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Estrogen: The necessary evil for human health, and ways to tame it

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ABSTRACT

Estrogen is a pivotal enzyme for survival and health in both genders, though their quantum, tropism, tissue-specific distribution, and receptor affinity varies with different phases of life. Converted from androgen via aromatase enzyme, this hormone is indispensable to glucose homeostasis, immune robustness, bone health, cardiovascular health, fertility, and neural functions. However, estrogen is at the center of almost all human pathologies as well-infectious, autoimmune, metabolic to degenerative. Both hypo and hyper level of estrogen has been linked to chronic and acute diseases. While normal aging is supposed to lower its level, leading to tissue degeneration (bone, muscle, neural etc.), and metabolite imbalance (glucose, lipid etc.), the increment in inflammatory agents in day-to-day life are enhancing the estrogen (or estrogen mimic) level, fueling 'estrogen dominance'. The resultant excess estrogen is inducing an overexpression of estrogen receptors (ERα and ERβ), harming tissues, leading to autoimmune diseases, and neoplasms. The unprecedented escalation in the polycystic ovary syndrome, infertility, breast cancer, ovary cancer, and gynecomastia cases are indicating that this sensitive hormone is getting exacerbated. This critical review is an effort to analyze the dual, and opposing facets of estrogen, via understanding its crosstalk with other hormones, enzymes, metabolites, and drugs. Why estrogen level correction is no trivial task, and how it can be restored to normalcy by a disciplined lifestyle with wise dietary and selective chemical usage choices has been discussed. Overall, our current state of knowledge does not disclose the full picture of estrogen's pleiotropic importance. Hence, this review should be a resource for general public as well as researchers to work in that direction.

1. Introduction

Estrogen is more than just an estrus-inducing sex hormone. In fact, this steroid hormone controls almost all aspects of female and even male health [1]. Critical functions like glucose homeostasis, lipid homeostasis, bone metabolism, brain function, follicular growth, skeletal growth, and ovulation, among a myriad other functions, depend on its signals [1,2]. Estrogens (C18) are formed by the demethylation of androgens (C19), the male hormone precursors [3]. Aromatase, a cytochromes P450 (CYP) class monooxygenase enzyme, encoded by CYP19 gene is extremely critical for estrogen biosynthesis [4–6]. Aromatase is responsible for the aromatization of androgen into estrogen. Most of the estrogen perturbation-caused ailments as breast cancer, polycystic ovary syndrome (PCOS), endometriosis, osteoporosis, ovarian cancer, gastric cancer, pituitary cancer, Alzheimer's disease, schizophrenia, male hypogonadism, and transgender issues, are linked to aromatase malfunction as well [3]. The same estrogen ligands when bound to different receptors, exert different physiological functions by autocrine or paracrine mechanisms, of which some are beneficial for the body, and some are detrimental [7]. Considering the gamut of diseases that are linked to estrogen, hormonal replacement therapy (HRT) is a common therapeutic option [8], which however is not side-effect-free. In both genders, the depletion of estrogen can lead to digestive issues, osteoporosis, Alzheimer's disease *etc*. In fact, it can be argued that chemotherapy blocking the essential estrogen signals lead totoxicity-related death in cancer patients. This critical review discusses the indispensable, dual and antagonizing function of estrogen in human body.

2. Estrogen and its receptors

Aromatase activity varies in different parts of the body, so does estrogen. Adipose tissues are the predominant steroidogenesis sites. Apart from ovary, placenta, and breasts, estrogens can occur in skin,

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bone, brain, liver, and adrenal glands [9]. Gender, age, and health status are factors deciding estrogen level in the body [10]. Puberty is a phase where estrogen level is high in females, which mediates sexual differentiation [11].

Estrogen (17 beta-estradiol) exerts its diverse functions by ligating to the nuclear hormone receptor protein, a form of transcription factor [12]. These classes of receptors are critical for the embryonic development, cell differentiation and homeostasis. Estrogen receptors (ER) occur in the nucleus, cytoplasm, and mitochondria of cells, and as a result of alternative splicing of the transcripts, they can be of several types. The two dominant types are alpha, and beta, which further occur in multiple isoforms. Alpha type ER (ERα) was discovered first, followed by the rather recent discovery of beta-type ER (ERβ). *In silico* analysis of the ERs from both types showed the presence of common domains/motifs *i.e.* N-terminal DNA binding domain, and C-terminal ligand binding domain [13]. As per the SMART (Simple Modular Architecture Research Tool)-based *in silico* analysis of some ER sequences retrieved from UniProt, both human ERα and ERβ had ZnF_C4 domain (c4 zinc finger) [14,15]. Zinc finger (Znf) domains are small DNA-binding motif with variation in binding modes. The classes under the Znf superfamily include ZnF_BED, ZnF_A20, ZnF_NFX *etc*. [16,17]. Homologues of all these zinc finger motifs have been detected in pathogenic viruses like HCV, HIV, and dengue. Another oft-occurring domain in these ERs include HOLI. This is a ligand binding domain of hormone receptors [18]. Further analysis showed that androgen receptor has a coiled-coil region, along with the above 2 domains. Glucocorticoid receptor has a HOLI domain; thyroid hormone receptor beta has ZnF_C4, and HOLI; Insulin-like growth factor 1 receptor has transmembrane region; G-protein coupled estrogen receptor 1 has 7 transmembrane regions. So, almost all the steroid receptors share the same motifs. Some other domains in the ERs with less-confident scores included Mcm10, ICA69, TR_THY, APC10, IL4_13, MAGE_N, AMA-1, B_lectin, Thymopoietin, C6, IBR, BowB, ZnF_GATA, IB, zf-AD, RPOLCX, PHD, RING, ZnF_NFX, LU, LDLa, C1_4, RINGv, ZnF_RBZ, SR, LRRCT, RGS, MADF, HTH_MARR, Rapamycin_bind, HTH_ARSR, BSD, FerA, CarD_TRCF, WH2, IDEAL, and ZM [15]. These domains regularly occur in pathogenesis-associated proteins from the organisms of diverse kingdoms [15,19]. It is suggested that all these virulence-associated domains have radiated from the same parent domain.

However, sequence variations in other parts of the ER proteins lead to different affinity for the estrogen. Once bound to the ligand estrogen, the ER becomes dimeric, and bind to estrogen response elements of DNA, regulating transcription [20]. The N-terminal DNA-binding domain of the ERs can elicit activating or repressing effects. On ligation with the ERs, estrogen acts as a mitogen, promoting cell division, neoplastic transformation and proliferation. Activity of estrogen is more pronounced in those tissues where its receptors are abundant, such as ovary, breast, brain (hypothalamus), kidneys, bone (bone marrow) *etc*. By binding to its receptors in the hypothalamus, it regulates anorexigenic/orexigenic stimuli, controlling food intake and glucose level.

Tissue distributions of both the ER types differ. As per the current state of knowledge, ERα occurs in the female reproductive system, while ERβ occurs in the prostate, colon, cardiovascular, and central nervous systems. Skeletal muscle expresses both ERs.

The antagonistic functions of ERα and ERβ have been documented. They have some common functions as well, but they regulate unique sets of genes, as revealed from microarray experiments [21]. ERα is the main regulator of GLUT4 (glucose transporter type 4) expression in adipose tissues, while ERβ is the repressor of the protein [22]. ERα induced leptin expression while ERβ inhibited its expression in 3T3-L1 adipocytes [23]. Leptin is a 16 kDa peptide formed by the white adipocytes, and is required for homeostasis [24]. This adipokine causes cardiac hypertrophy (thickening of myocardium) [25]. Leptin, along with adiponectin, and hepatocyte growth factor (HGF), enhances aromatase expression and inflammation [26–28].

ERα overexpression is a hallmark of estrogen +ve breast cancer [29]. ERα has ameliorative effects following trauma-hemorrhage [30]. Hyperinsulinemia activates DNA methyltransferases, which decrease ERα expression via their gene methylation [31]. ERα-ligated estrogen stimulates cell proliferation and induces neoplastic transformation [32].

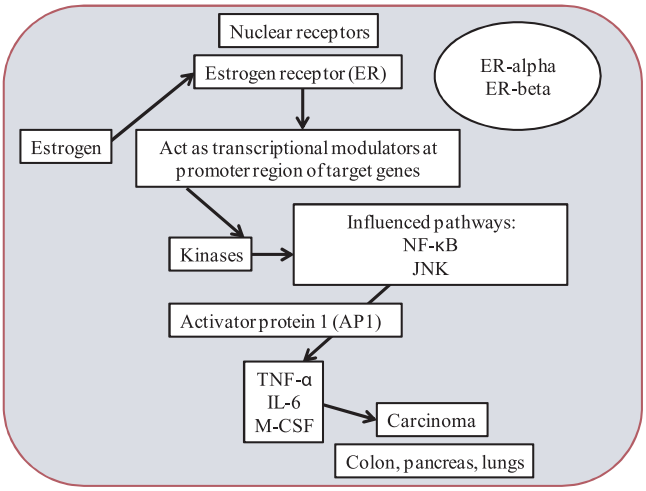

Fig. 1. Estrogen-ER complexation and the pathways activated. As the ligand estrogen binds to the ERs, they act as transcription regulators. The activated ER regulates the activation of the proinflammatory transcription factor NFκB. NFκB pathway activation induces M-CSF production which plays role in macrophage transformation by upregulating c-Jun, a major component of the transcription factor activator protein (AP)-1. Jun amino-terminal kinase (JNK), which phosphorylates c-Jun, is activated by the ligand-receptor complex as well. AP-1 induces the elaboration of the inflammatory cytokine TNF-alpha, which increases VEGF expression in breast cancer cells.

Polymorphism in ERβ has been associated with endometrioid carcinoma [33]. ERβ has been observed in TNBC (triple negative breast cancer) cell lines (MDA-MB-453, SUM-185-PE and MFM-223) [34].

A study reports that the net action of estrogen is an outcome of the relative ratio of each ER type [35]. The ERs and the pathways activated followed by estrogen binding has been presented in Fig. 1. Functions of ERs have been discussed in later sections as well, as the context required. Though much remains to be known about the role of both receptor types, Table 1 presents a list of pathologies and the dominant ER types.

3. Estrogen imbalance and consequent diseases

Both hyper and hypo level of estrogen sets off a diverse array of diseases *i.e.* autoimmune, metabolic, neural, and gender-specific, among others [12]. The section below briefly narrates the common pathologies, resultant of perturbed estrogen level. Also, the pathologies resultant of estrogen perturbation have been presented in Fig. 2 and Table 2.

3.1. Hyper-estrogen activity-driven pathologies

High estrogen level is causal of numerous health issues, some key of which have been discussed here. Polycystic ovary syndrome (PCOS) is characterized by the endocrine disturbance, leading to cysts in the

Table 1
Pathologies and the dominant ER types.

ER type	Pathologies	References
ERα	Thyroid tumors	[52]
	ER +ve breast cancer	[29]
ERβ	Endometrioid carcinoma	[33]
	Triple negative breast cancer	[34]

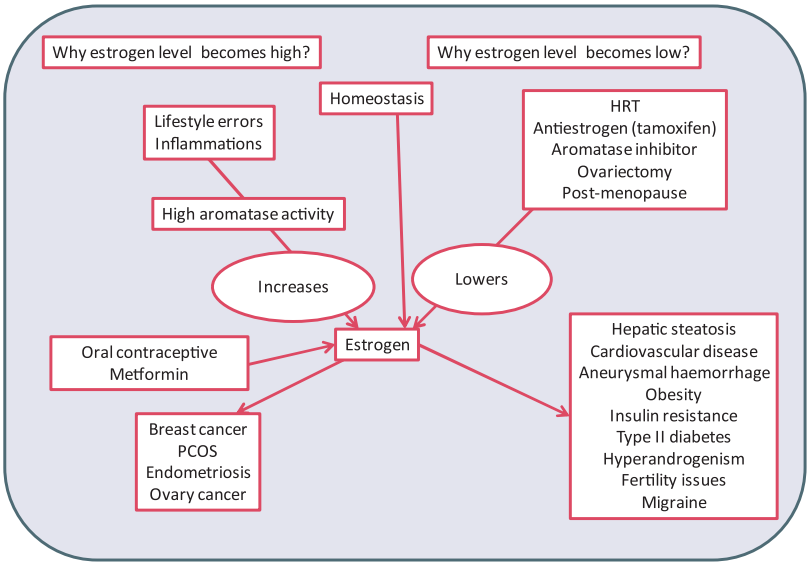

Fig. 2. Inflammatory lifestyle lowers body pH and activates aromatase enzyme, which increases the level of estrogen. The expression of estrogen in tissues lead to cancerous proliferations and other autoimmune pathologies. Estrogen inhibitors can block the hormone's adverse effects to some extent, but estrogen deficiency has its pathological consequences as well.

ovaries. Its symptoms include hirsutism, alopecia, amenorrhea, infertility, hypertension, type 2 diabetes mellitus, depression *etc.* [36–39]. Endometriosis is an uterine anomaly where uterus tissues grow outside, resulting in irregular periods, abdominal pain, chronic exhaustion, and infertility [40–42]. A number of cancers have been linked to ER expression in different tissues. Such cancers include endometrial/ovarian cancer, caused by the overexpression of estrogen in ovulatory follicles [43,44]. Breast cancer is a heterogeneous form of cancer, in the proliferation of which estrogen has predominant role [45,46]. In the estrogen receptor positive (ER +ve)-type breast cancer, estrogens or its mimics, bind to ER, driving cancerous epithelial hyperplasia [47]. Gastric cancer [6], lungs cancer [48], hepatic cancer [49], and pituitary cancer [50] are other forms of cancers, resultant of high estrogen level.

Thyroid carcinoma and adenomatous goiter have been linked to estrogens [51]. The presence of ERα in human thyroid tumors and normal thyroid glands has been reported [52]. Autoimmune diseases as systemic lupus erythromatosus (SLE) [53,54] and multiple sclerosis (MS) [55–57] are also the resultants of estrogen overactivity. Gender-specific effect of estrogen has been well-documented. High estrogen level leads to short stature (by early epiphyseal closure) in both genders, while it specifically causes hypogonadism and gynecomastia (the proliferation of male breast glandular tissue) in males [58,59], and breast hypertrophy in females [60].

3.2. Hypo-estrogen activity-driven pathologies

Estrogen level achieves a spurt in puberty which start menstrual cycle in females. In the late fourth or early fifth decade of life, estrogen depletes to a large extent. After menopause, ovary almost stops producing it, which pave the path for a number of pathologies, involving

Table 2
Pathologies associated with hyper and hypo level of estrogen.

Level of estrogen	Regulators of estrogen	Diseases	References
High estrogen	*The enhancers*	Breast cancer	[1,2]
	Inflammation	Prostate cancer	[3]
	Bisphenol A (BPA)	Polycystic ovary syndrome	[4,5]
	Alcohol, marijuana, heroin, cannabis, methadone, amphetamines	Ovarian cancer	[6]
	Cosmetic products (fragrance compounds), Antidepressants (diazepam)	Endometriosis	[7,8]
		Gastric cancer	[9]
		Pituitary cancer	[10]
		Thyroid carcinoma and adenomatous goiter	[11]
		Schizophrenia	[12,13]
		Systemic lupus erythematosus	[14,15]
		Multiple Sclerosis	[16,17]
		Male hypogonadism and oligospermia	[18]
		Gynecomastia	[19]
		Obesity	[20]
Low estrogen	*The inhibitors*	Osteoporosis	[21,22]
	Prolactin	Arthralgia (joint pain)	[23]
	Antidepressants	Alzheimer's disease	[24,25]
	Opiates	Parkinson's disease	[26]
	Estrogens	Diabetes	[27]
	Anti-androgens,	Eclampsia	
	Anti-hypertensive drugs		
	H2-receptor antagonists		
	Anticonvulsants		
	Immunosuppressive drugs (glucocorticosteroids, methotrexate)		
	Herbicides		

organs as well as systemic. Estrogen deficiency-caused imbalance between bone absorption and resorption, leading to osteoporosis, an ailment of bone fragility and porosity [61,62]. Arthralgia is characterized by joint pain, stiffness and functional disability. Depleting estrogen level in the geriatrics is responsible for this bone condition. Alzheimer's disease, a form of dementia, characterized by high amyloid beta (Aβ) production, and hyper-phosphorylation of tau protein, resulting in hippocampus degeneration, has been linked to the drop in estrogen level [63–65]. Tau protein is required for the stabilization of microtubules, but the post-translational modification leads to their aggregation [63]. Parkinson's disease, a neurodegenerative disease involving the degeneration of midbrain substantia nigra, affects the motor abilities like walking, balancing, and swallowing, because of tremor, bradykinesia (slow spontaneous movement), and pain [66–68]. Schizophrenia, a dopaminergic system-associated neuropathology, has been linked to estrogen effect [69,70]. Often these pathologies causal of low estrogen level, occur as co-morbidities [71]. Declining estrogen level affects blood glucose homeostasis, which results in adiposity and insulin resistance, and consequent cardiovascular disease risks and diabetes. Estrogen deficiency increases the risk of renal pathology in diabetics, via the overactivity of RAAS [72] and by altering renal calcium absorption [73]. Preterm delivery due to eclampsia (a form of seizure during pregnancy), is the resultant of aromatase inhibition, thus estrogen deficiency, and high blood pressure [74]. Low estrogen synthesis results in long stature due to delayed epiphyseal closure, and eunuchoid body [75].

In practical situation, estrogen is prone to oscillation between the extremes. It is a matter of serious concern as the fluctuataing level of the hormone can mislead the signaling system at as low as at picomolar to nanomolar level. The fetal and juvenile organisms are at higher risk by the ill effects of the endocrine disruptors. Unintentional or ignorance-driven exposure to aromatase and estrogen manipulators can perturb estrogen level. Personal care products and household consumables have chemicals (parabens, phthalates, nitro musks, benzophenones, bisphenol A, pesticides, fire retardants) with estrogenic property [76].

Apart from menopause, ovariectomy, and aging, the usage of aromatase inhibitors are one cause of the low estrogen production [77]. Anterior pituitary-secreted prolactin (luteotropic hormone or luteotropin) reduces aromatase activity, thus lowers estrogen level [78]. Antidepressants, antipsychotics, anticonvulsants opiates, estrogens, anti-androgens, anti-hypertensive drugs, and H2-receptor antagonists, increase prolactin level in the body, which reduces estrogen level [79]. Herbicides (glyphosates, Roundup etc.) and azole compounds (agricultural antifungals), immunosuppressive drugs (glucocorticosteroids, methotrexate), antimalarials, and anticancer drugs (anastrozole, exemestane, letrozole) are aromatase inhibitors [80–84]. Cigarette smoke is suspected to inhibit aromatase [85].

In this scenario, due to the intentioal or accidental lifestle mistakes, signaling pathways go haywire. The imbalance leads to gender-fluidity problems. High estrogen in males can cause feminization, while low estrogen in females can cause the dominance of androgen, thus masculinization. Oral contraceptive pills, such as ethinylestradiol and progestin, can bind to steroid receptors for androgen exerting masculinization effect on the female brain [86].

4. Interaction of estrogen with other body components

Estrogen as a pivotal signaling molecule, playing role in both health and ailments has been studied amply. Like most other body components, it behaves differently in homeostatic and non-homeostatic situations. When homeostasis prevails, estrogen protects against all invaders and stressors, maintaining health. For example, estrogen binds to ERα and promotes glucose transporter GLUT4 expression, and their internalization, promoting glucose homeostasis in skeletal muscles [87].

But, when stressors are recurrent, neuro-immune-endocrine axis perturbation is perpetual. These regulatory systems coordinate to create an extracellular acidic milieu, a requisite environment, evolutionarily-designed to neutralize the stressors. However, this defense strategy comes at a price. The acidosis activates hydrolyzing enzymes, which are instrumental in the elaboration of inflammatory cytokines (TNF-α (tumor necrosis factor-alpha), IL-6 (interleukin -6), and M-CSF (macrophage colony-stimulating factor)). These cytokines cannot distinguish between self and non-self in their destructive roles. So, human system and organs are damaged as well. Sensing the inflammation state, and the need to detoxify the system, aromatase and other cytochromes P450 (CYP) enzymes undergo hyperactivity. Higher production of estrogen completes this vicious cycle.

Estrogen is a master regulator, and its interacts with a spectrum of other hormones, and enzymes to mediate its versatile functions. Also, estrogen receptors can be expressed in response to drugs. Sex steroid imbalance leads to thyroid issues. Estrogen administration increases thyroxine-binding globulin level [88]. Estradiol stimulates the phosphorylation of Akt, AMPK (AMP-activated protein kinase) and the Akt substrate [89]. Prostaglandin PGE2 increases intracellular cAMP levels and stimulates estrogen biosynthesis via aromatase activity [90]. The synergy between cyclooxygenases (COX-1 and COX-2) and aromatase, the hormone which generates estrogen, has been observed in breast cancer tissues [91]. The hyper-produced estrogen regulates breast cancer proliferation, by autocrine or paracrine mechanisms [92]. Estrogen damages DNA and interferes with its repair via the manipulation of ATM, ATR, CHK1, BRCA1, and p53 proteins [93].

Studies are revealing the role of estrogen in areas of human physiology which was unthinkable years before. In rat model, it was observed that the fertilized eggs do not survive if exposed to proteases, as the enzymes lyse the embryo. ERα signaling can inhibit the protease, and in absence of the receptor, fertilization and fetus survival is affected [94]. On the other hand, a mice model study reports that estrogen increased the extracellular expression and IL-12-induced function of the inflammatory serine protease Granzyme A [95]. Such conflicting reports of estrogens functions is rampant in the literature. HIV protease inhibitor induces cholesterol accumulation in the macrophages and increases the risk of atherosclerosis. From mice model it came forth that ERα is involved in the macrophage cholesterol metabolism [96]. SERMs (selective estrogen receptor modulators) such as clomiphene and toremifene, could inhibit Ebola virus infection, by inhibiting the virus entry. If approved, the SERMs can be a breakthrough therapy for the deadly filovirus [97].

5. Therapies and regulators of estrogen-related pathologies

As both the high as well as low estrogen level is associated with separate sets of pathologies, their management modalities have been invented. Aromatase inhibitors (such as anastrozole, letrozole, and exemestane) are anti-estrogen agents, so used to treat cancers, endometriosis, PCOS, gynecomastia *etc*. [3,98–101]. Tamoxifen, a triphenylethylene derivative, an estrogen receptor antagonist, is the mainstay therapy for hormone-dependent breast cancers which interferes with the transcriptional regulation by the ERs [100]. However, estrogen being a versatile messenger, its manipulation via the aromatase inhibition or estrogen receptor modulation, is risky. It is akin to trying to cut the tree branch on which the lumberjack is perched on. Aromatase inhibitors can cause side effects which include bone fracture, osteoporosis, arthralgia, and Alzheimer's disease, among others [77,102–104]. Also, the therapeutic intervention is not guaranteed to be effective as two interferon response genes IFITM1 (interferon-induced transmembrane protein) and PLSCR1 (phospholipid scramblase 1) resist the aromatase inhibitors [105].

L-DOPA, dopaminergic agonists (dopamine receptor agonists), monoamine oxidase-B (MAO-B) [106], and ergot alkaloid derivatives, include available therapies to delay neural pathologies caused by

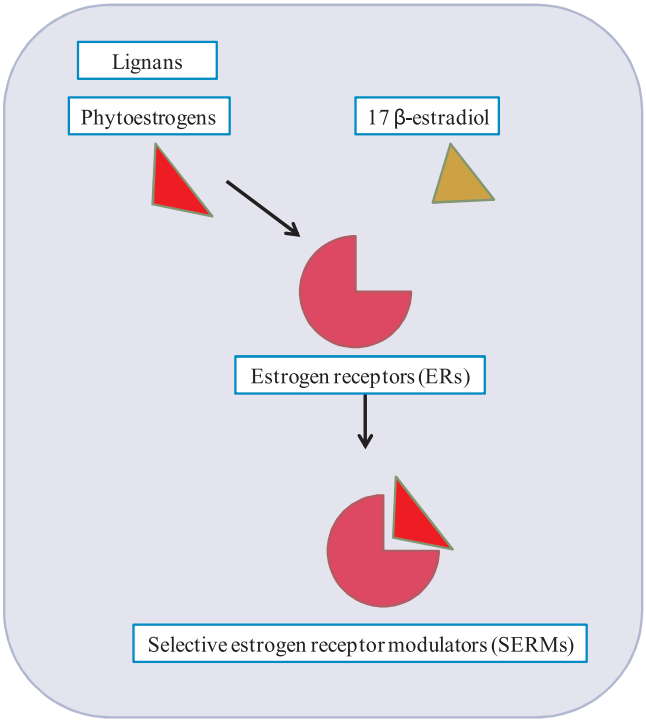

Fig. 3. Phytoestrogens like lignan, isoflavone and coumestan, act as estrogen agonists, and on ligation with the estrogen receptors, initiate estrogen signaling. It is debated that the phytoestrogens might be acting as antagonists, blocking estrogen from binding to the receptors, thus might hold potential as selective estrogen receptor modulators (SERMs).

estrogen deficiency. They alleviate some symptoms of the targeted pathologies, yet cause dyskinesia and dystonia [106].

Lignans are diphenolic compounds in plants (such as cereals, flaxseed, soy *etc*.), which on ingestion, are metabolized into enterolactone and enterodiol [107]. The role of these phytoestrogens in estrogen regulation is debatable. While one group believes that these steroids boost estrogen level, another group assumes that they can be an antagonists of estrogen. By binding to the ER, the phytoestrogens can exclude endogenous estrogen, preventing its downstream effects. SERMs have been proposed as a way to prevent cancerous attributes of estrogen. In this regard, plant lignans, rich in phytoestrogens are candidates for SERMs. The often-conflicting results, regarding their roles are obvious for different tissues, as they express different ERs with antagonizing functions. Binding of the lignans to the ERs will evoke opposing functions. This mechanism of estrogen inhibition by phytoestrogens has been illustrated in Fig. 3. Other phytochemicals as coumestrol, luteolin, kaempferol, resveratrol, curcumin, apigenin, catechin, nicotine, hesperitin *etc*. are known to lower aromatase activity [108,109]. Also, vitamin E being an antioxidant, can attenuate aromatase, by reducing oxidative stress level, though the mechanism is not well-published [110].

With aging, the hypothalamic-anterior pituitary-gonad axis weakens, leading to high adiposity, insulin resistance, dyslipidemia, tissue inflammation *etc*. [111,112]. Active form of vitamin D, the 25-hydroxyvitamin D can attenuate the instances of breast and ovarian cancer [113]. Calcitriol (1,25-dihydroxyvitamin D3) suppresses COX-2 enzyme expression, reducing the levels of inflammatory prostaglandins. Also, this form of vitamin D decreases the expression of aromatase, causing reduction in estrogen level [114]. Serum sex-hormone-binding globulins regulate circulating steroid level. Low level of the globulinsead to lincreased estrogen level [115].

Creatine kinase (CK) catalyzes ATP hydrolysis and the formation of ADP. CK has various isoforms which occur in diverse cellular regions and body tissues. *In vivo* studies have shown the link between CK and estrogen [116]. High CK level leads to muscle conditions as spasms, cramps, fatigue *etc*.Studies report that high CK level is often accompanied by high aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and aldolase level as well. Na-K-ATPase (sodium-potassium ATPase), an electrogenic pump located in the cell membranes, is vital for ionic balance. By transporting sodium and potassium ions across the membranes, the pump maintains physiological pH [117]. Among other regulators, endogenous hormones (some cardiotonic steroids), including estrogen, affect the performance of these pumps [118]. RAAS (renin-angiotensin-aldosterone system) maintains blood pressure by regulating extracellular fluid volume [119–121]. Kidney-secreted renin acts on its substrate angiotensinogen to form angiotensin I, which is acted upon by angiotensin-converting enzyme (ACE) to generate the versatile peptide angiotensin II [122,123]. This effector component can cause hypertension by exerting vasoconstriction. Estrogen as a vasodilator, protects against the detrimental hypertensive effects of the activated RAAS. It has been well-documented that the depleting estrogen level in post-menopausal females make them prone to cerebral, cardiovascular and renal pathologies [124,125]. However, like a lot of other ambiguous findings pertaining this hormone, its angiotensin-enhancing roles have emerged [126].

Androgen upregulates aromatase activity as it acts as the enzyme's substrate. Aromatase has an androgen-specific site which binds to androstenedione molecule and aromatizes its steroid ring, converting it into estrogen [127]. Androgen is anti-inflammatory, but inflammatory milieu induces the transformation of androgen to estrogen [128]. Progesterone metabolite 20 alpha-dihydroprogesterone (20αDHP) can act as an anti-estrogen agent [129]. There are ample evidences on the estrogen-opposing and hyperplasia-suppressing role of progesterone [130,131].

6. Discussion

Despite a wealth of information garnered on estrogen, our understanding is incomplete and full of misleading information. Estrogen can prevent inflammation, but can mediate inflammation as well. For example, estrogen boosts epithelial integrity and prevents pathogenesis of *Escherichia coli*-caused urinary tract infections (UTIs) in mice model [132]. Exogenous estrogen protects from postmenopausal rheumatoid arthritis, and osteoporosis [133]. However, the estrogen therapy can cause SLE, and thromboses [133].

While reporting and interpreting a pathological condition due to deficient or excess estrogen level, it should be remembered that same estrogen in interaction with different ER type is likely to exert different effects.

The precise distribution and regulators of the ERs are yet to be unraveled. Questions abound regarding the ERs. What is difference between ERα and ERβ? Which critical amino acid is substituted that makes the two ER behave differently? To prevent the expression of the problematic ER should be our goal. For hypo and hyper estrogen status, the objective will vary. The discovery of agonists for both alpha and beta forms of estrogen receptors is one approach. Agonists specific to either types of the receptors have been evaluated, but they often backfire, with undesirable results. The often-disparate tissue distributions, and antagonizing functions of the two forms of ERs add another layer of complications in the therapeutic efforts. Some observations of functional dichotomy have been mentioned here. ERα is the predominant isoform in cortical bone, while ERβ is the predominant form in trabecular bone. ERβ was involved in the prevention of geriatric hearing loss. So, it cannot be concluded that a particular receptor type is good or bad, as both types of ER have beneficial as well as evil roles. It is most likely that, the hormonal milieu decides the expression of the ER, just as the substrates induce enzyme expression. In fact, in the disturbed metabolic state, the human body's endocrine system is attempting to restore balance through the up-regulation of a distinct type of ER.

Cancer therapies often fail because they target the estrogen [93]. Inhibiting the aromatase enzyme, responsible for producing this hormone can shut down signaling between neuro-hormonal-immune components. It can lead to death. So, targeting estrogen is never in the best interest of the body.

Genetic polymorphisms have often been attributed to cause breast cancer. Mutations in BRCA1 and BRCA2 might be hereditary, but majority of the issues related to imbalanced estrogen are the resultant of lifestyle issues. All hormones are sensitive signaling molecules, vital for healthy life. Estrogen particularly is a violently alert hormone recruiting or recruited by other surveillance components essential for homeostasis. Unfortunately, unhealthy living conditions are perturbing estrogen level. Lifestyle revision can delay or prevent the pathological effects of estrogens. Modern living is full of encounter with endocrine-disrupting chemicals (parabens, phthalates, nitro musks, benzophenones, bisphenol A, pesticides, and fire retardants). These compounds are upregulators of aromatase, and are estrogenic [134]. Together they create an inflammatory, acidic milieu. The large repertoire of chemicals being used in daily life are perceived as stress to the body, to tackle which, high level of estrogen is produced. Perturbation in the estrogen level, in fact 'estrogen dominance' is responsible for the ER expression and activation [135]. So, this hormone level should not be allowed to fluctuate beyond normal level. The level of estrogen is a direct output of aromatase activity which in turn is the result of inflammations endured or being encountered. So, one's lifestyle should be such as to minimize inflammations. Lifestyle revision can delay or prevent the pathological effects of estrogens. Apart from reducing the usage of these endocrine-manipulating chemicals, dietary changes are assumed to help in the expression of the right type of ER in right tissues. Acidogenic food lead to drop in extracellular matrix pH, causing acidosis [136]. It causes aberrant enzyme activation, including that of matrix metalloproteinase, and aromatase. Tumor is one symptom of inflammation [137,138]. Just as other symptoms of inflammation such as swelling, redness, and heat resolve with care and time, tumor might be resolving, regressing on their own. However, recurrent abuse of the system or organs might be feeding aromatase to elaborate tissue-specific estrogen.

Authorities should take stringent actions to control environmental pollutants and to educate consumers to be aware of the risks of estrogen-begetting stressors and estrogenic chemicals. It is ironical and unfortunate that the life-giving estrogen itself is the clastogen, morbidogen, and carcinogen. But, that is how evolution has designed us, so nothing much can be done about it, except to being cautious, so as not to agitate it. The balanced activation of both receptor types is requisite for a healthy life. This critical review is expected to be of interest to general public as well as the researchers, as the mankind faces an enormous health challenge.

7. Conclusions

Estrogen's pleiotropic role and indispensability in homeostasis is adequately-proven. Its waveing in either extreme is hazardous. Excess estrogen will lead to autoimmune diseases and cancer, while less estrogen will lead to osteoporosis, and brain degeneration, among other pathologies. As being between Scylla and Charybdis is dangerous, both hyper as well as hypo estrogen level can push an individual towards morbidity or mortality. Current cancer management regimen appears insufficient. To normalize one stressor (hormone imbalance), subjecting the body to an array of other stressors (toxic drugs) appear paradoxical-yet it is the current convention. Long term usage of toxic chemotherapeutics is unadvisable as the battle arena is the human body, which already has lost its homeostasis (cancer is a reflection of lost homeostasis). Homeostasis can be maintained by a healthy, personalized lifestyle. The only sustainable way to ensure optimal estrogen level is to understand body type, estrogen dynamics with age, and through efforts to stay away from stressors. Intake of and exposure to detrimental chemicals by air, water, personal care products, and pesticides/additives in food need to be monitored. Research community ought to strive to unveil the hidden aspects of estrogen.

Compliance with ethical standards

The authors declare that there is no competing interest. This work does not involve human participants or animal models.

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