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Review Article

Investigation on the Involvement of Phytoconstituents in Endocrine Disorder: A Review

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Abstract

The endocrine system consists of various glands responsible for secreting hormones that regulate metabolism, growth, reproduction, and other physiological processes. Disruptions in this system, termed endocrine disorders, are linked to numerous health issues, such as obesity, diabetes, cardiovascular diseases, and metabolic syndromes. Moreover, the significance of factors such as life stage, gender and dietary habits in influencing health risks associated with endocrine disruption cannot be overstated. Synthetic medications for these conditions often have adverse side effects like hypoglycemia and heart complications, highlighting the need for alternative treatments. Herbal and natural remedies have shown promise in managing these disorders due to their lower toxicity and minimal side effects. Phytochemicals and poly-herbal therapies are emerging as effective strategies for addressing endocrine and metabolic disorders, influencing molecular targets like AMP-Activated Protein Kinase (AMPK) and nuclear factor erythroid-2-related factor (Nrf2). Specific disorders such as diabetes, Addison's disease and hyperthyroidism are characterized by hormone imbalances, with molecular mechanisms involving insulin resistance, cortisol dysregulation, and thyroid dysfunction. Additionally, the role of factors such as life stage, gender, and dietary habits in modulating endocrine disruption-associated health risks is crucial. Natural products, including flavonoids, catechins, resveratrol, and terpenes, are being explored for their therapeutic potential in regulating hormone levels and improving metabolic health.

Keywords: AMPK, Cardiovascular diseases, Diabetes, Endocrine system, Metabolic disorders.

1. INTRODUCTION

The endocrine system consists of various glands, such as the pituitary gland, the hypothalamus in the brain, and the adrenal glands in the kidneys. When these glands or their functions are impaired, it can lead to various disorders. Some commonly reported disorders include diabetes mellitus, which causes an overproduction of growth hormones; Addison's disease, which involves decreased production of growth hormones; Cushing syndrome, characterized by high levels of cortisol; Graves' disease, which results in excessive production of thyroid hormones; and Hashimoto's thyroiditis, an autoimmune disease that leads to hypothyroidism and low production of thyroid hormone. Other disorders include hyperthyroidism, which is an overactive thyroid, hypothyroidism, which is an underactive thyroid, and prolactinoma, characterized by the overproduction of prolactin by the pituitary gland.[1]

Different diseases can develop when these glands do not work properly. For example, diabetes mellitus occurs due to too much growth hormone, while Addison's disease comes from a lack of the same hormones. Cushing syndrome, which features high cortisol levels, and Grave's disease, caused by too much thyroid hormone, are other examples of these disorders. Additionally, Hashimoto's thyroiditis, an autoimmune disease, leads to hypothyroidism and less thyroid hormone production. Hyperthyroidism, hypo-thyroidism, and prolactinoma, which are caused by an overactive pituitary gland that produces too much prolactin, also show the range of problems in this complex system. Although these diseases are quite different, they all relate to issues in gland function. Because of this complex interaction, early detection and treatment are important for good health. However, the exact reasons for these issues can be hard to pinpoint, but ongoing research is providing more insight into these important health concerns.[2]

An endocrine disorder refers to a medical condition involving the endocrine system, which is responsible for producing and regulating hormones chemical messengers that control various functions in the body, including metabolism, growth, reproduction, and mood.

An endocrine disorder occurs when there is an imbalance in hormone levels- either too much (hyperfunction) or too little (hypofunction), or when the

body does not respond appropriately to hormones. Such an imbalance can be caused by various factors, including genetic mutations, autoimmune diseases, infections, or damage to the endocrine gland.[3]

2. VARIOUS ENDOCRINE DISORDERS

Diabetes Mellitus involves disrupted insulin signaling, often due to excess growth hormone (GH), which increases lipolysis and free fatty acids, impairing glucose uptake and leading to hyperglycemia. The pancreas compensates with increased insulin production, causing hyperinsulinemia. Over time, β-cell exhaustion can lead to Type 2 Diabetes. Complications include cardiovascular disease, retinopathy, nephropathy, and neuropathy.

Addison's disease is caused by insufficient cortisol and aldosterone production. Cortisol deficiency results in hypoglycemia, poor stress response, fatigue, muscle weakness, and mood disturbances. Low aldosterone causes sodium loss, dehydration, low blood pressure, and salt cravings.[4]

Cushing's syndrome arises from prolonged high cortisol levels due to steroid use or tumors. Cortisol promotes gluconeogenesis, protein breakdown, and fat redistribution, leading to hyperglycemia, muscle wasting, central obesity, and insulin resistance. Other effects include immunosuppression, osteoporosis, hypertension, and weight gain.

Graves' disease is an autoimmune disorder causing excessive thyroid hormone production. It results in hyperthyroidism, with symptoms like anxiety, tachycardia, weight loss, and heat intolerance. Long-term risks include thyroid storm and heart complications.

Hyperthyroidism is commonly caused by Graves' disease or nodules, leading to a hypermetabolic state with symptoms like sweating, palpitations, and weight loss.[5]

3. IDENTIFICATION OF PHYTOCONSTITUENTS

The study of phytoconstituents in endocrine disorders has gained significant interest due to their dual role as endocrine disruptors and therapeutic agents. Phytoconstituents—bioactive compounds such as alkaloids, flavonoids, terpenoids, glycosides, tannins, saponins, and phenolics—can influence endocrine function by interacting with hormone receptors, altering hormone synthesis, metabolism, or transport. Some act as hormone agonists or antagonists, especially phytoestrogens like genistein and daidzein from soybeans, which mimic estrogen and can either disrupt hormonal balance or aid conditions like menopause and osteoporosis.[6]

Certain phytochemicals impact thyroid health. Flavonoids like quercetin and apigenin may inhibit thyroid peroxidase, affecting hormone synthesis and potentially causing hypothyroidism. Goitrogens in cruciferous vegetables interfere with iodine uptake, disrupting thyroid hormone production. Conversely, withanolides from *Withania somnifera* (Ashwagandha) help maintain thyroid balance

Adaptogens such as *Panax ginseng* and *Rhodiola rosea* support the hypothalamic-pituitary-adrenal (HPA) axis, regulating cortisol and stress response. For diabetes, compounds in *Gymnema sylvestre* and *Momordica charantia* show insulin-like and insulin-sensitizing effects.

Overall, identifying these plant compounds is vital for understanding their therapeutic potential and risks. With proper dosing, phytoconstituents may offer effective, plant-based treatments for endocrine disorders while minimizing hormonal disruption.[7]

4. FACTORS MODULATING THE HEALTH RISKS ASSOCIATED WITH ENDOCRINE DISRUPTION

Endocrine disruption (ED) is influenced by life stage, gender, and dietary habits. Understanding these factors is essential for developing effective strategies to mitigate health risks associated with EDs.

Life Stage

Infancy & Childhood: Young children are especially vulnerable due to underdeveloped detox systems. ED exposure at this stage may lead to developmental delays and long-term health issues.

Puberty: Hormonal changes during this period can be disrupted by EDs, potentially causing early/delayed puberty, fertility issues, or increased cancer risk.[8]

Pregnancy: Hormonal interference can harm fetal development, leading to birth defects and growth issues, as some EDs cross the placental barrier.

Adulthood & Aging: Reduced detox capacity in older adults heightens vulnerability to ED-linked issues such as cancer, reproductive disorders, and metabolic diseases.[9]

Gender Differences

Women: Hormonal cycles, pregnancy, and menopause make women particularly susceptible. EDs may disrupt fertility, menstruation, and increase risks of osteoporosis and cardiovascular disease.

Men: EDs may lower testosterone, sperm count, and contribute to obesity and metabolic imbalances.[10]

Dietary Influence

Exposure: EDs enter the body through contaminated food (e.g., BPA, pesticides).

Nutritional Balance: Nutrients like iodine, zinc, and selenium support hormone function. A balanced diet can reduce ED effects and promote hormonal health.[11]

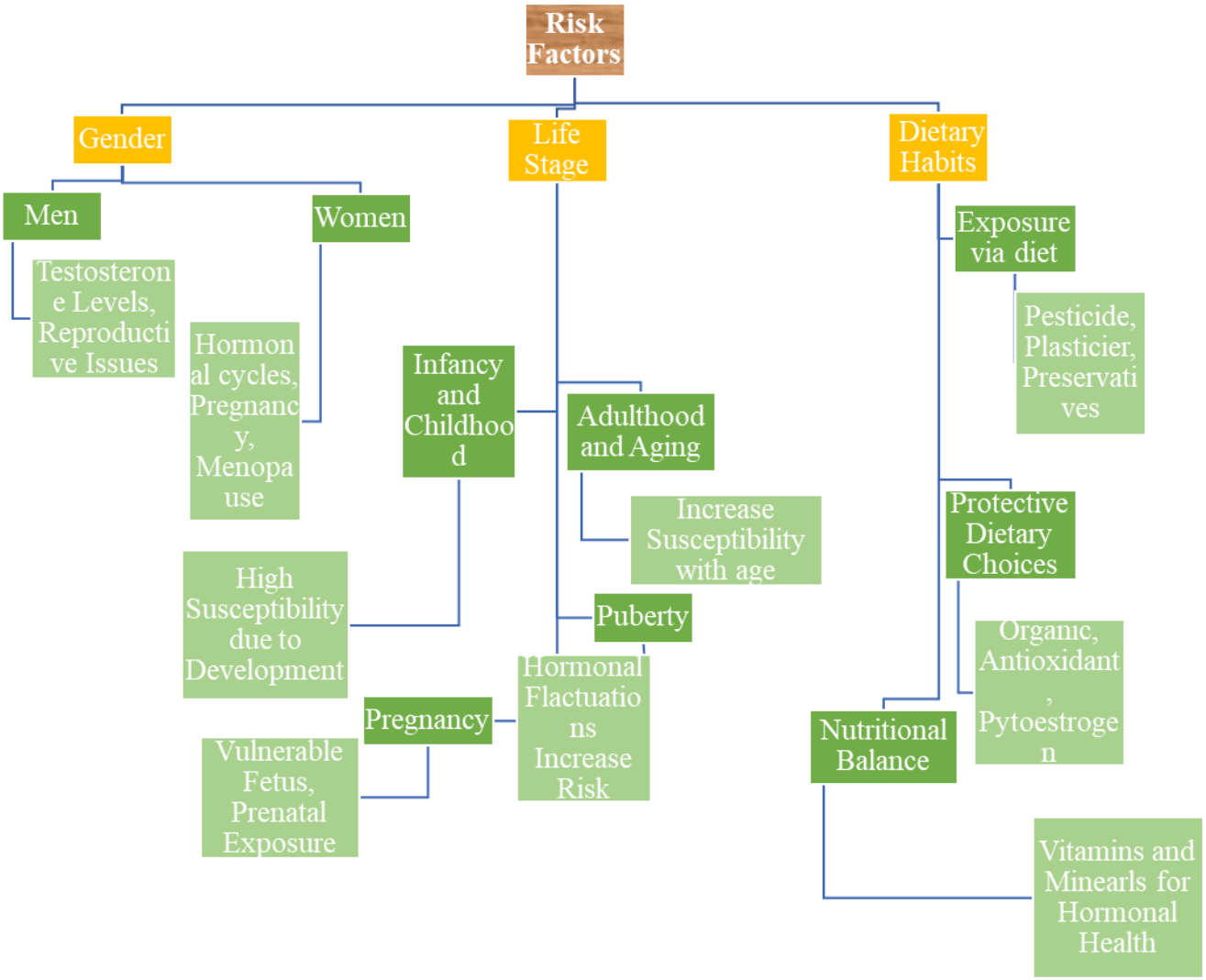

Figure 1: Risk Factors of Endocrine Disorders.

Molecular Targets and Signaling Pathways

Natural compounds influence key molecular targets involved in metabolic and cardiovascular disorders, including AMPK, COX-1/2, DPP-4, eNOS, NF-κB, Nrf2, PPAR, PTP1B, and 5-LO. These substances regulate fat and cholesterol synthesis, enhance fat oxidation, boost mitochondrial activity, and improve glucose uptake. AMPK activation, in particular, supports glucose absorption and insulin sensitivity. Compounds like flavonoids, terpenoids, and alkaloids suppress inflammation via NF-κB inhibition and activate Nrf2, promoting antioxidant gene expression while reducing lipogenesis. Polyphenols such as resveratrol and quercetin modulate AMPK and PPAR pathways, showing potential for diabetes management through improved metabolic regulation and reduced oxidative stress.[12]

5. ROLE OF PHYTOCONSTITUENTS IN ENDOCRINE DISORDER

Flavonoids and their role in Endocrine Disorders

Flavonoids are bioactive plant compounds with significant antioxidant, anti-inflammatory, and hormone-modulating properties. They show therapeutic potential in managing endocrine disorders such as diabetes, thyroid dysfunction, PCOS, and adrenal imbalances.

Flavonoids like catechins enhance glucose uptake by activating GLUT proteins and AMPK, improving insulin sensitivity. Quercetin, kaempferol, and luteolin protect thyroid tissues from oxidative stress and inflammation, while apigenin and genistein inhibit thyroid peroxidase, potentially lowering excess thyroid hormone in hyperthyroidism.[13]

In PCOS, flavonoids, especially isoflavones from soy, mimic estrogen and help regulate hormone levels. Quercetin and kaempferol also reduce inflammation, a core feature of PCOS. Flavonoids like epicatechin and apigenin enhance insulin sensitivity, supporting metabolic balance and reducing ovarian dysfunction.

In adrenal disorders such as Cushing's syndrome, flavonoids protect adrenal cells from oxidative damage and regulate enzymes involved in cortisol synthesis. Catechins like EGCG improve lipid profiles and reduce hyperglycemia by activating AMPK and suppressing hepatic glucose production.[14]

Resveratrol, a polyphenol, activates AMPK and SIRT1, reducing fat accumulation and protecting pancreatic cells. It enhances endothelial function, combats fatty

liver, and may aid in anti-obesity therapies. Other polyphenols such as rutin, diosmin, and myricetin support metabolic health through antioxidant activity.

Terpenes also show potential, reducing blood sugar more effectively than some drugs by inhibiting genes responsible for lipid synthesis and enhancing insulin response. Xanthine derivatives like caffeine improve insulin sensitivity and influence hormone regulation by modulating cAMP pathways.

Together, these natural compounds offer promising complementary strategies for managing endocrine and metabolic disorders.[15]

Table 1: Phytoconstituents, sources and mechanism used for EDs

Phytoconstituent	Source (Plant)	Molecular Formula and Type	Endocrine Disorder Use	Mechanism/Effects	Ref
Curcumin	Turmeric (*Curcuma longa*)	$C_{21}H_{20}O_6$ Diarylheptanoid	Diabetes, Metabolic Syndrome	Reduces insulin resistance, Anti-inflammatory effects.	16
Berberine	Barberry (*Berberis vulgaris*)	$C_{20}H_{18}NO_4$ Isoquinoline Alkaloid	Type 2 Diabetes	Activates AMPK, enhances glucose uptake, and improves lipid profile.	17
Resveratrol	Grapes (*Vitis vinifera*)	$C_{14}H_{12}O_3$ Polyphenol (stilbene)	Diabetes, Obesity, PCOS	Increases insulin sensitivity, antioxidant.	18
Quercetin	Onions, Apples (*Allium cepa*)	$C_{15}H_{10}O_7$ Flavonoid (polyphenol)	Obesity, Metabolic Syndrome	Anti-inflammatory reduces blood glucose.	19
Epigallocatechin Gallate (EGCG)	Green Tea (*Camellia sinensis*)	$C_{22}H_{18}O_{11}$ Catechin (polyphenol)	Obesity, Type 2 Diabetes, Thyroid issues	Enhances thermogenesis, antioxidant.	20
Ginsenosides	Ginseng (*Panax ginseng*)	$C_{42}H_{72}O_{14}$ Steroidal saponins	Diabetes, Adrenal insufficiency	Modulates glucose metabolism, adaptogenic effects.	21
Withaferin A	Ashwagandha (*Withania somnifera*)	$C_{28}H_{38}O_6$ Steroidal lactone	Thyroid imbalance, Adrenal fatigue	Balances cortisol, reduces inflammation, boosts thyroid function.	22
Diosgenin	Wild Yam (*Dioscorea villosa*)	$C_{27}H_{42}O_3$ Steroidal saponin	Menopausal symptoms, Adrenal issues	Precursor to steroid hormones supports hormone synthesis.	23
Forskolin	Co40leus (*Cole41us forskoh42lii*)	$C_{22}H_{34}O_7$ Labdane diterpenoid	Thyroid disorders, Weight management	Stimulates adenylate cyclase, increases thyroid activity.	24
Puerarin	Kudzu 43root (*Pueraria 44lobata*)	$C_{21}H_{20}O_9$ Isoflavone glycoside	Menopause, Osteoporosis	Phytoestrogenic activity supports estrogen balance.	25
Thymoquinone	Bl45ack Seed (*Nig46ella sativa*)	$C_6O_2(OH)_4$ Quinone derivative	Diabetes, Insulin resistance	Antioxidant, Anti-inflammatory, improves insulin sensitivity.	26

Genistein	Soy (*Glycine max*)	$C_{15}H_{10}O_5$ Isoflavone (phytoestrogen)	Menopausal symptoms, PCOS	Estrogenic effects, reduces oxidative stress.	27
Hesperidin	Citrus fruits (*Citrus sinensis*)	$C_{28}H_{34}O_{15}$ Flavanone glycoside	Metabolic Syndrome, Obesity	Improves lipid profile, reduces insulin resistance.	28
Salvianolic acid B	C36H30O16 Danshen (*Salvia miltiorrhiza*)	$C_{36}H_{30}O_{16}$ Polyphenolic acid	Diabetes, Thyroid-related heart conditions	Antioxidant, improves blood flow.	29
Silymarin	Milk Thistle (*Silybum marianum*)	$C_{25}H_{22}O_{10}$ Flavonolignan Complex	Liver support in Diabetes	Antioxidant, hepatoprotective, may improve insulin resistance.	30
Gallic acid	Pomegranate (Punica granatum)	C7H6O5 Phenolic acid	Type 2 Diabetes, PCOS	Antioxidant, Anti-inflammatory supports insulin sensitivity.	31,32

6. EVALUATION OF SAFETY AND TOXICITY

The assessment of safety and toxicity of flavonoids, a well-known class of phytoconstituents, assumes a central role in the scenario of endocrine diseases because of their ability to modulate hormonal processes. Flavonoids, such as quercetin, genistein, kaempferol, and apigenin, are plant-derived polyphenolic substances that occur naturally in fruits, vegetables, and medicinal herbs. They have antioxidant, anti-inflammatory, and hormone-modulating activities. In endocrine disorders, flavonoids have shown therapeutic effects by binding to estrogen receptors (ERα and ERβ), regulating thyroid function, and affecting insulin sensitivity. The hormone-like activity of flavonoids also poses safety issues, especially when taken at high concentrations or over a long period of time.[33]

One of the main issues with flavonoids is that they can function as endocrine disruptors. For instance, genistein, a soy isoflavone, acts as an estrogen mimetic and may interfere with the reproductive cycle, thus influencing fertility and fetal development. Flavonoids such as quercetin and apigenin can inhibit thyroid peroxidase (TPO), a vital enzyme for thyroid hormone production, which alters levels of thyroid hormones and induces potential hypothyroidism. The impacts are particularly significant in susceptible groups such as pregnant women, newborns, and those with pre-existing hormonal disturbances.[34]

Safety assessment of flavonoids is a blend of in vitro tests, animal experiments, and to a lesser extent, clinical studies. In vitro systems are useful for analyzing their binding capacity to hormone receptors and the possibility of enzyme inhibition. Animal testing indicates systemic toxicity, endocrine disruption, reproductive impact, as well as organ-specific effects. Although universally appreciated for safety at dietary exposure, flavonoid supplements in concentrated form can be dangerous, and long-term exposure is not entirely known.

In summary, though flavonoids hold great therapeutic potential in the control of endocrine diseases, their endocrine-modulating activity requires critical safety and toxicity assessment. Standardization of dosage, long-term investigations, and human trials are critical to making them available without hazardous endocrine effects.[35]

7. CONCLUSION

It becomes clear that a mix of herbal and pharmaceutical therapy may really be the most effective therapeutic option given the intricacy (and multivariate nature) of endocrine diseases. Poly-herbal treatments and drug-herb combinations seem particularly effective in addressing the multifaceted nature of metabolic and endocrine dysfunctions. Furthermore, the use of natural products as complementary or alternative treatments offers the potential to reduce reliance on synthetic medications: thereby minimizing the risk of adverse side effects while promoting overall health and well-being. However, this approach must be carefully considered because of the potential interactions between herbs and pharmaceuticals. Although natural products present numerous benefits, the intricacies of their interactions with conventional drugs require rigorous research. The investigation of natural materials, especially phytochemicals, offers a potential path towards safer and more comprehensive therapies, even if synthetic drugs remain a mainstay in the management of endocrine and metabolic problems. An alternate approach to treating complicated illnesses like diabetes, obesity, and cardiovascular diseases is provided by the therapeutic potential of natural

substances like flavonoids, resveratrol, and catechins, which target important molecular pathways involved in metabolic control. A more thorough approach to endocrine health can be attained by combining these natural therapies with traditional treatments which might improve patient results while reducing adverse effects.

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