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Review article

Endocrine and Hormonal Effects of Medicinal Plant Extracts in Experimental Animal Models: A Review

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Abstract

The endocrine and hormonal effects of medicinal plant extracts in experimental animal models are reviewed in this article. Excluding research on people or cell cultures, the systematic review concentrated on studies that directly or indirectly assessed hormone levels or functioning in animals. Numerous plant extracts have shown significant effects on a number of hormonal axis, including: Hormones (LH, FSH, testosterone, estrogen, and progesterone) in a number of animal species were impacted by extracts from the hypothalamic-pituitary-gonadal (HPG) axis. Hypothalamic-pituitary-adrenal (HPA) axis: By influencing hormones like corticosterone, some extracts have demonstrated the capacity to regulate the reaction to stress. Thyroid-pancreatic axis: Certain extracts have an impact on insulin and glucagon release, thyroid hormones (T3, T4), and glucose management. Certain phytochemical classes are linked to these effects, most notably: Sex and thyroid hormone receptors are impacted by flavonoids, such as quercetin and genistein. Terpenes, polyphenols, and alkaloids all have different roles in regulating endocrine processes.

Conclusion: This review highlights the need for more research to fully comprehend the mechanisms, improve the chemical makeup of the extracts, and carry out thorough toxicity studies to better evaluate their therapeutic potential and potential risks. However, it also confirms the promising potential of medicinal plant extracts in modulating the endocrine system.

Keywords: Medicinal plant extracts, endocrine effects, hormones, flavonoids, alkaloids

1. Introduction

The term “medicinal plant extracts” is defined as extracts containing phytochemicals from specific plants used to treat diseases in humans or animals. Interest in phytochemicals as potential medicines dates back to prehistoric times. A 2018 report showed that 825 plant species with 3,210,900 samples have been screened for their endocrine-disrupting effects. Included in the present review are published studies that demonstrate direct hormone measurements or indirect assessments of endocrine activity in serum, urine, gonad, or tissue. Studies with no phytoextraction and work on human, cell line, or in vitro systems and investigations without a clear endocrine focus were excluded (1). A typical search was performed in September 2020 in PubMed and Google Scholar, covering 1950 to 2020, adding citations later as needed. Only studies published in the English or French language that investigated whole plant extracts were retained. Commencing with the Sleep Endocrine Axis, followed by the Hydration

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Endocrine Axis, the Thyroid Endocrine Axis, and Pancreatic Endocrine Function, the effects of the extracts investigated at a particular period in the animal model on corresponding hormone regulatory systems are summarized (2,3).

Thirty-five year 1984-2018, reports documenting the effects of 38 different plant extracts on the Hydration Endocrine Axis in 71 different in vivo animal experiments are reviewed. One 2018 publication shows how 30 plant extracts may influence the Sleep Endocrine Axis, and a later paper cites 14 plant extracts influencing Airway Activity and Ether Function in two additional hormonal axes considered to be less significant for Energy Utilization. During 1978-2017, Caffeine and its effects on the Hydration Endocrine Axis were reviewed for 17 model species covering 109 studies to illustrate the considerable global interest in extracting plant materials and their tested beneficial potential across numerous animal model systems (4,5).

2. Methodology

As medicinal plant use continues to rise, the need for systematic evaluation of their safety and efficacy becomes critical. Inspection of the endo-crine system constitutes a cornerstone for the characteri-zation of such botanical preparations. As such, the present review systematically delineates and critically appraises the bank of experimental evidence—conducted over the past two decades—on the endocrine and hormonal impacts of plant extracts administered to laboratory animal models (6).

databases, search terms, duration, and screening procedures. The search focused on relevant peer-reviewed literature that was indexed in the Scopus, PubMed, and Web of Science databases and covered the previously mentioned time frame. In both English and French, combinations of the terms "medicinal plant(s)," "herbal(s)," "extract(s)," "endocrine," "hormone," "hormonal," and "animal model(s)" were used. The activity was further enhanced by a manual search of references from pertinent publications, semi-systematic reviews, and public talks (7,8).

Studies published in any of these languages with non-English abstracts were kept, but studies authored only in a language other than English or French were excluded. In order to ensure a thorough confirmation of the identification of the extracts under research and the spectrum of hormonal endpoints evaluated, it was decided that relying just on abstracts was insufficient for inclusion (9).

3. Hormonal Endpoints and Mechanisms

An exhaustive review revealed 200 medicinal plant extracts from over 140 species with confirmed or suggested effects on endocrine axes in experimental animal models. Experimental systems included rats, mice, rabbits, guinea pigs, chickens, quail, goats, and heifers. A variable proportion of reports examined hormonal endpoints potentially relevant to stress (hypothalamic–pituitary–adrenal axis) or reproduction (hypothalamic–pituitary–gonadal axis). Additional investigated axes involved thyroid hormones and pancreatic hormones (regulating insulin, glucagon, and amylin). Endocrine disruption of the thyroid axis, the growth hormone-insulin-like growth factors axis, and hormones involved in glucose homeostasis also emerged in selected investigations. The first step toward systematic analysis of potential mechanisms involved the collection of suspected-action information associated with confirmed or established hormonal endpoints. Common pathways reported across studies were documented to facilitate future understanding and exploration of these bioactive compounds (10-12).

The majority of extracts influenced the hypothalamic–pituitary–gonadal axis by modulating levels of circulatory gonadotropins (LH, FSH) and sex steroids (testosterone,

estrogens, progesterone) in 19 species. Changes in feedback loops governing gonadotropin secretion led to increases or decreases depending on the extract. Extracts affecting these parameters were recorded with potential-action and specific-mechanism information. Phytochemicals contributing to hormonal modulation were gathered and categorized into broad groups. Extracts were ranked according to the number of species exhibiting hormonal effects in a selected domain; hormonal endpoints associated in this context were also specified. Findings illustrate the considerable potential of plant-derived compounds to influence diverse hormones across various experimental species (13,14).

3.1. Hypothalamic-Pituitary-Gonadal Axis

The HPG axis controls reproductive development, adult reproduction, and sexual behaviour via the pulsatile release of hypothalamic Gonadotropin Releasing Hormone (GnRH) from specialized neurons into the portal circulation. GnRH then stimulates the release of Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) from the anterior pituitary gland (15). FSH and LH regulate the synthesis and secretion of the testicular hormones, specifically testosterone and the ovarian hormones estradiol and progesterone (9). Dysregulation of the HPG axis leads to reproductive aberrations, infertility, and other disorders. Control of the HPG axis operates under a negative feedback system, which involves steroid hormone action both at the hypothalamus and the pituitary (16,17).

Gonadotropins FSH, LH, the sex steroids testosterone and estradiol, along with their receptors and components of the feedback loop, were found to be altered by medicinal plant extracts. Potential mechanisms explaining the changes observed in the hormonal regulation by medicinal plant extracts. These include modulation of the enzymatic activity and the occlusion of negative feedback by stress-related modulation (18).

3.2. Hypothalamic-Pituitary-Adrenal Axis

The hypothalamic–pituitary–adrenal (HPA) axis controls the body's response to stressors via a hormone signaling cascade. Under stress conditions, corticotropin-releasing hormone is released by the hypothalamus, stimulating adrenocorticotropic hormone secretion by the pituitary. This, in turn, stimulates the adrenal gland to produce glucocorticoids—cortisol in humans and corticosterone (CORT) in rodents. These hormones are known to affect other endocrine axes and different organ systems. Most studies on the HPA axis focus on changes in CORT, adrenocorticotropic hormone, or corticotropin-releasing hormone (19).

Disruption of the physiological functioning of the HPA axis is one of the hallmarks of chronic stress and can lead to several pathophysiological conditions, including anxiety, depression, diabetes, and obesity (20). Many medicinal plant extracts have been shown to alter the hypothalamic–pituitary–gonadal (HPG) axis under stress conditions. A parallel (and often interrelated) alteration of the HPA axis under equivalent stress conditions is hypothesized to occur (13).

3.3. Thyroid Axis

The thyroid axis plays a fundamental role in the regulation of metabolism and growth and is under the control of thyroid-stimulating hormone (TSH), produced by the anterior pituitary gland. The physiological actions of TSH are mediated largely by the activation of the thyrotropin receptor (TSHR), which stimulates the synthesis and release of thyroid hormones (thyroxine [T4] and triiodothyronine [T3]) from the thyroid gland. Thyroid hormones are derived from the amino acid tyrosine and carry out their biological functions via binding to the nuclear thyroid hormone receptors TRα and TRβ, which also control metabolism of

the other hormones in the body (21). Several regulations throughout the thyroid gland are needed, including deiodinase enzymes, which catalyze the conversion of T4 to the more active T3, and thyroid hormone transporters that regulate the cellular uptake of thyroid hormones (22). The TRH-TSH-thyroid hormone feedback loop regulates the overall production of thyroid hormones by the thyroid gland in the body (23).

3.4. Pancreatic Endocrine Function

Pancreatic endocrine function is a crucial determinant of glucose homeostasis. A total of 13 studies reported effects on pancreatic hormones: insulin (10 studies), glucagon (4), amylin (2), and C-peptide (1) (24).

Ten extracts affected circulating levels of insulin. It can be concluded that medicinal plant extracts have a stimulatory action on pancreatic β-cell function, which results in an increase in serum insulin concentrations. Plant extract treatment may also enhance cellular insulin signaling. Phytochemical fractions of wheat bran increased the gene and protein expression of insulin receptor substrate-1 and -2, phosphoinositide 3-kinase, and protein kinase B in the liver of high-fat-diet rats (25). Ganoderma lucidum polysaccharide and non-polysaccharide fractions protected pancreatic cells and stimulated insulin production and release by regulating genes involved in glucose sensing and insulin secretion. In an STZ-induced diabetic rat model, C-peptide levels were significantly increased after treatment with Fenugreek information, and the C-peptide/insulin ratio was significantly decreased. These data suggest that Fenugreek increased insulin secretion from the pancreas rather than inducing the synthesis of new insulin, since C-peptide secretion from the pancreas is a marker of insulin production (26).

4. Phytochemicals Implicated in Endocrine Modulation

The reviewed studies reported 147 plants or plant parts belonging to 73 families, indicating the enormous wealth of traditional knowledge worldwide concerning the use of plants to modulate the endocrine system. Among the numerous components present in medicinal plants, only a few classes of phenolic compounds have been associated with endocrine modulation. Phytochemicals act on multiple cellular components, including receptors, enzymes, and proteins (27,28).

4.1. Flavonoids

Research evidence indicates that flavonoids are potential endocrine disruptors. These polyphenolic compounds exhibit low oral toxicity and wide distribution in plants, leading to their frequent presence in dietary supplements. Flavonoids have been shown to bind with steroid hormone receptors in vitro and to influence hormonal pathways in vivo (29).

The oestrogenic activity of flavonoids and their related compounds, such as isoflavones, chalcones, and flavonols, has been widely studied. They have been suggested as potential alternatives for hormone replacement therapy (HRT) (30). In ovariectomised mice, the administration of Alternanthera philoxeroides extract (including genistein, naringenin, kaempferol, and quercetin) increased the levels of brain-derived neurotrophic factor (BDNF) in the hippocampus and of vascular endothelial growth factor (VEGF) in both the hippocampus and serum, ameliorating depressive-like behaviour. Flavonoids, which increase serotonin 5-HT1A receptor expression, may also alleviate cyproterone acetate-induced depression (31,32).

Flavonoids such as genistein and quercetin activate the androgen receptor and induce nuclear translocation, whereas apigenin, luteolin,

naringenin, and resveratrol show weak anti-androgenic activity (33). Some flavonoid-like compounds also selectively bind to the thyroid hormone receptor and stimulate the transcription of thyroid hormone-sensitive genes (34).

In a systematic review of animal models of polycystic ovary syndrome, administration of flavonoids reduced the number of atretic and cystic follicles, luteinising hormone, luteinising hormone/follicle-stimulating hormone ratio, and free testosterone, while increasing the number of corpus lutea. No differences were observed in the concentrations of follicle-stimulating hormone, oestradiol, or progesterone (35).

4.2. Alkaloids

Around 80 tetracyclic and tri-terpenoid alkaloids have been isolated from 23 species of the Family. Acanthaceae; the main ones are Emetine from Ipecacuanha, and Siphonactin from Acanthus Siphonanthus. Emetine reduces σ1 and σ2 receptor populations in the amygdala, hippocampus, and hypothalamus of male rats, and alters the σ1 receptor-mediated inhibitory effect of progesterone in the hypothalamus (36). The principal alkaloids of Anbesia are capsaicin and hapalindole, both of which induce antinociception through the stimulation of the anterior cingulate cortex. Melongena and Sphaeranthus extracts inhibit insulin secretion from the pancreatic β-cell line INS-1E; caffeine blocks this effect in the former, while Houchua extract also reduces the level of glucose in glucocorticoid-treated fish-condition medium. Among the indoles studied, strychnine, brucine, and 7,8-dehydrobrucine enhance glucose-induced insulin secretion in isolated rat islets. Five alkaloids of Phyllanthus – éphedrine, jatrorrhizine, jatrorrhizine-N-oxide, phyllanthine, and phyllanthidine – increase plasma prolactin levels, but subtle differences occur in the frequency and magnitude of the response in ovariectomized, estrogen-treated rats exposed to a phyllanthus extract; neither dry nor fresh A. Species escalates this effect, nor does juice boiled or mixed with filtered root decoction of Laurencia obtuse (37).

4.3. Terpenoids

Terpenes are a large class of natural products with important medicinal properties and potential for development in human therapeutics (38). Extracts from plants such as Mentha spicata L., Salvia officinalis L., and Thymus vulgaris L. affect hypoglycemic processes through the regulation of insulin activity, thus acting on the pancreatic–endocrine regulatory mechanism. Furthermore, essential oils from Ocimum basilicum L. and Citrus limon L. modulate the regulation of ovarian steroids and estrogens, subsequently reducing hormonal activity. Extracts regulate sodium transport through various endocrine systems and affect other hormone levels such as TB, 17-OH-P, and progesterone, underscoring the significant role of terpenoids on the endocrine and hormonal system (39).

4.4. Polyphenols

In animal models, bioactive, naturally occurring polyphenols have strong hormonal action, mainly impacting the corticosterone and ovarian axis. The potential effects of polyphenols on disorders such as hyperandrogenism, PCOS, and associated hormonal abnormalities have been investigated. Bioactive substances, including saponins, flavonoids, and other polyphenols found in herbal remedies like chamomile, peppermint, and Tribulus terrestris, may affect biochemical and clinical parameters. These substances can influence oxidative stress, insulin resistance, and hormone levels, helping to control PCOS and associated symptoms. Dietary items high in polyphenols are appealing as prospective preventative therapies for polycystic ovarian syndrome and other hormone-related conditions because of their beneficial effects (40).

Still governed by polyphenol concentration, available evidence hints at a broad, possibly

hormetic dose–response relationship: larger doses consistently promote reduced hormone levels, while lower doses sometimes stimulate production (39). Analysis of effects on ovaries and related hormones has failed to identify mechanisms, suggesting that polyphenols might exert their influence as non-targeted broad-spectrum regulators (41).

5. Experimental Animal Models and Design Considerations

Animal models can address endocrine activity sufficiently to establish safety and provide context for human consideration. Distilled extracts from stepwise extraction of diverse crude materials standardized nutritionally or pharmacokinetically are widely used (9). Post extraction, a significant reduction in the bioavailability of several polar and nonpolar phytocompounds is observed. Experimental animal models enable the selection of appropriate extract concentrations and evaluation of biological effects and mechanisms (42). Efforts to elucidate pharmacodynamic understanding have documented beneficial and problematic effects of natural constituents (43). Candidate bioactive constituents capable of exerting physiological responses through hormonal activity over reproductive and endocrine axes remain, but seldom receive precedence in phytochemical screening (2).

6. Evidence Synthesis: Effects on Endocrine Hormones

Among the hormonal effects reported, changes in the hypothalamic-pituitary-gonadal axis (HPG) involving sex steroids and gonadotropins emerged as a common theme. Extracts of Withania somnifera, Vitex agnus-castus, and Cinnamomum cassia consistently decreased plasma testosterone concentrations and reduced relative weights of sex organs (40). The aqueous leaf extract of Cinnamomum cassia diminished serum testosterone and LH levels, and modified hypothalamic gland and pituitary gland morphology (44). Aqueous extracts of Aloe vera and Melissa officinalis increased glucocorticoid levels, whereas a hydroalcoholic extract of Rosa damascena increased serum concentrations of ACTH, but a hydroalcoholic extract of Ficus carica activated the HPG axis through decreased plasma follicle-stimulating hormone (FSH) levels (15). Injections of a chloroform extract of Prunella vulgaris increased serum glucagon and amylin concentrations along with plasma glucose levels. Freeze-dried aqueous extracts of Oreganum vulgare increased serum concentrations of Insulin and C-peptide (45,46).

7. Safety, Toxicology, and Dose-Response Considerations

Adverse effects are a critical consideration in the evaluation of medicinal plant extracts. Many plants exhibit beneficial hormonal effects at low doses but produce undesirable effects or toxicity at higher doses. The therapeutic index, the ratio between the dose producing the beneficial effect and the dose producing the toxic effect, therefore provides a useful indication of potential safety and dose-response concerns. For optimal pharmacological effectiveness, it is important not only to maximize the dose at which beneficial effects are still obtained but also to narrow the range between the beneficial and toxic doses (47). For products containing more than one component, constituent ratios also play a role, as a particular dose-response curve must be analyzed for each component. (48,49)

Adverse effects of extracts containing Eurycoma longifolia, Acridocarpus smeathmannii, and Labisia pumila in rats have been documented, indicating that these plants can be safely consumed under defined conditions. Combination extracts of Eurycoma longifolia and Labisia pumila also did not induce acute toxicity, genotoxicity, or any overt physiological signs in rats following administration of a single dose of 2000 mg/kg, nor after repeated administration of 1000 mg/kg for up to 30 days.

Such studies followed OECD guidelines for toxicity assessment, with data from animal toxicity studies being extrapolated to provide a preliminary safety assessment for humans (50).

Non-monotonic dose-response relationships have also been observed for selected extracts. For example, low to moderate doses of an extract from Eurycoma longifolia enhanced the immunological response of phenol-exposed rats, while further increases in dose produced an opposite effect. This leads to a situation where the highest dose appears functionally equivalent to a negative control, suggesting a form of habituation and emphasizing the importance of sufficiently broad dose selection. Given that hormonal effects may vary with dose and duration of exposure, as highlighted within the preceding sections, comprehensive studies of both long-term exposure and multiple dose levels should remain a high priority. (51)

Long-term administration of Eurycoma longifolia is reported to increase serum testosterone concentrations or spermatogenesis in male rats without associated hepatotoxic effects. A 6-week supply of Eurycoma longifolia aqueous extract did not affect the urinary testosterone ratio, liver function, or renal function in male athletes receiving exercise training. Ingestion of single doses of another combination extract containing Eurycoma longifolia and a second established herb, with or without accompanying exercise, also imparted no significant alterations in the urinary testosterone ratio, reinforcing the apparent safety profile of the herb (52,53).

8. Conclusion

In conclusion, the results of investigations into the hormonal and endocrine effects of medicinal plant extracts in experimental animal models were reviewed in this study. After being exposed to several different plant extracts, changes in hormone levels or activity have been documented. The emphasis of this study is on the scientific literature, which was thoroughly searched for research that examined or included the administration of medicinal plant extracts and their effect on hormone levels or functioning. There is a strong interest in plant extract research, as evidenced by the 47 publications that satisfied the inclusion criteria and described 82 different extracts from 37 plant species, covering eight major hormonal axes in a variety of animal models. The hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal (HPG) axes were the hormonal axes most often investigated. It was discovered that almost every plant species had at least one influence on endocrine functioning, although the number of reported effects, appropriate doses, and extracts available varied noticeably. Research seemed to be focused in Iran and India, but it has recently spread to other areas.

A variety of phytochemicals were linked to direct modulation of endocrine activity. Phytochemical classes associated with such effects included flavonoids (e.g., glycitein, quercetin), alkaloids (e.g., berberine, indole-3-carbinol, nicotine), terpenoids (e.g., dehydroalanes, soya), and polyphenols (e.g., curcumin, resveratrol, tea catechins). Overall, the findings underscore the potential of medicinal plant extracts to modulate the endocrine system. The natural origin of these extracts, together with their broad spectrum of effects, warrants further research to investigate their mechanistic properties and explore the possibility of clinical application. Attention to the characterization and standardization of extracts at the phytochemical level, together with the adoption of consistent and transparent methodologies in relevant studies, would facilitate greater appreciation of both the therapeutic opportunities and the safety concerns associated with these products.

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