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Review Article

Nutraceuticals as Therapeutic Agents for Management of Endocrine Disorders - Sources, Bioavailability and Mechanisms Underlying their Bioactivities

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Abstract

Nutraceuticals refer to health promoting bioactive compounds found in some foods or fortified food products/plant derived products. There is an increase in the consumption of nutraceuticals by mankind over the past decade due to their enriched biological activities and low or no side effects. Nutraceuticals can include inorganic mineral supplements, vitamins, probiotics, prebiotics, dietary fibres, antioxidants, phytochemicals like phytosterols, fatty acids, phenolics, flavonoid, isoprenoids, proteins etc. Dietary consumption of these neutraceuticals has shown to be effective endocrine modulators. However, detailed review with respect to endocrine modulators has not been clearly documented. Thereby, present review focuses on the sources, bioavailability and pharmacological properties of neutraceuticals towards endocrine modulation in detail.

Keywords: Endocrinology; Diabetes; Nutraceuticals; Obesity; Reproductive Dysfunctions

Abbreviations

PUFA: Polyunsaturated Fatty Acids: HbA1c: Glycated Haemoglobin; CRP: C-Reactive Protein; SOD: Superoxide Dismutase; GSH-Px: Glutathione Peroxidise; MDA: Malondialdehyde; IRS-1:Insulin Receptor Substrate 1; IR: Insulin Receptor; IGFBP4: Insulin-like growth factor binding protein 4; IGFBP5: Insulin-Like Growth Factor Binding Protein 5; AMPK: 5' Adenosine Monophosphate-Activated Protein Kinase; MAPK: Mitogen-Activated Protein Kinase; SIRT1: NAD-Dependent Deacetylase Sirtuin-1; LPS: Lipopolysaccharides; COX-2: Cyclooxygenase 2; NF-kB: Nuclear factor kB; IL-1β: Interleukin 1β ; IL-6:Interleukin 6; PPAR: Peroxisome Proliferator-Activated Receptors: FFA: Serum Free Fatty Acid; TG: Triglycerides; GLUT4: Solute Carrier Family 2: Facilitated Glucose Transporter Member 4; LXR-α: Liver X Receptor-alpha; LXR-β: Liver X Receptor-beta; ABCA1: ATP-binding Cassette Transporter A1; ABCG5: ATP-binding cassette transporter G5; ABCG8: ATP-Binding Cassette Transporter G8; SREBP1C: Sterol-Regulatory Element Binding Protein 1C; SCD1: Steroyl CoA Desaturase 1; FASN: fatty Acid Synthase; ACC: Acetyl-CoA Carboxylase; ZDF: Zucker Diabetic Fatty; CYP3A4: Cytochrome p450: Family 3: Subfamily A: Polypeptide 4; CYP1B1: Cytochrome p450: Family 1: Subfamily B: Polypeptide 1; CYP1A1: Cytochrome p450, Family 1, Subfamily A, Polypeptide 1; 16-OHE1: 16-Hydroxyestrone; 2-OHE1: 2-hydroxyestrone; 3β-HSD: 3β-Hydroxysteroid dehydrogenase; 17b-HSD: 17β- Hydroxysteroid Dehydrogenase; LHR: Luteinizing Hormone Receptor; P450scc: Cholesterol Side-Chain Cleavage Enzyme; ER- α: Estrogen Receptor alpha; AR: Androgen Receptor; StAR: Steroidogenic Acute Regulatory Protein; PCOS: Polycystic Ovary Syndrome.

Introduction

The word "neutraceutical" has been derived by combining two essential domains: "nutrition" and "cure", for the large number of plant derived compounds that possess both dietary importance and potential therapeutic activity. There has been an exponential increase in the number of studies focused on the various physiological roles of neutraceuticals, along with their contribution as a therapeutic agent towards management of various diseases [1-3], amongst which endocrine disorders are of major concern. Endocrine disorders are a major burden for the health care system all across the world and it is predicted that the prevalence and oc-

currence of metabolically incorrect pathologies like obesity, diabetes, polycystic ovarian syndrome and other endocrine disorders is going to increase in both developed as well as developing countries in the forthcoming decade [4]. The currently used conventional medications and surgical interventions are falling short of effectively controlling the unbridled spread of endocrine disorders. Additionally, these medications pose severe side-effects upon long term usage. In this regard, dietary interventions using natural bioactive food compounds have emerged as promising therapeutic tools for endocrine and metabolic disorders, with limited deleterious side effects. Phenolic compounds, flavonoids, fatty acids, phytosterols, and carotenoids of plant origin have been well-documented to exhibit protective effects against the prevention of chronic diseases such as coronary heart disease [5] as well as obesity [6], dyslipidemia [7], polycystic ovarian syndrome [8,9] and other endocrine disorders. In this context, the current review aims to understand the role and mechanisms of these neutraceuticals towards modulation of reproductive, metabolic and endocrine system. The neutraceuticals/plant derived biomolecules majorly fall over following categories like fatty acids, polyphenols and catechins, flavonoids, phytosterols, dietary fibers etc. The sources, bioavailability and pharmacological activities of each of these neutraceuticals towards endocrine modulation are reviewed in details.

Fatty acids

Fatty acids are straight chain hydrocarbons possessing a carboxyl (COOH) group at one end. Most of the fatty acids required for the proper functioning of the body are synthesized by the body itself. However, two essential fatty acids, linoleic and alpha-linolenic, which are responsible to build specialized fatty acids like omega-3 and omega-6 fatty acids, cannot be synthesized by the body and have to be obtained externally via food.

Sources

Fatty acids are mostly present in all different foods. The omega 6 fatty acids, Linoleic acid is present in abundance in corn oil, sunflower oil, soybean oil, animal meat etc whereas, Arachdonic acid can be found only from animal sources like meat, eggs etc [10]. Omega 3 fatty acids: alpha-linolenic acid is abundantly present in several vegetable oils, such as chia, linseed oil, walnut oil, faxseed oil, almonds etc. Omega-3 fatty acids like eicosapentaenoic acid and docosahexaenoic acid are found in abundance in cold water fishes such as salmon, mackerel, herring, and tuna. Fatty acids present in fishes, krills and their derived oils are mainly found in the triacylglyceride and free fatty acid forms [11]. Omega-3 fatty acids are present in smaller quantities in nuts, seeds, beans, vegetables, whole grains and soy products.

Bioavailability

The dietary intake of Omega-3 long chain polyunsaturated fatty acids ranges from 250 mg per day up to 2 g per day. After oral intake of fats, they get broken down into fine droplets due to the peristaltic movement of the stomach. The fat droplets get emulsified in the small intestine due to the action of bile. Emulsification is essential for the action of pancreatic lipases to cleave the triglyceride bound fatty acids. Fatty acid transport protein 4, present at the intestinal mucosal membrane are responsible for the transport of fatty acids to the lymph and blood. The bioavailability of long chain omega 3 fatty acids depends on numerous factors like the type of chemical bond, the fat content of the food, presence of calcium ions etc. Calcium ions can form complex with free fatty acids and thereby, reduce its bioavailability. The apparent bioavailability of ethyl ester fatty acids is the lowest whereas it is greatest for free fatty acids [12]. The omega-3 fatty acids are transported by the blood to the target tissues, where they are primarily incorporated in membranes of heart muscle cells, the brain/nervous system and retina cells [13].

Pharmacological activities towards endocrine disorders

There is a strong association of fatty acids with the normal functioning of the endocrine system. Dietary fatty acids have significant impact on hormone, neuropeptide concentrations as well as their receptors [14]. The bioactivities depend upon the type of fatty acids; saturated and trans-fatty acids were found to decrease insulin concentrations hence, leading to insulin resistance. On the other hand, polyunsaturated fatty acids (PUFA) increased plasma insulin concentration and decreased insulin resistance [15]. Insulin resistance lies in the core of all metabolic and endocrine disorders. Hence, supplementation with PUFAs can lead to amelioration of the symptoms associated with pathologies like diabetes and obesity.

Diabetes

Clinical studies have demonstrated that Type 2 Diabetes patients when supplemented food enriched with α-lipoic acid and omega-3 Poly Unsaturated Fatty acids (PUFA), they exhibited improvement in the body mass index, fasting plasma glucose, post-prandial glucose, glycated haemoglobin (HbA1c), fasting plasma insulin and HOMA-IR, lipid profile, high sensitivity C-reactive protein (Hs-CRP) and oxidative stress markers such as superoxide dismutase (SOD), Glutathione peroxidise (GSH-Px) and

malondialdehyde (MDA) [16]. Omega 3 fatty acid supplementation (4g/day) maintained renal function in patients suffering from diabetic nephropathy and hypertriglyceridemia [17]. Additionally, daily consumption of 500 mg/day of long-chain omega-3 polyunsaturated fatty acids reduces the incidence of severe diabetic retinopathy in older adults [18]. In addition to this, the components of the flaxseeds were also found to downregulate targets of insulin signalling pathway- IRS-1, IGFBP4, IGFBP5, AKT and NF-kB signalling [19]. These data suggest that α-linolenic acid can potentiate several metabolic targets. Nutritional supplementation of omega 3 PUFAs in early life can prevent the onset of Type 1 diabetes. Also, prolonged intake of these phytochemicals can suppress inflammation, regenerate pancreatic islets and reduce markers of autoimmunity and thereby, help in amelioration of type 1 diabetes [20]. These reports suggest that fatty acids play an important role in management of diabetes.

Obesity

With the rising epidemic of obesity, its management poses a greater threat to the Medicare system, leading to identification of alternative therapeutic options. Clinical trials demonstrate that daily intake of fish or omega-3 supplementation increased adiponectin levels in the blood by 14-60% [21]. Short-chain fatty acids suppress food intake by activating vagal afferent neurons [22]. Eicosapentaenoic and docosahexaenoic acids have been reported to improve chronic inflammation, insulin resistance and dyslipidaemia associated with obesity [23]. Dietary intakes of fish oil (400 mg/kg/day) for 4 weeks could restore brain alterations in high-fat diet-induced obesity model by partially restoring the inflammatory and oxidative damage parameters [24].

Reproductive endocrinology

Apart from their potential to modulate metabolic disorders, Omega-3 polyunsaturated fatty acids, present in abundance in fish oil was found to ameliorate high-fat diet induced reproductive dysfunction in male C57BL/6 mouse by modifying the rhythmic expression of testosterone synthesis related genes [25]. Studies in mice have shown that dietary intake of omega-3 and omega-6 fatty acids has positive association with the implantation rate by modifying the uterine phospholipid fatty acid composition and arachidonic acid levels [26]. Dikshit., *et al.* [27] demonstrated that α-linolenic acid, a major component of flaxseeds was found to reduce the inflammatory and pro-carcinogenic environment in the ovaries of normal hens by significantly decreasing inflammatory prostaglandin E2, ER-α, CYP3A4, CYP1B1, 16-OHE1. However, it increased CYP1A1 and 2-OHE1. These reports clearly suggest that fatty acids have efficacy to modulate steroidogenic targets.

Polyphenols

Epidemiological studies and meta-analyses robustly recommend that long term consumption of diets rich in plant polyphenols provides protection against development of cancers, cardiovascular diseases, diabetes, osteoporosis and neurodegenerative diseases [28]. Polyphenols and other related compounds are being researched immensely due to their varied bioactivities on several aspects of human physiology.

Sources

Polyphenols are secondary metabolites of the plants, derived from phenylalanine or shikimic acid prescursors. Majorly they are found in conjugated form, either with polysachcharides or monosachcharides or carboxylic and organic acids, amines, lipids or other phenols. They are present in abundance in fruits, vegetables, whole grains, cereal, legumes, tea, coffee, wine and cocoa. Fruits like grapes, apple, pear, cherries and berries contains up to 200–300 mg polyphenols per 100 grams fresh weight [29]. Typically a glass of red wine or a cup of tea or coffee contains about 100 mg polyphenols. Tea leaves contain up to 4.5 g/kg fresh wt of gallic acid [30]. Greater than 8000 polyphenolic compounds, including phenolic acids, flavonoids, stilbenes, lignans and polymeric lignans have been identified in whole plant foods [31]. Hydroxybenzoic acid and hydroxycinnamic acid are the major classes of phenolic compounds, amongst which hydroxybenzoic acid is found in less quantities in few fruits like strawberries, raspberries and black berries, black radish and onions [32]. On the other hand, hydroxycinnamic acids are more common and abundantly present in coffee, kiwis, plums, cherries, apples and blueberries [33]. Wheat grains contain 0.8–2 g/kg dry weight of ferulic acid, another phenolic compound found mostly in cereal grains [34].

Bio availability

It is estimated that dietary intake of polyphenols is approximately 1 g/day [35]. Inspite of being present abundantly in foods, polyphenols are not significantly bioactive, owing to their poor absorption from the intestines, high metabolization and rapid elimination from the body. Most of the polyphenols present in food are found to be conjugated with esters, glucosides or any other form which cannot be absorbed as such [36]. Hence, the metabolites those are present in the blood and the tissues vary from their native component in terms of biological activities. The gastrointestinal absorption of polyphenols is not well studied. The polyphenols are highly hydrophilic in nature and hence, don't passively diffuse through the gut wall. However, they can be taken up by Na- dependent membrane carriers [37].

Pharmacological activities towards endocrine disorders

Several biological activities and beneficial properties have been documented for dietary polyphenols, and some of the more well known ones include antioxidant [38], antiallergic [39], anti-inflammatory [40], anti-viral and anti-microbial [41], anti-proliferative [42], anti-mutagenic and anti-carcinogenic [43,44], free radical scavenging [45], regulation of cell cycle arrest [46] and apoptosis [47]. In addition to these, polyphenols are known to modulate endocrine disorders such as obesity and diabetes.

Diabetes

Green tea treatment (500mg/kg body weight) for 12 weeks in high- fat diet fed mice was found to increase the energy expenditure, reduce the body weight, alleviate insulin resistance and inflammation by down regulating the expression of miR-335, thereby, improving adipose tissue metabolism [48]. Revesterol, the main polyphenolic component of grapes was found to improve glucose homeostasis, decrease insulin resistance, protect pancreatic β- cells and improve insulin secretion by increasing the expression and/or activities of AMPK and SIRT1 in tissues of type 1 diabetes patients [49,50]. Revesterol could restore the skeletal muscle dysfunction by increasing the mitochondrial biogenesis, fatty acid metabolism, GLUT4 expression and decreasing the expression of NF-kB, IL-1β and IL-6 in muscle cells [51]. The therapeutic effect could be attributed to the anti-oxidative as well as anti-inflammatory activities of revesterol [52]. Animal studies have shown that revesterol can effectively ameliorate the glucose homeostasis in the liver of type 1 diabetic animals by decreasing the activity of phosphoenolpyruvate carboxykinase [53], lactate dehydrogenase and increasing the activities of hexokinase and pyruvate kinase [54]. Numerous studies have demonstrated dose and time dependent action of Revesterol in type 2 diabetes patients [55-57] and experimentally induced animal models of type 2 diabetes [58- 60]. Clinical studies demonstrate that 10 to 250 mg/day of revesterol for 1-3 months respectively improve insulin sensitivity and glucose homeostasis and thereby, manage Diabetes pathophysiology [61].

Obesity

Studies demonstrate that polyphenols present in bilberry [62,63], grapes [64], soy beans [65] have shown to possess anti-obesity property and act as an anti-inflammatory agent by modulating the body weight, BMI, adiposity, fat pad, adipocyte differentiation and decreased expression of NF-κB, TNF-α, IL-6, PPAR, SREBP-1C, ACC and CRP. These bioactive phytocomponents modulate cell signaling through the AMPK, MAPK and G-protein coupled receptor 120 signalling pathways and improve the balance of pro- and anti-inflammatory mediators secreted by adipose tissue and hence lowers systemic inflammation and risk for metabolic diseases [66]. Gingerols, the main pungent component of ginger, possesses excellent anti-inflammatory properties by inhibiting prostaglandin synthetase and Arachidonate 5-lipoxygenase activity in RBL-1 cells [67] and LPS induced COX-2 expression in U937 cells [68]. Saravanan., *et al*. [69] reported anti-obesity properties of gingerol through the inhibition of dietary fat absorption in the gastrointestinal tract, and its hypophagic and hypolipidaemic activity in male rats in the High fat diet-induced model of dietary obesity. "*In-vitro*" studies on mouse 3T3-L1 pre-adipocytes demonstrate that gingerols improve adipocyte differentiation and insulin-dependent glucose uptake [70].

Reproductive endocrinology

Currently, potential of plant derived compounds to improve fertility in humans and animals has been a burning topic of research. Polyphenols play an important role in the maintenance of healthy pregnancy by regulating targets associated with inflammation and oxidative stress [71]. Supplementation with Hydroxytyrosol in the maternal diet (1.5mg/kg of feed) during the early pregnancy bore offsprings having higher mean birth weight, suggesting that maternal supplementation with polyphenols improve the pre- and post natal development of the offsprings [72]. This can be attributed to the anti-oxidant, anti-inflammatory, immune-modulatory properties of polyphenols. Recently, dietary polyphenols like Epigallocatechin-3-gallate (EGCG) supplementation has been reported to improve the quality of male and female gametes, principally due to their ability to quench reactive oxygen species [73]. In addition, High doses (50 μM) of Quercetin, catechin and resveratrol can increase antioxidant activity in human and animal semen; thereby polyphenols are useful tools for semen cryopreservation. They improve the sperm motility, survival and integrity of the DNA in cryopreserved samples [74]. On the contrary, polyphenols derived from green tea reduced the testosterone levels in the animals by decreasing the activities of steroidogenic enzymes [75] or by direct or indirect inhibition of P450scc and 17β-HSD in a dose dependent manner. This property of polyphenols can be effectively used to design herbal drugs for reproductive endocrine disorders like polycystic ovarian syndrome (PCOS), wherein, hyperandrogenism lies in the core of the pathology.

Phytosterols

Phytosterols, products of the isoprenoid biosynthesis pathway are non-polar molecules with a molecular weight around 400-415 g/mol. They are highly hydrophobic and have very low solubility in water. The term phytosterols refers to more than 200 different compounds which are found in various plants and marine sources [76]. The most biologically relevant phytosterols are sitosterol, campesterol, stigmasterol and brassicasterol. Dietary consumption of phytosterols has shown to reduce cholesterol absorption. Phytosterols also affect other aspects of cholesterol metabolism and interfere with steroid hormone synthesis [77], suggesting it to be a potent herbal derived therapeutic agent towards management of metabolic and endocrine disorders.

Sources

Phytosterols may exist as free phytosterols or as conjugated phytosterols including steryl esters and steryl glycosides [78]. As a membrane component of plant cells, phytosterols are found in many different lipid-rich and fibre-rich fractions of all plant products. In particular, vegetable oils and products made from oils like spreads and margarine are good sources of plant sterols [79]. Canola oil contains 4.6-8.1 mg/g of total phytosterols, soybean oil contains 2.4-4.0 mg/g and sunflower oil contains 2.1-4.5 mg/g [80]. Corn oil contains even higher amounts of phytosterols with 8 to 15 mg/g [81]. Other foods which contribute to the daily intake of plant sterols are cereal grains, cereal based products, nuts, legumes, vegetables and fruits [82]. In general, the consumption of plant sterols in Asian cultures (including algae in their diets) and vegetarians is much higher.

Bioavailibility

The transport and metabolism of phytosterols within the human body is not yet completely understood. The absorption of phytosterols is promoted by the presence of a double bond. Moreover, the nature of the side chain plays an important role in this process -the more complicated the side chain is, the less phytosterol passes into the enterocytes in the gut [83]. When dietary sterols were supplemented at 2–3 g/day, the serum sitosterol and campesterol levels increased by 34–73% [84]. Phytosterols upon ingestion get emulsified by the action of bile acids in the small intestine to form micelles. The esterified phytosterols are converted to free phytosterols with the help of cholesterol esterase and pancreatic lipase enzymes [85]. Free phytosterols are then absorbed into enterocytes by ATP-binding cassette transporters that are encoded by ABC G5 and G8 genes [86]. Post absorption, the phytosterols form chylomicrons by combining with cholesterol, triacylglycerol and apolipoproteins [87]. It is in this form, that the transportation of phytosterols takes place through the lymph and bloodstream, where they are transformed to chylomicron remnants after the uptake of triacylglycerol by cells and transported to the liver. In the liver, the phytosterols may either be used for synthesis of bile salts [88] or be incorporated into very low density lipoproteins and be secreted into the blood, from where they are converted to low-density lipoproteins and presented to cells for uptake [89,90]. In the tissues, phytosterols are incorporated into the cell membranes [91] and have been found to be highly concentrated in the lungs, adrenal cortex, intestinal epithelia and ovaries [92].

Pharmacological activities towards endocrine disorders

Dietary phytosterols are thought to have a number of health benefits in humans.Small changes in the structure of sterol molecules confer them to highly distinct biological activities [93].

Diabetes

The phytosterols isolated from various plant and fungal sources have been extensively researched for their anti-diabetic potential (Table 1).

Obesity

Phytosterols can decrease the serum cholesterol by inhibiting the cholesterol absorption in the intestine [103]. Also, plant sterols activate nuclear hormone receptors in order to increase cholesterol excretion to the intestinal lumen [104]. The nuclear hormone receptors: LXRα and LXRβ are established regulators of cholesterol, lipid, and glucose metabolism and are attractive drug targets for the treatment of diabetes and cardiovascular diseases [105]. Extensive data from literature clearly suggests the phytosterols such as Stigmasterol and Ergosterol and their modified derivatives have the potential to assume a key role in the modulation of lipid metabolism and glucose homeostasis by altering LXR-alpha and beta expression by strongly inducing the expression of ABCA1 and inadequately/not activating the lipogenic genes SREBP1C and SCD1 or FASN, respectively [106]. Obesity is closely associated with inflammation; hence, a potential therapeutic agent should be in a position to combat the consequences associated with inflammatory responses. In this regard, phytosterols are known to suppress inflammatory responses, either by activating the genes that encode anti-inflammatory proteins or by suppressing the genes that are under the control of pro- inflammatory transcription factors [107].

Sl. No.	Plant Name	Active ingredients	Disease Model	Dose	Effect	References
1.	*Aloe barbadensis* MILLER (gel from the leaves)	lophenol, 24-methyl-lophenol, 24-ethyl-lophenol, cycloartanol, and 24-methylene-cycloartanol	Type 2 diabetic BKS. Cg-m$^{+/+}$Lepr$^{db/J}$ (db/db) male mice	1 µg of isolated phytosterols and 25µg of plant extract for 28 days	Reduction in the fasting and random blood glucose levels and HbA1c levels.	[94]
2.	*Aloe barbadensis* MILLER (gel from the leaves)	lophenol (Lo) and cycloartanol (Cy)	Zucker diabetic fatty (ZDF) male rats	25µg/kg for 44 days	Hypoglycemia, Reduction in the HbA1c levels, Improvised glucose tolerance, Reduction in the serum free fatty acid (FFA), triglyceride (TG) levels and visceral fat accumulation. No change in the total cholesterol levels.	[95]
3.	Unidentified sources	5-campestenone	Zucker diabetic fatty (ZDF) male rats	0.6% Dietary exposure	Reduction in plasma HbA1c, Total Cholesterol, TG and FFA, non esterified fatty acid (NEFA) and improved the glucose tolerance, visceral fat accumulation	[96]
4.	*Urena lobata* (leaves)	mangiferin, stigmasterol and β-sitosterol	In-vitro studies	IC_{50} for water extract- 6489.88 µg/ml IC_{50} for ethanolic extract- 1654.64 µg/ml	Inhibition of dipeptidyl peptidase IV activity	[97]
5.	*Erythrina indica* (Stem bark)	Oleanolic acid	Alloxan and dexamethasone induced diabetes in adult albino Wistar rats	200 and 400 m/kg aqueous and alcoholic extract orally for 3 weeks.	Hypoglycemic effect	[98]
6.	*Cassia alata* (leaves and flowers)	Kaempferol 3-O-gentiobioside			Anti diabetic	[99]
7.	*Pelvetia siliquosa* (sea weed)	Fucosterols	Streptozotocin-induced diabetic rats	30 mg/kg orally Single dose	Antidiabetic, inhibition of Sorbitol accumulation in the lenses.	[100]
8.	*Platycladus orientalis* (Leaves)	carbohydrates, proteins, amino acids, fixed oils, fats, phytosterols, tannins, phenolic compounds and	Streptozotocin-induced diabetic rats	100 and 200 mg/kg daily (aqueous extract) for 28 days orally	Reduced TC, TG, LDL, VLDL; increased HDL levels. Antioxidant property	[101]
9.	Chrozophora Plicata (seed oil)			IC_{50} value of 287.12 µM.	Inhibitors of α-Glucosidase and α-amylase	[102]

Table 1

Reproductive endocrinology

Data from literature shows that β-Sitosterol has estrogen-like effects and modulates the steroidogenic pathway by altering the P450scc activity, thereby, impairing the conversion of cholesterol to pregnenolone [108]. Fish exposed to phytosterols display altered sexual development, changes in hormone production, decreased egg production and decreased spawning rate [109]. Goldfish exposure to 75 µg/L 13 phytosterols resulted in a reduction of reproductive steroid levels and changes in gonadal steroidogenesis [110]. In subchronic rodent studies, it has been observed that even at small doses (0.5–50 mg/kg/day) phytosterols caused changes in the weights of reproductive organs. For example, when b-sitosterol was administered subcutaneously, it lead to reduced testicular

weight and sperm density in rats [111] and increased uterine weights in rats [112,113] and immature sheep (Ovis aries) [114]. Also, administration of 28- homobrassinolide (333 mg/kg body weight) to streptozotocin- induced diabetic male rats by oral gavage for 15 consecutive days to diminished LPO, increased antioxidant enzyme, 3β-HSD and 17β-HSD activities, and elevated StAR and Androgen Binding Protein expression and Testosterone level in rat testis [115]. Chronic effects of a dietary phytosterols mixture (5mg/kg/day), containing mainly beta sitosterol, on the reproduction of the mouse demonstrate increased the plasma levels of testosterone and decreased the relative uterine weights in the pups of F (2) and F (4) generations. Furthermore, phytosterol exposure increased the concentrations of plasma estradiol in the female pups of F (3) generation and testicular levels of testosterone in the male pups of F (2) generations [116]. Limited evidence from animal studies suggests that very high phytosterol intakes can alter testosterone metabolism by inhibiting 5a-reductase, a membrane-bound enzyme that converts testosterone to dihydrotestosterone, a more potent metabolite [117]. Dietary intake of Coumesterol decreases the amplitude of LH pulses in ewes [118]. Thereby, suggesting that phytosterols and its metabolites may act as GnRH modulators. Also, lower doses of phytosterol have found to be effective in treatment of Polycystic Ovarian Syndrome (PCOS). PCOS is a female endocrine disorder which is characterized by hyperandrogenism, insulin resistance and presence of multiple peripheral cysts in the ovaries. Maharjan and Nampoothiri [119] demonstrated that Letrozole induced PCOS rats when treated with phytosterol containing Non-polar extract of *Aloe vera* gel (25 µg/kg body weight) for 60 days, could effectively manage the reproductive as well as metabolic complication associated with PCOS. PCOS rats demonstrated a decrease in serum testosterone and insulin level with improved estradiol and progesterone levels after treatment with Non-polar extract of *Aloe vera* gel. Also, decrease in transcripts level of StAR, LHR, AR, Aromatase and IR as well as relative protein expression of StAR, 3β-HSD and aromatase expression was observed. Additionally, consumption of phytosterols is getting popularity among menopausal women [120] with increasing evidence that they are beneficial in relieving symptoms as well as in protection of certain cancers. Considerable emerging evidence supports the inhibitory actions of phytosterols on lung [121], ovarian [122] and breast [123] cancer. Phytosterols seem to act through multiple mechanisms of action, including inhibition of carcinogen production, cancer-cell growth, angiogenesis, invasion and metastasis, and through the promotion of apoptosis of cancerous cells [124]. Phytosterol consumption may also increase the activity of antioxidant enzymes and thereby reduce oxidative stress [125].

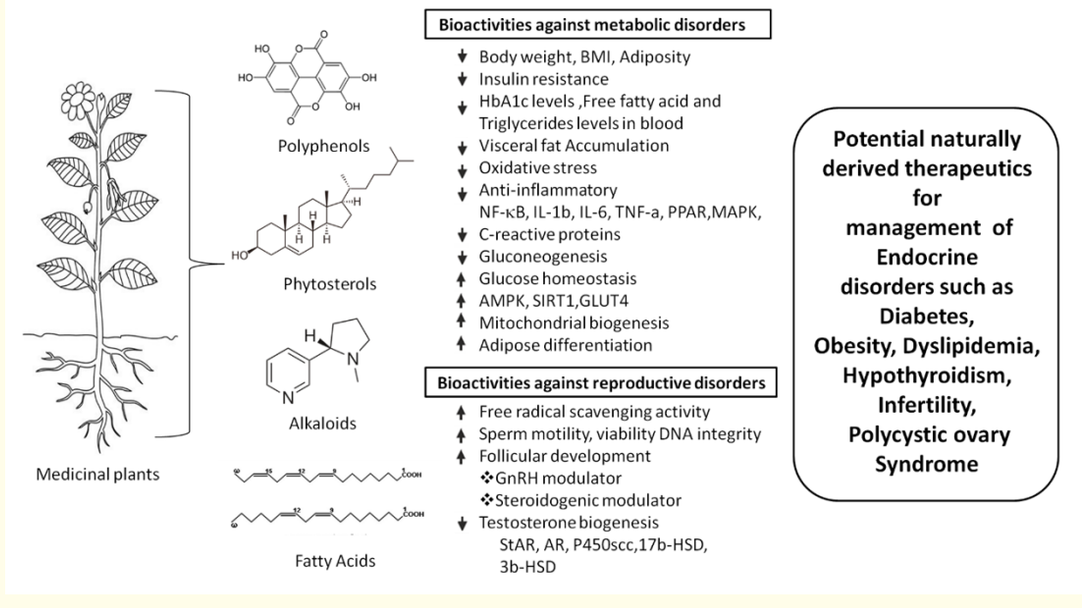

Figure 1: Schematic representation of the possible mechanism underlying endocrine modulation by plant derived nutraceuticals. Nutraceuticals derived from medicinal plants exhibit various health promoting activities, amongst which its role towards endocrine modulation has been described in this figure.They modulate several metabolic parameters linked with lipid and glucose homeostasis. Phytocomponents play an important role in the maintenance of endocrine disorders by regulating targets associated with inflammation and oxidative stress. Also, these phytocomponents can directly act as GnRH and steroidogenic modulators and thereby, manage the pathophysiological symptoms associated with reproductive disorders. Hence, suggesting that neutraceuticals are excellent naturally derived targets for management of endocrine disorders.

Conclusion

Dietary nutraceuticals appear to play an important role in the regulation of different aspects of human physiology. Recent studies have shown that these neutraceuticals are implicated in the treatment and management of cardiovascular diseases, cancers and metabolic syndromes. In this review, detailed description on the various sources of nutraceuticals, their chemical and physical properties, their bioavailability and the role and mechanisms of these phytochemicals towards modulation of reproduction and endocrine system has been summarized. The studies from several decades have clearly shown the potential of modulation of endocrine function and hence, can be effectively designed as drug targets for endocrine disorders. However, evidence for such promising effects is still at an elementary stage and more research is clearly needed to draw firm conclusions.

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Conflict of Interest Statement

The authors have declared no conflict of interest.

Highlights

- Plant derived neutraceuticals are potential therapeutic agents for management of endocrine disorders such as diabetes, obesity, dyslipidemia and reproductive disorders.
- Omega-3 PUFAs can modulate the glucose and lipid homeostasis in diabetes, obesity and dyslipidemia, also it can directly influence the testosterone biosynthetic genes.
- Plant derived polyphenols provides protection against development of cancers, cardiovascular diseases, diabetes, osteoporosis and neurodegenerative diseases due to their anti-inflammatory and anti-oxidant properties.
- Dietary intake of phytosterols restores the metabolic alterations associated with endocrine disorders like diabetes and obesity by directly activating nuclear receptors- LXR α and LXR β.
- Phytosterols and its metabolites can potentially act as GnRH modulators.

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