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# Aromatase enzyme: Paving the way for exploring aromatization for cardio-renal protection

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## Abstract

Documented male-female differences in the risk of cardiovascular and chronic kidney diseases have been largely attributed to estrogens. The cardiovascular and renal protective effects of estrogens are mediated via the activation of estrogen receptors (ERα and ERβ) and G protein-coupled estrogen receptor, and involve interactions with the renin-angiotensin-aldosterone system. Aromatase, also called estrogen synthase, is a cytochrome P-450 enzyme that plays a pivotal role in the conversion of androgens into estrogens. Estrogens are biosynthesized in gonadal and extra-gonadal sites by the action of aromatase. Evidence suggests that aromatase inhibitors, which are used to treat high estrogen–related pathologies, are associated with the development of cardiovascular events. We review the potential role of aromatization in providing cardio-renal protection and highlight several meta-analysis studies on cardiovascular events associated with aromatase inhibitors. Overall, we present the potential of aromatase enzyme as a fundamental contributor to cardio-renal protection.

### Keywords

Cardiovascular; Kidney; Estrogen synthase; Aromatase inhibitors; Meta-analysis

## 1. Introduction

### 1.1. Prevalence of cardiovascular and chronic kidney diseases

Cardiovascular disease (CVD) is one of the major causes of death worldwide, and can impose a significant financial and health burden on patients in the United States and globally [1]. The Global Burden of Disease study, conducted in 195 countries, reported that the



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prevalence of CVD cases almost doubled from 271 million in 1990 to 523 millions in 2019, while the number of CVD deaths progressively rose from 12.1 million in 1990 to 18.6 millions in 2019 [2]. In 2020, CVD was responsible for 928,741 fatalities in the United States and approximately 19.1 million deaths worldwide [3].

Chronic kidney disease (CKD) is also one of the leading causes of death in the 21st century, with over 850 million people worldwide suffering from CKD [4,5]. The latest estimations (2017–2020) of CKD prevalence in the United States adult population revealed a 14.5% overall prevalence [6]. Globally, a total of 3.16 million deaths from kidney disease were reported in 2019 according to the Global Burden of Disease study [2]. Notably, the relationship between CVD and CKD is reciprocal. In other words, CVD can be an underlying cause of CKD and vice versa [7,8].

### 1.2. Age and sex factors contributing to cardiovascular health

CVD is considered as an age-related pathology in both men and women, because age is a major factor that influences the cardiovascular health [9]. CVD is a major cause of death in individuals aged 65 years or older, accounting for 40% of mortality [9]. By 2030, it is projected that over 20% of the population in the United States will be 65 years or older [9,10]. According to the American Heart Association, the incidence of CVD among adult Americans is 40% between the ages of 40 and 59, 75% between the ages of 60 and 79, and 86% in individuals over the age of 80 [11].

The American Heart Association also reports that between 2013 and 2017, 77.8% of females and 70.8% of males aged 65–74 were diagnosed with hypertension; diagnosis rates were 85.6% for women and 80.0% for males over the age of 75 years [12]. Previous studies have also revealed that women are at higher risk of stroke than men [13,14]. On the contrary, men typically develop CVD at a younger age and have a higher risk of coronary heart disease than women [15]. Several clinical studies reported that women prior to menopause are more protected from CVD, but this risk sharply increases after menopause [16,17]. This difference in the cardiovascular risk between premenopausal and postmenopausal women is attributed to estrogen and its associated receptors, which consequently contribute to the disparities in disease outcomes between men and women [18].

### 1.3. Age and sex factors contributing to renal health

CKD is recognized as a common clinical problem with elderly patients. Recent estimates by the Center of Disease Control and Prevention showed that CKD is more prevalent in individuals over the age of 65 (38%) compared to those between the ages of 45–64 (12%) and 18–44 (6%) [19]. CKD is slightly more common in women (14%) than men (12%) [19]. A systematic meta-analysis showed that CKD is more prevalent in females and that its prevalence increases with age [20]. The estimations in this meta-analysis were based on the use of creatinine levels to determine the estimated glomerular filtration rate, while albuminuria or proteinuria was not detected in many of the included studies [20].. This alligns with reports of increased prevelance in CKD stage 3–5 among women, but not men, between 2002 and 2007 [21]. In contrast, other studies reported higher incidence of kidney failure in men [22]. Harris and Zhang concluded that although women have a larger

prevalence of CKD, the incidence of end stage renal disease is 50% higher in adult men than in women [23]. Therefore, further investigation is needed to better understand how sex affect CKD incidence, prevalence, and progression, in addition to potential sex-specific disease markers to determine whether sex hormones are related to the onset or progression of renal disease [24].

## 2. Estrogens

### 2.1. Types of estrogens and primary sites of production

Estrogens are steroidal sex hormones that include estrone ($E_1$), estradiol ($E_2$), estriol ($E_3$), and estetrol ($E_4$) [25]. The predominant circulating female hormone is $E_2$, which is commonly referred to as “estrogen”, due to its physiological importance and prevalence during the reproductive years [16,25]. $E_1$ is commonly detected at higher levels after menopause, while $E_3$, and $E_4$ are produced only during pregnancy [26].

The ovaries, specifically the granulosa cells, are the primary source of $E_2$ in premenopausal women, acting as a circulating hormone on distal tissues [25,27]. In men, $E_2$ is produced in minute amounts by the testes [28]. Estrogens are also produced in extra-gonadal sites such as adipose tissue, brain, skin, muscles, bones, vascular endothelium, vascular smooth muscles, intestine, liver, and adrenal glands, where they act locally in a paracrine or intracrine manner [27,29]. In a study investigating the source of elevated estrogen after menopause, an increase in the expression of aromatase (the enzyme catalyzing estrogen biosynthesis) was detected in the subcutaneous abdominal adipose tissue of ovariectomized rats [30]. This finding coincides with another study, which concluded that the conversion of androstenedione to estrogen was higher in obese women [31]. Additionally, a cross-sectional study on postmenopausal women found a link between rising body mass index and circulating estrogens ($E_1$ and $E_2$) [32]. However, the contribution of extra-gonadal $E_2$ biosynthesis in different organ systems to the systemic levels of sex hormones remains debatable.

### 2.2. Biosynthesis of estrogens

The biosynthesis of estrogen takes place through a series of reactions catalyzed by a number of cytochrome P450 enzymes and different hydroxysteroid dehydrogenases [33]. It starts by the conversion of cholesterol to pregnenolone by cytochrome P450 cholesterol side-chain cleavage enzyme (CYP11A) [33]. Pregnenolone can either be converted to 17-hydroxypregnolone and consequently to dehydroepiandrosterone by 17α-hydroxylase (CYP17), or it can be converted to progesterone by 3β-hydroxysteroid dehydrogenase (3β-HSD) [33]. Both dehydroepiandrosterone and progesterone are then converted to androstenedione by 3β-HSD and CYP17, respectively [33]. Afterwards, the androstenedione can be either converted to testosterone by 17β-hydroxysteroid dehydrogenase (17β-HSD), or to $E_1$ by the aromatase enzyme (CYP19A1) [33]. Then, 17β-HSD catalyzes the conversion of $E_1$ to $E_2$ [33]. Fig. 1 demonstrates the steps of estrogen biosynthesis.

### 2.3. Estrogen receptors

Estrogens exhibit a wide range of physiological functions on different body tissues, including the cardiovascular, reproductive, skeletal, adipose, and central nervous systems [34–36]. $E_2$ exerts its functions through acting on the estrogen receptors (ERα and ERβ) which are encoded by the ESR1 and ESR2 genes, respectively [37]. In addition, $E_2$ also binds to a recently discovered G protein-coupled estrogen receptor 1 (GPER1) or G protein-coupled receptor 30 (GPER30), also known as the membrane estrogen receptor [25]. Table 1 lists the gene and protein designations for estrogen receptors.

The expression of ERs has been identified in a wide range of cells and tissues. ERα is primarily found in the mammary glands, uterus, ovary (thecal cells), bones, male reproductive organs (testes and epididymis), prostate (stroma), liver, and adipose tissue [37,38]. ERβ is present in the prostate (epithelium), bladder, ovary (granulosa cells), colon, adipose tissue, and immune system [37,38]. In addition, both ERα and ERβ are markedly expressed in the cardiovascular and central nervous systems [37,38]. Within the cardiovascular system, ERα and ERβ are expressed in endothelial cells, vascular smooth muscle cells, and a variety of cardiac tissue, including cardiomyocytes, and cardiac fibroblasts [18,28]. Stained human renal biopsies showed that ERα is mainly expressed the renal glomeruli and tubules [39], while both ERα and ERβ are expressed in the kidney proximal tubule [40]. According to several studies on rodents and humans, GPER1 is ubiquitously expressed within the reproductive system [41], cardiovascular system [42], renal system [43], brain [44], adrenal glands [45], adipocytes [46], and bones [47].

### 2.4. The cardio-renal protective effect of estrogen

Postmenopausal women have a higher risk of CVD than premenopausal women [48,49]. The protection against CVD prior to menopause has been largely attributed to estrogens, which have a variety of advantageous effects on arterial walls, cardiac and renal functions, as well as tissue regeneration [18]. A direct effect of estrogen involves its vascular actions regulating vascular tone, cell proliferation, and migration [50]. Estrogens also act directly on cardiomyocytes in a favourable way [50]. Besides, estrogen can exert an indirect cardioprotective effect through regulating the lipid profile and reducing the coagulating factors and reactive oxygen species [51]. For instance, a comparative study showed that postmenopausal women had considerably higher serum total cholesterol, triglyceride and low density lipoprotein cholesterol levels than premenopausal women, which may be related to reduced estrogen levels [52]. Estrogen also inhibits low-density lipoprotein transcytosis by reducing the expression of endothelial scavenger receptor class B type 1 [53].

The vascular and cardiac protective effects of estrogens are exerted via ERα, ERβ and GPER1 [16]. $E_2$ binds to ERα and ERβ receptors, leading to activation of classical and non-classical pathways [54]. Previous studies conducted on ERα-knockout mice demonstrated the cardioprotective effect of ERα in cardiomyocytes in both males and females by improving the effectiveness of cardiac repair following a cardiac injury, such as ischemic-reperfusion injury or induced myocardial infarction (MI) [55,56]. ERα has been shown to contribute largely to the vasoprotective effects of $E_2$ as well [18]. In male and female transgenic mice model, the overexpression of ERβ in cardiomyocytes improved the survival

and the cardiac function, and decreased maladaptive remodeling following MI [57]. In a study on ERβ-deficient mice subjected to MI, there was an increase in mortality and exacerbated clinical and biochemical markers associated with heart failure (HF) [58]. In addition, ERβ activation rescues pre-existing severe HF in male mice by inducing cardiac angiogenesis, suppression of fibrosis, and restoration of hemodynamic parameters [59].

Emerging evidence points to the role of GPER1 in mediating cardiovascular protection and maintaining blood pressure [60]. Through activation of GPER1, estrogen can reduce ischemia and preserve heart function [61]. Kabir et al. found that GPER1-knockout hearts of male mice failed to demonstrate cardio-protection following ischemic-reperfusion after treatment with $E_2$, indicating the function of GPER1 in ameliorating cardiovascular disorders [62]. GPER1 activation also reduces cardiac myocyte hypertrophy and wall thickness and enhances myocardial relaxation in hypertensive female mRen2. Lewis rats placed on a high-salt diet [63]. The activation of GPER1 with G1 (a selective GPER1 agonist) demonstrated cardio protective effects against doxorubicin-induced cardiotoxicity in male rats [64], and reversed cardiopulmonary dysfunction in ovariectomized rats [65]. Recent studies showed that the infusion of G1 into the renal medulla promotes $Na^+$ excretion via an endothelin-1-dependent pathway in female, but not in male rats [66,67]. Additionally, GPER1 activation with G1 lowers blood pressure in ovariectomized rats [66]. These findings pave the way for additional clinical testing of novel GPER1 agonists for the treatment CVD in females following endogenous estrogen loss, perhaps removing the negative side effects of estrogen replacement therapy.

In terms of kidney function, women experience a slower decline in renal function than men, which supports the hypothesis that sex hormones play a significant role in the prevalence and severity of cardiovascular and kidney disorders [68]. $E_2$ was found to preserve kidney function and prevent the development of glomerulosclerosis in the female rat remnant kidney model [69]. A number of studies have also shown that targeting ERs signaling pathways might have protective effects against certain renal disorders [70], including acute kidney injury [71,72] and CKD [73,74]. For instance, $E_2$ was found to ameliorate glomerulosclerosis and tubulointerstitial fibrosis in the ageing Dahl salt-sensitive rat [73]. In addition, the activation of GPER1 via G1 demonstrated a protective effect against proteinuria and albuminuria in female Dahl salt-sensitive rats [75]. On the other hand, Mankhey et al. concluded that $E_2$ deficiency worsens the kidney function in diabetic ovariectomized female rats, which is antagonized by $E_2$ replacement therapy [76]. $E_2$ deficiency increases the risk of renal pathology specially in diabetic patients through the overactivity of renin angiotensin aldosterone system (RAAS) [77].

### 2.5. The RAAS-estrogen interactions

The RAAS plays a central role in the regulation of the cardiovascular and renal systems. It is a major contributor to the maintenance of blood pressure and body fluid homeostasis [78]. Hyper activation of the RAAS is associated with cardiovascular disorders and their complications, such as HF, hypertension, cardiac hypertrophy, atherosclerosis, coronary heart disease, myocardial dysfunction, and renal failure [79]. The inhibition of RAAS by

angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor type 1 (AT1) blockers were shown to improve cardiac and renal-related conditions [79].

The RAAS is composed of a series of enzyme–catalyzed interactions between its components, which regulate cardiovascular and renal function. The main precursor of the RAAS (angiotensinogen) is produced by the liver [80]. Angiotensinogen is cleaved by the renin secreted by the kidney to produce angiotensin I (Ang I), which is then hydrolyzed by ACE in the lungs to produce angiotensin II (Ang II) [80–82]. The latter acts on the cell-surface G protein-coupled receptor (AT1), causing an increase in blood pressure through different mechanisms, most importantly, vasoconstriction and aldosterone secretion [81,82]. Ang II also binds to cell surface type II receptors (AT2) to induce vasodilation, natriuresis, and nitric oxide generation [81,82]. Meanwhile, a biologically active heptapeptide Ang-(1−7) can be produced in response to the degradation of Ang I by endopeptidases or the degradation of Ang II by angiotensin-converting enzyme 2 (ACE2) [83]. Ang-(1−7) interact with AT2 receptors and Mas G protein-coupled receptors (MasR), which are present in the heart, vasculature, and kidneys, promoting vasodilation, nitric oxide production, and increased arterial baroreflex sensitivity [84]. Similar cardioprotective effects occur when Ang-(1−7) interacts with AT2 receptors [84]. In animal models, it has been shown that Ang-(1−7) has antihypertensive, antifibrotic, antiarrhythmogenic, and antithrombotic effects [84]. In the context of this review, we will pay more attention to the impact of estrogens on the components of the RAAS.

The angiotensinogen mRNA is expressed in several body organs including the heart, vascular system, kidneys, and adrenal glands [79]. The levels of angiotensinogen are generally higher in premenopausal women than in postmenopausal women [79]. In addition, oral estrogen replacement therapy considerably increases plasma angiotensinogen levels, which counteracts the beneficial cardioprotective effects of estrogen [79]. However, evidence indicates that plasma renin is lowered by estrogen due to the suppression of renin secretion from renal juxta-glomerular cells [79]. This may account for the cardiovascular protective effects of estrogen.

The effect of estrogen replacement therapy on Ang II levels is unclear. A study showed a protective effect against hypertension through estrogen-mediated reduction in the plasma levels of Ang II and amplification of the vasodilatory effect of Ang-(1−7) [85]. Estrogen also appeared to protect the heart against hypertrophy and fibrosis by demonstrating an inhibitory effect on Ang II-induced fibroblast-mediated remodeling and proliferation [86,87]. On the contrary, another study showed an increase in Ang II levels, which can be attributed to the suppression of RAAS by negative feedback [88]. Furthermore, a study revealed that Ang II induces albuminuria in male, but not female, rats during treatment with an ACE inhibitor [89]. Additional studies are needed to identify how estrogen dosing, route, and duration of administration and hormonal status of the recipient may impact key components in the RAAS system.

The expression of AT1 receptors in vascular smooth muscles is downregulated by estrogen, which can contribute to the association between estrogen deficiency and the incidence of CVD in post-menopausal women [90,91]. In the adrenal glands, estrogen reduces AT1

receptors and minimizes Ang II-induced aldosterone secretion [92]. It is thought that the activation of AT2 receptors will counteract the stimulation of AT1 receptors [93]. In estrogen-treated ovariectomized mice, the expression of AT2 receptors in the kidneys is increased, resulting in a reduced AT1/AT2 receptor ratio that favors vasodilation [81,94]. This may contribute to the preventive effects of estrogen on the progression of renal disease.

Estrogen was also found to regulate ACE. In ovariectomized rats, estrogen therapy reduces ACE activity in the plasma, kidneys, and aorta [85]. However, studies in ovary-intact female rats showed that during pregnancy, when estrogen level is elevated, ACE2 expression and renal and urinary Ang-(1−7) levels are increased [95,96]. Similarly, $E_2$ pro motes the production of Ang-(1−7) in human endothelial cells via ERα, which induces $E_2$-mediated vasodilatory effects [97]. Meanwhile, the expression of MasR varies between sexes in the renal system [98,99]. In comparison to males, the kidneys of female rats have greater levels of MasR mRNA, which can be attributed to sex hormonal factors [98,99].

Aldosterone is known to cause several types of tissue damage, including cardiac hypertrophy, cardiac fibrosis, proteinuria, vasoconstriction, and salt retention [79]. A number of studies showed that estrogen decreases Ang II-induced aldosterone secretion [100].

Thus, there are two major arms in the RAAS that has opposing actions. The first arm is the Ang II–ACE–AT1 that favors vasoconstriction and is known as the hypertensive axis, while the second arm is the Ang-(1−7)–ACE2–MasR/AT2 that favors vasodilation and is recognized as the antihypertensive axis [78,83]. Overall, estrogen promotes the production of angiotensinogen while inhibiting the production of renin and ACE. Also, the expression of AT1 is reduced by estrogen, while AT2 expression is increased. Therefore, estrogen shifts the balance of the RAAS towards the Ang-(1−7)–ACE2–MasR/AT2 receptor pathways, promoting cardiovascular protection [78]. Conversely, estrogen declination after menopause upregulates the vasoconstrictive arm of the RAAS [77]. However, the specific mechanisms by which estrogens interact with the RAAS to provide cardio-renal protection are still not fully understood and require further investigations. Fig. 2 illustrates the RAAS pathway and how estrogen modulates RAAS components favoring cardiovascular and renal protection.

### 2.6. Estrogen in ageing

With ageing, fluctuations in endogenous estrogen production as well as ERs expression start to emerge [101]. The expression of ERs is influenced by ageing in a tissue- and sex-specific manner, which may provide insight on the pleiotropic effects of estrogen on the cardiovascular system [43]. Further, this age-related change in the expression of ERs can be affected by illness and hormonal exposure, which consequently affect the response to estrogen [102,103].

In the context of CVD, the fall in estrogen levels accompanied by the alterations in ER expression and/or signaling brought on by ageing, plays a role in the reduced ability of estrogen to protect the arteries, which might be associated with cardiovascular and renal disorders [18]. For instance, ERs are lower in atherosclerotic human coronary arteries compared to normal human coronary arteries, regardless of menopausal state [104]. In a comparative study using a small sample of postmortem coronary arteries, the expression of

ER in vascular smooth muscle cells in postmenopausal women is lower than premenopausal women [104]. Gavin et al. reported a 30% reduction in the expression of ERα in endothelial cells during the early follicular (low estrogen) phase compared to the late follicular (high estrogen) phase of the menstrual cycle [105]. Similarly, the expression of ERα is 33% less in endothelial cells in postmenopausal women compared with the late follicular phase of the menstrual cycle in premenopausal women [105]. Animal studies also showed that endothelial ERα mRNA and protein expression decline after prolonged hypoestrogenic activity and is restored by estrogen replacement therapy [106]. Recently, Connelly et al. suggested that reduced estrogen levels cause a change in ERα:ERβ receptor ratios [103]. Meanwhile, the protein abundance of ERα and ERβ is slightly reduced with age in the aorta of female spontaneously hypertensive rats [107]. In a study conducted by Gurrala et al. to compare the transcript levels of murine ERs within the cardiovascular and renal systems across age and sex, it was revealed that the cardiac ERα mRNA transcript level is reduced in aged female mice compared to middle-aged females [43]. However, the level of cardiac ERα mRNA in male mice is not age-dependent [43]. Renal GPER1 increases with age only in female, but not male, mice; whereas cardiac GPER1 increases in both sexes with age [43]. Notably, other organ systems elicit changes in ER expression with ageing as well. For example, Arimoto et al. reported that ERα, but not ERβ, is increased with age in rat cortical astrocytes [108]. Whereas, the expression of ERα declines in the hippocampus with advancing age, causing a decrease in cognition [109]. Additional studies are required to determine the age-related changes in ER signaling and its role in the development of CVD.

## 3. Aromatase enzyme

The aromatase enzyme, alternatively known as estrogen synthase, is a mono-oxygenase that belongs to the cytochrome P450 family and is encoded by the CYP19A1 gene [33]. This enzyme catalyzes the demethylation of carbon 19 in androgens causing their aromatization into 18-carbon estrogens [110]. Androstenedione, testosterone, and 16-hydroxytestosterone are the physiological substrates of aromatase, which are then transformed into $E_1$, $E_2$, and $E_3$, respectively [111]. Collectively, the synthesis of estrogen is catalyzed by the aromatase enzyme, which converts endogenous androgens into estrogens [111].

### 3.1. The mechanism of aromatization

The aromatization process advances through a number of steps elaborated in Fig. 3. First, the methyl group at C19 in androstenedione is hydroxylated to produce 19-hydroxyandrostenedione, which is then followed by a second hydroxylation reaction to produce 19-dihydroxyandrostenedione [112,113]. The latter is then dehydrated to 19-oxoandrostenedione [112,113]. Finally, the steroid ring-A is subjected to oxidative cleavage of the C10-C19 bond followed by release of formic acid, leading to the formation of estrogen [112,113].

### 3.2. Distribution of aromatase

Estrogens are produced by gonadal and extragonadal sites. Gonadally and extragonadally-driven estrogens share the same chemical structure and biological activity, but differ in their metabolic pathways of synthesis [29]. Extra-gonadal estrogens are produced when C19

precursors are supplied to any tissue that expresses aromatase [29]. Noteworthy, aromatase is primarily produced by ovarian granulosa cells in premenopausal women and adipose cells in postmenopausal women [114].

On the gonadal level, aromatase is expressed in both ovaries and testis. In the ovaries, aromatase expression is limited to differentiated preovulatory granulosa cells and luteal cells, and it is not expressed by undifferentiated granulosa cells in preantral follicles [115]. The follicle-stimulating hormone stimulates the growth and maturation of preantral follicles to the preovulatory stage, and the differentiation of granulosa cells, inducing the activation of aromatase [115]. Aromatase is downregulated after ovulation as granulosa cells develop into luteal cells [115]. Meanwhile, the detection of high amounts of estrogens in the male semen can be explained by the expression of aromatase in different testicular cells. Carreau et al. reported the presence of physiologically active aromatase in Leydig cells, Sertoli cells, spermatocytes, spermatids, and ejaculated spermatozoa in males [116].

Aromatase is also highly expressed in the placenta of both human and non-human primates [117], as well as other extra-gonadal tissues including the thalamus, hypothalamus, and hippocampus, indicating that aromatase is expressed widely in numerous regions of human brain in both men and women [118]. Aromatase activity has also been reported in stromal cells and adipocytes [119]. In bone tissue, aromatase has been identified within the human fetal osteoblastic cell line (SV-HFO) [120], and human osteoblasts [121]. The human hepatocellular carcinoma cells and HepG2 hepatoma cells showed increase in estrogen biosynthesis upon treatment with androgen precursors such as testosterone or androstenedione, indicating elevated aromatase activity [122]. Western blotting and immunohistochemistry showed that aromatase is expressed in the adrenal cortex as well as in adrenocortical tumors [123,124]. In addition, aromatase activity was demonstrated by $^{3}[H_2O]$ assay and gas chromatography-mass spectrometry in the parietal cells of the gastric mucosa [125]. It has also been previously reported that aromatase is expressed in epidermal keratinocytes and dermal fibroblasts [126,127]. In situ, hybridization revealed the presence of aromatase in human vascular smooth muscle cells but not in endothelial cells [128]. In men, aromatase is also expressed in the prostate [129]. Although extra-gonadal estrogen is synthesized in small amounts, its concentration is high enough to exert a biological effect locally [29]. Therefore, the disruption of aromatase homeostasis, accompanied by a disturbance in estrogen levels, will result in organ-specific effects.

### 3.3. Disruption of aromatase homeostasis

Both high and low levels of aromatase, and consequently high and low levels of estrogen, can cause a wide range of diseases and side effects [130]. Aromatase or estrogen excess-driven pathologies include breast, prostate, lung, gastric, and hepatic cancers, polycystic ovary syndrome, endometriosis, obesity, short stature, male hypogonadism, gynecomastia, and testicular hypertrophy [130–132]. Aromatase or estrogen deficiency-induced pathologies include cardiovascular problems [36, 133], osteoporosis [36,130], hot flushes [134], vaginal dryness and vaginal atrophy [134], skin ageing, thinning and pigmentation [135, 136], schizophrenia [130], Alzheimer’s disease [130], depression [137], insomnia [134],

neuropathies [36], and elevated aldosterone levels [138,139]. Fig. 4 illustrates the sites of aromatase expression and estrogen disturbance-related effects.

### 3.4. Regulation of aromatase enzyme

Aromatase enzyme is highly expressed in the ovarian granulosa cells [140]. The expression of aromatase is mainly induced by the follicle stimulating hormone which activates the transcription factor GATA4 that afterward activates other kinases, including ERK1/2, PKA, and PI3K [141]. Cyclic adenosine monophosphate (cAMP) is also involved in the transcription of aromatase [142]. In addition, it has been shown that the transcription of cardiac aromatase was stimulated by the administration of $E_2$ therapy that can bind to ER to form a dimer which translocate into the nucleus where it can bind directly to the estrogen responsive element site on the aromatase gene (CYP19A1) [143]. $E_2$ can also act indirectly by stimulating transcription factors [143].

## 4. Aromatase inhibitors (AIs)

### 4.1. Discovery of AIs

Historically, oophorectomy and adrenalectomy have been used to treat breast cancer [144]. The anti-epileptic medication, aminoglutethimide, was found to reduce the production of adrenal steroid hormones by blocking cytochrome P450 enzymes [145]. It was then recommended as a potential medical substitute to adrenalectomy for the treatment of breast cancer [146,147]. Later, it was discovered that the key mechanism of aminoglutethimide was the suppression of aromatase enzyme, which subsequently leads to a reduction in estrogen levels [148,149]. Aminoglutethimide was recognized as the first-generation AI [114]. In 1981, the effect of using 4-hydroxy-androstenedione (4-OH-A) against breast cancer in post-menopausal women was reported [150, 151]. By the middle of the 1980 s, 4-OH-A was named formestane and was recognized as the first selective AI against breast cancer [152]. Formestane is considered as a second-generation AI [114].

Currently-used AIs (shown in Fig. 5) are classified into irreversible steroidal inhibitors (exemestane) and reversible non-steroidal inhibitors (anastrozole and letrozole) [153]. These AIs are nominated as third-generation AIs [114]. The third-generation AIs have an advantage over the first and second generations as they are well tolerated and highly selective for the aromatase enzyme [154]. In addition, third-generation AIs outperform the first- and second-generation AIs in terms of clinical benefit and near-complete specificity in clinical application [155]. However, long-term adverse effects of these drugs, such as skeletal and cardiovascular problems, must be carefully monitored [155].

### 4.2. Uses and side effects of AIs

AIs are currently approved by the United States Food and Drug Administration (FDA) for clinical use against ER-positive breast cancer in postmenopausal women [152,155]. However, AIs are not yet FDA-approved as risk-lowering agents in women who have not been diagnosed with breast cancer [156]. Although AIs demonstrated potential role against other estrogen-dependent conditions, their use is not yet FDA-approved. For instance, AIs showed therapeutic efficacy in improving endometriosis-associated pain [157–159], but their

use for endometriosis is still considered off-label [160]. Similarly, a case of male breast cancer responding to a combination of letrozole and palbociclib was reported [161]. Yet, AIs are not FDA-approved for male breast cancer [161].

Given that AIs work by suppressing the aromatization of androgens to estrogens, causing reduction in the estrogen level in the ovaries and peripheral organs [114,162], they reduce the favorable effects of estrogen on lipid profile and bone health [158]. The most common side effect associated with AIs is the joint pain and stiffness [158], which is probably associated with the suppression of cartilage-protective effect of estrogen [163]. Other side effects of AIs include hot flashes, mood disturbances, skin ulcers, and liver function abnormality, which are normally associated with the gradual decline in ovarian estrogen production after menopause [164].

The reduction in circulating estrogens caused by AIs, and subsequently, the decrease in estrogen-mediated protective effects on the cardiovascular system, may potentially lead to an increased risk of unfavorable cardiovascular events [157,158]. Indeed, several studies found that AI users had a higher incidence of adverse CVD outcomes, but the findings are not yet universally accepted [165]. In the next sub-section, we will discuss a number of meta-analysis studies analyzing randomized controlled trials (RCTs) and cohort studies. These studies report cardiovascular events associated with AIs vs. a comparator.

### 4.3. Controversies regarding the cardiotoxicity of AIs

Due to the documented role of estrogen in developing breast cancer, treatment options including ER blockers such as tamoxifen (TAM) or AIs [162] have been introduced as effective therapeutic options against invasive ER-positive breast cancer in postmenopausal women [166]. The use of AIs was evaluated in three different settings: (i) monotherapy/upfront therapy (AIs instead of TAM), (ii) sequential therapy (TAM switched to AIs or vice versa), and (iii) extended therapy (AIs following five years treatment with TAM) [162]. Although TAM is the gold standard breast cancer therapy, a shift from TAM to AIs in the management of ER-positive breast cancer has occurred [166]. On the other hand, some studies reported that AIs are associated with greater incidence of cardiovascular events compared to TAM. Yet, the increased risk of cardiovascular events is still unclear whether it is due to actual cardiac toxicity of AIs or due to the potential cardioprotective effect of TAM [162].

TAM appeared to have positive cardioprotective effect throughout different mechanisms. Particularly, TAM reduces acetylcholine-induced vasoconstriction and potentiates adenosine-induced vasodilatory response, which thereby reduces blood pressure and coronary artery disease in ovariectomized spontaneously hypertensive rats, pointing to potential beneficial actions of TAM on coronary vascular health after menopause [167]. TAM has also demonstrated lipid-lowering effects, which is one of the prominent factors of protection against developing CVD. A study on postmenopausalpatients with early breast cancer showed that TAM reduces the total cholesterol and low-density lipoprotein cholesterol levels while it does not affect high-density lipoprotein cholesterol [168]. A recent study also affirmed the favorable effect of TAM on lipid profile and ameliorating dyslipidemia [169]. Of note, TAM is a selective ER modulator that elicits antagonistic

activity against ERα and ERβ, however, it has been shown to elicit agonistic activity towards GPER1 [170]. Whether GPER1 agonistic activity contributes to the protective actions of TAM remains to be tested.

**4.3.1. Meta-analyses showing significant increase of CVD with AIs—**A number of meta-analysis studies reported an increase in the cardiovascular events associated with the use of AIs vs. a comparator. In general, the studied population in the clinical trials consisted of postmenopausal women with ER-positive breast cancer. Amir et al. conducted a meta-analysis on seven RCTs comparing AIs with TAM in postmenopausal women with early-stage breast cancer [171]. Data were extracted from two trials evaluating monotherapy with AIs vs. TAM, four trials evaluating switching from TAM to AIs vs. TAM, and one trial evaluating switching from TAM to AIs vs. AIs [171]. The findings revealed that only using AIs vs. TAM or switching from TAM to AIs vs. AIs showed a statistically significant association between AIs and CVD [171]. In addition, the pooled analysis of the data for all three treatment settings showed that the use of AIs for a longer duration was related to a significant increase in the risks of acquiring CVD compared to short duration of AIs or the use of TAM [171]. One meta-analysis study revealed that AIs used in monotherapy and sequential therapy settings are correlated with higher incidence of cardiovascular events when compared with TAM [172]. A meta-analysis conducted by Khosrow-Khavar et al. reported that the pooled analysis of eight RCTs comparing AIs (monotherapy) vs. TAM and four RCTs comparing AIs vs. TAM followed by AIs (sequential therapy), showed an elevated risk of CVD associated with the use of AIs [173]. Goldvaser et al. collated seven RCTs in order to compare AIs (extended therapy) to placebo or no treatment [174]. The pooled analysis of the included studies reported a significant increase in the likelihood of developing cardiovascular events with the extended AIs therapy [174]. In a recent meta-analysis, the findings revealed that patients receiving AIs (monotherapy or sequential therapy) vs. TAM alone or TAM followed by AIs, were at greater risk of developing cardiovascular events [175].

Recently, Yoo et. al conducted a meta-analysis of twenty five studies to investigate the CVD side effects associated with AIs and to evaluate the relation between AIs and the changes in lipid profile in adult female breast cancer patients above 19 years old [176]. By comparing the post-AIs lipid profile to the baseline group after six months of treatment, a significant reduction in high-density lipoprotein cholesterol was observed [176].

**4.3.2. Meta-analyses showing non-significant increase of CVD with AIs—**Despite the findings of the above studies that support the correlation between the use of AIs and cardiovascular events, some studies demonstrate statistically non-significant relationship between AIs and the occurrence of cardiovascular events. Yu et al. conducted meta-analysis study based on six RCTs, thirteen prospective cohort studies, and one retrospective cohort [177]. It was found that AIs were associated with an insignificant increase in the incidence of stroke, angina, MI, and HF in breast cancer patients compared to TAM [177]. Likewise, Sun et al. found that the pooled results of eight cohort studies revealed that there was no significant difference between AIs users and non-users in the incidence of MI, and HF [178]. Likewise, the combined analysis of four RCTs evaluating AIs (sequential therapy)

vs. TAM showed a non-statistically significant correlation between AIs and cardiovascular events [171]. In addition, some studies reported that the extended therapy with AIs is not associated with cardiovascular events [172,173, 175]. Further, the incidence of MI and HF was relatively higher in the AIs group than TAM group, but this difference did not reach statistical significance [176].

This lack of consistency in the data obtained from meta-analyes on the cardiovascular toxicity of AIs can be attributed to multiple factors. There is substantial population heterogeneity since some studies included subjects from different countries. Studies also varied in the inclusion of subjects with or without history of CVD and differed in the follow-up time after treatment with AIs. Importanly, there were differences in how cardiovascular events were defined as some meta-analyses included cardiovascular-related risk factors such as hypertension and hypercholesteremia. Finally, methodological difference in the meta-analyses, such as the type of studies included whether RCTs or cohort studies, and whether AIs are compared to TAM, placebo or without a comparator, also contribute to variation in the findings.

### 4.4. AIs and renal toxicity

The impact of AIs on the renal system has not been sufficiently studied. There is a lack of RCTs that investigate the relationship between AIs and kidney function. However, a case of anastrozole-induced glomerulonephritis [179], and a case of letrozole-induced acute interstitial nephritis [180] were previously reported. Animal studies also showed an increase in the biomarkers of renal proximal tubular injury by chronic aromatase suppression with anastrozole in female rats [181]. The levels of urinary albumin and plasma urea were elevated in anastrozole-treated female rats fed a high salt diet [181]. Anastrozole increased the urinary excretion of the renal proximal tubule injury biomarker (kidney injury molecule-1), but the level of the glomerular injury biomarker (nephrin) was not elevated [181]. AIs can also induce renal toxicity by altering calcium reabsorption in the kidneys [182]. However, anastrozole attenuates diabetic renal disease in male rats as demonstrated by decreasing albuminuria, glomerulosclerosis, and tubulointerstitial fibrosis [183]. Because the former study was conducted on male rats, the results cannot be extrapolated to include females. In another study, letrozole administration in female rats resulted in a reduction in renal functions as well as micromorphological deteriorations [184]. This is due to the direct oxidative damage caused by letrozole and its metabolites [184]. In particular, letrozole causes a decrease in the expression of cytoprotective detoxification genes (nuclear factor erythroid 2-related factor 2, cytochrome-c, and caspase-3), an increase in hepatorenal lipid peroxides, and a decrease in glutathione and catalase enzyme [184]. Anastrazole treatment also produced similar results in female rats [185]. In light of these findings, further investigation is needed to determine if renal toxicity is a potential adverse effect of AIs.

## 5. Extra-gonadal aromatase and cardio-renal protection

A unique feature of extra-gonadally synthesized estrogens is being produced locally in concentrations high enough to exert local biological effects with limited systematic effects [29]. Despite the documented cardioprotective effects of estrogen, the use of estrogen-

replacement therapy as a cardioprotective agent is still controversial [16]. This is due to the fact that estrogens have major off-target effects which include increased risks of breast and endometrial cancer, as well as thromboembolisms and strokes [186]. However, evidence suggests that the regulation of aromatase enzyme activity and expression protects against cardiac and vascular damage [187]. The aromatase enzyme was found to be expressed in the coronary endothelium and has an effect on the cardiac function and structural modelling as a result of the localized conversion of androgens to $E_2$ in an acute MI male mouse model [187]. Bayard et al. also demonstrated the activity of aromatase enzyme using female rat arterial smooth muscle cells and bovine coronary endothelial cells in in-vitro models [188,189]. Another research revealed that aromatase activity is demonstrated in human arterial smooth muscle cells and therefore hypothesized that $E_2$ produced in vascular smooth muscle cells regulates cardiac contractility and vascular tone (autocrine activity) while stimulating nitric oxide production and angiogenesis in endothelial cells (paracrine activity) [128]. In order to investigate whether upregulation of cardiac aromatase expression could improve ischemic resilience, Bell et al. conducted a study on hearts from male transgenic aromatase-overexpressing mice (AROM+), using an expression vector for human P-450 aromatase [190]. The male AROM+ mice have lower testosterone and higher $E_2$ levels than wild-type male mice. Interestingly, ischemic contracture are attenuated in AROM+ hearts, suggesting that aromatase regulation modulates cardiac performance after ischemia [190]. Another recent study found that HF is associated with local deficiency of cardiac estrogen and downregulation of aromatase, thus suggesting that the restoring the transcript level of cardiac aromatase can protect against HF [191]. Taken together, the abovementioned information indicate a need for more investigation into the potential role of extra-gonadal aromatization and the importance of restoring cardiac aromatase and enhancing estrogen signalling in conferring cardio-renal protection.

## 6. Conclusion and future prospects

Aromatase is localized in gonadal and extra-gonadal sites in the human body and plays a pivotal role in estrogen biosynthesis. For instance, it is established now that the brain can synthesize estrogen, and that brain aromatase is crucial for neuroprotection [192]. In this context, we propose that estrogenesis within the cardiovascular and renal systems may function to provide cardio-renal protection as well. We argue that aromatase has a fundamental effect in cardio-renal protection through increasing the level of estrogen. In other words, aromatase can function as a component of androgen metabolism that directly supplies estrogen to cardiovascular tissues. Future studies are required to properly understand this complex relationship, and identify the role of aromatization in preserving cardiovascular and renal health.

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## Data availability

No data was used for the research described in the article.

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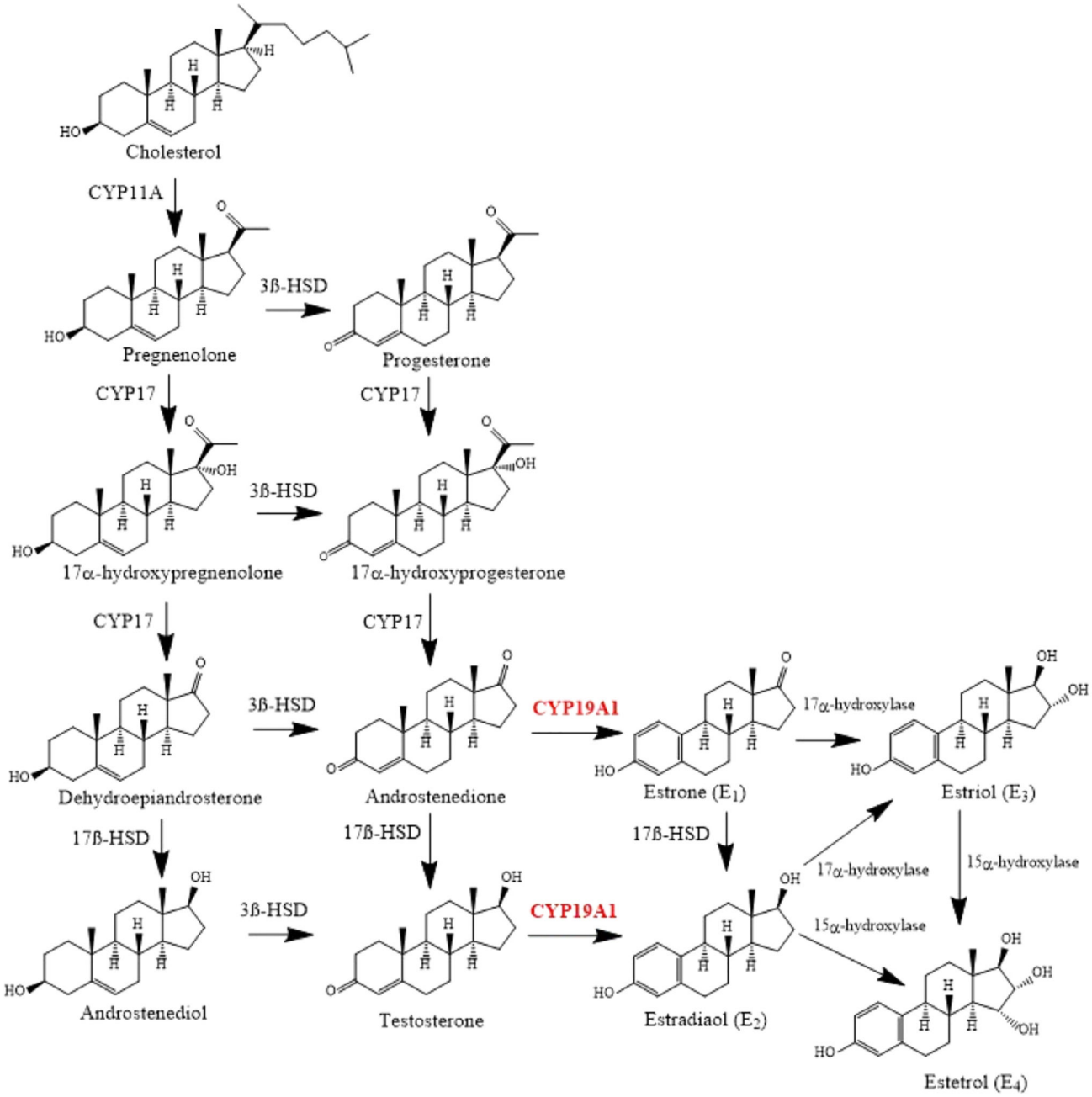


**Fig. 1.**
The Biosynthesis of estrogens. Created by Chemdraw Software.

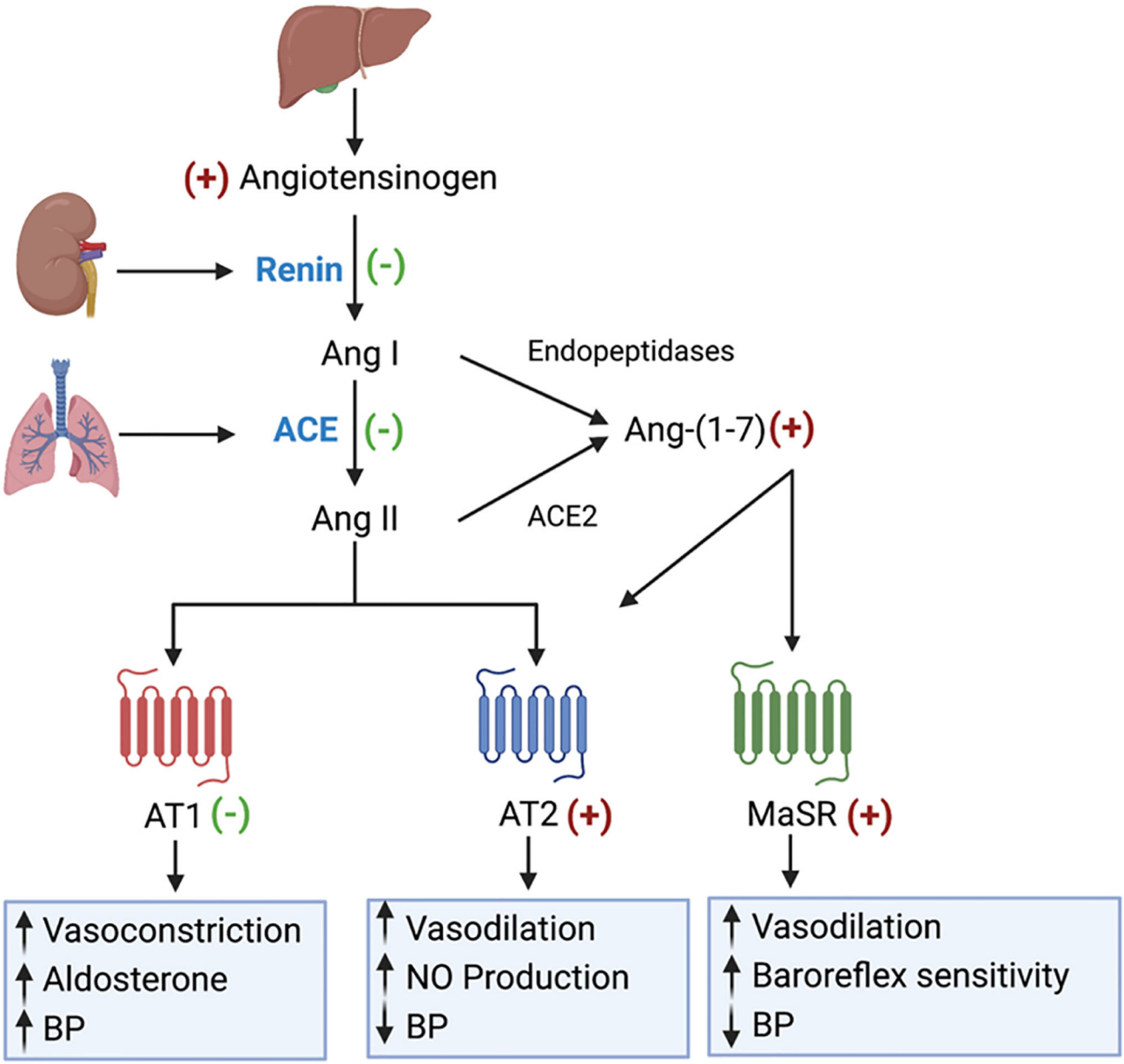


**Fig. 2.**

Overview of renin angiotensin aldosterone system (RAAS) pathways showing primary receptor-mediated cardiovascular effects and influence of estrogen on RAAS components. *ACE: angiotensin-converting enzyme, Ang I: angiotensin I, Ang II: angiotensin II, Ang (1 7): angiotensin 1–7, AT1: angiotensin II receptor 1, AT2: angiotensin II receptor 2, MasR: Mas receptor, (+) upregulation by estrogen, (-) downregulation by estrogen. Created in BioRender.com.

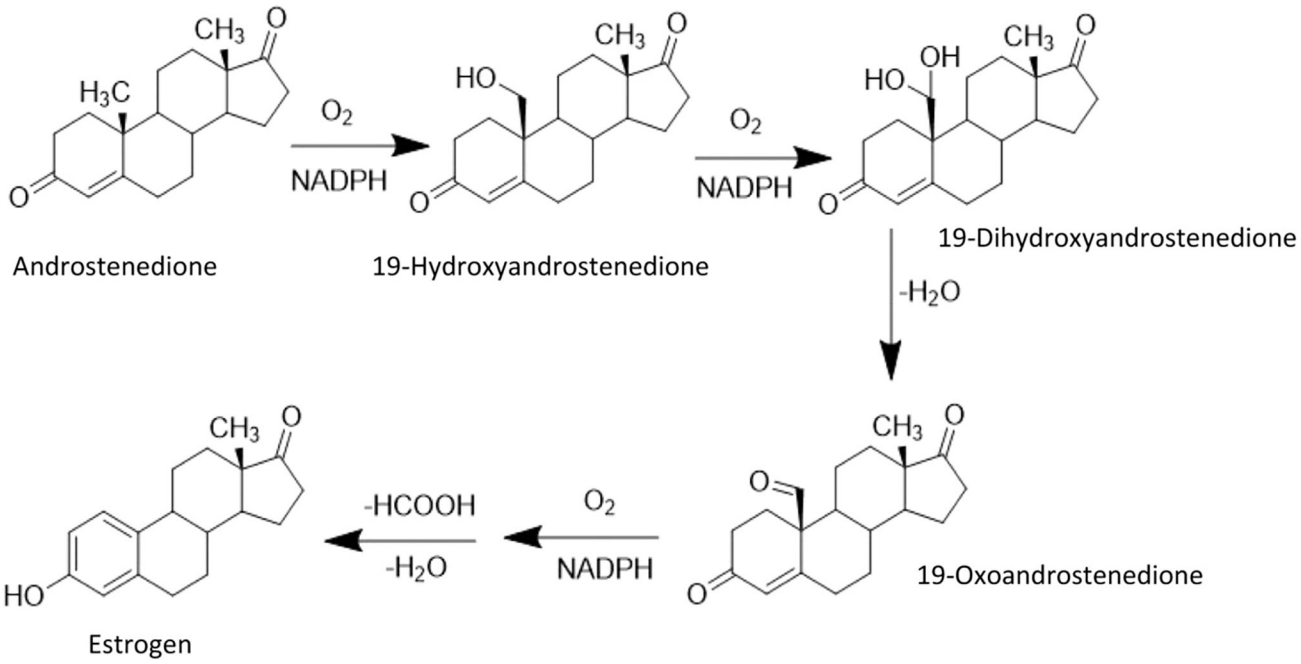


**Fig. 3.**
Biosynthesis of estrogen by aromatase. Created by Chemdraw Software.

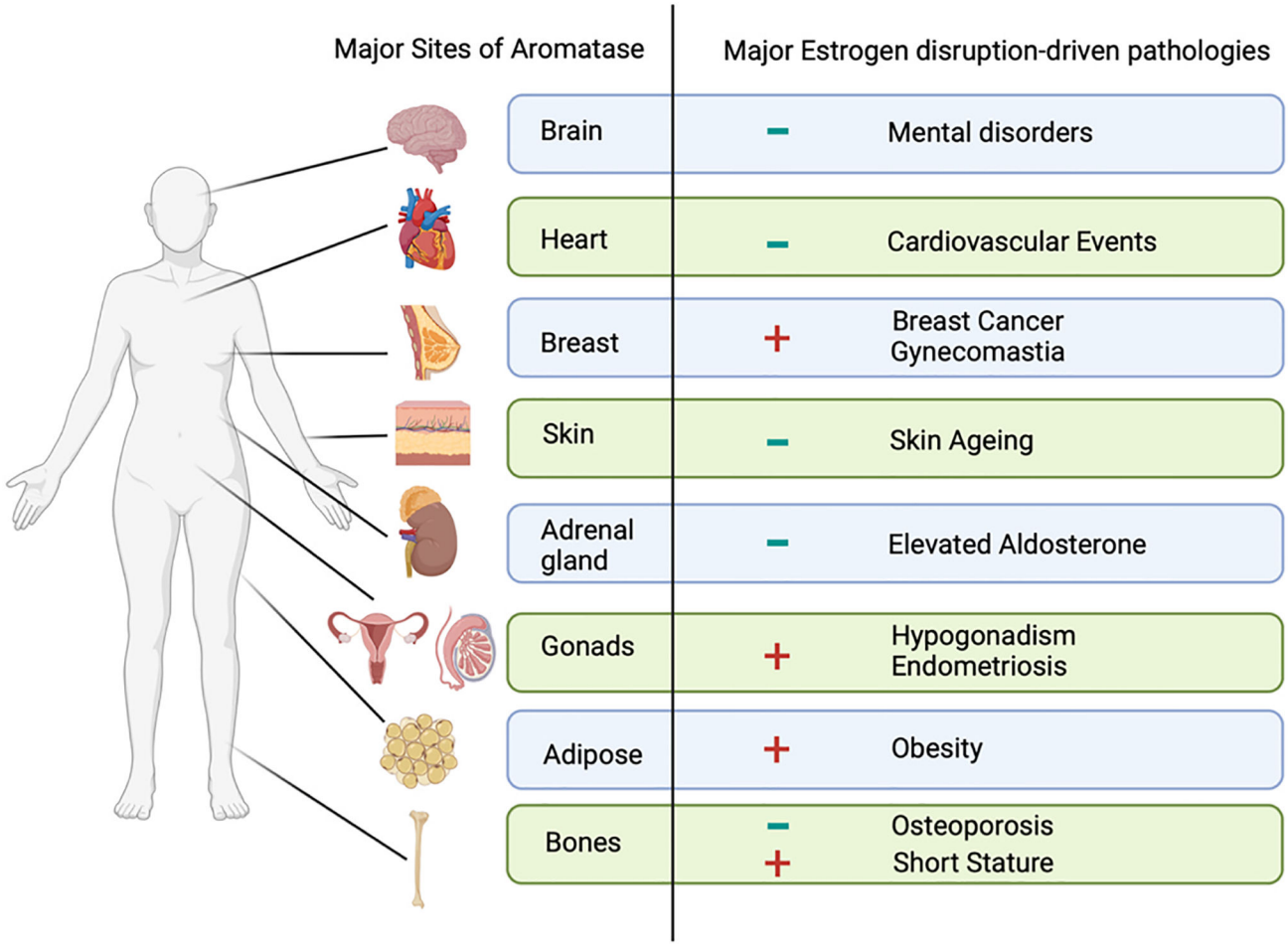


**Fig. 4.**

The major sites of aromatase and the associated estrogen-disruption pathologies. (-) estrogen deficiency, (+) estrogen surplus. Created in BioRender.com.

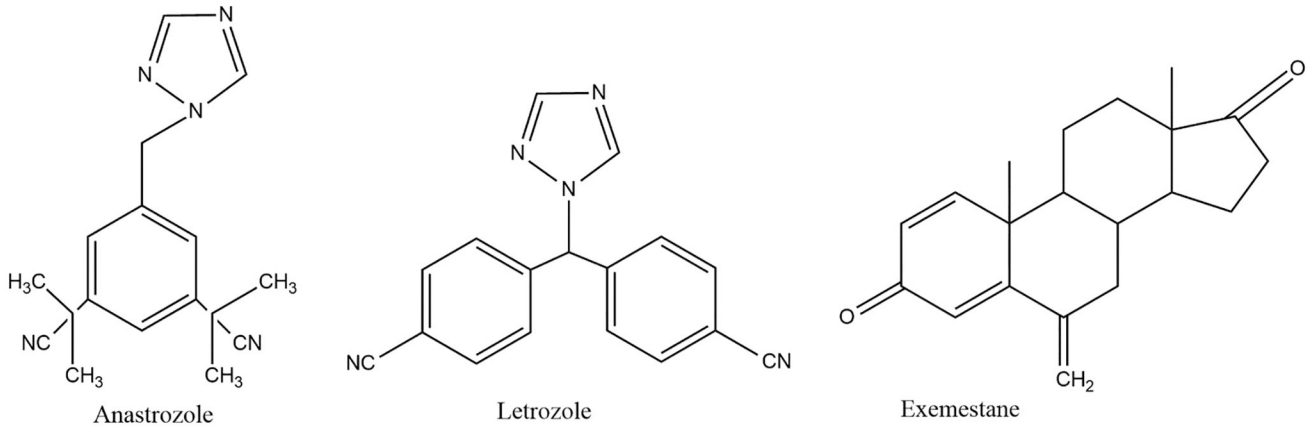


**Fig. 5.**
Third generation aromatase inhibitors. Created by ChemDraw Software.

**Table 1**

Protein, gene and HGNC ID designations for estrogen receptors.

| Protein | Gene | HGNC ID |
|---|---|---|
| Estrogen receptor alpha (ERα) | *ESR1* | 3467 |
| Estrogen receptor beta (ERβ) | *ESR2* | 3468 |
| G protein-coupled estrogen receptor 1 (GPER1) | *GPER1* | 4485 |