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Review Article

Role of estrogen receptors in cancer: a special emphasis on the therapeutic potential of estrogen receptor β

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ABSTRACT

Estrogen receptors are nuclear receptors that play a major role in both physiology and pathology. Estrogen receptor subtypes are currently divided into three groups: estrogen receptor alpha (ERα), estrogen receptor beta (ERβ), and G protein-coupled estrogen receptor 1 (GPER1 or formerly known as GPR30 or GPRx, a membrane-bound receptor). Overexpression of ERα and GPER1 are known to contribute to cancer, with ERα playing the most important impact. On the other hand, it is commonly acknowledged that ERβ inhibits ERα activity and has anti-cancer properties. As a result, the estrogen receptors ERα and ERβ are the most investigated, with ERα being recognized therapeutically as a therapeutic target for breast cancer. Unlike ERα, which must be blocked, ERβ is a target that has anti-cancer properties when activated. The potential anti-cancer efficacy of ERβ has been demonstrated in several pre-clinical and clinical investigations. In this review, we summarize the potential role of ERβ and ERβ agonists in various cancers.

Keywords:
ERβ, Lung cancer, Breast cancer, Prostate cancer, Skin cancer, Endometrial cancer, Bone cancer, Brain cancer, Blood cancer

1. INTRODUCTION

The nuclear receptor subfamily 3 (NR3A) of ligand-activated transcription factors 1 includes estrogen receptors (ERs)[1]. O'Malley et al., pioneered the work that established how ERs functioned as ligand-activated transcription in 2000[2]. Estrogen receptor subtypes are currently divided into three groups: estrogen receptor alpha (ERα), estrogen receptor beta (ERβ), and G-protein-coupled estrogen receptor (G-protein-coupled estrogen receptor) (GPER1 or formerly known as GPR30 or GPRx, a membrane bound receptor)[3]. ERα and ERβ are weakly attached to the nucleus and may disperse into the cytoplasm before being translocated back into the nucleus when bound to ligands[4]. This occurs by passive diffusion through the 'ever opened' central channel of the nuclear pore or active transport that is mediated by interaction of the nuclear localization sequences (NLSs) on the ERs with the NLS receptor-hsp90 complex[5]. As a result of this, NRs can regulate gene expression directly and indirectly and they are considered as transcription factors (TFs)[6]. GPER1 is a membrane-bound receptor[4] that cannot directly regulate gene expression but can do so indirectly by activating proteins that alter transcription factor activity[6]. These three ERs are found in distinct tissues and have varied functions, although having minor sex differences[7] and they perform different functions. For example, GPER1 regulates human neutrophil functions[8], and improves hippocampal synaptic transmission[3] while ERα and ERβ govern reproduction, mammary and bone growth, metabolic, and brain functions[9]. When estrogens (estrone or E1, estradiol or E2, estriol or E3) bind to these receptors, they perform physiological tasks[10]. Estrogens, or sex steroid-related hormones, were discovered by a German chemist Adolf Butenandt and colleagues in the 1920s and 1930s[11]. E1 and E3 are often considered weak estrogen and function via non-genomic signaling possibly via GPER1. While E2 is largely accepted to act via genomic signaling, i.e. via the activation of ERα and ERβ[10]. Thus, estrogen's physiological or pathological effects are mediated by these classic receptors, either directly or indirectly[12]. Interestingly, depending on the balance activities of ERα and ERβ in target tissues/organs, estrogen action can either be stimulatory or inhibitory[9]. Overexpression of ERα,

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along with estrogen stimulation, can result in breast cancer, endometrial cancer, venous thromboembolism, and autoimmune disorders[13]. In fact, through ERα, E2 promotes cell proliferation and tumor development[14]. In clinical practice, ERα inhibition is used to treat breast cancer. ERα inhibitors for breast cancer, on the other hand, can cause endometrial cancer by acting as an ERα agonist in the uterus. As a result, several pieces of research have concentrated on activating the ERα isoform, ERβ, to treat various types of cancer.

ERβ regulates several biological activities such as regulation of male sexual behavior[15], association and structural upkeep of the colon[16], mediate estrogens stimulatory effects on proliferation of granulosa cell[17], energy and glucose homeostasis[18], brain development[19], hierarchical social relationships[20], formation of multiple oocytes follicles (MOFs)[21], regulation of placental function and social learning-related food preference during human and animal pregnancy[22-23]. ERβ is also involved in pathological conditions such as muscle injuries, sarcopenia, and cachectic disease[24], delay in the onset of schizophrenia[25], global ischemia[26-27], dental caries[28], cancer[29], Alzheimer's disease[30-33], Parkinson's disease[32-35], trauma[32], acute bacterial meningitis[36], Leber's Hereditary Optic Neuropathy (LHON)[37], endometriosis[38], inflammatory bowel syndrome (IBS)[39]. ERβ also acts as a negative regulator of ERα under low levels of 17β-Estradiol (E2)[40]. These activities of ERβ may rely on the differential quantity of ERβ homodimer and heterodimer framed upon incitement by specific ligands[41]. ERβ heterodimerization with ERα prevents the ligand-induced transcriptional activity of ERα-ERE reporter gene[42]. Currently, the three classes of selective agonists of ERβ identified namely ERβ binder (ERbB-041): it binds 200-fold greater to ERβ than ERα; ERβ activator (MF101, liquiritigenin, nyasol): these bind to both ERα and ERβ in a similar pattern but cause gene activation only upon binding with ERβ; and ERβ binder/activator (DPN): it has a greater binding affinity and transcriptional activity for ERβ. These compounds could be used in the prophylaxis treatment of diseases related to menopause, such as breast cancer, hot flashes, and inflammatory disorders[43].

2. THE DEVELOPMENT OF ERβ AGONISTS: FROM STRUCTURE TO MECHANISM OF ACTION

The development of ERβ agonists and the elucidation of their mechanism of action have been focused on since the discovery of ERβ in 1996[44]. Naturally occurring compounds such as genistein show modest affinity for ERβ with 10-40 folds selective for ERβ when compared to ERα[45]. Similarly, other natural compounds such as liquiritigenin[46], calycosin[47], silymarin[48], toosendanin[49], and icaritin show modest effects on ERβ. These modest

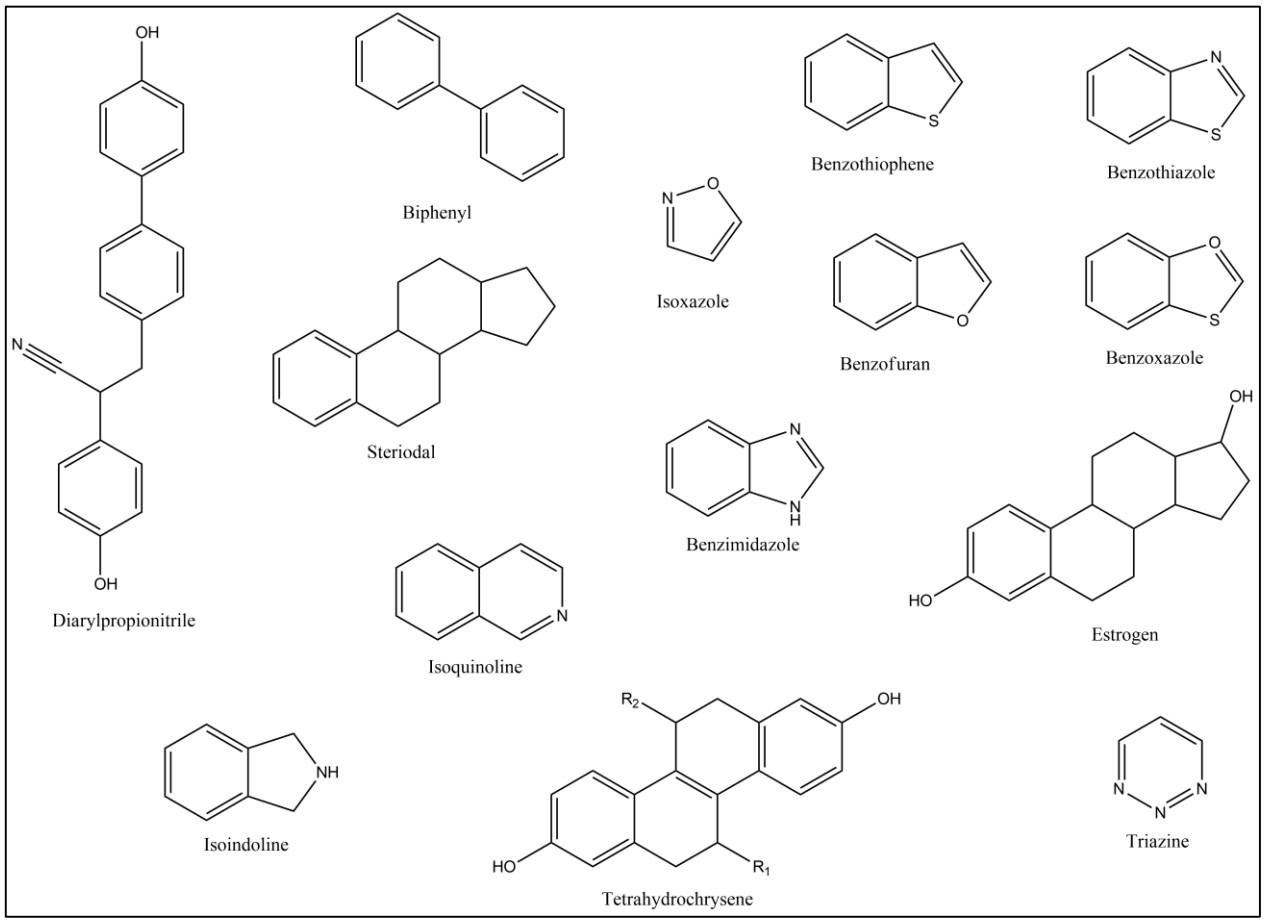


Figure 1. Examples of a few scaffolds that were employed for the design of ERβ agonists.

effects and selectivity of natural compounds are not enough to validate ERβ as a therapeutic target. For this reason, researchers have shifted to structure-based design for the design and development of highly selective and potent ERβ agonist[45]. The structure-based design focuses on the use of various scaffolds for enhancing ERβ selectivity. These scaffolds include biphenyls, tetrahydrochrysenes (THC), diarylpropionitrile (DPN) analogs, arylbenzothiophenes, isoxazoles, benzothiazoles/benzoxazoles, benzofurans, benzimidazoles, triazines, isoquinolines/ isoindolines, steroidal, and phytoestrogen analogs[45], Figure 1. Particularly for benzoxazole and benzofuran, two strategies were adopted to obtain a highly selective ERβ agonist. The first strategy is the manipulation of the relative orientation by constraining the bond and dihedral angles. The second strategy focus on inserting an sp2 or sp3 hybridized linker between the functional group and the benzofuran/benzoxazole ring system[45]. Other strategies for the development of ERβ include the modification of the scaffolds that compromise ligand-protein interactions. For example, Bryan and colleagues show that amino acids such as arginine 394 (Arg 394), glutamine 353 (Glu 353), histidine 535 (His535) of ERα, and arginine 346 (Arg 346), glutamine 305 (Glu 305), histidine 475 (H475) of ERβ are critical for the of development of ERβ agonist. They demonstrated that ligands that compromised either interaction are expected to be an agonist for ERα or ERβ[50]. Similarly, targeting methionine 336 (Met 336) and isoleucine 373 (Ile 373) of ERβ, the amino acids that are substituted by leucine 384 (Leu384) and methionine 421 (Met 421) in ERα is another strategy for the development of ERβ agonist. According to Wilkening and colleagues, ERβ agonists have been shown to form a van der Waals contact and hydrophobic interaction with Met 336 and Ile 373 of ERβ respectively. Whereas, these interactions with the Leu384 and Met 421 of ERα were not observed[51]. Examples of few ERβ agonists that have been explored in cancer are listed in Table 1.

Table 1. Few examples of ERβ agonists, their structure and mechanism of actions.

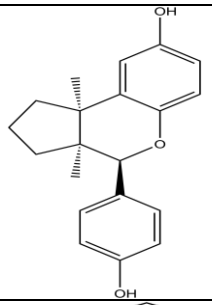
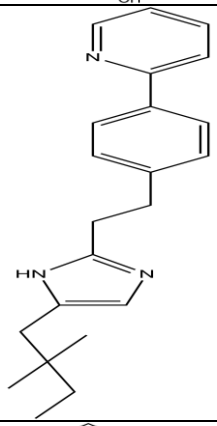
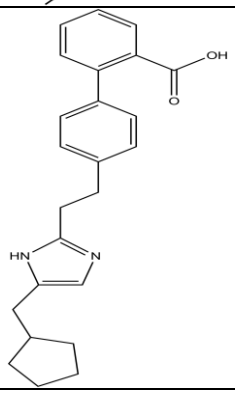
No	Name	Structure	Mechanism of action	Indication	Reference
1	LY500307		Induce the release of IL-1β by tumor cells	Lung cancer	52
2	BAG 1		Secretion of TNF-α and inhibition of tumor growth by activation of natural killer cells within tumor	Breast cancer	53
3	BAG 2		Secretion of TNF-α and inhibition of tumor growth by activation of natural killer cells within tumor	Breast cancer	53

Table 1. Few examples of ERβ agonists, their structure and mechanism of actions. (cont.)

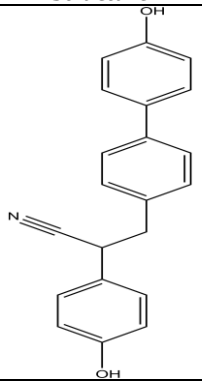
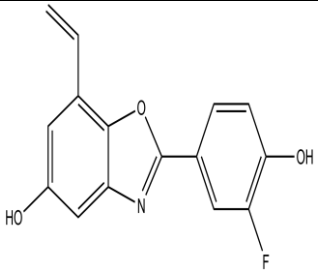
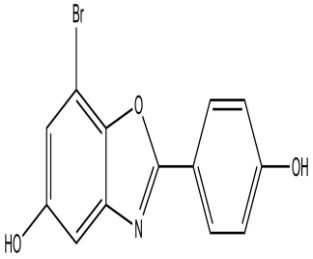
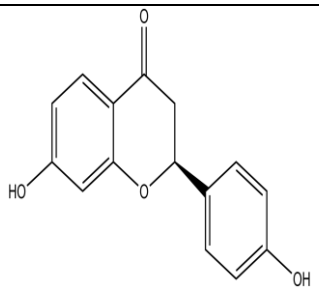
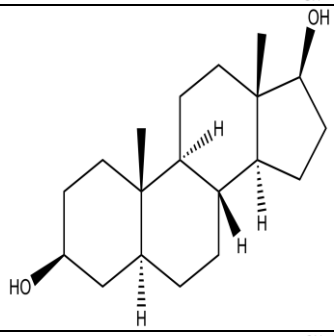
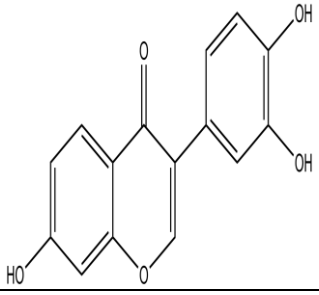
No	Name	Structure	Mechanism of action	Indication	Reference
4	DPN		Suppress ERα-mediated cell proliferation	Breast cancer	54,55
5	ERB-041,		Inhibit cancer invasion by downregulation of CYP24A1, MMP13, and TNC	Breast cancer	46
6	WAY200070		Inhibit cancer invasion by downregulation of CYP24A1, MMP13, and TNC	Breast cancer	46
7	Liquiritigenin		Inhibit cancer invasion by downregulation of CYP24A1, MMP13, and TNC	Breast cancer	46
8	3β-Adiol		Inhibit cancer invasion by downregulation of CYP24A1, MMP13, and TNC	Breast cancer	46
9	Calycosin		Modulate IGFR signaling	Breast cancer	47

Table 1. Few examples of ERβ agonists, their structure and mechanism of actions. (cont.)

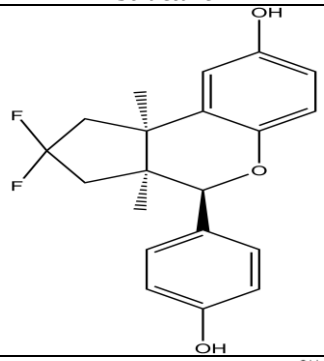
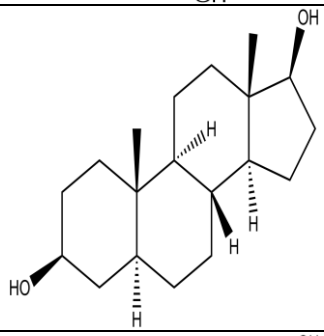
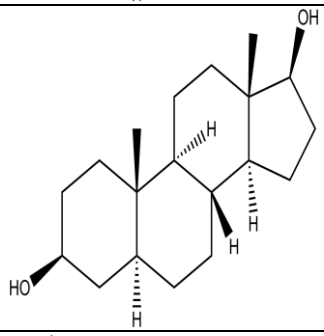
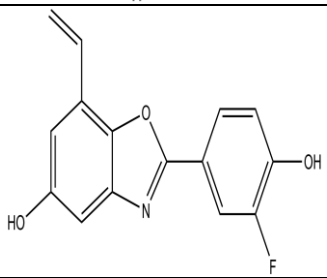
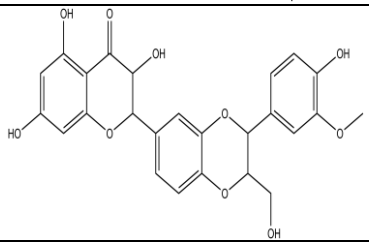
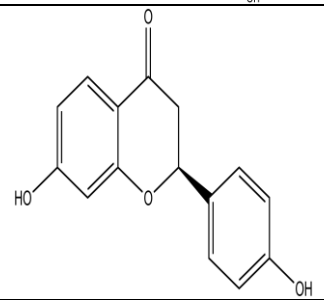
No	Name	Structure	Mechanism of action	Indication	Reference
10	LY3201		Inhibit AR signaling	Prostate cancer	44,56
11	3β-Adiol		Inhibit AR signaling	Prostate cancer	57
12	3β-Adiol		Activate FOXO3a/PUMA signaling	Prostate cancer	58
13	ERB-041,		Inhibit proinflammatory and Wnt/β-catenin signaling	Skin cancer	59,60
14	Silymarin		Inhibit Wnt/β-catenin signaling	Skin cancer	48
15	Liquiritigenin		Inhibit PI3K/AKT signalling Potential the anti-migratory/ anti-invasive effects of chemotherapeutic agents	Skin cancer	48

Table 1. Few examples of ERβ agonists, their structure and mechanism of actions. (cont.)

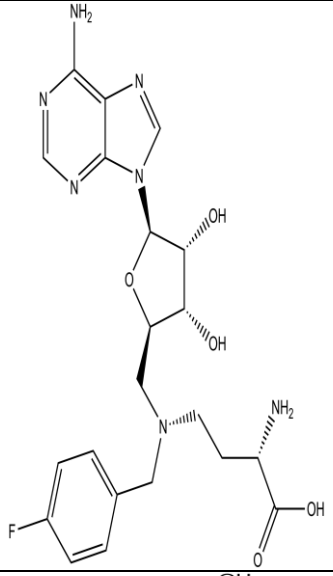
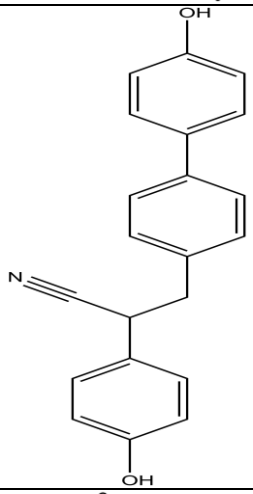
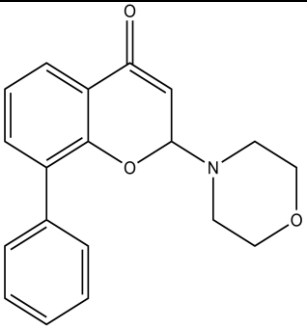
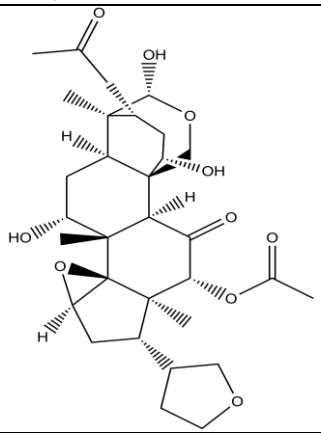
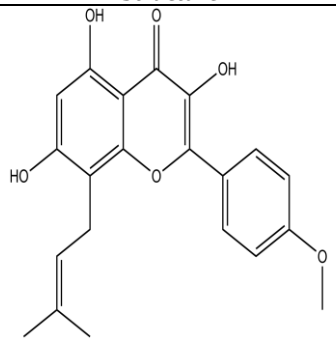
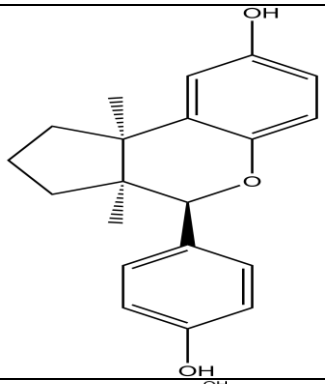
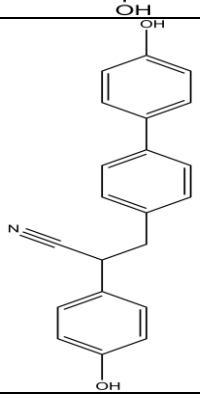
No	Name	Structure	Mechanism of action	Indication	Reference
16	KB1		Arrest the cell cycle at G1/S phase by decreased expression of cyclin D1 and cyclin D3, and increased expression of p27	Skin cancer	48
17	DPN		Arrest the cell cycle at G1/S phase by decreased expression of cyclin D1 and cyclin D3, and increased expression of p27	Skin cancer	48
18	LY294002		Inhibit integrin, IAP, NF-κB/ BCL2, and PI3K/AKT signaling pathways	Bone cancer	61
19	Toosendanin		Increase ERβ expression, inhibit proliferation and induced apoptosis	Brain cancer	49

Table 1. Few examples of ERβ agonists, their structure and mechanism of actions. (cont.)

No	Name	Structure	Mechanism of action	Indication	Reference
20	Icaritin		Increase ERβ expression, inhibit proliferation and induced apoptosis	Brain cancer	61
21	LY500307		Modulate apoptosis, cell cycle, and DNA damage. Sensitized cancer cells to chemotherapeutic agents	Brain cancer	62
22	DPN		Inhibit proliferation and induced apoptosis	Blood cancer	63

3. ROLE OF ERβ AND ERβ AGONIST IN CANCER

Cancer is the second leading cause of death globally. It is characterized by uncontrolled cell division, proliferation, invasion, and metastasis[64]. It is contributed by several factors[65] such as sex hormones[66], estrobolome (gastrointestinal tract microbiome)[67], histone lysine demethylase KDM4B, an important epigenetic modifier [68], lifestyle, and environmental factors. Of these, sex hormones, estrogens, and their receptors are the main contributors. In women, the predominant forms of estrogens depend on women's transitional period. For example, E1 predominates after menopause, E2 predominates in non-pregnant women before menopause, and E3 predominates during pregnancy. Estrogens exert a diverse biological effect and circulate in the blood as either free or protein-bound forms. Estrogens produced their biological effect upon binding to their receptors via reabsorption of its biologically significant proportion in the circulation. ~10%-15% of injectable E1, E2, and E3 are found in a conjugated form in feces, while ~65%, 48%, and 23% of injected radiolabelled E2, E1, and E3 are recovered in bile[67].

ERα and ERβ are two vital receptors widely expressed in human cancer. However, their expressional status is determined by transcriptional factors and events such as epigenetic and post-translational modification[69]. ERα is widely accepted to promote cancer progression and its role has been translated into clinical application, while ERβ is antiproliferative. According to recent research, therapy with the ERβ agonist LY500307 prevents lungs metastasis via inducing the release of IL-1β by tumor cells[52]. The loss of ERβ expression may lead to cancer progression and other disorders, implying that ERβ expression is favorable for cancer treatment[70]. In line with this, breast cancer cell line studies show that ERβ loss results from hypermethylation of the promoter ON gene (CpG islands)[53,71]. However, it was demonstrated by Margeret Warner et al., that ERβ need not be expressed in cancer cell to mediate its activity, but rather

it could be expressed in other cells such as natural killer (NK) cells. This was confirmed by the activation of NK cells within the tumor, secretion of TNF-α, and inhibition of tumor growth when breast tumors were treated with ERβ agonists, BAG 1 and BAG 2[53].

A study by Rocío Soldati et al., concluded that estrogen stimulatory or inhibitory effect in cancer is cell-context dependent and not ERs subtype-dependent effects[72]. Similarly, due to splice variations and conflicting data, some writers questioned ERβ's potential function in cancer. Some researchers found that ERβcx (ERβ2) variant expression is higher in breast and prostate cancer than ERβ1 (ERβ). The authors also discovered that the ERβ2 variation inhibited ligand-dependent ER reporter-gene activation via heterodimerization[53]. While others, such as in glioblastoma cells, found that ERβ expression increased chemotherapy-induced DNA damage response and malignant death[73]. The role of ERβ and ERβ agonists is depicted in Figure 2.

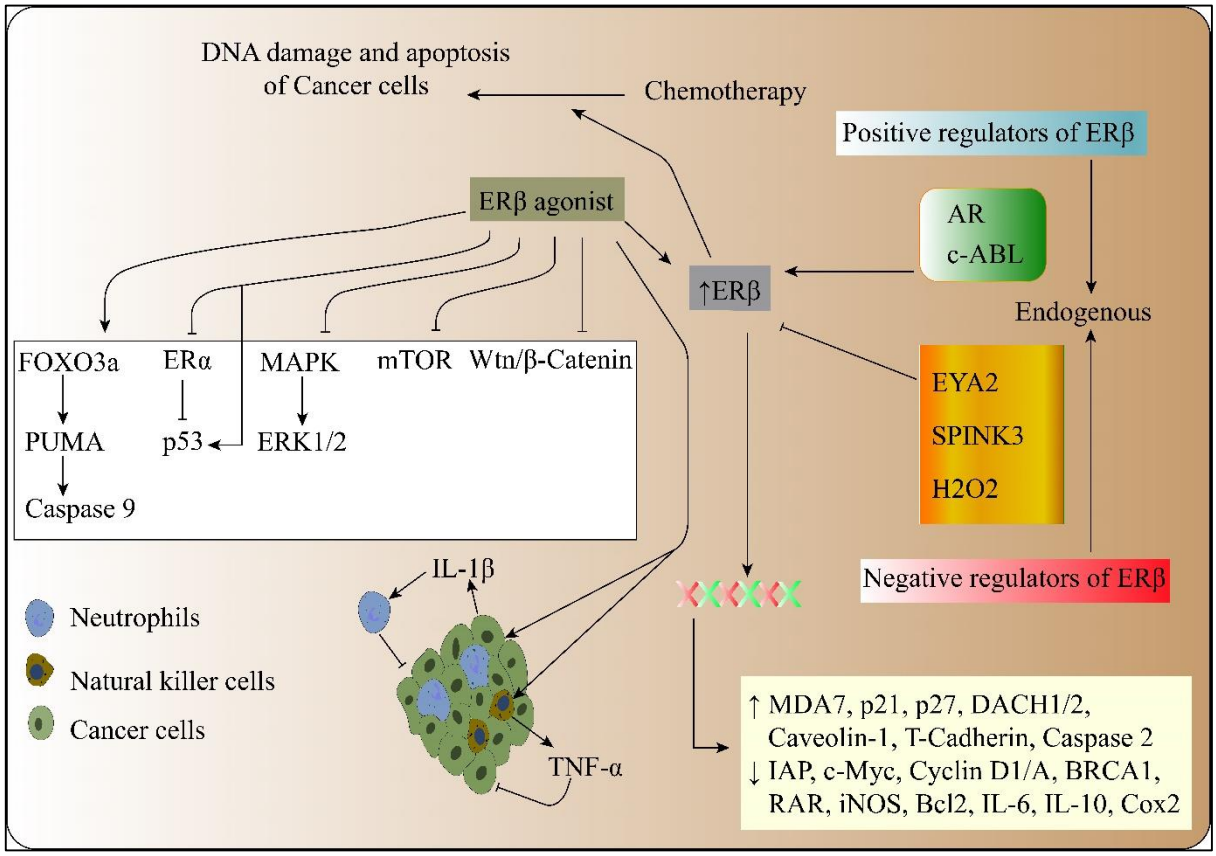


Figure 2. The potential mechanisms of ERβ agonist in cancer. ERβ agonist regulates a number of signaling pathways that are involve in halting and prevent cancer development. Furthermore, ERβ agonist can activate natural killer (NK) cells within the tumor leading to secretion of TNF-α and halt cancer cells development. Additionally, ERβ agonist helps in attraction of white blood cells, neutrophils, towards tumor microenvironment by releasing IL-1β from the activated cancer cells. ERβ agonist also act as sensitizer agent of cancer cells towards chemotherapeutic agents. Lastly, ERβ agonist is also involve in the expression and repression of genes that associated with halting and accelerating cancer development. Endogenous regulator (positive) of ERβ such as c-ABL activates ERβ via phosphorylation at tyrosine 36. While negative regulator such as EYA2 deactivates ERβ via dephosphorylation at tyrosine 36.

3.1. Lung cancer

Lung cancer ranks number one in cancer-related mortality. It is contributed and aggravated by factors such as smoking habit and estrogens[74]. Earlier study by Charles C. Canver et al., showed that ERs were abundance in lung tissue affecting with cancer only and not in normal lung tissue[75]. However, other researchers found that ERs are also expressed in normal lungs but are gender specific. In this study, ERα mRNA expression was shown to be more common in women's lungs, although ERβ frequency of expression was found to be comparable in men's and women's lungs. Consistently, the same pattern was observed in lung tumors, suggesting that women are at high risk of lung cancer due to higher circulating estrogen levels[76]. Similarly, hormone replacement therapy (HRT) use has been linked to an increased incidence of lung cancer, while smoking habit exacerbating the mortality rate[74,77]. In contrast, a population-based study of women (aged 18-74) from 488 patient cases and 498 controls found that postmenopausal women who took HRT had a lower risk of non-small cell lung cancer (NSCLC) in ERα and/or ERβ positive patients[78]. These intriguing results suggested the possibility that

early exposure of estrogen may promote lung cancer, but also protective in postmenopausal women with lung cancer; and that smoking may obstruct estrogen's protective effect in postmenopausal women, predisposing them to lung cancer risk[76].

Immunohistochemical of 132 resected NSCLC revealed that ERα expression (*P*=0.028) or ERβ absence (*P*=0.037) was associated with a worse prognosis. While, $ERα^+/ERβ^-$ patients showed significantly worse prognosis when compared to $ERα^-/ERβ^-$ patients. This suggests that the absence of ERβ could be used as a marker for identifying high-risk NSCLC patients even at an early stage of the disease[79]. Furthermore, the antagonistic blocking of cytoplasmic ERβ (cERβ) by fulvestrant may result in a better prognosis for nuclear ERβ (nERβ). While cytoplasmic co-expression of both ERs is linked to a poor prognosis in NSCLC[80] indicating the non-genomic action of ERα and ERβ. Irrespective of the cytoplasmic and nuclear expression of ERβ, LY500307, an ERβ agonist has been reported to prevent lungs metastasis via inducing the release of IL-1β by tumor cells[52]

3.2. Breast cancer

Breast cancer is the world's second most frequent cancer. Sir George Beatson, a British surgeon, was the first to publish on endocrine therapy for breast cancer, claiming that oophorectomy could lead to tumor regression[81]. As a result of this study, the significance of estrogens and ERs in the development of female breast tissue and, eventually, breast cancer, has now been well documented. This was corroborated by studies that revealed female mice with ER deletion mammary gland tissue lost their ability to grow despite increased levels of E2. Similarly, female patients with aromatase deficiency showed no sign of breast development due to failure of conversion of C_{19} steroids to estrogens[82]. In rodent mammary glands, ERβ expression varies during the conceiving (increased) and nursing period (decreased)[83]. In adult human breast, ERβ expression predominates in the mammary fibroblasts[84], benign and malignant breast [85]. ERβ has also been found to be evenly distributed in all the four subtypes of breast cancer: luminal A, luminal B, HER2, and triple-negative breast cancer (TNBC)[86]. ERs are known to play a contentious role in breast cancer; ERα is proliferative and ERβ is anti-proliferative in activity[87-89]. In line with this, ERα-knockout mice's breast has been reported to be atrophic and the breast epithelium of ERβ-knockout mice is hyperproliferative and prone to severe cystic breast disease as they age. Further, suppression of proliferation and up-regulation of CDK inhibitors or tumor suppressor genes such as p21 and p27, downregulation of c-myc, cyclins D1 and A upon transfection of ERβ and treatment of MCF-7 cells with ERβ agonist have been reported[84]. This anti-proliferative effect of ERβ, in part, results from the phosphorylation of tyrosine kinase (Y36) by c-ABL tyrosine kinase. Conversely, this phosphorylation of ERβ is dephosphorylated by the mammalian eye absent (EYE)-2 phosphatase, which is having oncogenic activity and promotes proliferation, migration, and invasion of breast cancer cells. The phosphorylation of Y36-specific ERβ was found to be highly related to both disease-free survival (DFS) and overall survival (OS) in patients with stage II and III disease[90].

The antiproliferative effect of ERβ has also been reported in HC11 mouse mammary cell line using ERβ-selective agonist, diarylpropionitrile (DPN); Hs578T TNBC cell line, MCF7, and T47D engineered to express ERβ. While this effect was not seen in cells expressing ERβ2[54]. However, a retrospective study conducted on patients with ERβ and ERβ2 expression found that tamoxifen-treated patients with ERβ2 expression reported a poor DFS and OS. It has been suggested that ERβ2 is linked to tamoxifen resistance and that it could be used as a negative prognostic biomarker in tamoxifen-treated patients[91]. In contrast, results from systematic review and meta-analysis reported that ERβ expression in breast cancer patients (ERα negative) is associated with improved DFS and but not OS while those with ERβ2 expression are associated with DFS as well as OS. Whereas, in breast cancer patients with ERα positive, ERβ expression has no impact on DFS and OS[92]. On the other hand, selective ERβ agonists also serve as a potential agent in ductal breast cancer by preventing it from becoming more invasive[93].

The expression of ERβ in several breast cancer cell lines has been demonstrated by E.A Vladusic et al. The authors show that treatment with anti-estrogen agents such as 4-hydroxy-tamoxifen (4OH-Tam) and ICI-182, 720 abolished estrogen-induced ERβ mRNA expression. However, the authors failed to report the effect of 4OH-Tam and ICI-182,720 on cell growth, proliferation, metastasis, and invasion when ERβ mRNA expression was abolished[94]. In another study, it was discovered that the loss of ERβ function and inactivation of p53 is linked to breast tumor initiation and progression[95]. Apart from the anti-proliferative effect, ERβ also mediates apoptosis by indirectly antagonizing ERα. ERα has been reported to repress the transcriptional activities of p53, suggesting that this could be one mechanism of how ERα promotes cancer[96-97]. As a result, the inhibition activity of ERβ on ERα would promote the transcriptional activity of p53, thereby arresting cancer development. ERβ forms a direct complex with p53 and activates its transcriptional activities[96-97]. This report is consistent with other studies and results conducted on MC4-L2, MCF7, LoVo cell lines[98], T47D[99], and TNBC[100], demonstrating the antagonistic activity of ERβ on ERα when there are low levels of endogenous E2[40]. While other studies show that p53 defection activity in breast cancer, ERβ

expression induction alone can damage and decrease the survival of cancer via BRCA1 downregulation and caspase-2 activation[101]. The increased expression of ERβ particularly in ER^+ breast cancer cells and its growth inhibition in breast cancer has also been reported as a result of androgen receptor (AR) activation. This effect was mediated via enhanced occupancy of RNA polymerase III and enhanced recruitment of AR to the AR element (ARE) site (TGTTCT motif) located at the -383 base pair of human ERβ promoter region[102].

The potential involvement of ERβ in TNBC is still being debated[103]. Jin wang et al. found that ERβ overexpression was detected in 30.4 percent of tumor samples and was directly associated with a better OS, DFS, and distance metastasis-free survival (DMFS). Additionally, increased PTEN phosphorylation (pPTEN) and decreased AKT phosphorylation (pAKT) expression was reported in a clinical study involving 571 patients with invasive TNBC. Notably, the study suggests the possible mechanism of ERβ-specific agonists via PTEN/PI3K/AKT signaling pathway activation[104]. In addition to this, Song I et al., also reported the overexpression of mitochondrial ERβ (mitERβ) that causes the inhibition of TNBC cells proliferation, and tumor masses[105] via suppression of CDK1/7[106]. Also, Schüler-Toprak S et al. reported that ERβ agonists, ERB-041, WAY200070, Liquiritigenin, and 3-Adiol reduced TNBC cell invasion, but ERβ knockdown by siRNA increased TNBC cell invasion by 3-fold[46]. In contrast to this, a study by Nalo Hamilton et al., on the TNBC cell line and human TNBC specimen showed that insulin-like growth factor-2 (IGF-2) along with ERβ significantly increased ERβ protein level, thereby contributing to cell proliferation and disease progression. Additionally, increased VEGF, amphiregulin, Wnt-10b production, and other tumor-promoting substances were also related to the stimulatory action of ERβ on cell growth[107]. This was further supported by a significant surge in proliferation and migration when TNBC cells were treated with ERβ agonist, DPN[108].

3.3. Prostate cancer

ERβ is mainly localized in differentiated luminal epithelial cells of rat and murine prostate but expressed throughout the epithelium of urogenital sinus and stroma in early fetal development in humans. This expression is maintained in most epithelial and stromal cells throughout the gestation period. Gestational period, suggesting the involvement of ERβ in cell differentiation and morphogenesis in the prostate. In adult men, dogs, monkeys, and rodents, ERα and ERβ are primarily localized in basal and epithelial cells of the prostate[44,109]. ERα mediates E2-induced squamous metaplasia is directly linked with epithelial and stromal expression in the periurethral ducts and peripheral prostatic acini. ERβ expression in epithelial prostate has been suggested to play a multi-role such as pro-differentiation, anti-proliferative, anti-inflammatory, and anti-oxidant genes inducer[109]. In line with this, the loss of ERβ expression in prostate cancer[110] is associated with cell hyperplasia, fibroblastic lesions, and inflammation[56]. Further, the loss of ERβ expression could be due to overexpression of the SPINK3 (TATI) gene which is believed to be a negative regulator of ERβ[53]. From another point of view, it was hypothesized that ERβ down-regulation in prostate cancer occurred as a result of its oxidation by H_2O_2 due to tissue inflammation. The oxidation of ERβ abolished its DNA binding and reduced E-cadherin expression[111]. E-cadherin is considered a key component in suppressing tumors and functions as a calcium-dependent to hold epithelial cells together. E-cadherin maintain cell-cell adhesion, tissue integrity, prevent invasion and cell migration, and regulate and maintain epithelial cell morphogenesis and differentiation under intact and normal conditions[112-113]. Loss or decreased expression of E-cadherin characterized epithelial to mesenchymal transition (EMT) and is associated with epithelial cell phenotype loss as well as promotes cell motility, migration[114], and metastasis in the case of prostate cancer[115-116].

In prostate cancer, androgen ablation or androgen receptor (AR) inhibition is the key approach and the most effective treatment, since AR is the regulator of prostate cell proliferation. Genistein, a potent ERs agonist with a higher affinity for ERβ rather than ERα, activate ERs and reduce AR in the LNCaP cell line originating from human prostate cancer. This positive effect of genistein was demonstrated in animal, clinical, and case-control trials[84]. Similarly, a recent study found that treatment of an engineered AR-positive LNCaP cell line that expressed ERβ with the ER agonist, LY3201, reduced AR transcription, protein levels, and translational activity[44]. Targeting ERβ and treatment with ERβ agonist in prostate cancer also promotes apoptosis, and/or differentiation as well as reduced tumor grade at the early stage of prostate cancer[117]. Additionally, ERβ agonist up-regulated the nuclear tumor suppressor PTEN, DACH1/2, stromal caveolin-1, and T-cadherin, and decreased AR, retinoic acid receptor (RAR)-related orphan receptor c, iNOS, Bcl2 and IL-6[56]. Similarly, the complex of ERβ with 5α-androstane-3β, 17β-diol (3β-Adiol) (testosterone metabolite having estrogenic) helps in restraining epithelial growth of rodent prostate which is useful in the prevention and/or clinical management of hyperplasia and neoplasia of prostate cancer[57]. The potential activity of 3β-Adiol in prostate cancer has been suggested to be a result of induction of cell apoptosis via ERβ/FOXO3a/PUMA signaling pathway[58].

3.4. Skin Cancer

Skin cancer is a malignant disease most commonly found in the Caucasian group and majorly caused by

ultraviolet (UV)-light. It is mainly categorized into two types: malignant melanoma (MM) and non-malignant melanoma (the most common type). Non-malignant melanoma is further subdivided into basal cell carcinoma and squamous cell carcinoma. These two subtypes of non-malignant melanoma are together referred to as nonmelanocytic skin cancer (NMSC)[118-119]. MM occurred in less than 5% of all skin cancers but with a high capacity of lymphogenic and hematogenic spread. This metastasis of MM to lymph and blood is responsible for 75.2% of death[120].

p53, a transcriptional factor and a tumor suppressor protein that is often described and called the 'guardian of the genome'. p53 is one of the most vital regulatory proteins responsible for cell cycle regulation, cell apoptosis, and DNA repair of damaged cells. In skin cancer, mutations in p53 (80% of mutation frequency rate in almost all types of cancer)[98] occurred as a result of the UV-light effect. These mutations are characterized by a transition in Cytosine to thymine (C→T) as well as CC→TT. The defect or mutations in p53 allows the damaged cells to resist apoptosis and pass through cell checkpoints, which ultimately leads to a positive selection of p53 mutant cell and clonal growth[121]. Since ERβ has also been reported to be present in the epidermis, dermal fibroblast, blood vessels, and hair follicles; it is, therefore, the main mediator of estrogen in human skin and hair follicles[122]. ERβ is also able to increase p53 transcriptional activity by antagonizing estrogen-mediated cytoplasmic translocation of p53. Thereby arresting cell growth and promoting apoptosis[98]. Most importantly, because the skin is by far the largest target on which estrogen acts[123], targeting ER becomes an appealing target for skin cancer prevention and treatment. In a study on nonmelanoma skin cancer (NSC), treatment with Erb-041, a highly specific ERβ-agonist cause inhibition of UV-light-induced skin cancer via the inhibition of proinflammatory signaling and EMT[59].

Another example of a cascade whereby modulation of ERβ shows promising activity in skin cancer is the Wnt signaling pathway. Wnt is a family of cysteine-rich glycoproteins that play a vital role in cell development and cancer. Wnt pathway is mainly classified into three branches, these are the β-catenin pathway, which is a nucleus-activated target genes pathway; the planar cell polarity pathway, which is involved in the rearrangements of cytoskeletal; and jun N-terminal kinase (JNK) and the Wnt/Ca^{2+} pathways. The former one is also known as the canonical or Wnt/β-catenin dependent pathway and the latter two are known as non-canonical or Wnt/β-catenin independent pathway. Events of cell proliferation and differentiation, and the formation of organ systems such as lungs, kidneys, heart, bone, and skin are regulated by the canonical Wnt cascade. Thus, abnormal activation in this cascade is associated with several human pathologies such as cancers of the colon, skin and breast, defects in skeletal, and human birth disorders such as spina bifida which is the most common human neural tube closure birth[124-126]. In the SKH-1 mice model UV-light-induced photocarcinogenesis, treatment with ERβ agonist, Erb-041 shows a promising therapeutic effect by downregulating Wnt/β-catenin pathway leading to reduced tumor invasion and EMT. Additionally, Erb-041 also significantly recovered the loss of ERβ expression in squamous cell carcinoma and diminished the activity of myeloperoxidase, and cytokines levels (IL-1β, IL-6, and IL-10). Erb-041 also decreased the activity of p-ERK1/2, p-p38, p-IkB, and expression of iNOS, COX-2, and nuclear NF-kBp65[60]. Whereas, on the contrary, abnormal inactivation of this pathway is also associated with disease development such as disorders of hair growth and pigmentation, pathology of wound healing, bone disease, neurodegenerative diseases, and chronic obstructive pulmonary diseases (COPD)[127]. In human melanoma cell lines (A375, BLM, WM115, and WM1552), ERβ is the ER subtype reported to be expressed but not ERα. The antitumor activity of ERβ agonists in these cell lines is a result of genomic and non-genomic effects. Genomic effects occurred as a result of ERβ/ERβ homo- or ERα/ERβ hetero-dimerization. Whereas non-genomic effects are mediated by inhibition of MAPK/ERK and PI3K/Akt signaling pathway[48].

3.5. Endometrial cancer

Endometrial cancer is a type of cancer where a tumor is originating in the endometrium. It is a common gynecological tumor in developed countries which is associated with exposure to endogenous and exogenous estrogen. Other diseases such as diabetes, hypertension, and obesity act as the main risk factors[128]. Endometrial cancer is reported to be ranked fourth as the most common cancer in women in the U.S after breast, lung, and colorectal cancers[129]. Based on histological characteristics, hormone receptor expression and grade, endometrial cancer is classified into Type I (estrogen-related) and Type II (estrogen unrelated). While based on molecular and genomic features endometrial cancer has been further sub-classified into serous, carcinosarcoma, and clear cell carcinomas. In addition to this endometrial cancer has also been classified based on surgical and histological characteristics[128,130].

The expression of ERs in endometrial adenocarcinomas[131] is associated with and promoted by disease states such as diabetes[132]. The activity of ERs in developing endometrial cancer is also driven by gene polymorphisms [133-135]. Nevertheless, the expression of ERs is associated with significant survival prognostic outcome[136] indicating the potential role of ERs as therapeutic targets. In comparison to ERα expression that promotes cell proliferation, siRNA-mediated ERβ knockdown in two endometrial cancer cell lines, HEC-1A and RL95/2 caused

the upregulation of several proliferation-associated genes and oncogenes. Whereas, gene expression which is linked with differentiation, apoptosis, or growth inhibition is associated with the expression of ERβ. This indicates the tumor suppressor activity of ERβ in endometrial cancer[137] and its activation could be useful in preventing and halting endometrial cancer.

3.6. Bone cancer

Estrogen plays a critical role in bone remodeling and bone mass via ERα in males while both ERs are reported in males and females[138]. Both ERs are predominantly expressed in the bone-remodeling cells, osteoblasts. While ERα's highest expression is reported in cortical bone (solid bone tissue) and ERβ's minor expression is observed in the bone-resorbing cells, osteoclast, and osteocytes of cancellous (spongy) bone[139]. Microarray assay on U2OS osteosarcoma (cells that stably over-expressed ERα/ERβ, or both) shows only 21% overlap in E2-regulated genes in U2OS-ERα and U2OS- ERβ cell line, demonstrating that ERs functioned differently in osteoblast-like cells. Whereas, when ERs are co-expressed together, distinct sets of E2-regulated genes were observed[140]. In estrogen-targeted tissues, growth factors such as IGF-1 that influence bone resorption[9] and TGF-β that positively regulate type I collagen genes synthesis, increased osteoblast proliferation, and decreased osteoclastic activity were observed[141]. ERα is heavily involved in osteoporosis[142] and its activation causes suppression and induction of apoptosis in osteoclast cells. Mechanistically, by i) osteoblast-induced Fas ligand (FasL) transcription, whereby further FasL cleavage from the cell surface is executed by matrix metallopeptidase-3 (MMP3), and the soluble FasL caused osteoclast apoptosis, ii) regulation of cytokine, receptor activator of NF-κB ligand (RANKL) which is essential for osteoclast differentiation, and decoy receptor (OPG) which inhibited RANKL pathway ratio[140]. Whereas, treatment with ICI-182,780 (fulvestrant), an ERα antagonist was found to abolish OPG/RANKL production[143]. The role of ERα in osteoporosis is demonstrated by ERαKO mice with a significant decrease in bone length and size, as well as in mineral density[9]. Thus, the overexpression of ERα may complicate the osteoclasts:osteoblasts ratio and increased bone cancer risk. While on the other hand, ERβ activity may be inhibitory to ERα possibly because ERβ contains a weak and repressor AF-1 domain, and has no contribution to bone cancer-related. This is evidence from a proximal tibial bone mineral density of ovariectomized rats which shows no sign of increasing upon treatment with ERβ agonist, ERB-041[140]. Further, ERβ agonist, LY294002 shows an anti-tumor effect in osteosarcoma cells via the regulation of integrin, inhibition of apoptosis protein (IAP), NF-κB/BCL-2, and PI3k/Akt signaling pathway[61].

3.7. Brain cancer

Glioblastoma (GBM) comprised of 16% of all primary brain and central nervous system neoplasms. Thus, it is often considered as the most common primary malignant brain tumor, arising mainly from glia cells but can also develop from other cells such as neural stem/progenitor cells. Currently, tumor-treating fields (TTFields), immunotherapy and drugs targeting molecular receptors are the promising approaches[144-145]. Based on pre-existing lesion, tumors of GBM are classified into primary and secondary GBMs. Primary GBMs accounts for 90-95% of GBMs and are common among elders (>50 years), while secondary GBMs accounts for 5-10% of GBMs and more common among young people[145].

In cancer, reduced T-cells or dysfunctional T-cells [146] and immunosuppression[147] are together considered as an important factors for tumor growth which is also seen in GBM via induction of anti-inflammatory response upon pericytes activation[148-149]. Apart from these, differential expression of ERβ and its splice variants have positively and negatively impacted on GBM progression. CRISPR-based ERβKO cells displayed high expression of two splice variants, namely ERβ and ERβ5. However, a contrasting role of these two were seen in the activation of mTOR signaling molecules, including p-mTOR, p-S6K, and pS6. The activation of molecules is decreased when ERβ is expressed and enhanced when ERβ5 is expressed[150]. In GBM cells the upregulation of ERβ occurred upon activation, and along with this, the activation of functional p53 and other gene-related apoptosis that inhibited cell proliferation, cell migration and increased apoptosis is observed[49,62,151]. Further, ERβ expression enhanced the chemotherapy in cells- and GBM-mice model treated with temozolomide (TMZ) by downregulation of genes involved in recombination and repair of DNA[73].

3.8. Blood cancer

The early history of leukemia may be dated back to 200 years ago where physicians namely, John Hughes Bennett, Rudolf Virchow, Alfred Donné, and Alfred Velpeau are often considered as 'the one' who discovered leukemia[152-153]. Leukemia was majorly classified into myeloid neoplasms and lymphoid neoplasms[154], out of which the most common form of acute leukemia in adults is acute myeloid leukemia that accounts for ~21000/ annual of new diagnoses in the U.S[155]. Notably, blood cancer such as chronic lymphatic leukemia is not considered as a sex-hormone related cancer. However, one study demonstrated that in male and female mice grafted with murine T-cell lymphoma cells, large tumors were seen in male when compared to females and upon ovariectomy, the difference was abolished[63] suggesting the role of estrogen. While other studies, suggests the incident

rate of leukemia to be statistically significant between the age group of 1-4 years old[156] with boys showing more prone (4 times) to be diagnosed with B-precursor acute lymphocytic leukemia when compared to girls[157]. These studies, suggests the gender risk of leukemia and role of sex-hormones such as of estrogen in the development of these diseases.

When compared to ERα, ERβ expression is highly expressed in AML patient[155-158]. While ERβ was also reported to be highly expressed in chronic lymphocytic leukemia along with ERβ2 which was stained in the nucleus and found specifically in B- but not T-lymphocytes[159]. Similarly, in lymphoma, murine T-cell lymphoma cell EG7, and human B-cell Burkitt's lymphoma cells Raji and Ramo, ERβ is the predominant ER to be expressed and associated with tumor growth inhibition [63,155]. Further, the role of ERβ in leukemia is demonstrated in mice by disruption of the *ESR2* gene which resulted in bone marrow hypercellularity and myeloproliferative neoplasm resembling chronic myeloid leukemia[155,160]. On the other hand, these effects were attenuated by ERβ expression. Mechanistically, this occurs via the activation of erythroid transcription factor, also called GATA-binding factor 1 (GATA-1)[155]. Additionally, ERβ activation reduces the proliferation and increased apoptosis in mice grafted with murine T-cell lymphoma[63].

Interestingly, a study by Vera Vanhentenrijk et al., pointed out the critical role of ERβ in leukemia. In their study, where they have applied comparative expressed sequence hybridization (CESH) technique in 12 hairy cell leukemia cases, they reported several chromosome regions with altered expression. Out of their identified regions, one region, 14q22-q24, a region which corresponded with ERβ gene region on the chromosome, was found to be significantly under expressed[161].

4. CONCLUSION

ERβ is a classical target that shows potential anti-cancer activity upon activation. In most cases of cancer, its expression is associated with beneficial effects and vice versa. So far, preliminary investigations of ERβ agonists in cancer and other diseases have been reported with positive come. While some of these investigations have been carried out at the clinical level (NCT00962390) and some are under consideration. Hence, from a drug discovery point of view, further study on the identification of more potent ERβ agonist, with better safety and efficacy is warranted.

Conflict of interest
None to declare.

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