REVIEW ARTICLE

Beneficiary and Adverse Effects of Phytoestrogens: A Potential Constituent of Plant-Based Diet

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ARTICLE HISTORY

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Abstract: ***Background*:** Phytoestrogens are non-endocrine, non-steroidal secondary derivatives of plants and consumed through a plant-based diet also named as "dietary estrogens". The major sources of phytoestrogens are soy and soy-based foods, flaxseed, chickpeas, green beans, dairy products, etc. The dietary inclusion of phytoestrogen based foods plays a crucial role in the maintenance of metabolic syndrome cluster, including obesity, diabetes, blood pressure, cancer, inflammation, cardiovascular diseases, postmenopausal ailments and their complications. In recent days, phytoestrogens are the preferred molecules for hormone replacement therapy. On the other hand, they act as endocrine disruptors via estrogen receptor-mediated pathways. These effects are not restricted to adult males or females and identified even in development.

***Objective*:** Since phytoestrogenic occurrence is high at daily meals for most people worldwide, they focused to study for its beneficiary effects towards developing pharmaceutical drugs for treating various metabolic disorders by observing endocrine disruption.

***Conclusion*:** The present review emphasizes the pros and cons of phytoestrogens on human health, which may help to direct the pharmaceutical industry to produce various phytoestrongen based drugs against various metabolic disorders.

Keywords: Phytoestrogens, diet, anti-cancer, anti-diabetic, anti-obesity, anti-oxidants, endocrine disruption.

1. INTRODUCTION

Phytoestrogens are the secondary derivatives of plants, which act as estrogen mimics, similar to estradiol (E_2) of mammals, and bind with the estrogen receptors to activate or inhibit the functions of estradiol [1, 2]. The word 'phytoestrogen' derived from Greek, where 'phyto' means plant and 'estrogen' means hormone for fertility. In Greek, the word 'estrus' means sexual desire and 'gene' means to generate. Since phytoestrogens are similar to that of mammalian estrogen and show similar functions or anti-estrogenic effects in animals and humans, they become potential dietary molecules in recent days.

Consciousness has increased for the consumption of phytoestrogen diet in developing countries due to their beneficiary effects in the prevention of various cancers like breast, colon, ovarian, endometrium and lung cancer [3]. In addition to this, phytoestrogens are used in the treatment of various metabolic disorders like inflammation, allergies, postmenopausal ailments, obesity, diabetes, and osteoporosis [3], including hormone replacement therapy. They also have a protective role in preventing cardiovascular diseases [4]. Apart from the positive effects, phytoestrogens also elevated with negative effects. Due to the estrogenic activity, they disrupt the endocrine system by binding to the estrogen receptors and show effects on the reproductive physiology of adults and the morphological development of offspring exposed prenatally [3]. Phytoestrogen (genistein) exposure alters estrus cycling and ovulation through the hypothalamus-pituitary-gonadal (HPG) axis [5]. These compounds are distributed in nature *via* paper, pulp mill and sewage water matter [6]. In view of the importance of phytoestrogens, the present review focuses on the pros and cons of these compounds in relation to pharmaceutical drug development.

2. HISTORY

Phytoestrogens were first identified in Australia (1940) and reported as endocrine disrupters. A female sheep grazing on the clover (*Trifolium subterraneum*, L.) plants rich in phytoestrogens, was observed with a syndrome called 'clovers disease' [7]. The noticed harmful effects in this syndrome are sterile in nature, abortion of pregnancy, abnormalities in young ones and reproductive disorders like ovarian tumors and delay in conceiving [7]. These clover phytoestrogens identified later as coumestrol and formononetin [8]. These findings of clovers disease made the phytoestrogens as one of the major research areas of reproductive toxicity. In addition to this, many disorders are noticed with plant-based foods. They reported infertility and liver damage [9], and disruption of the endocrine system [10-12]. Later, they reported with a number of beneficiary effects [3], which directed the researchers to promote a phytoestrogen-based diet for therapeutic use against various disorders.

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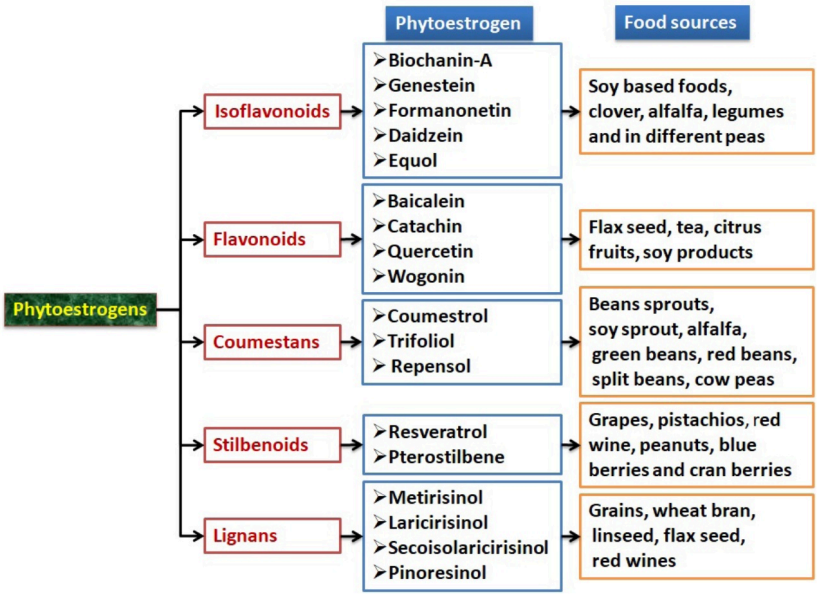

Fig. (1). Classification and various food sources of different phytoestrogens. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3. CLASSIFICATION OF PHYTOESTROGENS

Phytosterol is another name for phytoestrogen, which plays a crucial role in stabilizing the phospholipid bilayer of the plant cell membranes, whereas in animals, cholesterol stabilizes the cell membrane [13]. This is possible because the chemical structure of phytoestrogens is identical to cholesterol, having 28 or 29 carbon atoms with the exception of 24th carbon of the side chain along with a change in the position of unsaturated double bonds. A number of phytoestrogens were identified in various parts of the plant and they were primarily divided into five groups based on their chemical nature (Fig. **1**). They are presented hereunder.

3.1. Isoflavonoids

Isoflavonoids are a class of phytoestrogens, which are biologically active among all other classes of phytoestrogens. These are chiefly present in the *Fabaceae* family members [14]. Isoflavonoids are produced from the phenylpropanoid pathway, which starts with a precursor amino acid, phenylalanine. Isoflavones serve as a precursor for phytoalexin compounds produced, and act in defense mechanisms in the areas of infection [15]. Phytoalexins are also familiar with their antioxidant and antimicrobial functions [16]. In plants, phytoalexins are released as secondary metabolites holding high nutritional value and serve as food for humans. Isoflavonoids are having the beneficiary role in cardiovascular diseases, cognition, and reduction in various types of cancers, osteoporosis, obesity, menopause and skin diseases [17, 18]. Some isoflavonoids are involved in the synthesis of *Rhizobium* nodulation genes for nitrogen fixation, which is symbiotically associated with the legumes [19]. Dietary soy isoflavones are potent insulin-resistant molecules, and they reduce glycosylated hemoglobin (HbA1c) levels in pre-diabetic patients, body mass index (BMI; obesity), hypertension, lipid profiles, blood glucose and oxidative stress [20, 21]. Some of the isoflavonoids are toxic in nature. One such molecules is biliatresone, upon exposure, causes biliary atresia, a liver disorder in infants [22]. Soy-based foods are the richest source of isoflavonoids. A long-term administration of isoflavonoids causes infertility in rats [23]. The identified isoflavonoids from various plants are biochanin-A, genistein, daidzein, glicetin, formononetin, and equol (Fig. **2A**). Among all isoflavones, genistein is identified as potential candidates for estrogenic activity, whereas daidzein is the last one.

3.2. Flavonoids

Flavonoids are another class of phytoestrogens mainly used as anti-microbial (anti-bacterial and anti-viral), anti-inflammatory, anti-oxidants and anti-tumor pharmaceuticals [24]. Predominant flavonoid candidates identified in plants are baicalein, quercetin, campherol and catechin (Fig. **2B**). Generally, flavonoids are used as sunscreen lotions to protect the body against UV damage. The anti-oxidant role of flavonoids made them as therapeutic drugs for cardiovascular diseases [25]. Besides acting as an anti-depressant and neuroprotective drug, baicalein inhibits the animal lipoxygenase and thereby performs an anti-inflammatory role [26]. The control of disorders, such as obesity, diabetes, oxidative stress and its related complications, reported with flavonoids apigenin and naringenin [27, 28]. These studies are in agreement with the pharmaceutical importance of flavones in the control of metabolic disorders and its implications. The enzyme aromatase (Cytochrome P_{450}) is responsible for the conversion of androgens into estrogens. Flavonoids and isoflavonoids inhibit the activity of aromatase and decrease estrogen levels. The 4-hydroxyphenyl group located at the C3 position in isoflavonoids has the ability to bind with aromatase and inhibits its activity [29]. Whereas flavones show aromatase inhibition through possessing ring A and C, which mimics like androgen substrate respective rings D and C [12]. Though aromatase is a potential inhibitor of estrogen biosynthesis, it should not interfere with the other steroid biosynthesis [12]. Due to this kind of activity, developed aromatase inhibitors from several classes of phytoestrogen compounds used them as therapeutic agents [30].

3.3. Coumestans

Coumestans are holding the highest estrogenic activity compared to other phytoestrogens, and it is reported as much as 30-100

Table 1. List of phytoestrogen-rich common foods.

S.No.	Group of Food	Phytoestrogen Available Source
1	Fruits	Grapes, apples, pomegranates, strawberries, blueberries and cranberries
2	Vegetables	Carrot, yams, lentils, alfalfa sprouts, green beans and red beans
3	Soy and soy products	Soybeans, tofu, tempeh, miso soup and paste
4	Nuts and seeds	Flaxseeds, sunflower seeds, sesame seeds, almonds and walnuts
5	Dairy products	Milk, cheese and yogurt
6	Beverages	Coffee, bourbon, beer and red wine
7	Grains	Oats, barley and wheat germ
8	Oils	Vegetable oil, olive oil and jasmine oil

times more estrogenic than natural animal estrogens [31]. They lower the estrogen secretion and inhibit the process of ovulation [32]. The predominant coumestans are coumestrol, trifoliol and repensol, which are rich in food sources like alfalfa, sprouts of clover, split peas, lima beans, pinto beans and brussels sprouts (Fig. **2C**). They found anti-tumor, lipolysis, anti-obesity and anti-diabetic functions [33, 34]. Coumestans found to inhibit the steroidogenic pathway by lowering the activity of 3β-hydroxysteroid dehydrogenase and 17β-hydroxysteroid dehydrogenase [35].

3.4. Stilbenoids

Stilbenoids are predominant in plants and bacteria. In plants, they act as defense molecules similar to phytoalexin compounds. Resveratrol and pterostilbene are major stilbenoids isolated from grapes (Fig. **2D**). Chemically resveratrol is trans-3, 5, 40-trihydroxystilbene, rich in red wine and holds anti-fungal and anti-cancer activity [36]. Pistachios are another richest source of resveratrol. Another example of stilbenoid is pterostilbene, which is found in berries and grapes [37]. Resveratrol and its derivatives play a crucial role in the control of various metabolic disorders, including oxidative stress, obesity, diabetes, cancer, lipolysis, vasodilation, aging, platelet number, hypertension, *etc*., and are pharmaceutically potential molecules to develop natural plant-based drugs [38-40]. Stilbenoids modify the gene function by interacting with the estrogen receptors [41].

3.5. Lignans

Among all phytoestrogens, lignans are very familiar and greatly found in the diet as non-digestible fiber-like compounds. The main source of lignans includes whole grains, flax seeds, seedy fruits and vegetables. Matairesinol, secoisolariciresinol, lariciresinol and pinoresinol are the predominant lignans identified in plants (Fig. **2E**). The intestinal bacteria into its derivatives like enterolactone, enterodiol and equol metabolize these compounds. Actually, the activity of lignans is an outbreak by its derivatives in the intestine. These lignans are protective against breast and prostate cancers [42]. Pharmaceutically lignans are potential molecules with lipolytic, anti-obesity and anti-diabetic actions [43-48].

4. FOOD SOURCES OF PHYTOESTROGENS

Varieties of plant-based foods are rich in various types of phytoestrogens [49, 50]. Isoflavones are present in soy-based foods, including soymilk, clover, alfalfa, legumes, in different peas, fruits, vegetables and whole grains [51, 52]. Lignans are rich in grains, wheat bran, linseed and flaxseed [52] and poor in cereals, legumes, fruits and vegetables [51]. Coumestanes are present in soy sprout, alfalfa, green beans, red beans, split beans and cowpeas [53]. Red wine is the major source for stilbenoids and resveratrol [54]. They are present as glycosides in grains, nuts, cereals, seeds, vegetable oils and in fiber foods [55]. Rearick *et al.* [56] discuss the occurrence of environmental phytoestrogens and their effects on fathead minnows. Besides the occurrence in raw foods, phytoestrogens are also present in alcoholic beverages, dairy food products like milk, cheese and yogurt. They also identified in the plasma and urine of mammals who consume more phytoestrogenic foods [57]. Phytoestrogens can also enter into the offspring during the lactation period [58].

Most of the phytoestrogens enter into the human body through diet/food, and the predominant human foods are fruits, vegetables and dairy products. Lists of various phytoestrogen dietary sources and their functional importance in the maintenance of metabolic disorders and their related complications are represented in (Fig. **1** and Table **1**).

5. OCCURRENCE AND METABOLISM OF PHYTOESTROGENS IN ANIMAL AND HUMAN SYSTEMS

Biological synthesis of phytoestrogens is constrained only to the plants, but they enter into the animal and human body as dietary estrogens or by maternal origin *via* placenta and lactation [59, 58]. The predominant, biologically active glycosidic conjugated forms present in soy-based foods are genistein, glycitin and diadzin [60]. These molecules were then activated to aglycones (genistein and daidzein) through intestinal bacterial β-glucosidases and absorbed by the intestine [61]. Evidences are in support that there is an increase in the amounts of phytoestrogens (genistein) in the plasma of offspring's during lactation [62]. Chiefly phytoestrogens are absorbed in the small intestine and their biotransformation products are accumulated in the various parts of the body, including brain, lungs, heart, blood, small and large intestine, and reproductive organs (uterus, ovaries and testes) [57]. The occurrence of phytoestrogens in animal and human systems is not restricted to any body part; they appear even in the amniotic fluid, saliva and prostatic fluid [63, 64]. Phytoestrogens and their by-products can enter into urine and milk and the leftovers are appeared in the fecal matter [62, 65].

The metabolism of phytoestrogens primarily occurs in the liver. In the liver, phytoestrogens are reduced to their metabolic products, which enter into the systemic circulation and are distributed to different parts and tissues of the body where they show their mechanism of action. Due to its short half-life, the occurrence of phytoestrogens in the tissues and various parts of the body varies from compound to compound, and the reported range is 3-10 hrs [66]. For instance, genistein half-life is 8.4 hrs, whereas the daidzein is 5.8 hrs [67]. The complete metabolism of phytoestrogens, including absorption and excretion in humans, is presented in (Fig. **3**). The metabolic kinetic behaviour of phytoestrogens in human and animal systems may smooth the progress of developing dynamic pharmaceutical drugs.

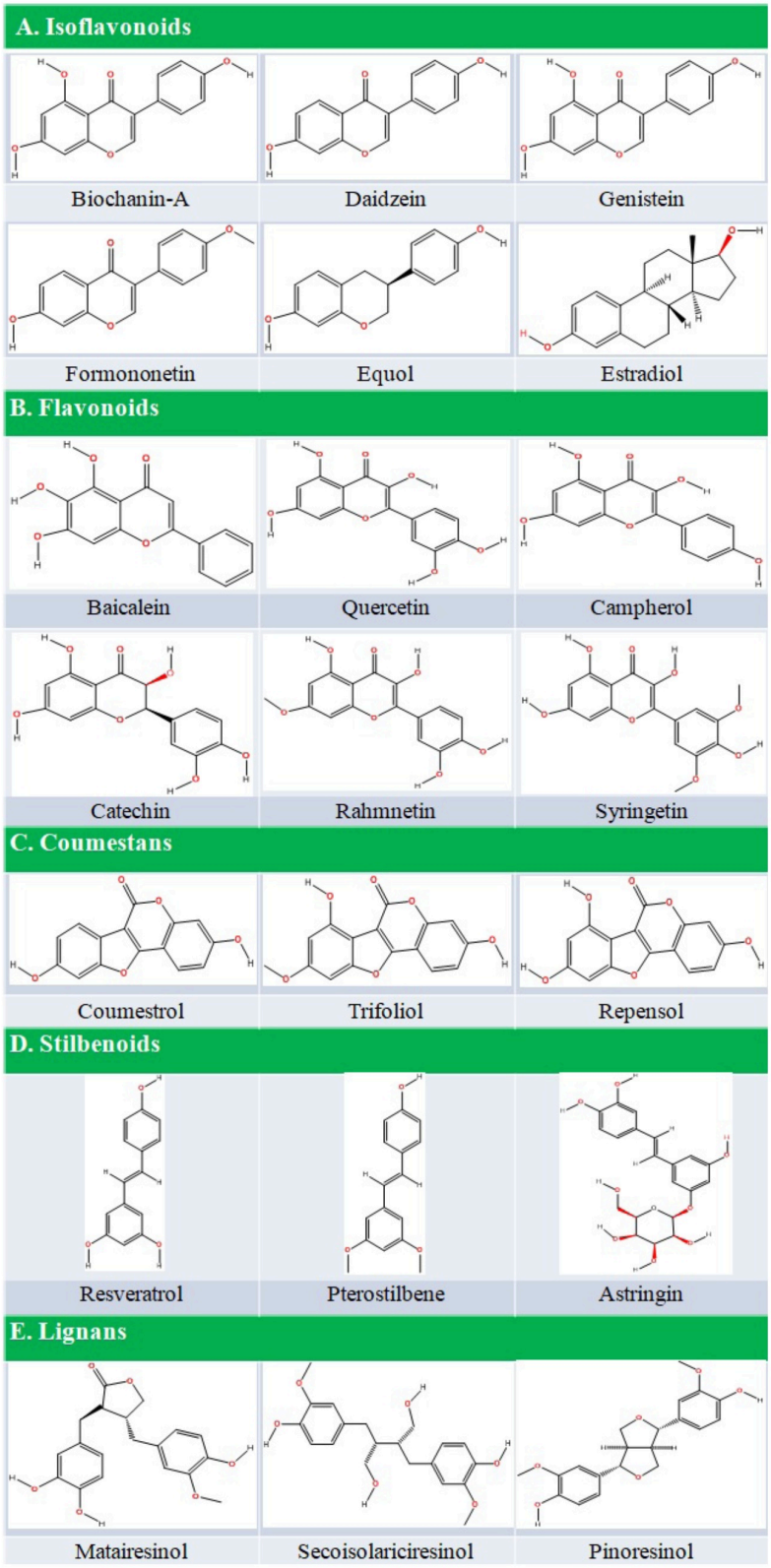

Fig. (2). Chemdraw **s**tructures of selected isoflavonoids (**A**), flavonoids (**B**), coumestans (**C**), Stilbenoids (**D**) and lignans (**E**). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

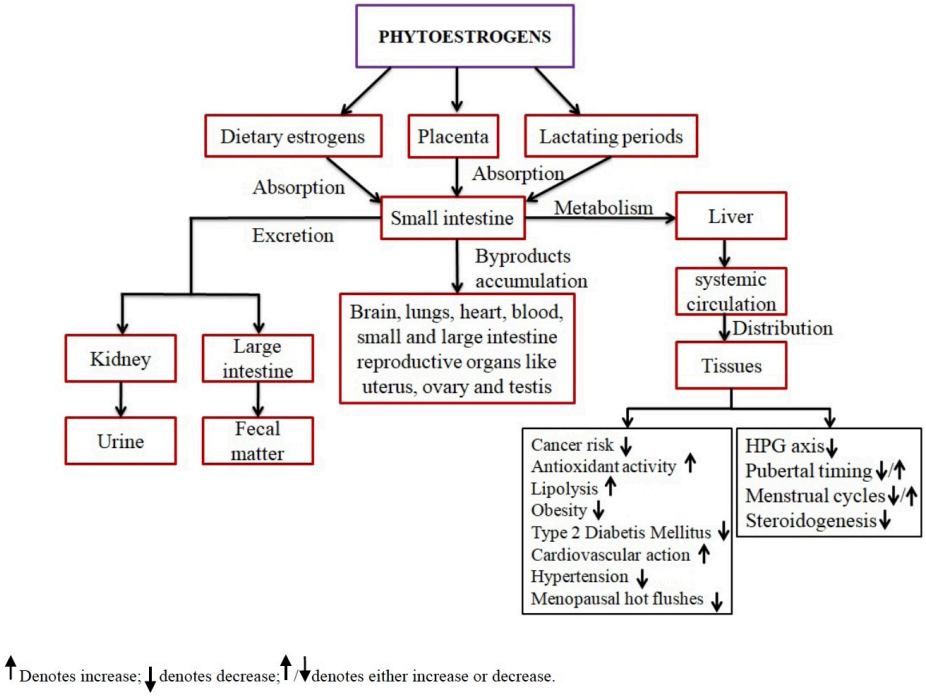

Fig. (3). Metabolism, absorption and excretion of phytoestrogens and their effects on tissues in human body.
(*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

6. EFFECT OF PHYTOESTROGENS IN ANIMALS AND HUMANS

The usage of a plant-based diet is not a recent practice and well immersed in various cultures in the world. It is important to know that a plant-based diet that we are following today was not introduced just like a snap. Ancient societies had more practice on these foods, and they introduced the best foods in society. Consumption of phytoestrogens naturally happens through eating herbivores and other animals who eat herbs directly or/and herbivores. Humans have no restrictions on eating food, and their meal includes all varieties of foods (direct plant-based and animal-based). However, all these varieties of foods are mostly rich in phytoestrogens. By means of the natural consumption of phytoestrogen-rich foods, human beings are protecting from many unidentified diseases. There are studies that explain the beneficiary role of dietary phytoestrogens on animal and human health, which may help in developing pharmaceutical drugs. Furthermore, recent studies discuss the adverse health effects of phytoestrogens in animals and humans. The Vedas, the best-suited ancient Indian literature, tells about the beneficiary and harmful effects of plant-based foods and drugs besides Ayurveda, Yunani and Homeopathy.

6.1. Beneficiary Effects of Phytoestrogens

Consumption of phytoestrogenic foods is increasing worldwide due to their beneficiary effects and protective role in the treatment of various disorders (Table **2**). The natural selective estrogen receptor modulating (SERM) role of phytoestrogens makes them act agonist to estrogens and brings positive regulation [68]. Plant-based foods consisting of phytoestrogens have vast therapeutic potential. Based on the SERM role of phytoestrogens, they used in the treatment of various cancers (breast and endometrial cancers) and in hormone replacement therapy (HRT) [3]. Especially in postmenopausal women, HRT or estrogen replacement therapy (ERT) is in usage for the treatment of osteopenia or osteoporosis. In postmenopausal woman, phytoestrogens certainly improve bone strength and lower menopausal disorders and osteoporosis [69-71]. More interestingly, phytoestrogens are identified as beneficiary phytochemicals that protect from various cancers, including breast, prostate, colon cancers, and other metabolic disorders (Fig. **3** and **4**).

6.1.1. Obesity, Diabetes, Hypertension and Oxidative Stress

Obesity is an impairment of health due to abnormal fat deposition in the body and is a major public health threat on the globe. Obesity has increased thrice since 1975. According to the World Health Organization (WHO), over 650 million populations are obese in which 340 million are aged between 5 to 19 years. Consuming high fat and glucose diets leads to overweight (obese), which causes more deaths than underweight. Obesity is linked to the initiation of impaired metabolic disorders like oxidative damage, hypertension, type-2 diabetes Mellitus and other chronic diseases in the body. Burning reserve fat is a part of weight reduction programmes and is becoming popular on the globe with many side effects. The natural way of weight reduction is preferable, and suggestible, and may be possible by developing plant-based pharmaceutical drugs consisting of phytoestrogens, which may help to control obesity, diabetes and its associated disorders.

The social health problem type 2 diabetes mellitus (DM2) is growing in an uncontrolled manner in the world. The supplementation of laflavon, provided as a new formulation that increases the bioavailability of the individual components (Laflavon CamMedica contains 7 mg of Lycopene and 50 mg of Soy Isoflavones), which determines improvement in glucose tolerance and insulin resistance in patients with the metabolic syndrome and reduces HbA1c in patients with mild DM2 (https://clinicaltrials.gov/ct2/show/NCT01377961). Bakhtiari *et al.* [21] conducted a short-term study in women with the intake of roasted soy-nut and textured soy protein

(TSP; isoflavon rich food) to find out its role in metabolic disorders. They found that moderate intake (snack or meal) of soy-nut and TSP can maintain the lipid profiles, glucose levels and oxidative stress. Especially in pre-diabetic conditions, soy-nut and TSP stop the progression of the disease. Moreover, BMI (obesity) and blood pressure reduced with soy diet [20].

The apigenin and naringenin are the identified flavones that shows normalized endothelial dysfunctions through regulating nitric oxide and ROS/caspase-3 pathways [27]. Similarly, reported reduction in serum lipids, blood glucose levels, insulin resistance index and malandialdehyde levels in diabetic induced rats by apigenin and naringenin. These drugs also lower the glucose intolerance in diabetic rats through reduced oxidative stress by the enhanced release of superoxide dismutase [27, 28].

Coumestrol found to reduce the cancer cell growth by lowering the methylation in tumor suppressor genes [33]. It is also observed that coumestrol is effective in increasing thermogenesis (lipolysis), which reduces obesity and glucose intolerance through the up-regulation of AMPK (adenosine monophosphate-activated protein kinase) and sirtuin 1 [34]. Lignans lower the levels of plasma tri-glycerides, total cholesterol and visceral obesity [43, 44], insulin, glucose and IR [45-47], fasting insulin and c-peptide [48], suggesting its pharmaceutical role in the control of obesity and diabetes.

Resveratrol is a magic compound isolated from grapes. Resveratrol and its metabolites are pharmaceutically most important due to their pleiotropic effects, such as oxidative stress release, anti-obesity, anti-diabetic, anti-cancer, anti-viral, vasodilatory, anti-aging, anti-platelet, controls hypertension, *etc*., in humans [38]. Zhang *et al.* [39] found that resveratrol lowers the release of glucose from polysaccharides through suppressing the activity of intestinal α-glucosidases, thereby reduces the levels of post-load insulin and postprandial glucose. AMPK typically controls energy metabolism through AMP/ATP ratio. Activation of AMPK through elevated mitochondrial AMP/ATP ratio by resveratrol might be an essential requirement in the treatment of obesity and controlling its related complications [38]. Moreover, the lipolytic action of resveratrol is due to the activation of sirtuins, which promotes a) down-regulation of sterol biosynthesis b) deacetylation of PPARγ (peroxisome proliferator-activated receptors) c) deacetylation of LXR (liver x-receptors) to maintain lipid homeostasis [40].

The above studies emphasize the pharmaceutical importance of isoflavonoids, flavonoids, coumestans, stilbenoids and lignans in the control of obesity, diabetes, hypertension, oxidative damage and its related implications.

6.1.2 Cardiovascular Disease

The predominant cause of death in postmenopausal women is due to heart diseases. This occurs due to the decrease or loss of estrogen levels in those women [72]. The reason for the cardiac arrest includes high lipid content, vascular reactivity, rapid cell multiplication and blood clots [73]. These conditions would be reverted by the frequent consumption of phytoestrogenic food. In a study, Van der Schouw *et al.* [4] demonstrated the intake effects of phytoestrogens on cardiovascular disease. They found reduced cardiovascular disease by dropping the plasma lipid and cholesterol levels along with reduced blood clots. This activity of phytoestrogens is due to the activation of estrogen receptors, which in turn bind to the estrogen response element in the DNA and promote the lipid and cholesterol-lowering gene expression [4]. United States Food and Drug Administration (FDA) approved the usage of phytoestrogens for short-term therapy in postmenopausal women [74].

6.1.3. Prostate Cancer

Male-specific cancer that occurs in the world is prostate cancer. Programmed cell death is a method to control any cancer. The increase in prostate cancer in the Western and developing countries is mainly due to the reduced dietary composition of phytoestrogens and other natural components of foods. People are more fascinated to eat fried and artificial flavoured foods, which are lacking essential growth components and are present in natural foods, including plant-based foods. Phytoestrogens initiate the programmed cell death in prostate tumors. Soy-based diet inhibits tumor cell growth in humans [75]. It is very much clear from the study of Peterson and Barnes [76] that *In vitro* incubation of genistein and biochanin-A along with prostate cancer cell lines inhibited the growth of human prostate cancer cells. The best way to protect men from prostate cancer is by going back to traditional foods and promoting the consumption of balanced phytoestrogen-rich foods. Analysis of various components of a plant-based diet should assist in developing natural drugs against prostate cancer.

6.1.4. Menopausal Symptoms and Osteoporosis

There are many problems associated with menopause in women, like hot flushes, cognition, vaginal dryness, and osteoporosis. Studies indicate that phytoestrogen consumption can reduce menopausal problems in women. The inclusion of soy isoflavones in the diet reduced the menopausal flushes in women [77]. Lower doses of genistein improved the bone mineral density, whereas, at higher doses, no improvement was observed in ovariectomized rats [78]. In humans, the intake of phytoestrogens improves memory [79]. In general, menopausal problems have not been observed in women who are taking a balanced diet with the inclusion of plant-based foods. More specifically, the green salads, leafy vegetables and other types of phytoestrogen-rich foods should be included in their diet to stay away from menopausal and osteoporosis problems in women. However, once osteoporosis and menopausal problems occur, women are generally subjected to estrogen replacement therapy. Therefore, phytoestrogens replaced (instead of estrogens) in the therapy and administered to the menopausal women for sinking the hot flushes and improving the mineral density in bone, suggest the role of developing phytoestrogen based drugs pharmaceutically.

6.1.5. Ovarian Cancer

In women, a prolonged menopausal problem and other known and unknown factors may lead to the occurrence of ovarian cancer [80]. However, evidences are showing a reduction of ovarian cancer with phytoestrogen intake or administration. Genistein inhibited ovarian cancer cell growth through pleiotropic action such as promoting apoptosis, inhibiting cell proliferation, angiogenesis and metastasis in cancer cells [81]. *In vitro* studies proved that the genistein and quercetin inhibit the cell growth of ovarian cancer in women [82]. Long-term dietary intake of soy foods rich with genistein and daidzein inhibits ovarian cancer [83]. These studies are emphasizing the development of plant-based drugs against ovarian cancer.

6.1.6. Other Cancers

Phytoestrogens not only act against the growth of prostate and ovarian cancers; they also inhibit other cancers named as stomach, bladder and lung cancers. In broad, phytoestrogens enter into the bloodstream and promote the signal transduction pathway in cancer tissues, which enhances the process of apoptosis, thereby inhibits tumor growth. Biochanin-A and genistein inhibit the growth of stomach cancer cell lines [84]. Besides all, consumption of coumestrol was found to reduce gastric cancer risk [85]. Furthermore, *in*

vitro and *in vivo* clinical studies proved the usage of phytoestrogens in treating the different cancers, menopausal disorders and cardiovascular diseases [77, 85].

6.1.7. Drug or Xenobiotic Toxicity

Cytochrome P_{450} monooxygenases (CYPs), a set of enzymes metabolizes xenobiotics (foreign compounds), such as pollutants, carcinogens, drugs, food toxicants, *etc*. into less toxic compounds [86, 12]. Flavonoids are involved in the detoxification of xenobiotics and drugs in interaction with CPYs. Flavonoids induce several CPYs biosynthesis, inhibit or stimulate CPYs mediated cyto-toxic reactions and metabolized by many CPYs [87-89]. Nevertheless, flavonoids interact with hepatic, intestinal CYP3A4 *via* its substrates, thereby altering the drug, and other xenobiotic detoxification processed by the enzyme. The binding of flavonoid with drug alters the pharmacokinetics of the drug, but it purely depending on the type of drug and flavonoid participated in the interaction. Subsequently, the binding of the flavonoid-drug (or xenobiotic) complex to CYP3A4 enhances its metabolic activity. The phytoestrogens flavones and tangeretins stimulate CYP3A4 action, whereas flavonolignan and sylimarin inhibit its activity [89, 90]. These studies suggest the pharmaceutical importance of phytoestrogens in detoxification drug development.

6.1.8. Controversial Reports on Breast Cancer

Studies of phytoestrogen-based diets and its administration are very specific in inhibiting the tumor growth of many cancers except breast cancer, where reported controversial results [91, 92]. Genistein exposure on breast cancer cells revealed the relation between the amounts of phytoestrogen intake and its positive or negative effects on breast cancer. Hsieh *et al.* [93] demonstrated that the high amounts of genistein intake increase the risk of breast cancer due to its elevated estrogenic activity. Baicalein present in the plant *Scutellariae baicalensis* is a natural compound used in the herbal tea preparations. It is found as a potential anti-breast cancer molecule and is used in breast cancer therapy [94]. On the other hand, Hsieh *et al.* [94] describe the possible anti-cancer molecular mechanism of phytoestrogens on breast cancer. They explained the possible ways for the usage of phytoestrogens with reference to studies on *in silico*, *in vitro* breast cancer cell lines, *in vivo* preclinical studies with animal models and xenograft studies. These studies suggest the beneficiary or adverse effects of phytoestrogens decided by its concentration in humans and other organisms. The threshold level of phytoestrogens may not be the same from one individual to another in case of breast cancer. However, the data available on phytoestrogen effects on breast cancer is a limited, and in-depth focus on this area can enhance our understanding and its mechanism of action in both the ways. Furthermore, these few studies may not help us decide the functionary activities of phytoestrogens on breast cancer.

6.2. Harmful Effects of Phytoestrogens

The beneficiary effects of phytoestrogens to maintain health have been briefly discussed in Subsection 6.1; in contrast, this section exerts harmful effects (Table **3**). This is possible because structurally, phytoestrogens mimic estradiol and bind to steroid receptors in the reproductive tissues and cause endocrine disruption. This disruption is specific towards reproduction and inhibits reproductive performance in both males and females (Fig. **3** and **4**).

6.2.1. Brain-Pituitary-Gonad Axis

Together with the brain and nervous system, endocrine hormones play a major role in controlling the physiological activities of vertebrate animals. Hypothalamo-hypphyseal-gonadal axis plays a key role in regulating the human reproductive system. Gonadotrphic hormones like follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are released from the pituitary gland, which is under the control of the brain axis, *i.e*., hypothalamus. Gonadotrophins of the pituitary stimulate the release of estrogens such as progesterone in females and testosterone in males, where these sex hormones majorly functioned in the ovule formation and spermatogenesis, respectively in females and males. The estrogen receptor-α (ER-α) found on the membrane of the epithelium and stroma cells of both vagina and uterus, whereas β-receptors (ER-β) are present in the pituitary gland, nervous system, mammary gland and ovary [95]. The α-receptors were found high during the gestation period in females. Phytoestrogens act as reproductive disrupters by inhibiting the hypothalamo-pituitary-ovary (HPO) axis. The high amounts of phytoestrogen exposure alter the normal functioning of the HPO axis, which results in decreased amounts of gonadotrophic hormones, thereby disrupts the reproductive system and its function. It is proved that reproductive inhibition of phytoestrogens is carried through binding with the receptor ER-α [96].

6.2.2. Thyroid Metabolism

Thyroid hormones are essential for the growth, development, metabolism and temperature regulation of the body. These hormones are synthesized and released from the thyroid gland. Mammalian estradiol has receptors in the thyroid tissue and is involved in the production of thyroid hormones [97]. Mimicking the capacity of phytoestrogens with estradiol that makes them compete for estrogen receptors on the thyroid gland for binding [98], leads to alteration in thyroid hormones synthesis and secretion. The thyroperoxidase, an enzyme involved in T3 and T4 biosynthesis inhibited by isoflavones. The dose-dependent decrease in iodine uptake was reported with Fischer rat thyroid cells after treatment with soy proteins *in vitro* [99]. Protein levels of thyroglobulin (a known autoimmunogen) and sodium/iodide symporter in Fischer rat thyrocytes elevates in the presence of novasoy and genistein, found as potential molecules for thyroid dysfunction [100]. In the case of human subjects, phytoestrogens (66mg of soy protein) reported no alteration in deteriorated thyroid gland function [101]. Phytoestrogens are effective to alter the thyroid gland function up to a certain concentration, and beyond that, they exert the same effect without any alteration and is an open challenging area to work further.

6.2.3. Food Intake

The growth of any animal depends on the amount of food intake. Many hormones are responsible to maintain food intake in humans and animals. The adipose tissue protein hormones leptin (16 KD) and ghrelin are mainly involved in the regulation of food intake. Ghrelin, consists of 28 amino acids present in the stomach, small and large intestine, kidneys, placenta, and the pancreatic islets of alpha cells [102]. Leptin inhibits the appetite and ghrelin is a hunger hormone [103]. Leptin acts as a signal component between adipose tissue and the reproductive system [104, 105]. Experimental evidence reported that the phytoestrogen diet results in the decrease of leptin levels in the plasma of male rats [106]. The genistein reduces leptin levels [107]. Reduced leptin has no control over appetite and hence high food intake, which leads to obesity. In contrary to leptin, low levels of ghrelin decrease appetite, which leads to weight loss. In women, soy-isoflavonoids caused weight loss due to reduced ghrelin and appetite [108]. It is clear from the above studies that phytoestrogens regulate food intake and weight by altering the appetite hormones. The ghrelin lowering isoflavonoids may help in developing drugs to reduce obesity.

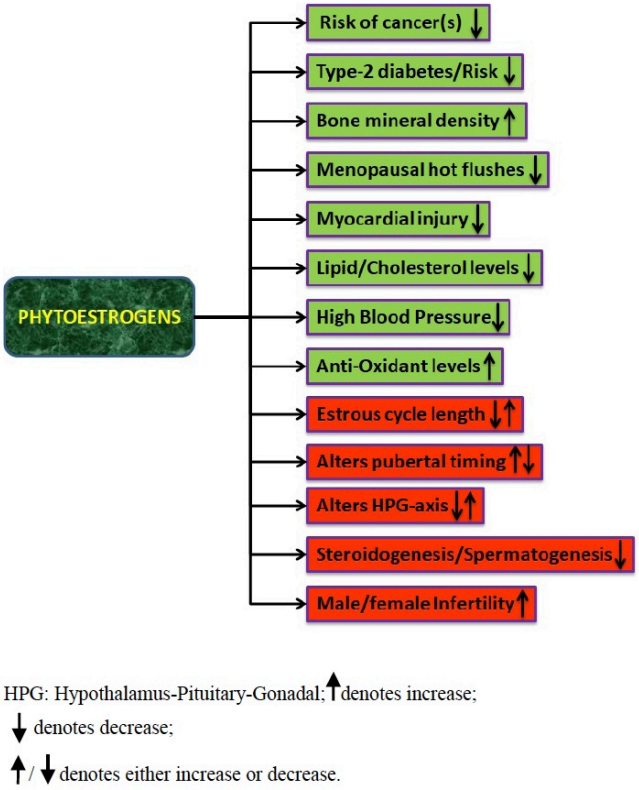

Fig. (4). The overall picture on effects of dietary/administered phytoestrogens in humans and animals. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

6.2.4. Gene Expression

Phytoestrogens alter the gene function. Chiefly, isoflavonoids inhibit the enzymes, which play a key role in estrogen metabolism. Aromatase is an enzyme involved in the conversion of androgens to estrogens and the process of steroidogenesis. At low concentrations, phytoestrogens inhibit the mRNA expression of the aromatase enzyme in human granulosa luteal cells [109]. This enzyme is a CYP19 A1 member that belongs to the family of cytochrome P_{450}. Altered aromatase activity lowers the estrogen levels in women, which leads to the induction of breast cancer. This was proven in a study by the administration of biochanin-A and formononetin, which inhibited the CYP19 gene expression and aromatase activity, and low estrogen levels caused breast cancer [110]. Furthermore, studies are needed to explain the mechanistic action of phytoestrogens on gene(s) function in humans and animals.

6.2.5. Male Reproductive System

Male infertility, most commonly, low sperm number and motility, is becoming a well-linked problem worldwide [111]. Administration or consumption of supra-normal levels of phytoestrogens is one of the factors that influence male infertility. The consumption of soy foods at a moderate level is healthy, but high amounts can act as endocrine disrupters [112]. It is clear that soy compounds cross the placental barrier and show its adverse effects on the developing embryo [113] and infants [114]. A series of reports are available on various types of phytoestrogens induced infertility in different animal models. The dietary isoflavones cause infertility in male rats [115]. Genistein exposure through drinking water (25 µl/kg body weight/day) caused infertility [111] with a decreased weight of testis [116], seminal vesicle and prostate gland in adult mice [117]. Moreover, the subcutaneous administration of genistein reduces the testosterone levels in adult mice [118]. Perinatal exposure of genistein (5-300 mg/kg/day), decreases testosterone and dihydrotestosterone levels in adult mice [116]. In adult rats, exposure of dietary phytoestrogens disrupts the testicular steroidogenesis and decreases the quality sperm in caudal epididymis, thereby reduction in fecundity [119]. Phytoestrogens more promptly bind to testicular key enzymes in steroidogenesis, *i.e.*, 3β- and 17β- hydroxysteroid dehydrogenases. Sowjanya *et al.* [120] proved the reduced activity levels of 3β- and 17β- hydroxysteroid dehydrogenases in adult male offspring exposed prenatally to biochanin-A. In another study, both lignans and isoflavonoids reduced the activity level of 5α-reductase, thereby inhibition of the steroidogenic pathway [121]. Akingbemi *et al.* [122] in adult rats reported the reduced androgen secretion in testicular Leydig cells by prenatal exposure of phytoestrogens.

Spermatogenesis is the process where the sperms are produced from testicular spermatozoa and their maturation. Dietary phytoestrogens at high concentrations promote germ cell apoptosis and inhibit spermatogenesis with increased lipid peroxidation in the caudal epididymis [128]. Excess amounts of biochanin-A cause infertility by lowering the quality and motility of sperm [129]. Genistein decreases the motility of sperm and alters the process of spermatogenesis [130]. Sperm capacitation is the activation/maturation of sperm, which is an important reaction required to fertilize the oocyte. Genistein exposure alters the capacitation reaction in cryopreserved bull sperm. Genistein affects the signal transduction pathway in sperms, which plays a key role in the acrosomal reaction and sperm capacitation [131]. Hence, the spermatozoa do not mature, and the fertilization reaction does not occur, which results in male infertility. The events such as steroidogenesis, spermatogenesis, acrosomal reaction and circulatory hormone levels play a crucial role in the male reproductive system, and these are altered by the high amount of phytoestrogen exposure and caused infertility in males.

Table 2. Beneficiary effects of various phytoestrogens on human and animal systems.

S.No	Phytoestrogen	Beneficiary Effect	References
1	Genistein and Quercetin	Anti-ovarian cancer	Shen and Waber [82]
2	Genistein	Anti-diabetic	Fu *et al.* [46]
3	Baicalein	Breast cancer therapy	Hsieh *et al.* [94]
4	Soy isoflavones	Decreases menopausal flushes	Howes *et al.* [77]
		Anti-diabetic and anti-oxidative stress and maintain lipid levels	Bakhtiari *et al.* [21]
		Reduces BMI and blood pressure	Yamori [20]
5	Genistein and Biochanin-A	Inhibits human prostate cancer cell growth.	Peterson and Barnes [76]
6	Biochanin-A	Treating asthma or chronic obstructive pulmonary disease	Chang Ko *et al.* [123]

S.No	Phytoestrogen	Beneficiary Effect	References
7	Stilbene and Lignan compounds	Weak Aromatase inhibitors and decreases the cancer risks.	Edwin [124]
8	Coumestrol and Zearalanol	Reduces oophorectomy-induced bone loss	Draper *et al.* [125]
9	Coumestrol	Anti-obesity	Kim *et al.* [34]
		Anti-cancerous	Pundenz *et al.* [33]
10	Genistein and Daidzein	Prevents Insulin dependent diabetic mellitus (Auto immune disorder)	Choi *et al.* [126]
11	Daidzein	Reduces myocardial injury	Kim *et al.* [127]
12	Daidzin and glycitin	Anti-obesity and anti-diabetic	Zang *et al.* [47]
13	Coumestrol	Reduces Gastric cancer risk	Hernandez-Ramiez *et al.* [85]
14	Apigenin and naringenin	Normalizes endothelial dysfunction, anti-diabetic and anti-oxidative stress	Qin *et al.* [27]; Ahuja *et al.* [28]
15	Resveratrol	Anti-oxidant, anti-inflammatory; lipid homeostasis Anti-fungal and anti-cancer activity	Kurylowicz [40] Jang *et al.* [36]
		Anti-obesity and anti-diabetic	Zhang *et al.* [39]; Springer and Moco [38]
17	Piceatannol	Anti-obesity and anti-diabetic	Zhang *et al.* [39]; Springer and Moco [38]
18	Lignans	Decreases plasma tri-glycerides, total cholesterol and visceral obesity	de Kleijn *et al.* [43]; Glisic *et al.* [44]
		Lowers insulin, glucose and IR	Song *et al.* [45]; Fu *et al.* [46]; Zang *et al.* [47]
		Decreases fasting insulin and c-peptide	van der Schouw *et al.* [48]

Table 3. Harmful effects of various phytoestrogens on human and animal systems.

S. No	Phytoestrogen	Harmful Effect	References
1	Genistein and Daidzein	Causes Infertility and liver disease in rats.	Setchell *et al.* [9]
2	Baicalein	Affect developmental landmarks like delay in testes descend and early in vaginal opening in mice.	Sridevi *et al.* [140]
3	Biochanin-A	Developmental abnormalities like delay in vaginal opening and testes descend in rats. Alters male reproduction and testicular oxidative stress. Alters female reproduction.	Soujanya *et al.* [141] Sowjanya *et al.* [120] Soujanya *et al.* [23]
4	Genistein and Daidzein	Female infertility in rats, increases the resorption sites and decreases the implantations	Romero *et al.* [142]
5	Genistein and Daidzein	Decreases the biosynthesis of reproductive steroid hormones by reducing the activity of 3β-HSD.	Tieman *et al.* [143]
6	Soy isoflavones (Genistein and Daidzein)	Delay in Puberty, alters steroidogenenic pathway.	Fan *et al.* [144]
7	Genistein	Decreases sperm motility and also alters spermatogenesis	Eustache *et al.* [130]
8	Resveratrol	Sociosexual behaviour was reduced in rats	Henry and Witt [145]
9	Genistein	Decreases testosterone levels	Wisniewski *et al.* [116]
10	Genistein	Body and reproductive organ weights were decreased	Kyselova *et al.* [117]
11	Biochanin A and Formononetin,	Strong aromatase inhibitors, development of breast cancer.	Wang *et al.* [110]
12	Coumestrol	Inhibits steroidogenesis	Blomquist *et al.* [35]
13	Genistein	Alters HPG axis	Kim and Park [5]

HSD: Hydroxy Steroid Dehydrogenase; HPG: Hypothalamus-Pituitary-Gonad.

6.2.6. Female Reproductive System

Exposure to high amounts of phytoestrogens prolongs/shortened the length of estrous cycle, abnormalities in ovarian differentiation, ectopic pregnancy, pre-mature delivery and an increased incidence of uterine fibroids in females [132]. Balanced maintenance of hormones is the key to the healthy female reproductive system. A high intake of phytoestrogens reduces the serum female reproductive hormone levels. Similar to testosterone in male, female produces estradiol, a 'female-specific hormone' from the ovaries and is responsible for the growth and differentiation of reproductive organs. Alteration in estradiol levels disgusts the female reproductive health. Genistein exposure decreases the progesterone and estrogen levels in female rats [133]. Low levels of estradiol were reported in women fed with soymilk daily for one month [134]. Phytoestrogen intake during puberty and pregnancy period causes serious complications. Reports suggest that genistein in rats alters the pubertal timing, *i.e*., early in puberty and the prolonged estrous cycle [135], abnormalities like low fertility rates with delayed birth [136] and reduced number of offspring [137]. Soy-based diet in teenage girls caused menstrual abnormalities like irregular cycles and prolonged bleeding periods [138]. The prolonged estrous cycle is due to the delay in the LH surge during the process of ovulation, and this delay of LH surge observed in the Japanese women taken more soy food in their diet [139]. Pubertal timing is also altered in the mice and rat exposed to baicalein and biochanin-A, respectively, where the altered vaginal opening period is reported [140, 141]. An adult woman consuming phytoestrogen (isoflavones/ lignans) rich diet, show abnormal changes in the length of the menstrual cycle [42]. The intake of more amount of flavonoid containing products like caffeine increased the conception time in married women of New Haven in USA [146]. Alteration in the hormone levels is a major change that happens due to consumption/exposure to phytoestrogenic foods, which ultimately leads to changes in female genitalia and reduced fertility.

However, to explore the beneficiary role of phytoestrogens while developing pharmaceutical drugs requires attention while using them for various metabolic disorders. Most critically, the dosage of these drugs has been evaluated before releasing them into the market to avail beneficiary effects and to avoid the adverse effects.

CONCLUSION

In vitro and *in vivo* studies on phytoestrogens clinically proved the beneficiary role of these molecules in treating various disorders, and in contrary, the endocrine disruption. The pros and cons of these plant-based compounds mainly depend on the amount of

its intake and assimilation. Mitochondrial biogenesis is another aspect of phytoestrogens in developing potential therapeutic drugs for cancer therapy [147]. Similarly, phytoestrogen based pharmaceuticals against various metabolic disorders like obesity, type-2 diabetes, hypertension, inflammation, cardiovascular, prostate and ovarian cancers, menopausal problems and osteoporosis are appropriate. Pharmacologically, genistein was tested in rats to verify its detoxification potency against pesticide methoxychlor and altered the toxicological behaviour of methoxychlor [148]. These compounds undergo sulfonylation and glucuronidation vital detoxification modifications in humans. Moreover, it is most valuable to keep an eye on the adverse effects of these compounds while developing the drugs, especially on endocrine-disrupting activity. Considering altogether, developing various phytoestrogen-based drugs under estrogen-deficient state and their clinical approvals with specified dosage may address the prevention or treatment of many metabolic disorders and its related complications.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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