterohepatic circulation. Absorbed aglycones are rapidly glucuronidated and sulphated in the enterocyte and the liver. The conjugates circulate at concentrations far above those of the free aglycone, but only the free form binds receptors, and the conjugates excreted in bile are hydrolysed again in the gut. Curcumin is the extreme case: oral doses of several grams produce plasma concentrations in the low nanomolar range, because of poor solubility, rapid conjugation and chemical degradation [22]. Co-administration of piperine, which inhibits glucuronidation, increased the bioavailability of curcumin about twentyfold in





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human volunteers [23]. Nanoparticle, phospholipid complex and micellar formulations are designed to address the same barrier.

These processes produce large inter-individual variation. Gut microbiota composition, antibiotic use, diet, sex and genetic polymorphism in conjugating enzymes all alter exposure, and the same dose of the same extract can yield a several-fold range of active metabolite concentration in a trial population.

2.5 Multi-Target Action, Synergy and Network Pharmacology

A crude or standardised extract contains many constituents that may act on different targets within the same disease pathway. Synergy is present when the combined effect exceeds the sum of the individual effects. Several mechanisms have been described: constituents acting on separate targets in the same pathway, constituents improving the solubility or absorption of others, inhibition of efflux transporters such as P-glycoprotein, and the neutralisation of adverse effects [24]. In the gynaecological setting the concept is illustrated by *Vitex*, in which dopaminergic diterpenes and opioid-active flavonoids contribute to a single clinical effect, and by the classical Ayurvedic formulations that combine *Asparagus racemosus* with other rasayana drugs.

Network pharmacology describes these interactions formally. Constituents, their predicted or measured protein targets, and the disease-associated genes are represented as a network, and the overlap between the compound–target and disease–gene networks identifies the probable mechanism of action [25]. The approach has been applied widely to herbal formulations for PCOS, endometriosis and menopausal symptoms. Its output is a hypothesis: target predictions depend on databases of variable quality, and docking scores do not establish that a constituent reaches the tissue at a sufficient concentration. Network predictions acquire meaning only when they are confirmed experimentally.

2.6 Limits of Mechanistic Evidence

Four limitations recur in the literature and should govern the interpretation of any mechanistic claim.

The first is concentration. Many in vitro effects are reported at 10–100 μM , whereas plasma concentrations of free aglycones after dietary or therapeutic doses are commonly below 1 μM .





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A mechanism demonstrated only at supraphysiological concentrations is not an explanation of a clinical effect.

The second is the identity of the test material. Mechanistic studies often use a pure compound, clinical trials use an extract, and the commercial products used by patients may differ from both in composition. Findings transfer only when the materials are chemically comparable.

The third is assay interference. Compounds such as curcumin, and many catechols and quinones, give false-positive signals in high-throughput assays through aggregation, redox cycling or covalent reactivity [17]. Activity against a long list of unrelated targets should raise suspicion of such interference rather than confidence in pleiotropy.

The fourth is species. Rodent reproductive physiology differs from human physiology in cycle length, the role of prolactin in luteal function, and isoflavone metabolism (rodents are almost uniformly equol producers). Animal data identify mechanisms; they do not establish dose or efficacy in women.

2.7 Conclusion

The phytochemicals used in women's health act through a limited number of identifiable mechanisms: partial and subtype-selective agonism at oestrogen receptors, dopaminergic, serotonergic and opioidergic modulation of neuroendocrine circuits, inhibition of steroidogenic enzymes, suppression of prostaglandin and inflammatory signalling, and activation of metabolic regulators such as AMPK. Several long-held assumptions have not survived scrutiny; black cohosh is not a phytoestrogen in the classical sense, and diosgenin is not a precursor of progesterone in the human body. Whether a mechanism operates in a patient depends on pharmacokinetics, in which gut microbial metabolism and conjugation often matter more than the intrinsic potency of the parent compound. Mechanistic understanding is most useful when it is tied to a chemically defined extract, a measured concentration and a clinical endpoint. That combination is the standard against which the herbal agents described in the following chapters should be judged.





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