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Review Article

A comprehensive review on estrogen, estradiol, and estriol binding receptors: computational approaches and therapeutic implications

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Estrogen and its types of estradiol and estriol are diverse and robust molecules which influence metabolism in health and disease conditions. A comprehensive literature review was conducted using defined selection criteria and a focused search strategy. The SwissTargetPrediction Tool was employed as the primary computational approach to predict and categorize receptor targets, grouping them into functional classes such as nuclear receptors, kinases, enzymes, and others. The binding receptors to these molecules observed in this study are categorized under electrochemical transporters, kinases, enzymes, Transferases, Lyases, Proteases, Nuclear receptors, Erasers, Cytochrome P450, secreted proteins, oxidoreductases, Family AG protein coupled receptors, hydrolases, other ion channels and cytosolic proteins. Few common binding receptors were observed indicating structural similarity and receiving and transducing signals through the same metabolic pathway. Our analysis reveals that estrogen and its derivatives exhibit variable binding efficiencies across different receptor classes, with several common targets indicating potential structural and functional similarities. The work also emphasizes how crucial computational techniques are for methodically finding new receptor interactions, providing a high-throughput and economical means of drug development. Estrogen and its derivatives' ability to alter cellular signaling pathways highlights its potential as therapeutic agents for a variety of metabolic and pathological illnesses, such as hormone-dependent malignancies, heart disease, and neurological disorders. The unprecedented data in the form of list of receptors broadens the scope of these hormones to be prominent players in various diseased conditions. Additionally, the discovery opens the door for tailored treatment approaches by offering important insights into receptor specificity. The positive aspect makes us look deeper into these targets and new drugs developed mediating the role in health and adverse health conditions of peri and post-menopausal women ultimately advancing patient care and enhancing the quality of life across diverse population.

Keywords: *Estrogen, estradiol, estrone, receptors, SwissTargetPrediction Tool*

Introduction

Our body operates through a complex network of hormones, serving as chemical messengers crucial for maintaining a holistic and intricate environment. Released in specific amounts into the bloodstream, hormones orchestrate the organization and function of tissues and organs. Any disturbance, from synthesis to function, can lead to direct or indirect adverse effects on the body (Novella et al., 2012). Notably, estrogen plays a protective role, particularly in menopause, where the decline in endogenous estrogen production is linked to physiological dysfunction. This deficiency is associated with increased central fat, reduced lean body mass, heightened hypercoagulability, and a pro-inflammatory state. Additionally, studies indicate the involvement of oxidant enzymes in post-menopausal females with type-2 diabetes, highlighting the intricate interplay of hormones in maintaining overall health (Kumawat et al., 2012). In the ovary,

synthesis of Tissue Specific Estrogen takes place with the help of Theca Cells and Granulosa Cells (Zhao et al., 2016). Among the types of estrogen, each plays a distinct role in the body's hormonal balance. Estrogen (E1) predominates during post-menopause and is primarily synthesized in adipose tissues and skin. Estradiol (E2) is the most potent estrogen and is abundant in premenopausal women, primarily originating from the ovarian synthesis and released into circulation. Estriol (E3), the weakest estrogen, is primarily found in the placenta of pregnant women, contributing to the unique hormonal milieu of pregnancy (Samavat & Kurzer, 2015). A study utilizing radioligand assays to measure hormone levels in pregnant women discovered a gradual increase in progesterone, unconjugated estrone, estradiol, and estriol during later stages of pregnancy. Additionally, levels of 17-hydroxyprogestrone surged notably after the 33rd week of gestation (Zhao et al., 2016). Androstenedione, a precursor to estrogen, is initially found in the theca cells and subsequently localized within the granulosa cells. Under the influence of aromatase (P450arom) and 17β-hydroxysteroid dehydrogenase (17B-HSD), it undergoes conversion into estrogen, highlighting the intricate biochemical processes involved in estrogen synthesis (Tulchinsky et al., 1972). Surprisingly, elderly males exhibit higher circulating levels of androgens in comparison to females, suggesting unexpected hormonal dynamics in aging populations (Anawalt & Matsumoto, 2022).

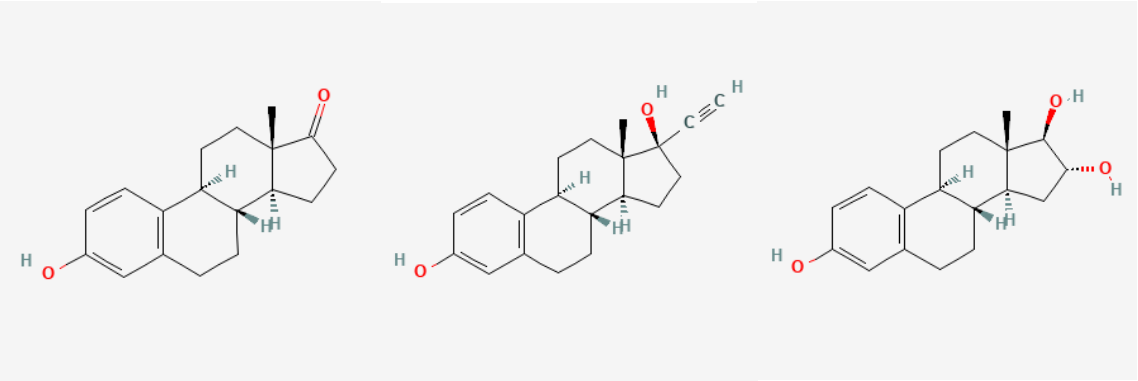

Figure 1. Estrone (E1) and Estradiol (E2), and Estriol (E3)

The estrogen binds to the nuclear transcription factors, estrogen receptors ERα/ ESR1, ERβ / ESR2 and cell surface or membrane estrogen receptors- mERs (Thomas & Potter, 2013). The mERs are a group of estrogen binding receptors such as GPER1(GRP30) and non-GPER receptors as mERα and mERβ, ER-X and Gq-mER (Wnuk et al., 2023). The mERs have proved to be neuroprotective players in the estrogen modulation of the signaling and have ruled out the deleterious effects of conventional ERs. Alpha receptors are known to increase cell proliferation and beta receptors that inhibit cell growth. Estrone binds with alpha receptors in 5:1 ratio, hence, increases cell growth. Estradiol binds alpha receptors and beta receptors in equal proportion. Estriol activates beta receptors in a 3:1 ratio, inhibiting cell growth. Reports show presence of ERβ protein in the ovarian granulosa cells, kidney, brain, bone, heart (Arslan et al., 2014; Cui et al., 2013; Hammond, 2016; Samavat & Kurzer, 2015), lungs, intestinal mucosa, prostrate and endothelial cells (Janicki & Schupf, 2010). The distribution of the estrogen receptors provides a perspective of the repercussions of estrogen level alterations.

Because estrogen signaling plays a part in hormone-regulated diseases such breast cancer, osteoporosis, and cardiovascular disorders, it is essential to understand it. There are still gaps in our understanding of all possible receptor interactions and their therapeutic consequences, despite a great deal of research. To improve drug-targeting tactics, this review attempts to comprehensively assess both known and new estrogen receptors using computational techniques. Incomplete knowledge of receptor interactions presents a major challenge in the development of effective and targeted therapeutic approaches. Despite extensive research on estrogen signalling, many potential receptor targets remain unexplored or insufficiently characterized, limiting our ability to design precise drug interventions. Traditional experimental techniques, while invaluable, are often time-consuming and resource-intensive, which can delay the identification of novel therapeutic targets and hinder the progress toward personalized treatment strategies. Computational analysis offers a promising solution to overcome these limitations. By leveraging high-throughput tools such as the Swiss Target Prediction Tool, researchers can systematically identify and categorize receptor interactions on a large scale. This approach not only accelerates the discovery process but also provides a more comprehensive understanding of the molecular mechanisms underlying hormone signalling. In doing so, it lays the groundwork for more precise drug development, enabling the formulation of personalized therapies that can effectively address the multifaceted nature of hormone-related disorders. The objective of this review is to fill critical gaps in the current literature by systematically assessing both known and novel estrogen receptor interactions using advanced computational techniques. By compiling an extensive list of receptor targets and classifying them into functional categories—such as nuclear receptors, kinases, enzymes, and more—this work aims to provide a detailed molecular map that can inform future experimental validation and clinical applications. Ultimately, the insights gained from this analysis are expected to pave the way for more targeted

and individualized therapeutic strategies, enhancing patient care in the treatment of metabolic and pathological conditions associated with estrogen signalling.

An attempt has been made to identify the probable targets in *Homo sapiens* for the small biologically active molecules using SwissTargetPrediction tool. The ligands narrowed the search to specific targets and have been listed in the following tables with UniProt and ChEMBL ID along with the class to which the target belongs. It is interesting to learn that a significant number of targets have not been judiciously explored (Daina et al., 2019). The results are given in tables 1, 2 and 3 as the strongest binding targets are stated first at the top of the table with continuous decrease in binding of targets as Sr. no. of the target decreases. These results have also been summarized as pie charts in figure 2, 3, and 4.

Table 1. List of estrogen binding proteins in homo sapiens

Sr. no.	Target	Common name	Uniprot ID	ChEMBL ID	Target Class
1	Serotonin 2b (5-HT2b) receptor	HTR2B	P41595	CHEMBL1833	Family A G protein-coupled receptor
2	Androgen Receptor *(by homology)*	AR	P10275	CHEMBL1871	Nuclear receptor
3	Cytochrome P450 19A1	CYP19A1	P11511	CHEMBL1978	Cytochrome P450
4	Estrogen receptor alpha	ESR1	P03372	CHEMBL206	Nuclear receptor
5	Serotonin transporter	SLC6A4	P31645	CHEMBL228	Electrochemical transporter
6	Estrogen receptor beta	ESR2	Q92731	CHEMBL242	Nuclear receptor
7	Estradiol 17-beta-dehydrogenase 1	HSD17B1	P14061	CHEMBL3181	Enzyme
8	Testis-specific androgen-binding protein	SHBG	P04278	CHEMBL3305	Secreted protein
9	Steryl-sulfatase	STS	P08842	CHEMBL3559	Enzyme
10	Glucocorticoid receptor	NR3C1	P04150	CHEMBL2034	Nuclear receptor
11	LXR-alpha	NR1H3	Q13133	CHEMBL2808	Nuclear receptor
12	LXR-beta	NR1H2	P55055	CHEMBL4093	Nuclear receptor
13	Tyrosine-protein kinase SRC	SRC	P12931	CHEMBL267	Kinase
14	Focal adhesion kinase 1	PTK2	Q05397	CHEMBL2695	Kinase
15	Vascular endothelial growth factor receptor 2	KDR	P35968	CHEMBL279	Kinase
16	ALK tyrosine kinase receptor	ALK	Q9UM73	CHEMBL4247	Kinase
17	Insulin-like growth factor I receptor	IGF1R	P08069	CHEMBL1957	Kinase
18	Estrogen-related receptor alpha	ESRRA	P11474	CHEMBL3429	Nuclear receptor
19	Estrogen-related receptor beta	ESRRB	O95718	CHEMBL3751	Nuclear receptor
20	G-protein coupled estrogen receptor 1	GPER1	Q99527	CHEMBL5872	Family A G protein-coupled receptor
21	Adenylate cyclase type 10	ADCY10	Q96PN6	CHEMBL5854	Enzyme
22	Arachidonate 15-lipoxygenase	ALOX15	P16050	CHEMBL2903	Enzyme
23	Arachidonate 12-lipoxygenase	ALOX12	P18054	CHEMBL3687	Enzyme
24	DNA polymerase alpha subunit	POLA1	P09884	CHEMBL1828	Transferase
25	Aldo-keto-reductase family 1 member C3	AKR1C3	P42330	CHEMBL4681	Enzyme
26	Estradiol 17-beta-dehydrogenase 2	HSD17B2	P37059	CHEMBL2789	Enzyme
27	Estradiol 17-beta-dehydrogenase 3	HSD17B3	P37058	CHEMBL4234	Enzyme
28	Solute carrier family 22 member 2	SLC22A2	O15244	CHEMBL1743122	Electrochemical transporter
29	Leukotriene B4 receptor 1	LTB4R	Q15722	CHEMBL3911	Family A G protein-coupled receptor

30	Arachidonate 5-lipoxygenase	ALOX5	P09917	CHEMBL215	Oxidoreductase
31	Histone deacetylase 6	HDAC6	Q9UBN7	CHEMBL1865	Eraser
32	Cyclooxygenase-2	PTGS2	P35354	CHEMBL230	Oxidoreductase
33	Serotonin 7 (5-HT7) receptor	HTR7	P34969	CHEMBL3155	Family A G protein-coupled receptor
34	Serotonin 6 (5-HT6) receptor	HTR6	P50406	CHEMBL3371	Family A G protein-coupled receptor
35	Cytochrome P450 24A1 *(by homology)*	CYP24A1	Q07973	CHEMBL4521	Enzyme
36	DNA polymerase beta *(by homology)*	POLB	P06746	CHEMBL2392	Enzyme
37	Carbonic anhydrase II	CA2	P00918	CHEMBL205	Lyase
38	Carbonic anhydrase I	CA1	P00915	CHEMBL261	Lyase
39	Acetylcholinesterase	ACHE	P22303	CHEMBL220	Hydrolase
40	Matrix metalloproteinase 9	MMP9	P14780	CHEMBL321	Protease
41	Sterol 26-hydroxylase, mitochondrial	CYP27A1	Q02318	CHEMBL5992	Enzyme
42	Cyclin-dependent kinase 5/CDK5 activator 1	CDK5R1 CDK5	Q15078 Q00535	CHEMBL1907600	Kinase
43	Cyclin-dependent kinase 2/cyclin E	CCNE2 CDK2 CCNE1	O96020 P24941 P24864	CHEMBL2094126	Other cytosolic protein
44	Cyclin-dependent kinase 1/cyclin B	CCNB3 CDK1 CCNB1 CCNB2	Q8WWL7 P06493 P14635 O95067	CHEMBL2094127	Other cytosolic protein
45	Cyclin-dependent kinase 2/cyclin A	CDK2 CCNA1 CCNA2	P24941 P78396 P20248	CHEMBL2094128	Other cytosolic protein
46	Glycogen synthase kinase-3 beta	GSK3B	P49841	CHEMBL262	Kinase
47	Glycogen synthase kinase-3 alpha	GSK3A	P49840	CHEMBL2850	Kinase
48	Cyclin-dependent kinase 5/CDK5 activator 1	CDK5	Q00535	CHEMBL4036	Kinase
49	Cystic fibrosis transmembrane conductance regulator	CFTR	P13569	CHEMBL4051	Other ion channel
50	Dopamine transporter	SLC6A3	Q01959	CHEMBL238	Electrochemical transporter
51	Beta-3 adrenergic receptor	ADRB3	P13945	CHEMBL246	Family A G protein-coupled receptor
52	Protein kinase C theta	PRKCQ	Q04759	CHEMBL3920	Kinase
53	Rho-associated protein kinase 2	ROCK2	O75116	CHEMBL2973	Kinase
54	11-beta-hydroxysteroid dehydrogenase 1	HSD11B1	P28845	CHEMBL4235	Enzyme
55	Kinesin-1 heavy chain/ Tyrosine-protein kinase receptor RET	RET	P07949	CHEMBL2041	Kinase
56	Mu opioid receptor	OPRM1	P35372	CHEMBL233	Family A G protein-coupled receptor
57	Delta opioid receptor	OPRD1	P41143	CHEMBL236	Family A G protein-coupled receptor
58	Kappa Opioid receptor	OPRK1	P41145	CHEMBL237	Family A G protein-coupled receptor

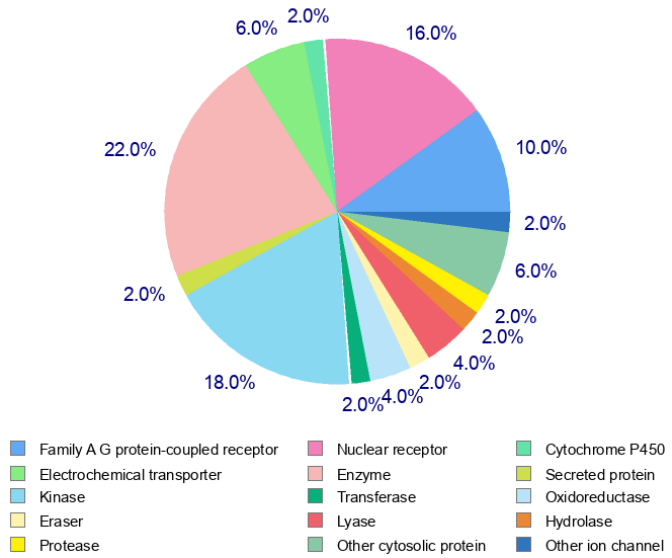

Figure 2. Distribution percentage of Estrogen binding protein

Table 2. List of estradiol binding proteins in homo sapiens

Sr. No.	Target	Common name	Uniprot ID	ChEMBL ID	Target Class
1	Estrogen receptor alpha	ESR1	P03372	CHEMBL206	Nuclear receptor
2	Estrogen receptor beta	ESR2	Q92731	CHEMBL242	Nuclear receptor
3	Testis-specific androgen-binding protein	SHBG	P04278	CHEMBL3305	Secreted protein
4	Androgen Receptor	AR	P10275	CHEMBL1871	Nuclear receptor
5	Cytochrome P450 19A1	CYP19A1	P11511	CHEMBL1978	Cytochrome P450
6	Serotonin transporter	SLC6A4	P31645	CHEMBL228	Electrochemical transporter
7	Estrogen-related receptor alpha	ESRRA	P11474	CHEMBL3429	Nuclear receptor
8	Estrogen-related receptor beta	ESRRB	O95718	CHEMBL3751	Nuclear receptor
9	G-protein coupled estrogen receptor 1	GPER1	Q99527	CHEMBL5872	Family A G protein-coupled receptor
10	Steryl-sulfatase	STS	P08842	CHEMBL3559	Enzyme
11	Adenylate cyclase type 10	ADCY10	Q96PN6	CHEMBL5854	Enzyme
12	Glucocorticoid receptor	NR3C1	P04150	CHEMBL2034	Nuclear receptor
13	Estradiol 17-beta-dehydrogenase 1	HSD17B1	P14061	CHEMBL3181	Enzyme
14	DNA polymerase alpha subunit	POLA1	P09884	CHEMBL1828	Transferase
15	Solute carrier family 22-member 2	SLC22A2	O15244	CHEMBL1743122	Electrochemical transporter
16	Norepinephrine transporter	SLC6A2	P23975	CHEMBL222	Electrochemical transporter
17	Dopamine transporter	SLC6A3	Q01959	CHEMBL238	Electrochemical transporter
18	Nuclear receptor subfamily 1 group I member 3	NR1I3	Q14994	CHEMBL5503	Nuclear receptor
19	Insulin-like growth factor I receptor	IGF1R	P08069	CHEMBL1957	Kinase
20	Tyrosine-protein kinase SRC	SRC	P12931	CHEMBL267	Kinase
21	Vascular endothelial growth factor receptor 2	KDR	P35968	CHEMBL279	Kinase
22	ALK tyrosine kinase receptor	ALK	Q9UM73	CHEMBL4247	Kinase
23	Progesterone receptor	PGR	P06401	CHEMBL208	Nuclear receptor
24	Arachidonate 15-lipoxygenase	ALOX15	P16050	CHEMBL2903	Enzyme
25	Arachidonate 12-lipoxygenase	ALOX12	P18054	CHEMBL3687	Enzyme

26	Serotonin 2b (5-HT2b) receptor	HTR2B	P41595	CHEMBL1833	Family A G protein-coupled receptor
27	LXR-alpha	NR1H3	Q13133	CHEMBL2808	Nuclear receptor
28	LXR-beta	NR1H2	P55055	CHEMBL4093	Nuclear receptor
29	Aldo-keto-reductase family 1 member C3	AKR1C3	P42330	CHEMBL4681	Enzyme
30	Tyrosine-protein kinase FYN	FYN	P06241	CHEMBL1841	Kinase
31	Focal adhesion kinase 1	PTK2	Q05397	CHEMBL2695	Kinase
32	Histone deacetylase 3	HDAC3	O15379	CHEMBL1829	Eraser
33	Cytochrome P450 24A1 *(by homology)*	CYP24A1	Q07973	CHEMBL4521	Enzyme
34	Transthyretin	TTR	P02766	CHEMBL3194	Secreted protein
35	Leukotriene B4 receptor 1	LTB4R	Q15722	CHEMBL3911	Family A G protein-coupled receptor
36	Serotonin 1a (5-HT1a) receptor	HTR1A	P08908	CHEMBL214	Family A G protein-coupled receptor
37	Serotonin 1b (5-HT1b) receptor	HTR1B	P28222	CHEMBL1898	Family A G protein-coupled receptor
38	Serotonin 7 (5-HT7) receptor	HTR7	P34969	CHEMBL3155	Family A G protein-coupled receptor
39	Serotonin 6 (5-HT6) receptor	HTR6	P50406	CHEMBL3371	Family A G protein-coupled receptor
40	Acetylcholinesterase	ACHE	P22303	CHEMBL220	Hydrolase
41	DNA polymerase beta *(by homology)*	POLB	P06746	CHEMBL2392	Enzyme
42	Estradiol 17-beta-dehydrogenase 2	HSD17B2	P37059	CHEMBL2789	Enzyme
43	Alpha-2b adrenergic receptor	ADRA2B	P18089	CHEMBL1942	Family A G protein-coupled receptor
44	Muscarinic acetylcholine receptor M2	CHRM2	P08172	CHEMBL211	Family A G protein-coupled receptor
45	Muscarinic acetylcholine receptor M1	CHRM1	P11229	CHEMBL216	Family A G protein-coupled receptor
46	Serotonin 2c (5-HT2c) receptor	HTR2C	P28335	CHEMBL225	Family A G protein-coupled receptor
47	Beta-3 adrenergic receptor	ADRB3	P13945	CHEMBL246	Family A G protein-coupled receptor
48	Adenosine A3 receptor	ADORA3	P0DMS8	CHEMBL256	Family A G protein-coupled receptor
49	Delta opioid receptor	OPRD1	P41143	CHEMBL236	Family A G protein-coupled receptor
50	Vanilloid receptor	TRPV1	Q8NER1	CHEMBL4794	Voltage-gated ion channel
51	Sonic hedgehog protein *(by homology)*	SHH	Q15465	CHEMBL5602	Unclassified protein
52	Mu opioid receptor	OPRM1	P35372	CHEMBL233	Family A G protein-coupled receptor
53	Kappa Opioid receptor	OPRK1	P41145	CHEMBL237	Family A G protein-coupled receptor
54	Histone deacetylase 6	HDAC6	Q9UBN7	CHEMBL1865	Eraser
55	Alpha-2a adrenergic receptor	ADRA2A	P08913	CHEMBL1867	Family A G protein-coupled receptor
56	Adrenergic receptor alpha-2	ADRA2C	P18825	CHEMBL1916	Family A G protein-coupled receptor
57	Neurokinin 2 receptor	TACR2	P21452	CHEMBL2327	Family A G protein-coupled receptor
58	Muscarinic acetylcholine receptor M3	CHRM3	P20309	CHEMBL245	Family A G protein-coupled receptor

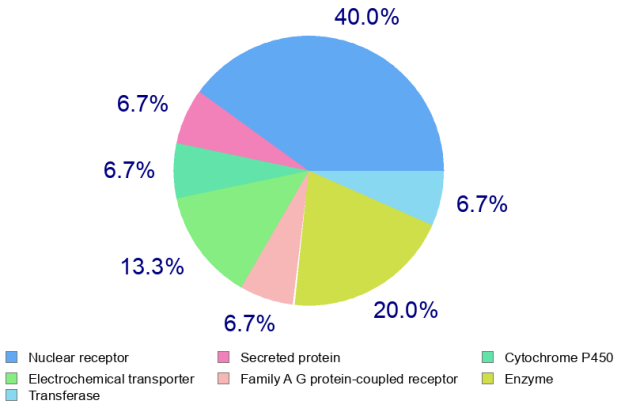

Figure 3. Distribution percentage of Estradiol binding proteins

Table 3. List of estriol binding proteins in homo sapiens

Sr. No.	Target	Common name	Uniprot ID	ChEMBL ID	Target Class
1	Estrogen receptor alpha	ESR1	P03372	CHEMBL206	Nuclear receptor
2	Serotonin transporter	SLC6A4	P31645	CHEMBL228	Electrochemical transporter
3	Estrogen receptor beta	ESR2	Q92731	CHEMBL242	Nuclear receptor
4	Testis-specific androgen-binding protein	SHBG	P04278	CHEMBL3305	Secreted protein
5	DNA polymerase alpha subunit	POLA1	P09884	CHEMBL1828	Transferase
6	Steryl-sulfatase	STS	P08842	CHEMBL3559	Enzyme
7	Adenylate cyclase type 10	ADCY10	Q96PN6	CHEMBL5854	Enzyme
8	Estradiol 17-beta-dehydrogenase 1	HSD17B1	P14061	CHEMBL3181	Enzyme
9	Androgen Receptor	AR	P10275	CHEMBL1871	Nuclear receptor
10	Insulin-like growth factor I receptor	IGF1R	P08069	CHEMBL1957	Kinase
11	Tyrosine-protein kinase SRC	SRC	P12931	CHEMBL267	Kinase
12	Vascular endothelial growth factor receptor 2	KDR	P35968	CHEMBL279	Kinase
13	ALK tyrosine kinase receptor	ALK	Q9UM73	CHEMBL4247	Kinase
14	Cytochrome P450 19A1	CYP19A1	P11511	CHEMBL1978	Cytochrome P450
15	Glucocorticoid receptor	NR3C1	P04150	CHEMBL2034	Nuclear receptor
16	Solute carrier family 22 member 2	SLC22A2	O15244	CHEMBL1743122	Electrochemical transporter
17	Nuclear receptor subfamily 1 group I member 3	NR1I3	Q14994	CHEMBL5503	Nuclear receptor
18	Estrogen-related receptor alpha	ESRRA	P11474	CHEMBL3429	Nuclear receptor
19	Estrogen-related receptor beta	ESRRB	O95718	CHEMBL3751	Nuclear receptor
20	G-protein coupled estrogen receptor 1	GPER1	Q99527	CHEMBL5872	Family A G protein-coupled receptor
21	Progesterone receptor	PGR	P06401	CHEMBL208	Nuclear receptor
22	Serotonin 2b (5-HT2b) receptor	HTR2B	P41595	CHEMBL1833	Family A G protein-coupled receptor
23	Arachidonate 15-lipoxygenase	ALOX15	P16050	CHEMBL2903	Enzyme
24	Arachidonate 12-lipoxygenase	ALOX12	P18054	CHEMBL3687	Enzyme
25	Norepinephrine transporter	SLC6A2	P23975	CHEMBL222	Electrochemical transporter
26	Dopamine transporter	SLC6A3	Q01959	CHEMBL238	Electrochemical transporter
27	Aldo-keto-reductase family 1 member C3	AKR1C3	P42330	CHEMBL4681	Enzyme
28	LXR-alpha	NR1H3	Q13133	CHEMBL2808	Nuclear receptor

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30	Tyrosine-protein kinase FYN	FYN	P06241	CHEMBL1841	Kinase
31	Focal adhesion kinase 1	PTK2	Q05397	CHEMBL2695	Kinase
32	Histone deacetylase 3	HDAC3	O15379	CHEMBL1829	Eraser
33	Cytochrome P450 24A1 *(by homology)*	CYP24A1	Q07973	CHEMBL4521	Enzyme
34	G-protein coupled receptor 55	GPR55	Q9Y2T6	CHEMBL1075322	Family A G protein-coupled receptor
35	Cannabinoid receptor 1	CNR1	P21554	CHEMBL218	Family A G protein-coupled receptor
36	N-arachidonyl glycine receptor	GPR18	Q14330	CHEMBL2384898	Family A G protein-coupled receptor
37	Cannabinoid receptor 2	CNR2	P34972	CHEMBL253	Family A G protein-coupled receptor
38	Transthyretin	TTR	P02766	CHEMBL3194	Secreted protein
39	Leukotriene B4 receptor 1	LTB4R	Q15722	CHEMBL3911	Family A G protein-coupled receptor
40	Serotonin 1a (5-HT1a) receptor	HTR1A	P08908	CHEMBL214	Family A G protein-coupled receptor
41	Serotonin 1b (5-HT1b) receptor	HTR1B	P28222	CHEMBL1898	Family A G protein-coupled receptor
42	Serotonin 7 (5-HT7) receptor	HTR7	P34969	CHEMBL3155	Family A G protein-coupled receptor
43	Serotonin 6 (5-HT6) receptor	HTR6	P50406	CHEMBL3371	Family A G protein-coupled receptor
44	Estradiol 17-beta-dehydrogenase 2	HSD17B2	P37059	CHEMBL2789	Enzyme
45	Acetylcholinesterase	ACHE	P22303	CHEMBL220	Hydrolase
46	DNA polymerase beta *(by homology)*	POLB	P06746	CHEMBL2392	Enzyme
47	Kappa Opioid receptor	OPRK1	P41145	CHEMBL237	Family A G protein-coupled receptor

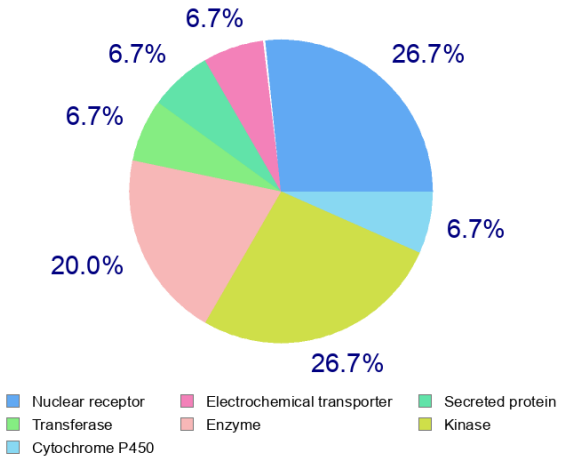

Figure 4. Distribution percentage of estriol binding protein

Estrogen is not confined to sex type. It shows its importance in regulating the metabolic processes for rolling the wheel of life (Thomas & Potter, 2013). Other than its active role in metabolism, it is important to understand the fate of estrogen or how it gets metabolized (Janicki & Schupf, 2010). Estrogen gets metabolized in the liver in two phases. Phase I is a process of Hydroxylation and Phase II is methylation and glucuronidation pathways. During Phase I, 3 biologically active estrogens are contributed to the body. 2-hydroxyestrone (2-OH) or catechol estrogen is labelled as good estrogen and thus potentially beneficial. The elevated levels of 2-hydroxyestrone have proved to be antitumoral. Whereas, 16α-OH and 4-OH are actively involved in not so friendly tissue growth which later can be alarming. 4-hydroxyestrone has been selective in its effects. Its cancer promoting report (Babiker, 2002) and neuroprotective effects involving cytoplasmic translocation

of p53 resulting from SIRT1 mediated p53 deacetylation (Choi et al., 2020). Similar observations have been reported for 16α-OH (Charneira et al., 2020). Thus, estrogen overall or its metabolites have been found to be instrumental in the diverse pathophysiological conditions emerging from genetic or epigenetic reasons. The deleterious effects of 4-OH are reduced by methylation and the activation of 2-OH is simultaneously conducted by converting it into 2-methoxyestrone (2-MeOE 1 and 2). Phase II (glucuronidation) facilitates the detoxication of estrogen and its excretion.

The 4- Hydroxyestradiol can do metabolic redox cycling leading to generation of chemically reactive estrogen semiquinone/quinone intermediates along with free. It is studied to be a strong carcinogen in hamster kidney of hamster (Li & Li, 1987; Liehr et al., 1986). The reaction of amino acids and 16α-hydroxyestrone leading to formation of Schiff base, theoretically implying same reaction with other macromolecules like DNA (Xu et al., 2002). It is a crucial molecule which is requisite in bone formation, neural function, cardiovascular health, immunity, and glucose homeostasis (Babiker, 2002).

Estrogen imbalance

The pathophysiology emerging due to estrogen imbalance preferably occurs with increasing age but can also be preponed with stressful and unhealthy lifestyle. Reportedly, there are around 6000 (approx.) endocrine disorders that are being caused by hormone imbalance (Ali et al., 2018). One of the recurrent complaints in daily ophthalmic practice is dry eye. It is a chronic inflammatory disorder that results in visual disturbances, discomforted eyes, and ocular surface damage. Ocular surface is an integrated unit, any affliction in it leads to unstable preocular tear film. It was investigated that increasing percentage of dry eye is directly related to the increasing age, mostly in females probably because of the decrease in the level of sex hormones. However, it is still contradictory to conclude whether estrogen or androgen imbalance results in dry eye onset (Stevenson et al., 1993; Versura et al., 2015).

Estrogens and progestins are found to have profound impact on central serotonergic and opioid neurons, governing both neuronal activity and receptor density. Menstrual related migraine is provoked primarily by estrogen abolition rather than sustaining high or low estrogen level. Variation in estrogen level with pregnancy (increased) and menopause (decreased) is found to aggravate headache (Versura & Campos, 2005). Reports also claim estrogen dominance to be associated with uterine cancer, polycystic ovarian syndrome, fibroids, and endometriosis (Kim et al., 2013).

In 234th national meeting of the American Chemical Society, researchers have shown through series of animal experiments on how estrogen receptors on hypothalamus serve in controlling food intake, fat distribution and energy expenditure. Estrogen receptor alpha accounts for regulation in energy expenditure and food intake. These receptors are densely located in two of the sub-areas of ventromedial hypothalamus, the ventrolateral region, and the Arcuate region. Deactivation of ER alpha in both these regions leads to plummeting metabolic rate and energy expenditure along with increase in weight, primarily in females (Shufelt et al., 2017). Estrogen combines with the adipose tissue (AT) genes and increases gluteofemoral adipose tissue mass and decreases central adipose tissue mass, in reproductive females, this reduces the chances of cardiovascular disorders (CVD) and type 2 diabetes mellitus (T2DM). Decline in the level of estrogen during menopause, increases total AT mass and reduces lean body mass (Bjørndal et al., 2011; Leeners et al., 2017). Nonetheless, estrogen is required in sufficient amounts to maintain the levels of serotonin which is a neurotransmitter that prevents headaches, temperament regulation, irritability, and depression. It leads to the decreasing serotonin breakdown or changing mRNA and protein levels of certain serotonin markers (Silberstein & Merriam, 1993). Temporomandibular disorders (TMD), a type of musculoskeletal condition manifesting in pain and dysfunction of mastication muscles and temporomandibular joint are found to mostly affect the women in their reproductive age (Furquim et al., 2015; Ribeiro-Dasilva et al., 2017). The role of estrogen in TMD demands more understanding.

Estrogen affects muscles, ligaments, and tendons and hence has an indirect effect on health of bones (Chidi-Ogbolu & Baar, 2019). Sarcopenia, osteoporosis, and osteoarthritis is commonly observed in post and perimenopausal women leading to affect normal life. Osteoarthritis and osteoporosis lead to disability in women more than men (Van Dijk et al., 2015).

Estrogen imbalance

The estrogen imbalance is not a result of a single cause but a group of allies including aging which can be responsible for the natural cause. Among the others include unhealthy lifestyle practices, excessive consumption of non-organic and animal products with excessive amount of estrogen and cosmetics, consumption of alcohol and undesired intake of food. Increased consumption of alcohol hinders the estrogen detoxification in liver and increases estradiol level, which is correlated to breast cancer (Singletary & Gapstur, 2001). Smoking is known to have a significant impact on the reproductive health of women, it affects the estrogen metabolism and leads to elevated level of steroid hormone binding

globulin, this together leads to low level of free circulating estrogen, causing alteration in menstrual cycle, and increases risk of anovulation. This has also been related to increase osteoporosis cases in female with smoking history (Kapoor & Jones, 2005). Toxins present in the environment in the form of pesticides, insecticides and fertilizers interfere with the hormonal level, especially in estrogens. Plethora of studies have reported that DDT (Dichlorodiphenyltrichloroethane) which is a synthetic chemical shows estrogenic effect and acts as an endocrine disruptor. An observation stated that DDT had significantly reduced the hatchability of eggs in pelagic birds (Darbre, 2018; Rogan & Ragan, 2007). Endocrine disrupting chemicals (EDCs) can affect the functioning of hormones at various steps, which includes altering the endocrine gland hormone synthesis, manipulating transport of hormones to target organs, or by competing for protein receptor binding. While doing so, they mimic the role of hormones secreted by body and causes hindrance in the functioning of naturally secreted hormones (Ali et al., 2018). Hormone imbalance has direct relation with food consumption, use of drugs and several other factors like workload and depression (Kim et al., 2013; Silberstein & Merriam, 1993), which is personalized and only little can be done to overcome.

Ways involved in the treatment of estrogen imbalance

Hormone replacement therapy

Fluctuating hormone levels during menopause can lead to various discomforts like vaginal dryness, osteoporosis, night sweats, and hot flashes. To alleviate these symptoms, hormone replacement therapy (HRT) was introduced. Numerous approaches have been explored, including estrogen therapy, combined estrogen and progesterone therapy, tissue selective estrogen complex, androgens, selective estrogen receptor modulators, tibolones, offering women relief from the challenges of menopause through scientific advancements (Kutlesic et al., 2016a, b). The history of hormone replacement therapy dates to the 1960s, gained popularity in 1990. The first results of women's health initiative (WHI) in 2002 revealed that effects of hormone replacement therapy were detrimental than beneficial, and the use of HRT plummeted. Later another study was put forth to stem the correction of estrogen using HRT as downregulating the deleterious effects of cardiovascular disorders and in eliminating coronary disorders (Cagnacci & Venier, 2019). In non-hysterectomised women, providing estrogen alone during hormone replacement therapy is associated with greater risk of endometrial cancer. The risk is reduced when progesterone is assisted with estrogen (Emons et al., 2004). Tibolone therapy is mainly preferred by women who have history of endometriosis and face side effects with conventional menopausal hormone therapy (MHT) (Fait, 2019). It curbs vasomotor problems, improves vaginal atrophy, and has protective effect on bone mass and prevents cell proliferation of breast epithelial cells. Selective estrogen receptor modulator (SERM): Tamoxifen shows anti-estrogenic effects and plays a major role in preventing breast cancer. Bazedoxifine helps in reducing bone mass loss in postmenopausal women, thus reducing the chances of developing osteoporosis (Fait, 2019; Lee et al., 2018). Genito-urinary syndrome of menopause (GSM) can be treated through intra vaginal estrogens (Roberts & Hickey, 2016). Bioidentical hormone therapy is gaining popularity for its anti-aging properties on skin, at the same time dearth of evidence is found about the side effects and efficacy of this therapy (Borda et al., 2019). It is also used as a replacement for conventional hormone replacement therapy thereby having a similar molecular structure to that of naturally synthesized hormones. Recently, symptomatic women of less than 60 years of age are found to have more benefits of menopausal hormone therapy with lesser risk than the older women (Stuenkel, 2015).

Non hormonal therapy

This therapy is mainly used for patients that have contraindications for menopausal hormone therapy.

Serotonin uptake inhibitors

Paroxetine has shown great effects in reducing severity and frequency of hot flashes when compared to placebo. It was the first drug approved by US food and drug administration (FDA) for curbing vasomotor symptoms (Fait, 2019; Rahimzadeh et al., 2018). It also ameliorates anxiety, depression, and sleep in the menopausal females (Kutlesic et al., 2016a, b). Phytoestrogens and diet supplementing phytoestrogens including isoflavonoids, soy, flavonoids, stilbenes, and lignans (Dixon, 2004; Fait, 2019) are crucial for the treatment of menopausal symptoms, osteoporosis, cardiovascular diseases, metabolic and immune diseases, skin aging, and cancer (Sirotkin & Harrath, 2014). Phytoestrogens help in protection and treatment of several types of cancers (Qadir & Cheema, 2017). According to a demographic study, Asian women consuming phytoestrogen rich diet showed lower occurrence of climacteric syndrome and osteoporosis along with lifestyle disorders like breast carcinoma, when compared to the women population of Europe and North America (Fait, 2019). Pollen extract: Though the pollen extracts do not have estrogenic properties, they are reported to block the reuptake of serotonin in the hypothalamus and influence sleep and thermoregulation. The study showed that a dosage of 160mg (twice a day) of pollen extract significantly reduced the menopausal symptoms (Fait, 2019; Fait et al., 2019). Black cohosh: It is a medicinal plant derived from buttercup family, native to North America, shows estrogenic properties and

was found to be effective in sleep management in menopausal women (Jiang et al., 2015). ("LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases," 2012). Xenoestrogen, an estrogen mimicking synthetic chemical with selective and variable binding efficacy for estrogen receptors show resemblance to 17B-estradiol. Consumed via mostly unhealthy sources may lead to estrogen dominance and become the major cause of hypothyroidism (Silberstein & Merriam, 1993).

Conclusion

This review systematically assesses our current understanding of known and novel estrogen and its related hormones-estradiol and estriol interactions with diverse receptors using the SwissTargetPrediction tool. The observations reveal a complex and wide-ranging network of interactions involving different types of receptors, including nuclear receptors, enzymes, kinases, and G protein-coupled receptors, all of which are associated with a range of physiological and pathological conditions. These findings not only confirm the intricate role of estrogen and its co-hormones but also highlight several new targets that could be useful in developing future therapies. By mapping binding efficiencies across different receptor classes, our findings provide a clear molecular framework that underpins the groundwork for future experimental validation and targeted drug development. A summary of Estrogen binding proteins shows enzymatic receptors made up the largest group (22%), followed by kinases (18%), nuclear receptors (16%), and GPCRs (10%). Estradiol demonstrated effective binding with nuclear receptors (40%), Enzymatic receptors (20%) and Electrochemical Transporters (13.3%). Estriol exhibited affinity for nuclear proteins (26.7%), Kinases (26.7%) and Enzymes (20%). With subject to type of hormone, although other proteins shared smaller percentages marking trivial contribution they should not be overlooked as they may offer valuable insights. Irrespective of the share percentage disparity in the classes observed, the targets uncovered hold equal potential for novel therapeutic targets. There have been several common binding targets among the molecules under examination. By understanding these networks better, we can effectively overcome limitations inherent in traditional experimental techniques, paving the way for precision medicine and personalized treatment strategies in hormone-related disorders. Integrating multi-omics approaches, comprehends and enhances the interpretation of complex datasets and advances the research in recommending molecular approach for personalized treatment strategies and innovative therapeutic approaches, ultimately advancing patient care, and enhancing the quality of life for women across diverse populations.

Author contributions

The first two authors have contributed to bioinformatics data compilation. The third author helped in the framework and finalization of manuscript. The concept and finalization of the manuscript was conducted by the corresponding author.

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