The Effect of Phytoestrogens as Endocrine Disruptors

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Abstract: Health effects attributed to endocrine disrupting compounds include a range of reproductive problems (reduced fertility, male and female reproductive tract abnormalities, and skewed male/female sex ratios, loss of fetus, menstrual problems), changes in hormone levels; early puberty; brain and behavior problems; impaired immune functions; and various cancers. Human exposure may cause some health effects, such as lower IQ and adult obesity. These effects may lead to lost productivity, disability, or premature death in some people. The health effects from endocrine disruptors (EDs) will depend on the specific endocrine disruptors (EDs) involved, the level of exposure, the time course of exposure (hours, days, and years) and the underlying health status of the exposed individual. The key to good health is avoiding as much as we can the ingestion of estrogen containing substances (phytoestrogens) and other endocrine disruptors (EDs) in our environment.
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1. Introduction

Estrogens are hormones that are important for sexual and reproductive development, mainly in women. They are also referred to as female sex hormones.

The term "estrogen" refers to all of the chemically similar hormones in this group, which are estrone, estradiol (primary in women of reproductive age) and estriol (Rettner, 2014).

1.2 Construction and Production of Estrogens

Estrogens are a group of chemically similar steroid hormones. Steroids are a special kind of fat molecule with a four-ringed, carbon atom backbone, or core, like their cholesterol predecessor.

A series of chemical reactions, spurred by proteins called enzymes, remove and add groups to cholesterol's core. These actions transform it first into the steroid pregnenolone and then into androgens. Special aromatase enzymes convert androgens into the estrogens estradiol and estrone.

In humans and other vertebrates, estrogens are made primarily in the female ovaries and in small amounts in the male testes and the adrenal glands, brain, and fat of both sexes. 17-beta estradiol is the most abundant and potent natural estrogen in all vertebrates.

Estrogen-like chemicals play a poorly understood role in the reproductive cycle of some invertebrates, including mollusks and corals (Tarrant *et al*., 1999 and Di Cosmo *et al*., 2001).

1.3 Functions of Estrogen

In women, estrogen is produced mainly in the ovaries, but it is also produced by fat cells and the adrenal gland. Estrogen is involved in the onset of puberty, playing a role in the development of so-called secondary sex characteristics, such as breasts, and pubic and armpit hair (Bradford, 2016). Estrogen also helps regulate the menstrual cycle, controlling the growth of the uterine lining during the first part of the cycle. If the woman's egg is not fertilized, estrogen levels decrease sharply and menstruation begins.

If the egg is fertilized, estrogen works with progesterone, another hormone, to stop ovulation during pregnancy (Bradford, 2016). Estrogen controls lactation and other changes in the breasts, including at adolescence and during pregnancy. During pregnancy, the placenta produces estrogen, specifically the hormone estriol (Bradford, 2016).

Estrogen is instrumental in bone formation, working with vitamin D, calcium and other hormones to effectively break down and rebuild bones according to the body's natural processes. As estrogen levels start to decline in middle age, the process of rebuilding bones slows, with postmenopausal women eventually breaking down more bone than they produce.

This is why postmenopausal women are four times more likely to suffer from osteoporosis than men, according to the Cleveland Clinic (Bradford, 2016). Estrogen also plays a role in blood clotting, maintaining the strength and thickness of the vaginal wall and the urethral lining, vaginal lubrication and a host of other bodily functions.

It affects skin, hair, mucous membranes and the pelvic muscles. The hormone also affects the brain,

and studies also show that chronically low estrogen levels are linked with a reduced mood (Rettner, 2014). Men produce estrogen as well, but at lower levels than women. In men, estrogen is thought to affect sperm count.

1.4 Changes in Estrogen Levels

Estrogen levels naturally increase during puberty, and also during pregnancy. Estrogen levels fall after menopause, or when a woman stops menstruating.

This reduction in estrogen production can cause symptoms such as hot flashes, vaginal dryness and loss of sex drive. Other conditions that can cause estrogen levels to drop include hypogonadism (or diminished function of the ovaries) and polycystic ovarian syndrome.

Extreme exercise and anorexia can also cause a decrease in estrogen levels because women with low body fat may not be able to produce adequate amounts of estrogen (Bradford, 2016).

1.5 The Endocrine System

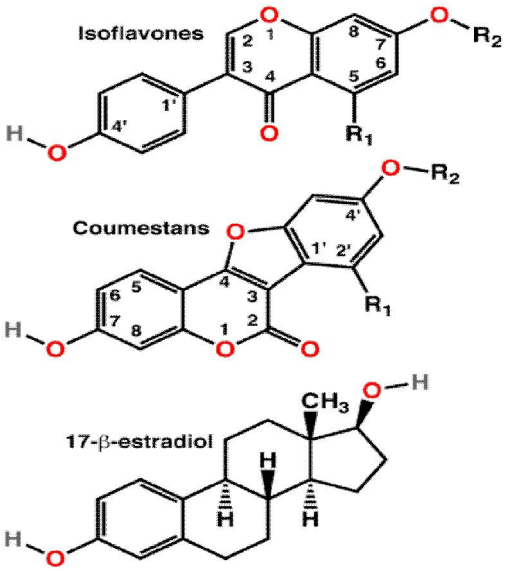
The endocrine system is a network of glands that secrete chemicals called hormones to help your body function properly. Hormones which are chemical signals coordinate a range of bodily functions.

The endocrine system produces stores and releases hormones. The body functions properly when the endocrine system is well coordinated.

1.6 Phytoestrogens

Phytoestrogens are naturally occurring substances in plants that have hormone-like activity. Phytoestrogens are plant-derived xenoestrogens not generated within the endocrine system but consumed by eating phytoestrogenic plants.

Also called "dietary estrogens", they are a diverse group of naturally occurring non-steroidal plant compounds that, because of their structural similarity with estradiol (17-β-estradiol), have the ability to cause estrogenic or/and anti-estrogenic effects,(Yildiz*et al*., 2005) by sitting in and blocking receptor sites against estrogen.



	R_1	R_2
daidzein	H	H
formononetin	H	CH_3
genistein	OH	H
biochanin A	OH	CH_3

	R_1	R_2
coumestrol	H	H
4'-methoxycoumestrol	H	CH_3
repensol	OH	H
trifoliol	OH	CH_3

Source: Wikipedia.org/wiki/phytoestrogen

Chemical structures of the most common phytoestrogens found in plants (top and middle) compared with estrogen (bottom) found in animals. Their name comes from the Greek word phyto ("plant") and estrogen, the hormone which gives fertility to mammals.

The word "estrus" - Greek οίστρος - means "sexual desire", and "gene" - Greek γόνο - is "to generate". It has been proposed that plants use phytoestrogens as part of their natural defence against the overpopulation of herbivore animals by controlling male fertility (Mascie-Taylor *et al.,* 2000).

The similarities, at molecular level, of estrogens and phytoestrogens allow them to mildly mimic and sometimes act as antagonists of estrogen (Yildiz *et al.*, 2005). Phytoestrogens were first observed in 1926 (Varner *et al.,* 1966 and Yildiz *et al*., 2000) but it was unknown if they could have any effect in human or animal metabolism.

In the 1940s, it was noticed for the first time that red clover (a phytoestrogens-rich plant) pastures had effects on the fecundity of grazing sheep (Yildiz *et al*., 2005 and Bhagwat, 2008) Researchers are exploring the nutritional role of these substances in the regulation of cholesterol and the maintenance of proper bone density post-menopause.

Evidence is accruing that phytoestrogens may have protective action against diverse health disorders,

such as prostate, breast, bowel, and other cancers, cardiovascular disease, brain function disorders and osteoporosis, (Johnston, 2003; Yildiz*et al*., 2005 and Bhagwat, 2008).

Phytoestrogens cannot be considered as nutrients, given that the lack of these in the diet does not produce any characteristic deficiency syndrome nor do they participate in any essential biological function (Yildiz *et al*., 2005). Analytical methods are available to determine phytoestrogen content in plants and food (Zhao *et al.,* 2011).

Phytoestrogens mainly belong to a large group of substituted natural phenolic compounds: the coumestans, prenylflavonoids and isoflavones are three of the most active in estrogenic effects in this class. The best-researched are isoflavones, which are commonly found in soy and red clover.

Lignans have also been identified as phytoestrogens, although they are not flavonoids (Yildiz *et al*., 2005) Mycoestrogens have similar structures and effects, but are not components of plants; these are mould metabolites of *Fusarium*, a fungus that is frequently found in pastures as well as in alfalfa and clover. Although mycoestrogens are rarely taken into account in discussions about phytoestrogens, these are the compounds that initially generated the interest on the topic (Committee on Toxicity Group, 2011).

1.7 Phytoestrogens Found in Foods

Nine common phytoestrogens in a Western diet, foods with the highest relative phytoestrogen content were nuts and oilseeds, followed by soy products, cereals and breads, legumes, meat products, and other processed foods that may contain soy, vegetables, fruits, alcoholic, and non-alcoholic beverages (Women living naturally, 2016).

Flax seed and other oilseeds contained the highest total phytoestrogen content, followed by soy bean and tofu. The highest concentrations of Isoflavones are found in soy bean and soy bean products followed by legumes, whereas lignans are the primary source of phytoestrogen found in nuts and oilseeds (e.g. flax) and also found in cereals, legumes, fruits and vegetables (Women living naturally, 2016).

Phytoestrogen content varies in different foods, and may vary significantly within the same group of foods (e.g. soy beverages, tofu) depending on processing mechanisms and type of soy bean used. Legumes (in particular soybeans), whole grain cereals, and some seeds are high in phytoestrogen (Women living naturally, 2016).

A more comprehensive list of foods known to contain phytoestrogens includes: soy beans, tofu, tempeh, soy beverages, linseed (flax), sesame seeds, wheat, berries, oats, barley, dried beans, lentils, yams, rice, alfalfa, mung beans, apples, carrots, pomegranates, wheat germ, rice bran, soy linseed bread, ginseng, bourbon and beer fennel and anise.

1.8 Phytoestrogens Found in Herbs

Herbalists have discovered that many of the herbs traditionally used by women for the health concerns unique to women contain some of the highest amounts of these beneficial phytonutrients.

The list includes black cohosh (*Cimicifugaracemosa*), dong quai (*Angelicasinensis*), red clover (*Trifoliumpratense*), alfalfa (*Medicagosativa*), licorice (*Glycyrrhizaglabra*), Korean ginseng (*Panaxginseng*), wild American ginseng (*Panaxquinquefolius*), Kudzu root (*Puerariaelobata*), and many others.

Mexican wild yam (*Dioscorea villosa*) is not a phytoestrogen but contains a phyt-nutrient that is a precursor for progesterone, which is also important for balancing a women's glandular system (Women living naturally, 2016).

1.9 Phytoestrogen as Endocrine Disruptors

Endocrine disruptors are chemicals that may interfere with the body's endocrine system and produce adverse developmental, reproductive, neurological, and immune effects in both humans and wildlife (NIEHS, 2015).

A wide range of substances, both natural and man-made, are thought to cause endocrine disruption, including pharmaceuticals, dioxin and dioxin-like compounds, polychlorinated biphenyls, DDT and other pesticides, and plasticizers such as bisphenol A.

Endocrine disruptors may be found in many everyday products– including plastic bottles, metal food cans, detergents, flame retardants, food, toys, cosmetics, and pesticides. Research shows that endocrine disruptors may pose the greatest risk during prenatal and early postnatal development when organ and neural systems are forming (NIEHS, 2015).

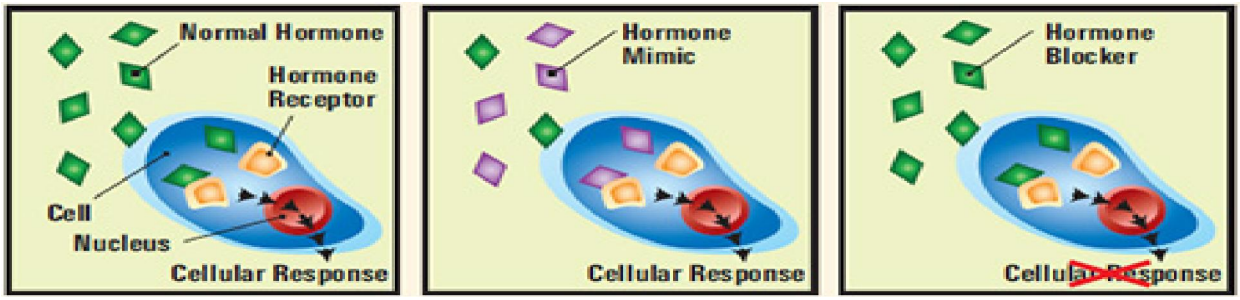
1.10 Mechanism of Endocrine Disruptors

From animal studies, researchers have learned much about the mechanisms through which endocrine disruptors influence the endocrine system and alter hormonal functions.

Endocrine disruptors can mimic or partly mimic naturally occurring hormones in the body like estrogens (the female sex hormone), androgens (the male sex hormone), and thyroid hormones, potentially producing overstimulation (NIEHM, 2015); secondly, it can bind to a receptor within a cell and block the endogenous hormone from binding. The normal signal then fails to occur and the body fails to respond properly.

Examples of chemicals that block or antagonize hormones are anti-estrogens and anti-androgens; thirdly, interfere or block the way natural hormones or

their receptors are made or controlled, for example, by altering their metabolism in the liver.



Source: National Institute of Environmental Health Sciences (2015).

When absorbed in the body, an endocrine disruptor can decrease or increase normal hormone levels (left), mimic the body's natural hormones (middle), or alter the natural production of hormones (right). Endocrine disruptors (EDs) are interesting chemicals because they can mimic hormones.

In doing so, they can bind hormone receptors and create a powerful response, even more powerful than the original hormone; create a less powerful response than the original hormone; or create a totally different response than the original hormone (NIEHM, 2015).

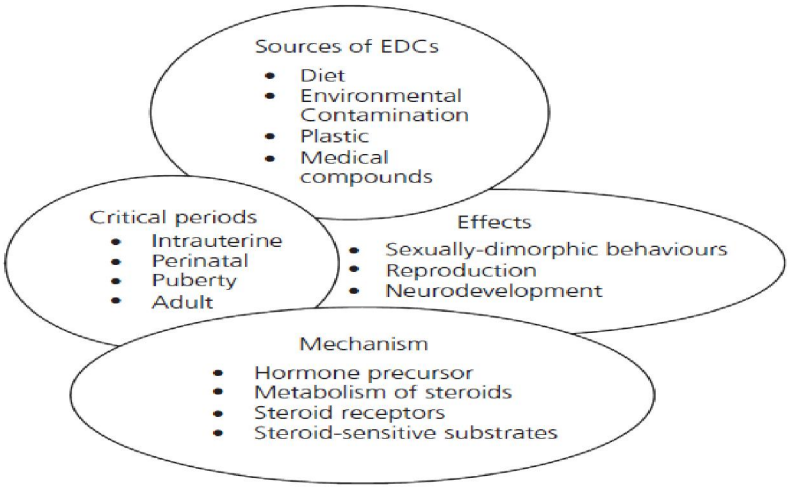


Fig. 1. A schematic representation of varied sources of endocrine disrupting chemicals (EDCs) and how they may influence sexually-dimorphic, reproductive and neurodevelopmental processes, in particular through their actions during critical periods of development. Some of the steroids mechanisms that may mediate the actions of EDCs are included.

In the end, Endocrine disruptors (EDs) can change hormone creation (synthesis), transport, binding, and breakdown; and even very small amounts can have an influence.

That is why Endocrine disruptors (EDs) are often measured in parts per trillion (ppt). Also, Endocrine disruptors (EDs) are very stable, meaning they do not break down quickly. This is why many manufacturers include them in products in the first place.

Of course, it also means they stick around in water, air, soil, (and our bodies) for a long time. Since our hormonal systems are critical to body function and health, when they are changed by Endocrine disruptors (EDs).

Potential outcomes include oxidative stress, altered testicular function and suppression of testosterone synthesis; early onset of menarche, sensory impairment and social problems (especially when exposed at early ages), altered conversion of cholesterol to steroid hormones, promotion of obesity (by altering metabolism, fat cell signaling, glucose uptake, inflammation, and appetite), (NIEHM, 2015). Source: Frye., *et al*. (2011).

1.11 Some Endocrine Disruptors

A wide and varied range of substances are thought to cause endocrine disruption. Chemicals that are known endocrine disruptors include diethylstilbestrol (the synthetic estrogen DES), dioxin

and dioxin-like compounds, polychlorinated biphenyls (PCBs), DDT, and some other pesticides. Bisphenol A (BPA) is a chemical produced in large quantities for use primarily in the production of polycarbonate plastics and epoxy resins (NTP, 2008).

Di-2-ethylhexyl phthalate (DEHP) is a high production volume chemical used in the manufacture of a wide variety of consumer food packaging, some children's products, and some polyvinyl chloride (PVC) medical devices (NTP, 2006).

Phytoestrogens are naturally occurring non-steroidal compounds in plants that connect to and stimulate estrogen receptors. Examples of phytoestrogens are genistein and daidzein, which can be found in soy-derived products.

1.12 Phytoestrogens Mechanism of action

Phytoestrogens exert their effects primarily through binding to estrogen receptors (ER), (Turner, *et al*., 2007). There are two variants of the estrogen receptor, alpha (ER-α) and beta (ER-β) and many phytoestrogens display somewhat higher affinity for ER-β compared to ER-α (Turner*et al*., 2007).

The key structural elements that enable phytoestrogens to bind with high affinity to estrogen receptors and display estradiol-like effects are (Yildiz, 2005). The phenolic ring that is indispensable for binding to estrogen receptor.

The ring of isoflavones mimicking a ring of estrogens at the receptors binding site, having a low molecular weight similar to estrogens (MW=272) and distance between two hydroxyl groups at the isoflavones nucleus similar to that occurring in estradiol (optimal hydroxylation pattern).

In addition to interaction with estrogen receptors(ERs), phytoestrogens may also modulate the concentration of endogenous estrogens by binding or inactivating some enzymes, and may affect the bioavailability of sex hormones by depressing or stimulating the synthesis of sex hormone-binding globulin (SHBG), (Johnston, 2003).

Emerging evidence shows that some phytoestrogens bind to and transactivate peroxisome proliferator-activated receptors (PPARs), (Dang *et al*., 2005 and Dang, 2009). *In vitro* studies show an activation of peroxisome proliferator-activated receptors (PPARs) at concentrations above 1 μM, which is higher than the activation level of ERs, (Dang *et al*., 2003, 2004). At the concentration below 1 μM, activation of ERs may play a dominant role.

At higher concentrations (>1 μM), both ERs and PPARs are activated. Studies have shown that both ERs and PPARs influence each other and therefore induce differential effects in a dose-dependent way. The final biological effects of genistein are determined by the balance among these pleiotrophic actions, (Dang *et al*., 2003, 2005 and 2009).

1.13 Soy as a Classic Example

Soy phytoestrogens disrupt endocrine function and have the potential to cause infertility and to promote breast cancer in adult women. Soy phytoestrogens are potent anti-thyroid agents that cause hypothyroidism and may cause thyroid cancer. In infants, consumption of soy formula has been linked to autoimmune thyroid disease (Mercola, 2010).

Vitamin B12 analogs in soy are not absorbed and actually increase the body's requirement for B12. Soy foods increase the body's requirement for vitamin D. Fragile proteins are denatured during high temperature processing to make soy protein isolate and textured vegetable protein.

Processing of soy protein results in the formation of toxic lysinoalanine and highly carcinogenic nitrosamines. Free glutamic acid or MSG, a potent neurotoxin, is formed during soy food processing and added to many soy foods. Soy foods contain high levels of aluminum which is toxic to the nervous system and the kidneys.

1.14 Soy Infant Formula — Birth Control Pills for Babies

Babies fed soy-based formula have 13,000 to 22,000 times more estrogen compounds in their blood than babies fed milk-based formula. Infants exclusively fed soy formula receive the estrogenic equivalent of at least five birth control pills per day (Mercola, 2010).

Male infants undergo a "testosterone surge" during the first few months of life, when testosterone levels may be as high as those of an adult male. During this period, baby boys are programmed to express male characteristics after puberty, not only in the development of their sexual organs and other masculine physical traits, but also in setting patterns in the brain characteristic of male behavior.

Pediatricians are noticing greater numbers of boys whose physical maturation are delayed, or does not occur at all, including lack of development of the sexual organs. Learning disabilities, especially in male children, have reached epidemic proportions (Mercola, 2010).

Soy infant feeding, which floods the bloodstream with female hormones that inhibit testosterone, cannot be ignored as a possible cause for these tragic developments (Mercola, 2010). In animals, soy feeding indicates that phytoestrogens in soy are powerful endocrine disrupters.

1.15 Potential Endocrine Disruptors in Males

Exposure to diethylstilbestrol (DES) induces persistent structural and functional alterations in the developing reproductive tract of males. It is possible that xenoestrogens other than DES alter sexual

differentiation in males and account for the increasing incidence of developmental disorders of the reproductive tract in men and wild animals.

Phytoestrogens (coumestans, isoflavonoids, flavonoids, and lignans) present in numerous edible plants are quantitatively the most important environmental estrogens when their hormonal potency is assessed *invitro*. They exert their estrogenic activity by interacting with estrogen receptors (ERs) *invitro* (Santti *et al*., 1998).

They may also act as anti-estrogens by competing for the binding sites of estrogen receptors or the active site of the estrogen biosynthesizing and metabolizing enzymes, such as aromatase and estrogen-specific 17 beta-hydroxysteroidoxidoreductase (type 1).

In theory, phytoestrogens and structurally related compounds could harm the reproductive health of males also by acting as antiestrogens(Santti *et al*., 1998), however, there are very little data on effects of phytoestrogens in males. Estrogenic effects in wildlife have been described but the evidence for the role of phytoestrogens is indirect and seen under conditions of excessive exposure.

In doses comparable to the daily intake from soybased feed, isoflavonoids such as genistein were estrogen agonists in the prostate of adult laboratory rodents. When given neonatally, no persistent effects were observed. In contrast, the central nervous system (CNS)-gonadal axis and the male sexual behavior of the rat appear to be sensitive to phytoestrogens during development.

The changes were similar but not identical to those seen after neonatal treatment with DES, but higher doses of phytoestrogens were needed, (Santti *et al*., 1998). Estrogen is essential for maintenance and normal activity of the male reproductive tract (Eddy *et al*., 1996, Hess *et al*., 1997). Exposure to exogenous estrogen or inhibition of endogenous estrogen, either during development or adulthood, induces structural and functional changes in the male reproductive tract.

Exposure of neonatal rats to estrogenic chemicals reduces sperm concentrations, plasma testosterone (Goyal *et al*., 2003, Sharpe *et al*., 2003), Sertoli cell number (Atanossova*et al*., 2005), gene expression (Adachi *et al*., 2004), rete tubule distension, and height of efferent duct epithelium (Aceitero*et al*., 1998 and Fisher *et al*., 1998, 1999).

Similarly, distension of the rete testes, efferent ducts, and epididymides, and subsequent infertility, is seen in ERα null mice (Lubahn*et al*., 1993; Eddy *et al*., 1996 and Hess *et al*., 2000).

Similar structural and functional abnormalities can be induced by anti-estrogen treatment of adult rats (Oliveira *et al*., 2001), while exposure to low levels of the potent synthetic estrogen diethylstilbestrol (DES) reduces weights of reproductive organs, decreases epididymal sperm, and decreases fertility (Goyal *et al*., 2001).

Apoptosis of select germ cells occurs normally in the testis and is required to maintain homeostasis (Huckins 1978; Blanco Rodriguez, 1998 and Print and Loveland 2000). Increased apoptosis may be induced following physical or toxicological insult (Richburg 2000).

Apoptosis is induced by disruption of the endocrine actions of estrogen by the synthetic DES due to suppression of gonadal testosterone. ERβ inactivation decreases apoptosis of spermatogonia in neonatal mice (Delbès *et al*., 2004), while in adult human testes *invitro* estradiol has been shown to inhibit apoptosis of spermatocytes and spermatids (Pentikäinen *et al*., 2000).

Furthermore in aromatase-deficient mice, spermatid development is disrupted with increased germ cell apoptosis (Robertson *et al*,. 1999). This mouse model has also demonstrated that dietary phytoestrogen exposure through a soy-containing rodent feed, influences spermatogenesis independently of the hypothalamo–pituitary–gonadal axis (Robertson *et al*., 2002).

While many studies have demonstrated the effects of fetal and neonatal phytoestrogen exposure on testis development and subsequent fertility of the adult male (Atanassova *et al*., 2000, Roberts *et al*., 2000), very few studies have investigated the effects of adult male exposure to dietary phytoestrogens on spermatogenesis, and none have controlled for effects of exposure during the fetal, neonatal, or pubertal periods.

1.16 Conclusion

This review concludes that uncontrollable intake of phytoestogen could lead to oligospermia (low sperm count) and azoospermia (no sperm at all) which is a complicated medical condition that is mostly responsible for childlessness caused by males and responsible for marital issues. The damage caused by phytoestrogens does not have symptoms and cannot be known without proper medical screening.

Recommendation

Proper Medical checkup should be conducted on males who are up to reproductive age in order to know their reproductive status this will help to know if their fertility has been affected through uncontrollable intake of phytoestrogen containing plants and herbs.

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