Phytopharmaceuticals for Hormonal Imbalance Management

Lukas F Becker [1*], Mia K Schneider [2], Jonas H Wagner [3]
[1] Institute of Pharmaceutical Technology, University of Heidelberg, Germany
[2] Department of Nanobiotechnology, Technical University of Munich, Germany
[3] Max Planck Institute for Colloids and Interfaces, Germany

* Corresponding Author: **Lukas F Becker**

Article Info

ISSN (online): 3107-393X
Volume: 06
Issue: 04
July-August 2025
Received: 13-06-2025
Accepted: 15-07-2025
Published: 16-08-2025
Page No: 48-55

Abstract
Hormonal imbalances constitute a significant burden in contemporary clinical medicine, underpinning a diverse array of metabolic, reproductive, and endocrine disorders including hypothyroidism, polycystic ovary syndrome, type 2 diabetes mellitus, and adrenal insufficiency. While conventional hormone replacement therapies and pharmacological interventions have demonstrated clinical utility, their long-term use is associated with substantial risks such as cardiovascular complications, hepatotoxicity, thromboembolism, and hormone-dependent malignancies, necessitating the exploration of safer therapeutic alternatives. Phytopharmaceuticals, comprising bioactive compounds derived from medicinal plants, have garnered increasing scientific and clinical interest due to their capacity to interact with hormonal axes, modulate endocrine gland function, and restore hormonal homeostasis with comparatively favourable safety profiles. This article presents a comprehensive and critically evaluated review of the current understanding of phytopharmaceuticals in hormonal imbalance management, with emphasis on major bioactive classes including phytoestrogens, flavonoids, alkaloids, and terpenoids. The mechanisms underlying their endocrine activity, encompassing receptor binding, enzyme modulation, and regulation of hormone biosynthesis and metabolism, are systematically examined. Preclinical models, clinical trial evidence, pharmacokinetic challenges, and advanced formulation strategies are analysed. The review further discusses regulatory and commercialisation challenges and identifies priority areas for future translational research, with the goal of advancing plant-based therapies into evidence-based clinical practice for hormonal disorders.

Keywords: Phytopharmaceuticals, Hormonal imbalance, Endocrine regulation, Phytochemicals, Hormone therapy, Translational research

1. Introduction

Hormonal regulation is fundamental to the maintenance of physiological homeostasis, orchestrating processes ranging from cellular metabolism and growth to reproduction, immune function, and stress adaptation. Disruption of endocrine balance gives rise to a spectrum of clinically significant disorders that collectively affect hundreds of millions of individuals worldwide [1, 2]. Hypothyroidism and hyperthyroidism alter metabolic rate and cardiovascular function; polycystic ovary syndrome (PCOS) impairs reproductive capacity and metabolic health in women of reproductive age; type 2 diabetes mellitus represents a pandemic of insulin signalling dysregulation; and adrenal disorders disrupt cortisol and aldosterone homeostasis with profound systemic consequences [3, 4].

The clinical management of hormonal imbalances has traditionally relied upon synthetic hormone replacement therapies, receptor agonists and antagonists, and enzyme inhibitors. While such interventions offer precise pharmacological targeting, they are encumbered by significant adverse effects. Long-term oestrogen-progestin therapy is associated with elevated risks of breast

and endometrial carcinoma, venous thromboembolism, and cardiovascular disease [5]. Glucocorticoid administration induces osteoporosis, glucose intolerance, and adrenal suppression [6]. Synthetic thyroid hormone replacement may precipitate cardiac dysrhythmias and bone mineral loss [7]. These limitations have stimulated renewed interest in plant-derived therapeutics as adjunctive or alternative options for endocrine management.

Phytopharmaceuticals represent a broad category of plant-derived preparations and isolated bioactive compounds with demonstrated pharmacological activity. Ethnobotanical traditions across multiple civilisations have long employed herbal preparations for the management of reproductive disorders, thyroid conditions, and metabolic disease [8, 9]. The advent of modern analytical chemistry, molecular pharmacology, and clinical trial methodology has enabled rigorous scientific evaluation of these traditional claims, yielding a growing body of evidence for the endocrine-modulating properties of compounds such as isoflavones, lignans, withanolides, berberine, and ursolic acid [10, 11]. The present review aims to synthesise current knowledge regarding phytopharmaceuticals in hormonal imbalance management, critically evaluating mechanisms of action, clinical efficacy, translational challenges, and future research trajectories.

2. Physiology of the Endocrine System

The endocrine system comprises a network of specialised glands and diffusely distributed secretory cells that synthesise and release hormones into the systemic circulation, enabling long-range chemical communication between tissues [12]. Principal glands include the hypothalamus, anterior and posterior pituitary, thyroid, parathyroid, adrenal cortex and medulla, pancreatic islets, gonads, and pineal gland. Hormonal output is governed by hierarchical feedback loops, the most prominent of which involve the hypothalamic-pituitary axis and its downstream target glands, namely the hypothalamic-pituitary-thyroid (HPT), hypothalamic-pituitary-adrenal (HPA), and hypothalamic-pituitary-gonadal (HPG) axes.

Hormone biosynthesis encompasses peptide, steroid, and amine biochemical pathways. Steroid hormones, including glucocorticoids, mineralocorticoids, androgens, oestrogens, and progestogens, are synthesised from cholesterol through a series of cytochrome P450-mediated enzymatic conversions localised in the mitochondria and endoplasmic reticulum [13]. Thyroid hormones are iodinated tyrosine derivatives whose synthesis depends upon functional thyroid peroxidase activity and adequate dietary iodine availability. Insulin and glucagon, secreted by pancreatic beta and alpha cells respectively, regulate glucose homeostasis through opposing actions on hepatic glucose production and peripheral glucose uptake [14].

Regulatory feedback mechanisms operate primarily through negative feedback, wherein rising concentrations of target gland hormones suppress hypothalamic and pituitary secretion of releasing and trophic hormones. This principle underpins the tight physiological regulation of cortisol, thyroxine, and gonadal steroids. Disruption of these feedback circuits, whether through intrinsic glandular pathology, autoimmune mechanisms, environmental endocrine disruptors, or pharmacological intervention, results in hormonal excess or deficiency and the clinical manifestations thereof [15]. Understanding the molecular architecture of these regulatory systems is essential for identifying rational targets for phytopharmaceutical intervention.

3. Phytopharmaceuticals and Their Bioactive Compounds

Phytopharmaceuticals encompass a heterogeneous array of secondary metabolites produced by plants, principally serving roles in chemical defence, pollinator attraction, and environmental adaptation [16]. From a pharmacological perspective, four major classes are of particular relevance to endocrine modulation: phytoestrogens, flavonoids, alkaloids, and terpenoids.

Phytoestrogens are polyphenolic compounds with structural homology to 17beta-oestradiol that are capable of binding to oestrogen receptors (ERalpha and ERbeta) and exerting oestrogenic or antioestrogenic effects depending upon tissue context, receptor subtype distribution, and endogenous oestrogen levels [17]. Major subclasses include isoflavones (genistein, daidzein, formononetin), lignans (enterolactone, secoisolariciresinol), coumestans, and stilbenes. Isoflavones are abundant in soy (Glycine max) and red clover (Trifolium pratense), whereas lignans are prevalent in flaxseed (Linum usitatissimum) and sesame.

Flavonoids constitute a broad class of polyphenolic compounds characterised by a 15-carbon benzo-gamma-pyrone skeleton. They include flavones, flavonols, flavanones, isoflavones, anthocyanins, and chalcones. Quercetin, kaempferol, apigenin, and naringenin have been identified as modulators of steroidogenic enzyme activity and thyroid function [18, 19]. Alkaloids represent nitrogen-containing secondary metabolites with considerable pharmacological diversity. Berberine, isolated from Berberis species, has demonstrated potent insulin-sensitising effects mediated through AMP-activated protein kinase (AMPK) activation and modulation of gut microbiota composition [20]. Terpenoids, including withanolides from Withania somnifera and ginsenosides from Panax ginseng, exert adaptogenic effects on the HPA axis and modulate glucocorticoid receptor signalling [21, 22].

4. Mechanisms of Action in Hormonal Regulation

The endocrine-modulating effects of phytopharmaceuticals are mediated through multiple, often intersecting molecular mechanisms. Nuclear receptor binding represents a primary pathway through which phytoestrogens exert their biological activity. Genistein and daidzein bind ERbeta with affinity approximately 20 to 30 times lower than 17beta-oestradiol; however, in tissues with high ERbeta-to-ERalpha ratios such as bone, vasculature, and brain, phytoestrogens may elicit biologically relevant oestrogenic responses [17, 23]. Conversely, in oestrogen-rich environments, phytoestrogens may competitively antagonise endogenous oestrogens at ERalpha, potentially attenuating oestrogenic stimulation in breast and endometrial tissues.

Enzyme modulation constitutes another critical mechanism of phytopharmaceutical action. Several plant-derived compounds inhibit steroidogenic enzymes including aromatase (CYP19A1), which catalyses the conversion of androgens to oestrogens, and 5alpha-reductase, which converts testosterone to the more potent dihydrotestosterone. Flavonoids such as apigenin, chrysin, and naringenin have been shown to inhibit aromatase activity *in vitro*, suggesting utility in oestrogen-dependent conditions [19]. Berberine activates AMPK, suppresses hepatic gluconeogenesis, and

downregulates the expression of gluconeogenic enzymes including phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, thus reducing fasting plasma glucose in a manner mechanistically analogous to metformin [20].

Effects on the HPT axis have been documented for several phytochemicals. Guggulsterones from Commiphora mukul stimulate thyroid hormone biosynthesis, potentially through enhanced thyroid-stimulating hormone (TSH) sensitivity, and have been investigated in hypothyroidism management [24]. Ashwagandha (Withania somnifera) root extract modulates the HPA axis by reducing cortisol secretion, attenuating stress-induced HPA hyperactivity, and restoring adrenal responsiveness, effects attributed to the withanolide content of the extract [21]. Additionally, phytopharmaceuticals may influence hormone transport proteins, including sex hormone-binding globulin (SHBG) and thyroid-binding globulin, thereby altering the bioavailable fraction of circulating hormones and producing downstream endocrine effects [25].

5. Preclinical and Translational Research

The preclinical evaluation of phytopharmaceuticals for hormonal disorders has been conducted across a range of experimental models, including *in vitro* cell culture systems, rodent models of endocrine disease, and ex vivo tissue preparations. Oestrogen receptor binding assays employing MCF-7 breast cancer cells and Ishikawa endometrial cells have been widely used to characterise the oestrogenic and antioestrogenic potency of phytoestrogens [17, 23]. Streptozotocin-induced diabetic rodent models have been extensively employed to assess the antidiabetic efficacy of berberine, metformin-like compounds, and insulinotropic plant extracts, consistently demonstrating reductions in fasting glucose, HbA1c, and insulin resistance indices [20, 26].

Pharmacokinetic profiling of phytochemicals has revealed several characteristics that pose challenges for clinical translation. Many phenolic compounds, including flavonoids and isoflavones, undergo extensive first-pass metabolism in the intestinal wall and liver, resulting in low oral bioavailability [27]. Genistein and daidzein are subject to microbial conversion by intestinal flora, particularly to equol in the case of daidzein, a metabolite with higher oestrogenic potency; however, equol-producing capacity varies substantially among individuals, introducing significant inter-subject pharmacokinetic variability [28]. Withanolides from ashwagandha and ginsenosides from ginseng similarly display complex metabolic profiles, with active metabolites differing in pharmacological potency from parent compounds.

Translational challenges are compounded by the complexity of herbal preparations, which typically contain multiple bioactive constituents with potentially additive, synergistic, or antagonistic interactions. The identification of principal active compounds, establishment of dose-response relationships, and development of validated analytical methods for standardisation remain critical unmet needs in the field [29]. Furthermore, species variations in phytochemical content, geographic origin, cultivation conditions, and post-harvest processing practices introduce batch-to-batch variability that complicates reproducibility across studies and hinders regulatory approval.

6. Clinical Evidence: Efficacy and Safety

The clinical evidence base for phytopharmaceuticals in hormonal disorders is growing but remains heterogeneous in quality and consistency. Randomised controlled trials of soy isoflavone supplementation in menopausal women have reported modest but statistically significant reductions in vasomotor symptom frequency and severity compared to placebo, with improvements in bone mineral density also documented in several trials [30, 31]. A meta-analysis of soy isoflavone interventions concluded that supplementation was associated with a mean reduction of approximately 21% in hot flush frequency, though considerable inter-trial heterogeneity was noted, partly attributable to differences in isoflavone dose, formulation, and population equol-producer status [30].

Berberine has attracted particular clinical interest for its insulin-sensitising properties. Clinical trials in patients with type 2 diabetes mellitus have demonstrated reductions in fasting plasma glucose, postprandial glucose, and HbA1c comparable in magnitude to those achieved with metformin, without the latter's gastrointestinal adverse effects in head-to-head comparisons [20, 26]. A systematic review of berberine clinical trials reported mean HbA1c reductions of 0.9% to 1.1% across trials, supporting its potential as an adjunct antidiabetic agent. Withania somnifera extract has demonstrated significant reductions in serum cortisol, improvements in thyroid function indices, and amelioration of stress-related psychological and physiological parameters in several randomised controlled trials [21, 22].

Safety considerations for phytopharmaceuticals are generally favourable compared to synthetic hormone therapies, though important caveats apply. High-dose phytoestrogen supplementation may exert proliferative effects on oestrogen-sensitive tissues in susceptible individuals, necessitating caution in women with a history of oestrogen-receptor-positive breast cancer [17, 31]. Herb-drug interactions represent a clinically significant safety concern; for example, St John's Wort (Hypericum perforatum) induces cytochrome P450 enzymes and P-glycoprotein, potentially reducing plasma levels of co-administered medications including oral contraceptives and thyroid hormone preparations [32]. The absence of mandatory pre-market clinical safety data for herbal supplements in many jurisdictions further limits the evidence base for safety characterisation.

7. Formulation Strategies and Advanced Delivery Systems

The limited oral bioavailability of many phytochemicals has catalysed considerable research into advanced drug delivery systems aimed at enhancing their pharmacokinetic profiles and therapeutic efficacy. Nanoparticle-based delivery platforms, including polymeric nanoparticles, solid lipid nanoparticles, and nanostructured lipid carriers, have been extensively investigated for isoflavones, curcumin, and resveratrol, with studies demonstrating substantially improved dissolution rates, intestinal permeability, and systemic bioavailability compared to conventional oral formulations [33, 34].

Liposomal encapsulation has been applied to hydrophilic phytochemicals to enhance cellular uptake and extend plasma half-life. Phytosomes, proprietary complexes in which phytochemicals are bound to phosphatidylcholine to form

amphiphilic structures, have demonstrated enhanced oral bioavailability for compounds such as silymarin, curcumin, and green tea catechins [34]. Self-emulsifying drug delivery systems (SEDDS) exploit the emulsification capacity of lipid-surfactant mixtures to enhance the solubilisation and intestinal absorption of lipophilic phytochemicals, including withanolides and ginsenosides [35]. Cyclodextrin inclusion complexes improve aqueous solubility and chemical stability of poorly soluble phytochemicals without altering their pharmacological activity.

Beyond oral delivery, transdermal and mucosal administration routes have been explored for steroid-like phytochemicals. Topical formulations of phytoestrogens have been investigated for localised management of vulvovaginal atrophy associated with postmenopausal oestrogen deficiency, potentially offering tissue-selective oestrogenic effects with minimal systemic exposure [36]. The rational design of delivery systems tailored to the physicochemical properties of specific phytochemicals and the pharmacokinetic requirements of the target indication represents a priority area for formulation research.

8. Regulatory, Ethical, and Commercialisation Challenges

The regulatory landscape for phytopharmaceuticals varies substantially across jurisdictions, creating inconsistencies in quality standards, safety requirements, and evidence thresholds for market authorisation. In the European Union, herbal medicinal products are subject to the Traditional Herbal Medicinal Products Directive, which permits marketing based on established traditional use without requiring proof of clinical efficacy for simplified registration, while full marketing authorisation demands conventional clinical evidence [37]. In the United States, botanical products may be marketed as dietary supplements under the Dietary Supplement Health and Education Act with minimal pre-market regulatory oversight, substantially limiting consumer protections and creating a permissive environment for products of inadequate quality or safety characterisation [38].

Standardisation of phytopharmaceutical preparations presents fundamental scientific and commercial challenges. Unlike synthetic pharmaceuticals, where chemical identity and purity can be precisely specified, herbal preparations are complex matrices whose phytochemical composition varies with botanical source, geographical origin, climate, agricultural practices, and extraction methodology. The identification of reliable chemical markers for standardisation, development of validated analytical methods, and establishment of acceptable specifications for batch consistency are essential prerequisites for regulatory compliance and clinical reproducibility [29, 39].

Ethical considerations in phytopharmaceutical research include the equitable sharing of benefits arising from the commercialisation of traditional knowledge, as mandated by the Nagoya Protocol on Access and Benefit Sharing under the Convention on Biological Diversity [40]. Indigenous communities possessing traditional knowledge of medicinal plant use should receive recognition and fair compensation when such knowledge underpins commercial product development. The risk of biopiracy and the appropriation of traditional knowledge without community consent remain ongoing ethical concerns that the pharmaceutical industry and academic research community must actively address.

9. Conclusions and Future Directions

This review has systematically examined the scientific and clinical evidence for phytopharmaceuticals as therapeutic agents for hormonal imbalance management. The accumulated evidence supports the view that plant-derived bioactive compounds, including isoflavones, lignans, berberine, withanolides, and ginsenosides, possess genuine endocrine-modulating activities mediated through receptor binding, enzyme modulation, and HPA or HPG axis regulation. Clinical trials for specific compounds and indications, notably soy isoflavones for menopausal symptoms and berberine for glycaemic control, have generated promising results, though the evidence base remains constrained by heterogeneity in study design, standardisation, and outcome measures.

Future research should prioritise the conduct of rigorously designed, adequately powered, long-duration randomised controlled trials employing well-characterised and standardised phytopharmaceutical preparations. Mechanistic research in advanced *in vitro* and *in vivo* models, including three-dimensional organoid cultures and humanised mouse models, should be employed to elucidate the molecular targets and signalling networks through which key phytochemicals exert their endocrine effects. Pharmacogenomic and gut microbiome research holds particular promise for explaining inter-individual variability in pharmacokinetic and pharmacodynamic response, with equol-producer status exemplifying the importance of individualised approaches to phytopharmaceutical therapy.

Advanced delivery systems, particularly nanoparticle-based platforms and phytosomes, should be further developed and clinically validated to address the pharmacokinetic limitations that have historically impeded the translation of promising preclinical findings into clinical efficacy. Regulatory frameworks must be strengthened and harmonised to ensure consistent standards of quality, safety, and evidence across jurisdictions. Collaborative engagement between academic researchers, pharmaceutical developers, regulatory agencies, and indigenous knowledge holders will be essential for the responsible and equitable translation of phytopharmaceuticals into evidence-based clinical practice. The convergence of traditional ethnobotanical knowledge with modern pharmacological science offers a compelling paradigm for the development of novel endocrine therapeutics that are both effective and contextually appropriate.

Figures

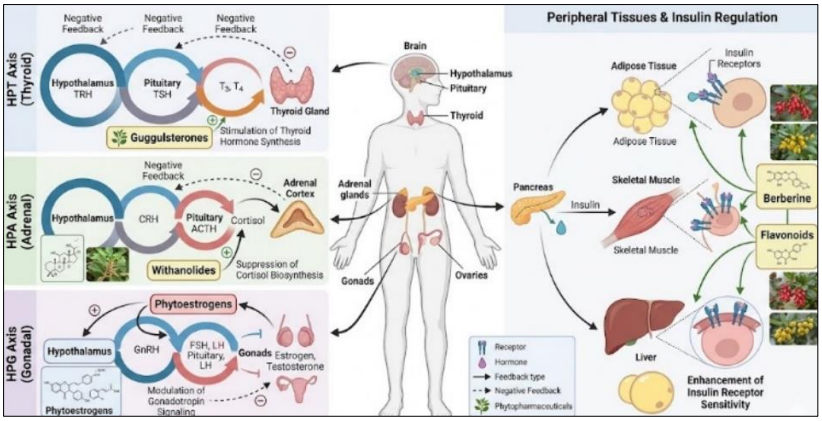

Fig 1: Schematic representation of the principal endocrine glands and their hormonal regulatory axes as targets for phytopharmaceutical intervention.

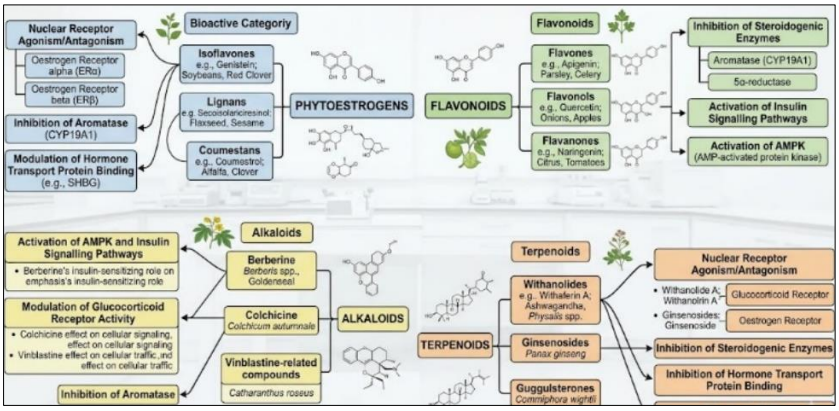

Fig 2: Classification diagram of major phytopharmaceutical classes and their principal mechanisms of endocrine action.

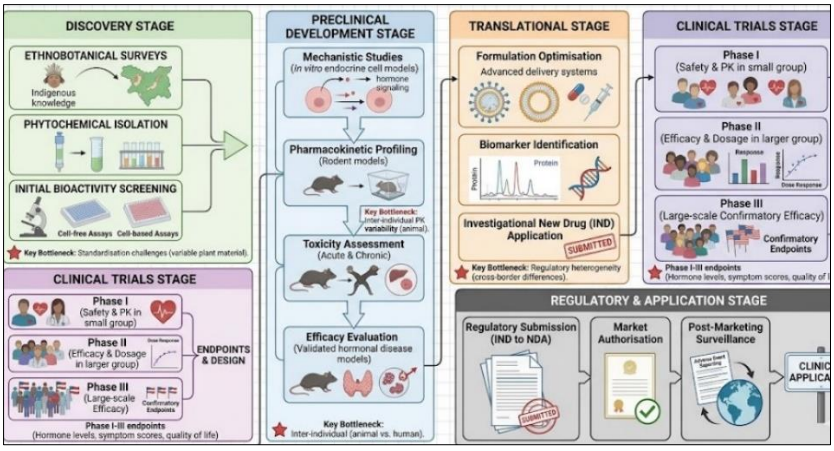

Fig 3: Translational pathway from initial phytopharmaceutical discovery to clinical application in endocrine disorders, presented as a multi-stage pipeline.

Tables

Table 1: Comparative Overview of Major Phytopharmaceuticals, Their Sources, and Mechanisms of Action in Hormonal Regulation

Phytopharmaceutical	Bioactive Class	Plant Source	Primary Mechanism of Action	Target Hormonal Axis
Genistein / Daidzein	Isoflavones (Phytoestrogens)	Glycine max (Soya)	Selective ERalpha/ERbeta binding; aromatase inhibition	HPG axis; menopausal hormone balance
Secoisolariciresinol	Lignan (Phytoestrogen)	Linum usitatissimum (Flaxseed)	Weak oestrogenic activity; SHBG modulation	Oestrogen regulation; breast tissue
Berberine	Protoberberine Alkaloid	Berberis vulgaris / B. aristata	AMPK activation; inhibition of hepatic gluconeogenesis; gut microbiome modulation	Insulin/glucose axis; HPA axis
Withanolides	Steroidal Lactone (Terpenoid)	Withania somnifera (Ashwagandha)	Glucocorticoid receptor modulation; cortisol suppression; thyroid stimulation	HPA axis; HPT axis; adaptogenic effects
Ginsenosides Rb1, Rg1	Triterpene Saponin (Terpenoid)	Panax ginseng	Glucocorticoid receptor binding; HPA axis attenuation; insulin receptor sensitisation	HPA axis; HPG axis; glucose metabolism
Guggulsterones E & Z	Diterpenoid	Commiphora mukul (Guggul)	Farnesoid X receptor antagonism; thyroid peroxidase stimulation	HPT axis; thyroid hormone synthesis
Quercetin / Kaempferol	Flavonol (Flavonoid)	Allium cepa; Camellia sinensis	CYP19A1 aromatase inhibition; ER binding; anti-inflammatory effects on adrenal tissue	Oestrogen metabolism; adrenal function
Metformin-like Alkaloids	Biguanide-related Alkaloid	Galega officinalis (Goat's Rue)	Mitochondrial complex I inhibition; AMPK activation; reduced hepatic glucose output	Insulin signalling; glucose homeostasis

Table 2: Summary of Clinical Applications and Efficacy of Plant-Based Therapies for Hormonal Disorders

Phytopharmaceutical	Clinical Indication	Study Design	Principal Clinical Outcomes	Limitations and Caveats
Soy Isoflavones (50-100 mg/day)	Menopausal vasomotor symptoms; osteoporosis prevention	Multiple RCTs; meta-analyses	~21% reduction in hot flush frequency; modest BMD improvement	Variable equol-producer status; inconsistent standardisation across trials
Berberine (500 mg three times daily)	Type 2 diabetes mellitus; insulin resistance; PCOS	RCTs; head-to-head vs metformin	HbA1c reduction 0.9-1.1%; improved fasting glucose and lipids	Small sample sizes; short follow-up duration; limited long-term safety data
Withania somnifera Extract (300-600 mg/day)	Hypothyroidism; HPA dysfunction; stress-related cortisol excess	RCTs; open-label pilot studies	Significant cortisol reduction; improved TSH and T4 levels; improved subjective stress indices	Small cohort sizes; lack of multicentre replication
Red Clover Isoflavones (40-160 mg/day)	Menopausal symptoms; cardiovascular risk reduction	RCTs; systematic reviews	Modest symptom relief; improved lipid profiles; cardiovascular risk factor reduction	Concerns regarding ER-positive breast tissue exposure; interaction potential
Panax ginseng (200-400 mg/day)	HPA dysregulation; fatigue; glucose intolerance; erectile dysfunction	RCTs; observational studies	Improved glycaemic control; reduced fatigue; enhanced erectile function in men	Heterogeneous ginsenoside profiles; variability in preparation and dose
Flaxseed Lignans (10-25 g/day)	Menopausal symptoms; hormone-sensitive cancer risk reduction	Pilot RCTs; cohort studies	Modest vasomotor symptom improvement; favourable effects on oestrogen metabolism ratios	Limited large-scale clinical data; individual variation in lignan bioconversion

Table 3: Advantages, Limitations, and Pharmacokinetic Considerations of Phytopharmaceuticals in Endocrine Management

Parameter	Advantages	Limitations	Pharmacokinetic Considerations
Safety Profile	Generally favourable compared to synthetic hormone therapy; lower risk of thromboembolic and malignant adverse effects	Herb-drug interactions (e.g., CYP450 induction); potential toxicity at high doses; lack of comprehensive adverse event reporting	Variable metabolic profiles; toxicological data incomplete for most constituents
Bioavailability	Some compounds show adequate oral absorption; nanoformulations can markedly enhance systemic exposure	Poor aqueous solubility of many polyphenols; extensive first-pass metabolism; efflux transport limitations	Low absolute bioavailability for most flavonoids (2-20%); high variability influenced by food matrix and gut microbiota
Standardisation	Chemical marker-based standardisation increasingly feasible with modern analytical methods	Complex, variable phytochemical matrix; batch-to-batch variability; difficulty defining full active complement	Pharmacokinetic parameters must be referenced to defined marker compound concentrations
Mechanism Selectivity	Multi-target activity may address the pleiotropic pathophysiology of endocrine disorders; potential for synergistic benefit	Off-target effects may occur; mechanistic specificity difficult to establish with whole plant extracts	Tissue-selective distribution may be advantageous but is incompletely characterised for most compounds
Cost and Accessibility	Plant-derived compounds generally lower cost than biologics; wide cultural acceptance and availability	Quality inconsistency in commercial products; risk of adulteration; regulatory oversight variable	Pharmacokinetic equivalence between commercial and research-grade preparations often unverified

Table 4: Current Research Status and Development Stages of Selected Phytopharmaceutical-Based Therapies for Endocrine Disorders

Compound / Preparation	Target Disorder	Development Stage	Key Findings to Date	Priority Research Needs
Soy Isoflavones	Menopause; postmenopausal osteoporosis	Phase III trials completed; marketed supplements available	Clinically relevant vasomotor symptom reduction; favourable bone density data in long-duration trials	Standardised equol-stratified trials; long-term breast tissue safety data
Berberine	Type 2 diabetes; PCOS; dyslipidaemia	Phase II/III trials; increasingly used in clinical practice	Comparable glycaemic efficacy to metformin; additive lipid-lowering effects; PCOS hormonal improvements	Long-term cardiovascular outcome trials; gut microbiome mechanistic studies
Withania somnifera Extract	Stress-induced HPA dysregulation; subclinical hypothyroidism	Phase II trials; marketed nutraceuticals	Consistent cortisol reduction across trials; preliminary thyroid-stimulating evidence	Larger phase III trials; standardised withanolide content definition; long-term safety profiling
Guggulsterone Complex	Hypothyroidism; dyslipidaemia	Preclinical to Phase II; marketed in Ayurvedic systems	Thyroid stimulation demonstrated in animal models; mixed human trial results for lipids	Rigorous standardised clinical trials; bioavailability enhancement research
Quercetin Nanoformulation	Oestrogen-dependent conditions; adrenal inflammation	Preclinical; early Phase I	Aromatase inhibition confirmed *in vitro* and *in vivo*; nanoparticle formulations show markedly improved bioavailability	Clinical dose-finding studies; safety in oestrogen-sensitive populations; CYP interaction profiling
Flaxseed Lignan Extracts	Menopausal symptoms; hormone-sensitive cancer prevention	Phase II trials; dietary supplement stage	Modest vasomotor symptom benefit; favourable urinary oestrogen metabolite ratios	Phase III trials with validated biomarker endpoints; gut microbiome stratification

References

1. Melmed S, Polonsky KS, Larsen PR, Kronenberg HM. Williams textbook of endocrinology. 14th ed. Philadelphia: Elsevier; 2020.
2. Golden SH, Robinson KA, Saldanha I, Anton B, Ladenson PW. Prevalence and incidence of endocrine and metabolic disorders in the United States: a comprehensive review. J Clin Endocrinol Metab. 2009;94(6):1853–78.
3. Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. Endocr Rev. 2012;33(6):981–1030.
4. Pearce EN, Farwell AP, Braverman LE. Thyroiditis. N Engl J Med. 2003;348(26):2646–55.
5. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, *et al*. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA. 2002;288(3):321–33.
6. Fardet L, Petersen I, Nazareth I. Prevalence of long-term oral glucocorticoid prescriptions in the UK over the past 20 years. Rheumatology. 2011;50(11):1982–90.
7. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. Endocr Rev. 2008;29(1):76–131.
8. Fabricant DS, Farnsworth NR. The value of plants used in traditional medicine for drug discovery. Environ Health Perspect. 2001;109(Suppl 1):69–75.
9. Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. Front Pharmacol. 2014;4:177.
10. Patisaul HB, Jefferson W. The pros and cons of phytoestrogens. Front Neuroendocrinol. 2010;31(4):400–19.
11. Ehrlich SD. Herbal medicine. University of Maryland Medical Center; 2015.
12. Boron WF, Boulpaep EL. Medical physiology. 3rd ed. Philadelphia: Elsevier; 2017.
13. Miller WL, Auchus RJ. The molecular biology, biochemistry, and physiology of human steroidogenesis and its disorders. Endocr Rev. 2011;32(1):81–151.
14. Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. Nature. 2001;414(6865):799–806.
15. Zoeller RT, Brown TR, Doan LL, Gore AC, Skakkebaek NE, Soto AM, *et al*. Endocrine-disrupting chemicals and public health protection: a statement of principles from the Endocrine Society. Endocrinology. 2012;153(9):4097–110.
16. Cragg GM, Newman DJ. Natural products: a continuing source of novel drug leads. Biochim Biophys Acta. 2013;1830(6):3670–95.
17. Messina M. Soy and health update: evaluation of the clinical and epidemiologic literature. Nutrients. 2016;8(12):754.
18. Lecomte S, Demay F, Ferriere F, Pakdel F. Phytochemicals targeting estrogen receptors: beneficial or adverse effects? Int J Mol Sci. 2017;18(7):1381.
19. Rice S, Whitehead SA. Phytoestrogens and breast cancer – promoters or protectors? Endocr Relat Cancer. 2006;13(4):995–1015.
20. Yin J, Xing H, Ye J. Efficacy of berberine in patients with type 2 diabetes mellitus. Metabolism. 2008;57(5):712–17.
21. Chandrasekhar K, Kapoor J, Anishetty S. A prospective, randomized double-blind, placebo-controlled study of safety and efficacy of a high-concentration full-spectrum extract of Ashwagandha root in reducing stress and anxiety in adults. Indian J Psychol Med. 2012;34(3):255–62.
22. Ambiye VR, Langade D, Dongre S, Aptikar P, Kulkarni M, Dongre A. Clinical evaluation of the spermatogenic activity of the root extract of Ashwagandha (Withania somnifera) in oligospermic males. Evid Based Complement Alternat Med. 2013;2013:571420.
23. Kuiper GG, Carlsson B, Grandien K, Enmark E, Haggblad J, Nilsson S, *et al*. Comparison of the ligand binding specificity and transcript tissue distribution of

estrogen receptors alpha and beta. Endocrinology. 1997;138(3):863–70.
24. Panda S, Kar A. Guggulu (Commiphora mukul) potentially ameliorates hypothyroidism in female mice. Phytother Res. 2005;19(1):78–80.
25. Mueller SO, Simon S, Chae K, Metzler M, Korach KS. Phytoestrogens and their human metabolites show distinct agonistic and antagonistic properties on estrogen receptor alpha (ERα) and ERβ in human cells. Toxicol Sci. 2004;80(1):14–25.
26. Zhang Y, Li X, Zou D, Liu W, Yang J, Zhu N, *et al*. Treatment of type 2 diabetes and dyslipidemia with the natural plant alkaloid berberine. J Clin Endocrinol Metab. 2008;93(7):2559–65.
27. Manach C, Williamson G, Morand C, Scalbert A, Remesy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. Am J Clin Nutr. 2005;81(1 Suppl):230S–242S.
28. Setchell KD, Clerici C. Equol: history, chemistry, and formation. J Nutr. 2010;140(7):1355S–62S.
29. Calixto JB. Efficacy, safety, quality control, marketing and regulatory guidelines for herbal medicines (phytotherapeutic agents). Braz J Med Biol Res. 2000;33(2):179–89.
30. Howes LG, Howes JB, Knight DC. Isoflavone therapy for menopausal flushes: a systematic review and meta-analysis. Maturitas. 2006;55(3):203–11.
31. Lethaby A, Marjoribanks J, Kronenberg F, Roberts H, Eden J, Brown J. Phytoestrogens for menopausal vasomotor symptoms. Cochrane Database Syst Rev. 2013;(12):CD001395.
32. Henderson L, Yue QY, Bergquist C, Gerden B, Arlett P. St John's wort (Hypericum perforatum): drug interactions and clinical outcomes. Br J Clin Pharmacol. 2002;54(4):349–56.
33. Nair A, Jacob S, Al-Dhubiab B, Attimarad M, Harsha S. Basic considerations in the dermatokinetics of topical formulations. Braz J Pharm Sci. 2013;49(3):423–34.
34. Kidd PM. Bioavailability and activity of phytosome complexes from botanical polyphenols: the silymarin, curcumin, green tea, and grape seed extracts. Altern Med Rev. 2009;14(3):226–46.
35. Pouton CW. Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and self-microemulsifying drug delivery systems. Eur J Pharm Sci. 2000;11(Suppl 2):S93–8.
36. Genazzani AR, Stomati M, Valentino V, Pluchino N, Palumbo M, Genazzani AD, *et al*. Effect of 1-year, low-dose DHEA therapy on climacteric symptoms and female sexuality. Climacteric. 2011;14(6):661–8.
37. European Medicines Agency. Guideline on good agricultural and collection practice (GACP) for starting materials of herbal origin. Amsterdam: EMA; 2006.
38. Dietary Supplement Health and Education Act of 1994. Public Law 103-417. Washington, DC: US Congress; 1994.
39. Canter PH, Thomas H, Ernst E. Bringing medicinal plants into cultivation: opportunities and challenges for biotechnology. Trends Biotechnol. 2005;23(4):180–5.
40. Secretariat of the Convention on Biological Diversity. Nagoya protocol on access to genetic resources and the fair and equitable sharing of benefits arising from their utilization to the convention on biological diversity. Montreal: SCBD; 2011.