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Clinical Pharmacology Of Selective Oestrogen Receptor Modulators In The Prevention Of Breast Cancer, Osteoporosis, Coronary Heart Disease, Alzheimer's Disease, Use In Hormone Replacement Therapy, Cholesterol Metabolism

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Abstract:
Oestrogen is the key regulatory hormone for the development and maintenance of reproductive functions and affects various physiological systems, including the skeletal, cardiovascular, and central nervous systems. oestrogen replacement therapy (ERT) is highly effective in postmenopausal women, addressing menopausal symptoms and providing beneficial effects on osteoporosis and coronary heart disease. However, ERT is associated with significant side effects, such as an increased risk of breast cancer. To mitigate these risks, selective oestrogen receptor modulators (SERMs) have been developed. SERMs are a growing class of synthetic nonsteroidal compounds that act as oestrogen receptor agonists or antagonists in a tissue-specific manner. They can selectively activate or inhibit oestrogen receptors in different tissues throughout the body. SERMs are used to treat a variety of conditions, including ER-positive breast cancer, osteoporosis, coronary heart disease, Alzheimer's disease, and cholesterol metabolism disorders in postmenopausal women. Specific SERMs are employed for different conditions: raloxifene for osteoporosis, tamoxifen and toremifene for breast cancer, clomiphene for the induction of ovulation, and ormeloxifene for oral contraception. Arzoxifene is used for altering cholesterol metabolism. Each SERM forms a unique complex with oestrogen receptors, influencing target tissues and resulting in a tissue-selective pharmacological profile. This unique mechanism of action translates into specific safety and efficacy profiles for each SERM. The surprising pharmacology of SERMs has sparked interest in developing new selective medications, allowing for precise treatment of various diseases. This article reviews the pharmacological properties of SERMs and explains how they differ from oestrogen in their actions.

Keyword: *SERM, ERT, Osteoporosis, breast cancer, cholesterol metabolism, Alzheimer's disease*

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I. Introduction

Oestrogen-containing medications are widely utilized to treat conditions associated with menopause [1]. Oestrogen is a crucial hormone for the development and maintenance of reproductive functions and has significant impacts on various physiological systems, including the skeletal, cardiovascular, and central nervous systems [2]. Oestrogen replacement therapy (ERT) is particularly effective for postmenopausal women, not only alleviating menopausal symptoms but also providing benefits for osteoporosis and coronary heart disease [3]. For instance, oestrogen can inhibit bone resorption, making it useful in treating osteoporosis [4]. Additionally, various studies suggest oestrogen has positive effects on the cardiovascular system, potentially reducing the incidence of coronary heart disease [5]. It also benefits the central nervous system by possibly enhancing cognitive function and delaying the onset of Alzheimer's disease [6]. ERT has been shown to positively impact mortality and morbidity in postmenopausal women [7]. However, despite these medical benefits, the number of women who continue ERT for longer than one year is relatively low due to concerns about an increased risk of breast cancer associated with oestrogen. This concern has driven the need for novel oestrogen receptor modulators, which retain oestrogen's beneficial effects on most target organs while remaining inactive in the breast. Developing such modulators is the first step towards creating the best hormone replacement therapy [8].

Oestrogen exerts its effects by binding to oestrogen receptors (ER), which are nuclear receptors functioning as ligand-inducible transcription factors. These receptors regulate the expression of target genes involved in metabolism, development, and reproduction. A key role of these receptors is to modify the transcriptional response in target cells to hormones such as oestrogens, androgens, and progestins[9].

MOA: The function of oestrogen is to switch the inactive receptor to a transcriptionally active form[9]. Figure no 1: illustrates the Dual action mechanism of SERMs on gene regulation through oestrogen receptors (ER). Figure no 2: Depicts types of oestrogen receptors.

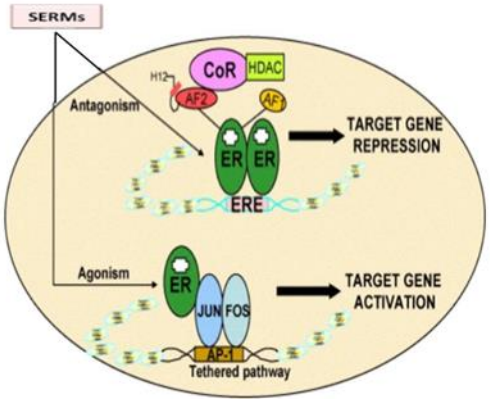

Fig:1 Dual action mechanism of SERMs on gene regulation through oestrogen receptors (ER)

ER receptors are of 2 types a

- ER α
- ER β

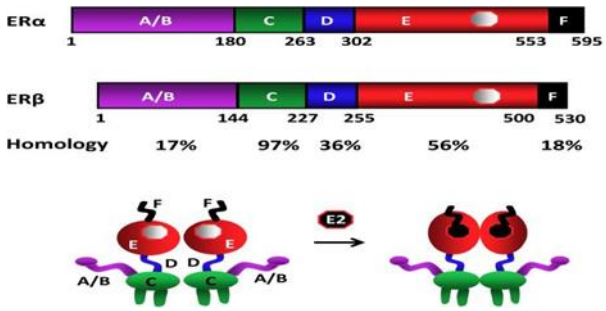

Fig:2 Types of oestrogen receptors

ER α is present in the uterus, vagina, breast, blood vessels, mammary glands, ovary
ER β is present in the prostate, bone, heart, intestine, adipose tissue, immune system

In the absence of a ligand, the oestrogen receptor (ER) exists in an inactive form within the nucleus of target cells. Upon binding with an agonist, the ER undergoes an activation event, interacting with specific DNA response elements in the promoters of target genes, thereby altering the phenotype of the cells[10]

Classification Of Serm:

Table no 1: Classification of SERM based on chemical structure

S.no	Name of the class	Examples
1	Phytoestrogens	Genistein, Daidzein
2	Triphenylethylenes	Tamoxifen Clomifene Droloxifene Fispemifene Idoxifene Miproxifene Ospemifene Toremifene
3	Benzothiophenes	Raloxifene Arzoxifene
4	Naphthalenes	Lasoxifene Trioxifene

		Nafoxifene
5	Benzopyrans	Acolbifene Levormeloxifene Ormeloxifene
6	Indoles	Pipendoxifene Bazodoxifene

Triphenylethylenes

Triphenylethylenes are primarily used in the treatment of oestrogen-dependent breast cancer, benefiting around 10 million women. First-generation selective oestrogen receptor modulators (SERMs) are effective in treating all types of breast cancers except ER-negative tumours in premenopausal women.

Clomiphene is the first SERM used clinically, specifically for ovulation induction, with no effect in postmenopausal women. It has potent anti-tumour effects for breast cancer and decreases high cholesterol levels, though it does not affect triglycerides induced by ovariectomy.

Toremifene is used for the treatment of breast cancer as an alternative to tamoxifen. Both drugs are similar in reducing serum lipids, but their effects on bone mineral density differ. Tamoxifen potently increases bone mineral density but is associated with hepatocarcinogenesis due to CYP450 enzymatic system oxidation. It also carries a risk of developing pre-malignant endometriosis, raising concerns about uterine safety.

Fesmiphene acts as an antagonist in breast tissue, an agonist in bone, and promotes re-endothelialisation.

Benzothiophenes

Raloxifene is the first selective oestrogen receptor modulator (SERM) effective in treating bone metabolic disorders and postmenopausal osteoporosis, preventing cardiovascular disease in postmenopausal women, and treating ER-positive breast cancer [12].

Arzoxifene is a SERM that acts as a potent oestrogen antagonist in mammary and uterine tissues while functioning as an oestrogen agonist to maintain bone density and lower serum cholesterol. It is highly effective in preventing mammary cancer induced by the carcinogen nitrosomethylurea and is significantly more potent than raloxifene in this regard. Unlike tamoxifen, Arzoxifene lacks uterotrophic effects, suggesting it is unlikely to increase the risk of developing endometrial carcinoma.

Napthalenes

Lasoxifene used for the treatment of male osteoporosis secondary to hypothyroidism significantly decreases the LDL cholesterol.

Indoles

Pipendoxifene is hormone-dependent and inhibits oestrogen-stimulated growth of cell line MCF1 and inhibits the proliferation of endothelial and ovarian cancers that are resistant to tamoxifen[11] Figure no 3: depicts the different types of selective oestrogen receptor modulators

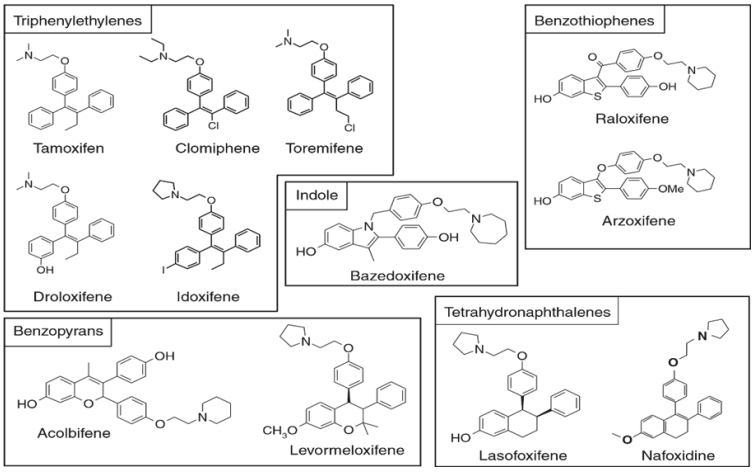

Fig: 3 Types of SERM structures.

Clinical pharmacology of SERM

Selective oestrogen receptor modulators (SERMs) are diverse compounds that interact with intracellular oestrogen receptors in target organs either as agonists or antagonists[12]. Over the past decade, these

drugs have been extensively studied and proven highly versatile for treating various conditions related to the health of postmenopausal women, such as hormone-responsive cancers and osteoporosis[13].

Osteoporosis: It is a systemic skeletal disorder characterized by low bone mass, leading to decreased bone strength and an increased risk of fractures. Often referred to as a "silent disease," osteoporosis typically presents without symptoms until a fracture occurs. It is a significant cause of fractures in postmenopausal women and older men[14]. In postmenopausal women, fractures are primarily due to oestrogen deficiency after menopause and an imbalance between bone resorption by osteoclasts and bone formation by osteoblasts. Additional contributing factors include vitamin D deficiency, secondary hyperparathyroidism, and reduced mechanical loading, all of which can exacerbate bone loss[15].

Bone strength and the risk of osteoporotic fractures are determined by bone mineral density (BMD), which is assessed using Dual Energy X-ray absorptiometry (DEXA). According to WHO criteria, osteoporosis is diagnosed when BMD values fall more than 2.5 standard deviations below the young adult reference mean. Treatment with selective oestrogen receptor modulators (SERMs) is recommended, as these drugs selectively target ERα receptors on osteoclasts, reducing bone resorption and increasing bone mineral density[16].

Oestrogen has positive effects on bone health by decreasing the production and lifespan of osteoclasts (bone-resorbing cells), stimulating osteoblast (bone-forming cells) activity, and influencing calcium homeostasis. The antiresorptive action of oestrogen is mediated through its effects on the receptor activator of the NF-kappa B ligand (RANKL)/RANK/osteoprotegerin system, which is the primary regulator of osteoclast activity. Oestrogen also reduces the production of various proresorptive cytokines and has direct effects on osteoclasts. Figure no:4 describes MOA of oestrogen on different cells.

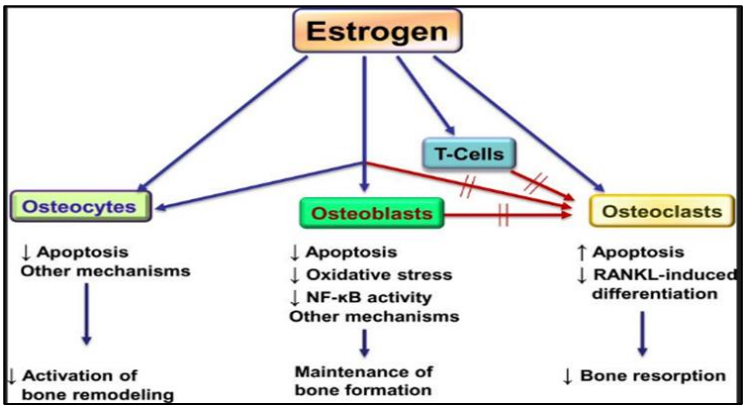

Fig:4 MOA of oestrogen on different cells

Positive effects on osteoporosis have been observed with SERMs such as raloxifene and tamoxifen. These drugs, along with other SERMs like arzoxifene, Idoxifene, bazedoxifene, and toremifene, prevent bone loss in vertebral, distal femur, and trabecular-rich bone sites[17]. Raloxifene, for example, suppresses mediators of osteoclast differentiation by binding to nuclear receptors (RANK receptors), leading to an increase in antiresorptive factors like osteoprotegerin. Biochemical markers of bone turnover, such as serum osteocalcin and urinary collagen, are also suppressed by SERMs. Furthermore, in MLO-Y4 osteocyte cells, raloxifene prevents stress-induced apoptosis and inhibits the generation of reactive oxygen species such as hydrogen peroxide[18].Figure no :5 demonstrates the impact of oestrogen deficiency on different cells

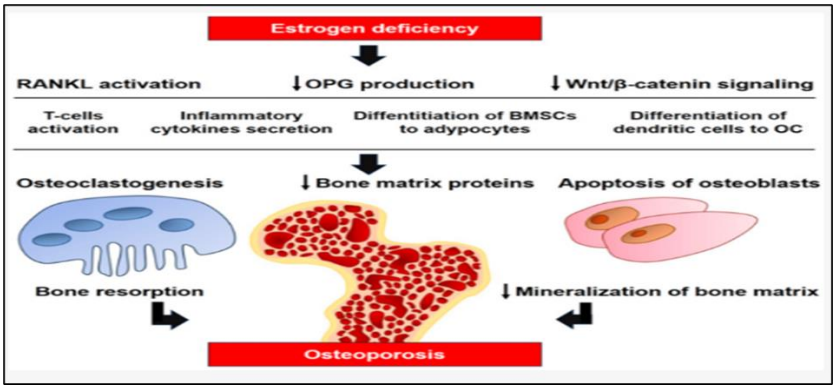

Fig:5 Impact of oestrogen deficiency on different cells

MOA of SERMs on different pathways to protect bone health by inhibiting bone resorption and promoting bone formation is shown in Figure no 6.

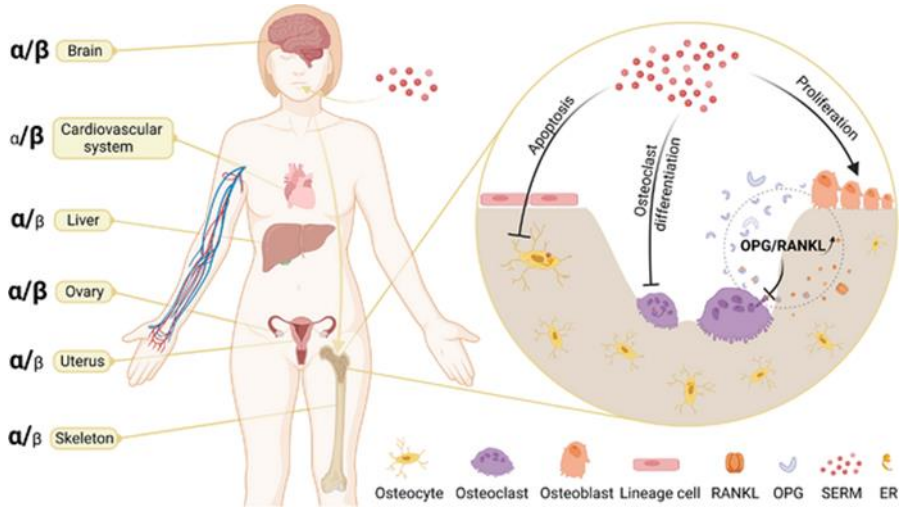

Fig:6 MOA of SERMs on different pathways to protect bone health by inhibiting bone resorption and promoting bone formation.

Uterus: SERM inhibits endometrial proliferation. These changes can be evaluated by ER mediated alkaline phosphate production, creatinine kinase production[19].

Ovarian Effects: It is indirectly regulated via oestrogen action on HPO [Hypothalamus pituitary ovarian] axis. SERM increases serum luteinizing hormone inhibition of ovarian follicle maturation. Antagonist of 17-B oestradiol in pituitary suggest the elevation of LH related to blockade of feedback inhibitory properties of oestrogen on HPO Axis [20]

Hormonal Effects: In premenopausal women SERM predominantly exert a stimulatory effect on HPO Axis and ovulation with excitatory effects on GNRH, FSH, LH with clomiphene derivatives or tamoxifen. In postmenopausal women SERM exhibits a partial agonist action on HPO Axis and decrease in LH and FSH, Prolactin [21].

Vaginal Effects: A decrease in oestradiol levels associated with menopause are the causes for various vaginal related symptoms like aching, drying, dyspareunia. Hormonal replacement therapy provides relief for postmenopausal women. SERM demonstrate a range of properties on vaginal symptoms of menopause. Most reports in postmenopausal women indicates oestrogen like maturation of vaginal epithelial cells with tamoxifene and tormitefene[17].

Breast Cancer: It is a disease in which cells in the breast grow uncontrollably, forming a mass of tissue known as a tumor. It is one of the most common cancers among women, second only to skin cancer, and primarily affects women over the age of 50. Breast cancer can originate in different parts of the breast, which is composed of three main components: lobules, ducts, and connective tissue. Lobules produce milk, ducts carry milk to the nipple, and connective tissue, made up of fibrous and fatty tissue, surrounds and supports the lobules and ducts. Most breast cancers begin in the ducts or lobules

Prolonged use of oestrogen can induce the proliferation of cancerous MCF-7 cells. Selective oestrogen receptor modulators (SERMs) inhibit the proliferation of these cells. Raloxifene and tamoxifen, developed as antagonists of oestrogen in oestrogen-dependent tumor tissue lining the breast cells, are used in the treatment of breast cancer[17]. Figure no : 7 depicts the action of tamoxifen on the breast cancer cell

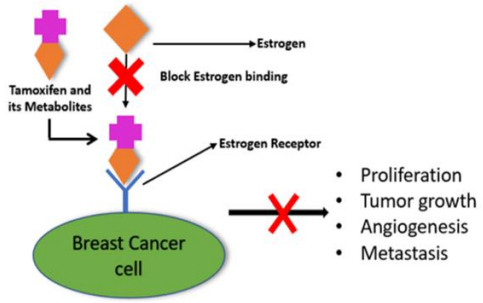

Fig:7 The action of tamoxifen on the breast cancer cell.

Cholesterol Metabolism: Cholesterol is a complex substance that can either be obtained from the diet (exogenous) or synthesized de novo by various cells in the body (endogenous). The liver is the primary site for endogenous cholesterol synthesis. Cholesterol is essential for various body functions, including the synthesis of cell membranes, hormones, and the production of substances necessary for fat digestion. Hypercholesterolemia, also called high cholesterol, is the presence of high levels of cholesterol in the blood. It is a form of hyperlipidemia (high levels of lipids in the blood), hyperlipoproteinemia (high levels of lipoproteins in the blood), and dyslipidemia (any abnormalities of lipid and lipoprotein levels in the blood [22].

Elevated levels of non-HDL cholesterol and LDL in the blood may be a consequence of diet, obesity, or inherited (genetic) diseases. Hypercholesterolemia increases the risk of coronary artery disease, and peripheral arterial disease.

Selective oestrogen receptor modulators (SERMs) decrease **Sterol regulatory element- binding proteins (**SREBP-2) protein levels by binding to oestrogen receptors, leading to changes in the transcription of target genes in the liver that regulate cholesterol metabolism. This modulation reduces the activity of HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis, and interferes with the proteolytic activation of SREBP-2, preventing its cleavage and release into the nucleus. By lowering intracellular cholesterol levels, SERMs also reduce the activation of SREBP-2 through feedback regulation. Additionally, SERMs may induce post-translational modifications of SREBP-2 or its regulatory proteins, further decreasing its stability or nuclear localization. These actions collectively decrease the expression of genes involved in cholesterol synthesis and uptake, lowering cholesterol levels in postmenopausal women[23]. Figure no :8 describes the role of SERM in cholesterol metabolism

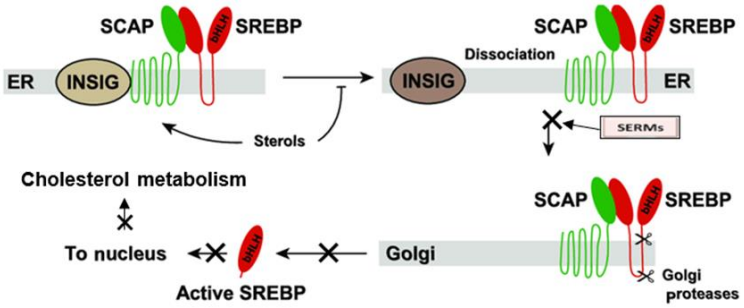

Fig:8 The role of SERM in cholesterol metabolism

ANTI-Inflammatory Action: Selective oestrogen Receptor Modulators (SERMs) exert their anti-inflammatory effects by interacting with oestrogen receptors (ERs), specifically ERα and ERβ. These receptors play a critical role in modulating the NF-κB signalling pathway, which is pivotal in inflammation. NF-κB regulates the expression of genes involved in immune responses, including pro-inflammatory cytokines, chemokines, and adhesion molecules. By binding to ERs, SERMs inhibit NF-κB activation, thereby preventing its translocation into the nucleus and reducing the production of these inflammatory mediators[24].

Moreover, SERMs influence gene expression in immune cells and vascular endothelial cells, suppressing the synthesis of inflammatory molecules such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and cytokines like IL-1 and IL-6. These actions collectively contribute to attenuating inflammation in various tissues, including the vascular system[25].

Different SERMs possess varying affinities for ERα and ERβ, resulting in tissue-specific effects. For example, tissue-selective oestrogen complexes (TSECs) activate ERs selectively in specific tissues, offering targeted anti-inflammatory benefits without affecting oestrogen receptors in reproductive tissues. This specificity enhances their potential therapeutic applications in managing inflammatory conditions across different physiological contexts[26]. Figure no 9: depicts the role of SERM in inhibition of NF-kB thereby decreasing inflammation and increasing neuroprotection**.**

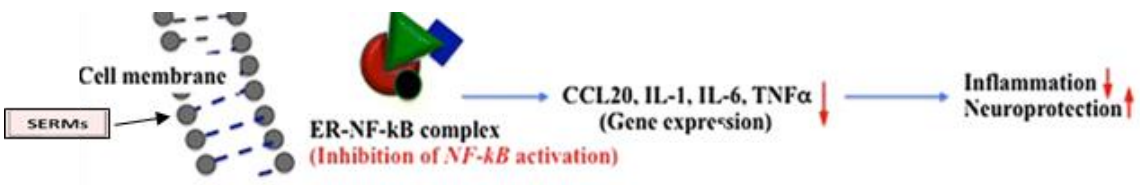

Fig:9 SERM's role in inhibiting NF-kB, thereby decreasing inflammation and increasing neuroprotection.

Coronary Heart Disease: Oestrogen receptors alpha and beta, found in coronary vessels of both men and women, play a significant role in vascular function. They contribute to endothelial vasodilation and influence processes like proliferation and apoptosis. Various selective oestrogen receptor modulators (SERMs) are utilized in treating coronary heart disease, including raloxifene, tamoxifen, lasofoxifene, bazedoxifene, acolbifene, and levormeloxifene

Raloxifene induces acute vasodilation in coronary arteries by activating endothelial nitric oxide synthase, leading to increased nitric oxide release, reduced production of free oxygen radicals, and elevated prostacyclin levels, which collectively help mitigate ischemic heart disease

Tamoxifen, on the other hand, counters hypertrophy caused by the deletion of the gene encoding FK506-binding protein by interfering with calcium cycling. Selective oestrogen receptor agonists, such as tamoxifen, offer vasoprotection through these mechanisms[27]

Pharmacology of SERM on Alzheimer's disease:

Oestrogen receptors are broadly distributed throughout the brain, with a predominant presence in the hypothalamus. In the hypothalamus, oestrogen receptors are involved in regulating reproductive hormones in the periventricular nucleus and in thermoregulation in the lateral hypothalamus. ERβ receptors are highly concentrated in regions such as the hippocampus (specifically CA1 and CA3), which are associated with learning and memory[28].

Oestrogen has neurotrophic effects, including the inhibition of acetylcholinesterase activity, which results in increased acetylcholine levels—a neurotransmitter crucial for cognition. Additionally, oestrogen reduces neural damage. SERMs mainly raloxifene and tamoxifen have demonstrated neuroprotective effects in neuroepithelial cell lines by conferring resistance to beta-amyloid-induced toxicity. They achieve this by elevating levels of seladin-1, a factor known to be downregulated in brain regions affected by Alzheimer's disease. This elevation in seladin-1 increases acetylcholine transferase activity in the hippocampus, leading to enhanced acetylcholine transmission, which supports cognitive function. Raloxifene and tamoxifen, however, produce distinct profiles regarding serotonin neurotransmission in the brain. Figure no:10 This diagram highlights the effects of SERM on cellular signaling pathways that result in neuroprotective and regenerative outcomes in the brain.

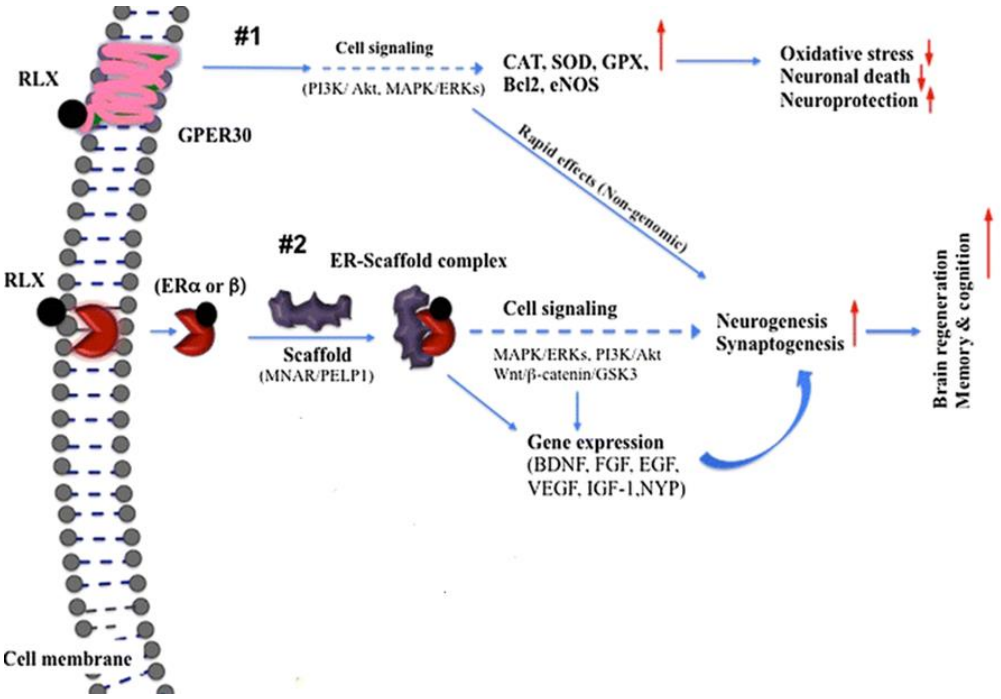

Fig:10 Effects of SERM on cellular signaling pathways that result in neuroprotective and regenerative outcomes in the brain.

II. Discussion

The use of oestrogen-containing medicines, particularly oestrogen replacement therapy (ERT), has been a cornerstone in managing menopausal symptoms and related conditions such as osteoporosis and cardiovascular diseases. Oestrogen plays a crucial role in regulating various physiological systems, including the reproductive, skeletal, cardiovascular, and central nervous systems. ERT effectively alleviates menopausal

symptoms, reduces bone resorption, and lowers the risk of osteoporosis and coronary heart disease. Moreover, it has shown potential benefits in enhancing cognitive function and delaying the onset of Alzheimer's disease. ERT works primarily through binding to oestrogen receptors (ERs) which function as transcription factors to regulate genes involved in metabolism, development, and reproduction. Despite its benefits, the increased risk of breast cancer associated with prolonged oestrogen use has limited its long-term application. This risk has driven the development of selective oestrogen receptor modulators (SERMs). Despite these advantages, the long-term use of ERT is limited due to concerns about an increased risk of breast cancer. This has led to the development of selective oestrogen receptor modulators (SERMs), which offer the advantages of oestrogen in target organs without the associated breast cancer risk. SERMs, such as raloxifene and tamoxifen, exhibit tissue-specific actions, acting as oestrogen agonists in bones to prevent osteoporosis and as antagonists in breast tissue to inhibit cancer cell proliferation. Additionally, SERMs improve cholesterol metabolism by modulating SREBP-2 protein levels, reducing cholesterol synthesis, and enhancing anti-inflammatory responses by interacting with oestrogen receptors and inhibiting NF-κB.

III. Conclusion

In summary, the advent of SERMs represents a significant advancement in hormone replacement therapy, offering a safer alternative to traditional ERT by mitigating the associated risks of breast cancer. SERMs effectively modulate oestrogen receptors to maintain bone density, reduce cholesterol levels, and exert anti-inflammatory effects, making them versatile agents in managing postmenopausal women's health. Their ability to selectively target oestrogen receptors in different tissues without uniformly activating them across all oestrogen-sensitive organs highlights their therapeutic potential. Continued research and development of novel SERMs aim to optimize their efficacy and safety profiles, potentially offering postmenopausal women an effective and safer alternative to ERT. The strategic use of SERMs could revolutionize the management of menopausal symptoms and related health issues, improving the quality of life for many women.

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