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(REVIEW ARTICLE)

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Selective Estrogen Receptor Modulators (SERMs) in non-cancer therapeutics: expanding horizons beyond oncology

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Abstract

Selective Estrogen Receptor Modulators (SERMs) represent a class of compounds that demonstrate tissue-specific agonist or antagonist activity on estrogen receptors, allowing for selective modulation of estrogenic effects across different tissues. Originally developed for the treatment of hormone receptor-positive breast cancer, SERMs have revealed significant potential for use in non-cancer therapeutics due to their diverse pharmacological profiles. This review thoroughly examines the expanding applications of SERMs beyond oncology, elaborating on their mechanisms of action, pharmacokinetics, and clinical applications.

Compounds such as raloxifene, bazedoxifene, tamoxifen, and lasofoxifene have proven effective in managing osteoporosis by enhancing bone mineral density and reducing the risk of fractures. Moreover, their cardiovascular benefits include improved lipid profiles and endothelial function, albeit with an awareness of associated thromboembolic risks. SERMs also display neuroprotective properties, suggesting potential advantages in cognitive disorders such as Alzheimer's disease, in addition to alleviating menopausal symptoms through tissue-selective estrogen complex therapies.

A comparative analysis reveals variations in efficacy, safety, and tissue selectivity among the different SERMs. Despite their therapeutic potential, challenges such as thromboembolic risks, inconsistent patient responses, and adverse effects demand careful clinical consideration. Future efforts will focus on developing next-generation SERMs that offer improved tissue selectivity, reduced side effects, and personalised treatment strategies informed by pharmacogenomic insights. This review emphasizes the necessity for continued research to broaden the therapeutic landscape of SERMs, highlighting the importance of balancing efficacy and safety to optimize patient outcomes across various non-cancer conditions.

Keywords: Selective Estrogen Receptor Modulators; SERMs; Non-Cancer Therapeutics; Bone Health; Cardiovascular Protection; Neuroprotection

1. Introduction

Estrogen receptors are ligand-activated transcription factors belonging to the nuclear receptor family. They play a crucial role in regulating various physiological processes, including reproduction, bone density maintenance, cardiovascular health, and brain function. These receptors exist in two primary isoforms: estrogen receptor alpha and estrogen receptor beta, each encoded by separate genes and exhibiting distinct tissue distributions and functions. ERα is predominantly expressed in reproductive tissues, whereas ERβ is more prevalent in the central nervous system, bone, and cardiovascular tissues. Upon activation by estrogen, these receptors influence gene expression, modulating cellular

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growth, differentiation, and apoptosis. The intricate roles of ERs in numerous biological systems underline their significance in both health and disease[1–4].

Therapeutic Potential of Selective Estrogen Receptor Modulators: In the quest to harness the therapeutic potential of estrogen signalling, Selective Estrogen Receptor Modulators have emerged as a class of compounds that selectively agonise or antagonise ERs in a tissue-specific manner. Initially developed for the treatment of breast cancer, where they exhibit anti-estrogenic effects in breast tissue, SERMs have since been explored for their potential in various non-cancer indications[5]. Compared to their estrogen counterparts, SERMs offer the advantage of targeted modulation of ER activity, thereby mitigating the systemic side effects associated with hormone replacement therapy[6, 7].

Selective Estrogen Receptor Modulators (SERMs) are compounds that exhibit tissue-specific estrogen receptor agonist or antagonist activity. The development of SERMs was driven by the need for therapeutics that could harness the beneficial effects of estrogen in specific tissues while avoiding its undesirable actions in others. The first SERM, tamoxifen, was introduced in the 1960s as a treatment for breast cancer, marking a breakthrough in cancer therapeutics. Tamoxifen acts as an estrogen antagonist in breast tissue, inhibiting ER-mediated proliferation of cancer cells, while simultaneously exerting estrogenic effects on bone and lipid metabolism. This duality of action set the stage for the development of a new class of drugs with tailored tissue selectivity[8, 9].

Over the decades, several SERMs have been developed, including raloxifene, toremifene, and bazedoxifene, each with unique receptor-binding profiles and therapeutic indications. While tamoxifen and raloxifene have been extensively studied for breast cancer prevention and osteoporosis treatment, respectively, the spectrum of potential SERM applications has widened significantly. Beyond their role in oncology, SERMs are now being investigated for various non-cancer conditions, such as cardiovascular diseases, neurodegenerative disorders, and metabolic syndromes[10, 11].

The growing interest in SERMs beyond cancer can be attributed to their ability to selectively modulate estrogenic activity, offering targeted therapeutic benefits while minimizing systemic adverse effects[7]. For instance, raloxifene has shown efficacy in reducing the risk of vertebral fractures in postmenopausal women, while exhibiting favourable effects on cholesterol levels[12]. Furthermore, emerging evidence suggests that SERMs may have neuroprotective properties, potentially mitigating the progression of Alzheimer's disease and other cognitive disorders. Such findings underscore the need to explore the full therapeutic potential of SERMs in a broader range of diseases[13, 14].

1.1. Purpose of the Review

This review aims to explore the therapeutic potential of SERMs beyond their traditional role in cancer management. While SERMs have established efficacy in treating hormone receptor-positive breast cancer and preventing osteoporosis, their expanding utility in non-cancer therapeutics warrants a comprehensive evaluation. This article seeks to provide an in-depth analysis of the current state of research on SERM applications in non-cancer conditions, highlighting key findings, limitations, and future research directions.

Objective of the Review

The primary objective of this review is twofold:

- To summarize and critically analyse current research on the therapeutic applications of SERMs in non-cancer conditions, including but not limited to cardiovascular health, neuroprotection, metabolic regulation, and bone health.
- To identify gaps in existing knowledge and propose future research directions that could further elucidate the role of SERMs in non-cancer settings.

By addressing these objectives, this review aims to contribute to the ongoing scientific discourse on SERMs, fostering a deeper understanding of their potential to improve patient outcomes across a range of non-oncological diseases.

2. Mechanism of action of SERMS

2.1. Estrogen Receptor Subtypes and Tissue Selectivity

Estrogen receptors exist primarily in two subtypes, ERα and ERβ, which exhibit differential expression across various tissues. ERα is predominantly found in reproductive tissues such as the breast, uterus, and ovaries, where it mediates

estrogen's proliferative effects. Conversely, ERβ is expressed in tissues such as the brain, bone, cardiovascular system, and lungs, where it generally exhibits anti-proliferative and protective roles. The distinct distribution and functional differences of these receptors underpin the tissue-selective actions of SERMs[15].

SERMs exert their effects by binding to ERs and inducing conformational changes that influence receptor interaction with co-regulator proteins. Depending on the tissue context, these changes determine whether the SERM acts as an agonist or antagonist. For example, tamoxifen acts as an ER antagonist in breast tissue by recruiting co-repressors to inhibit transcription, while functioning as an agonist in bone tissue by recruiting co-activators to promote gene expression[16, 17].

2.2. Molecular Pathways Affected by SERMs

SERMs influence multiple molecular pathways through their interactions with ERs and subsequent modulation of transcriptional activity. Upon binding to a SERM, ERs can either promote or inhibit the recruitment of co-regulator proteins, such as co-activators (e.g., SRC-1, CBP) or co-repressors (e.g., NCoR, SMRT)[18]. This interaction dictates the receptor's ability to modulate gene expression in a tissue-specific manner. Additionally, SERMs have been shown to impact non-genomic signalling pathways, including the activation of intracellular kinases such as PI3K/Akt and MAPK, which play roles in cell survival, metabolism, and neuroprotection[18, 19].

Beyond transcriptional regulation, SERMs can influence downstream signalling cascades involved in inflammation, oxidative stress, and apoptosis. These pathways are critical in the therapeutic effects of SERMs in non-cancer conditions, such as cardiovascular health and neurodegeneration[20].

2.3. Pharmacokinetics and Pharmacodynamics of SERMs

The pharmacokinetics of SERMs, including absorption, distribution, metabolism, and excretion, play a significant role in their therapeutic efficacy. SERMs are typically well-absorbed orally, with hepatic metabolism primarily involving cytochrome P450 enzymes. Tamoxifen, for instance, is metabolized into active metabolites such as 4-hydroxytamoxifen and endoxifen, which exhibit a higher affinity for ERs[16].

Binding affinity and half-life are crucial factors influencing the duration of action of SERMs in different tissues. Tamoxifen has a long half-life (approximately 5 to 7 days), contributing to its sustained effects, while raloxifene has a shorter half-life (approximately 27 hours) but exhibits high binding affinity to ERs in bone and cardiovascular tissues. These pharmacokinetic properties underpin the tissue-selective efficacy and safety profiles of various SERMs[16, 21].

In summary, the mechanism of action of SERMs involves complex interactions with estrogen receptors, modulation of transcriptional activity, and influence on key signalling pathways. Understanding these mechanisms is essential for developing novel therapeutic applications of SERMs in non-cancer conditions[18, 22].

3. Established and emerging non-cancer therapeutic applications of SERMS

3.1. Bone Health and Osteoporosis

Estrogen plays a critical role in maintaining bone density by regulating the balance between bone resorption and bone formation. It inhibits osteoclast activity, thereby reducing bone resorption, and promoting osteoblast survival, enhancing bone formation. The decline in estrogen levels during menopause leads to increased bone turnover and a subsequent decrease in bone mineral density (BMD), heightening the risk of osteoporosis and fractures[23, 24].

SERMs, such as raloxifene and bazedoxifene, have been extensively studied for their efficacy in preventing and treating osteoporosis in postmenopausal women. Raloxifene, for instance, has been shown to increase BMD at the spine and hip while reducing the risk of vertebral fractures[25]. Clinical trials, such as the Multiple Outcomes of Raloxifene Evaluation (MORE) study, demonstrated a 30% to 50% reduction in vertebral fractures among postmenopausal women treated with raloxifene. Bazedoxifene, a third-generation SERM, has similarly shown efficacy in reducing vertebral fracture risk, with the added benefit of fewer adverse effects on endometrial and breast tissues compared to earlier SERMs[16, 25].

Mechanistically, SERMs exert their bone-protective effects by acting as estrogen agonists on ERs in bone tissue. This action promotes the recruitment of co-activators, enhancing the transcription of genes involved in bone matrix production and osteoclast inhibition. Unlike estrogen, however, SERMs do not stimulate breast or uterine tissues, reducing the risk of estrogen-dependent cancers[21, 26].

When compared to other osteoporosis therapies, such as bisphosphonates, SERMs offer unique advantages. While bisphosphonates primarily inhibit bone resorption by inducing osteoclast apoptosis, SERMs modulate both bone resorption and formation, providing a more balanced approach to bone remodelling. Additionally, SERMs have favourable effects on lipid profiles, which are not observed with bisphosphonates. However, bisphosphonates tend to have greater efficacy in reducing non-vertebral fractures[27, 28].

Overall, the role of SERMs in bone health is well-established, with significant evidence supporting their use in reducing vertebral fracture risk and improving BMD. Future research may focus on combination therapies involving SERMs and other agents, such as bisphosphonates or parathyroid hormone analogues, to enhance therapeutic outcomes[29–31].

3.2. Cardiovascular Health

Estrogen has long been recognized for its protective effects on cardiovascular health, primarily through its ability to improve lipid profiles, enhance endothelial function, and reduce vascular inflammation. Postmenopausal women experience an increased risk of cardiovascular disease (CVD) due to the loss of estrogen's cardioprotective effects[32, 33].

SERMs have the potential to mimic some of estrogen's beneficial cardiovascular effects while minimizing associated risks. Raloxifene, for example, has been shown to improve lipid profiles by reducing low-density lipoprotein (LDL) cholesterol levels without significantly affecting high-density lipoprotein (HDL) cholesterol or triglycerides. Evidence from clinical trials indicates that raloxifene may reduce the risk of coronary events in certain subgroups of postmenopausal women, particularly those at lower baseline cardiovascular risk[34, 35].

Despite these benefits, the use of SERMs in cardiovascular health is not without risks. One of the primary concerns is the increased risk of venous thromboembolism (VTE) associated with SERM therapy[36]. Studies have consistently reported a two- to three-fold increased risk of VTE in women using raloxifene or tamoxifen. Strategies for mitigating this risk include careful patient selection and monitoring, particularly in individuals with a history of thromboembolic events or other predisposing factors[37].

Mechanistically, SERMs exert their cardiovascular effects by acting as partial estrogen agonists in vascular tissues, promoting nitric oxide production and improving endothelial function. Additionally, SERMs may exert anti-inflammatory effects by modulating the expression of inflammatory cytokines and adhesion molecules involved in atherosclerosis development[28, 38].

In summary, while SERMs offer promising cardioprotective benefits, their use must be carefully balanced against potential thromboembolic risks. Future research may explore the development of novel SERMs with improved safety profiles or combination therapies that mitigate VTE risk while preserving cardiovascular benefits[39, 40].

3.3. Cognitive Function and Neuroprotection

Estrogen has significant effects on cognitive health, with evidence suggesting its role in reducing the risk of neurodegenerative diseases such as Alzheimer's disease (AD). The neuroprotective effects of estrogen are thought to be mediated through its antioxidant properties, modulation of neuroinflammation, and promotion of synaptic plasticity[41, 42].

SERMs have been investigated as potential therapeutic agents for cognitive decline and neurodegenerative disorders. Preclinical studies have demonstrated that SERMs, such as raloxifene, can reduce amyloid-beta deposition and neuroinflammation in animal models of AD. Clinical evidence, although limited, suggests that raloxifene may have cognitive benefits in certain subgroups of postmenopausal women[43]. For instance, a secondary analysis of the MORE trial indicated improved verbal memory and attention in women receiving raloxifene[24, 44].

Mechanistically, SERMs exert their neuroprotective effects by acting as estrogen agonists in the brain, particularly in regions involved in memory and learning, such as the hippocampus. SERMs may also reduce oxidative stress and inflammation by modulating the activity of microglia, the resident immune cells of the central nervous system[30, 45].

However, the evidence for SERM efficacy in cognitive function remains mixed, with some studies reporting no significant cognitive benefits. Limitations of current research include small sample sizes, short follow-up periods, and heterogeneity in study populations. Ongoing clinical trials are expected to provide more definitive evidence regarding the role of SERMs in neuroprotection[46–48].

In conclusion, while SERMs show potential as neuroprotective agents, further research is needed to establish their efficacy in preventing or slowing cognitive decline. Future studies should focus on identifying the most responsive patient populations and optimizing dosing regimens[49, 50].

3.4. Menopausal Symptoms and Quality of Life

SERMs have also been explored for their role in managing menopausal symptoms, particularly vasomotor symptoms (e.g., hot flashes) and improving overall quality of life in postmenopausal women. While traditional hormone replacement therapy (HRT) effectively alleviates menopausal symptoms, its use is associated with increased risks of breast cancer and cardiovascular events[51–55].

Bazedoxifene, in combination with conjugated estrogens, has been approved for the treatment of menopausal symptoms and the prevention of osteoporosis. This combination therapy, known as tissue-selective estrogen complex (TSEC), provides the benefits of estrogen on menopausal symptoms and bone health while minimizing the risk of endometrial hyperplasia. Clinical trials have shown significant improvements in vasomotor symptoms, sleep quality, and overall quality of life in women receiving TSEC therapy[51, 56, 57].

The safety profile of SERMs in managing menopausal symptoms is generally favourable, with a lower risk of breast and endometrial cancer compared to traditional HRT. However, as with other SERM therapies, the risk of VTE remains a concern and warrants careful patient selection and monitoring[56–59].

In summary, SERMs offer a promising alternative to traditional HRT for managing menopausal symptoms, with the added benefit of bone protection. Future research may focus on optimizing combination therapies to enhance efficacy and safety.

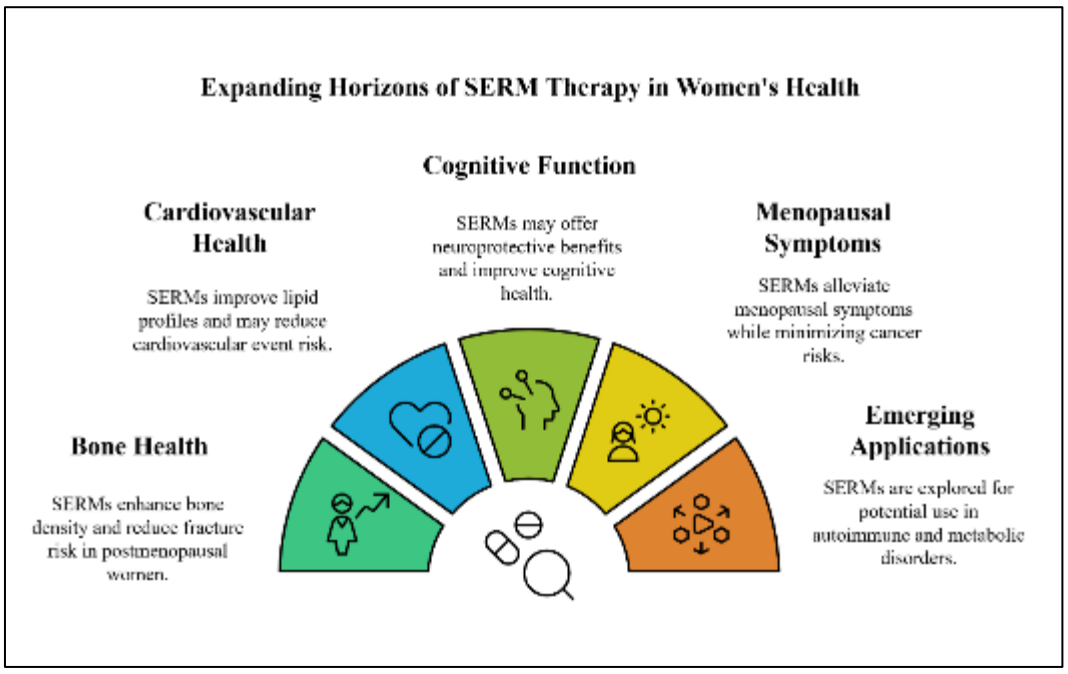

Figure 1 Established and emerging non-cancer therapeutic applications of SERMs

3.5. Other Emerging Applications

Beyond their established roles, SERMs are being investigated for potential applications in autoimmune disorders and metabolic syndrome. Preliminary evidence suggests that SERMs may modulate immune function, offering therapeutic potential in conditions such as lupus and rheumatoid arthritis[60]. Additionally, SERMs have been shown to influence metabolic parameters, including weight gain and insulin sensitivity, making them potential candidates for managing metabolic syndrome[25].

However, the evidence for these emerging applications is still limited. Additional research is needed to fully elucidate the therapeutic potential of SERMs in these areas and determine their efficacy and safety profiles. Further clinical trials

and experimental studies will be crucial to advancing our understanding of SERMs beyond their established uses[40, 45].

The development of novel SERMs with improved tissue selectivity and safety profiles continues to be an area of active research. As our understanding of SERM pharmacology and mechanisms of action advances, the scope of their clinical utility is likely to expand, providing new opportunities for the management of various estrogen-responsive conditions[61].

Future research directions include large-scale clinical trials to validate these emerging applications and the development of next-generation SERMs with improved efficacy and safety profiles. By expanding the therapeutic indications of SERMs, researchers may unlock new treatment options for a variety of non-cancer conditions[62].

4. Comparative analysis of key SERMS

4.1. Discussion on Safety Profiles

The safety profiles of SERMs vary depending on their receptor-binding selectivity and pharmacokinetics. Common adverse effects associated with SERM therapy include hot flashes, leg cramps, and an increased risk of venous thromboembolism (VTE). The risk of VTE is a significant concern, particularly in older patients or those with a history of thromboembolic events. Careful patient selection and regular monitoring are essential strategies to mitigate this risk[63, 64].

Contraindications for SERM use include a history of thromboembolic disorders, active or past breast cancer (for non-cancer indications), and pregnancy. Drug interactions may occur with anticoagulants and other medications metabolized by cytochrome P450 enzymes, necessitating caution in polypharmacy cases[65–67].

Table 1 Summary of Key SERMs in Non-Cancer Therapeutics

SERM	Indications	Mechanism of Action	Clinical Outcomes	Common Side Effects
Raloxifene	Osteoporosis, cardiovascular health	Estrogen agonist in bone; antagonist in breast	Increased BMD, reduced vertebral fractures	Hot flashes, VTE risk
Bazedoxifene	Osteoporosis, menopausal symptoms	Estrogen agonist in bone; antagonist in uterus	Improved BMD, reduced vertebral fractures, improved QoL	Hot flashes, leg cramps
Tamoxifen	Neuroprotection (investigational)	Estrogen antagonist in breast; partial agonist elsewhere	Potential cognitive benefits, reduced cholesterol levels	Hot flashes, VTE risk, endometrial hyperplasia
Lasofoxifene	Osteoporosis, breast cancer prevention	Estrogen agonist in bone; antagonist in breast	Increased BMD, reduced vertebral fractures	Hot flashes, VTE risk

In conclusion, while SERMs offer substantial therapeutic benefits in non-cancer conditions, their use requires a balanced consideration of efficacy and safety. Future research should focus on developing next-generation SERMs with improved safety profiles, particularly concerning thromboembolic risks[68].

5. Challenges and future directions

5.1. Challenges in Clinical Use

One of the primary challenges in the clinical use of SERMs is achieving an optimal risk-benefit balance. While SERMs offer significant therapeutic benefits, such as improved bone density and cardiovascular health, they also pose risks, notably venous thromboembolism. The risk of VTE necessitates careful patient selection and monitoring, particularly

in older individuals and those with a history of thromboembolic events[69, 70]. Patient-specific factors, including age, sex, comorbidities, and genetic variability, also influence the efficacy and safety of SERMs. For instance, variations in cytochrome P450 enzymes can affect the metabolism of SERMs, leading to differences in drug levels and therapeutic outcomes. These factors underscore the need for personalized medicine approaches in SERM therapy to optimize treatment and minimize adverse effects[71, 72]. Furthermore, the potential for drug interactions is a key consideration in SERM therapy, particularly when patients are taking anticoagulants or other medications metabolized by the cytochrome P450 system. Careful monitoring and dose adjustments may be required to ensure the safe and effective use of SERMs in a polypharmacy setting[73].

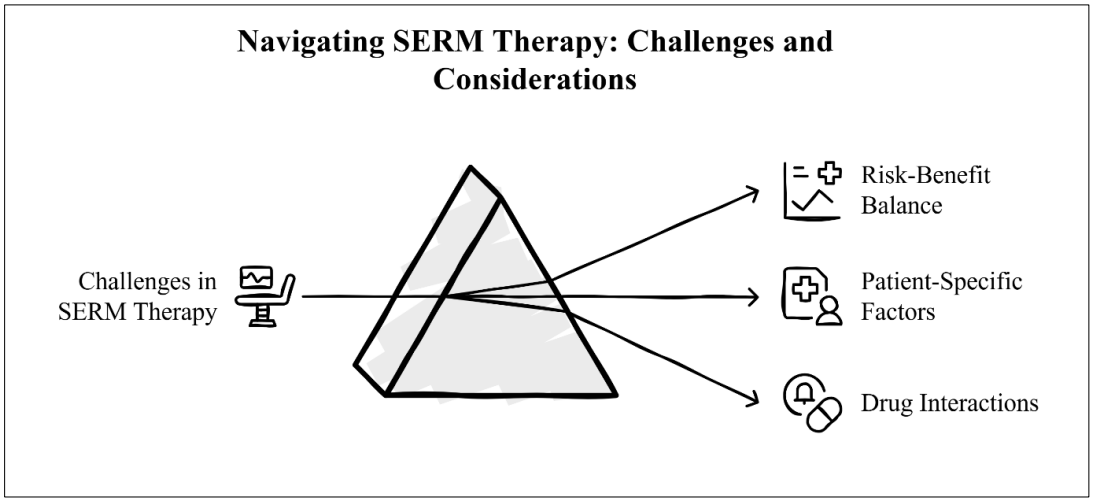

Figure 2 Navigating SERM Therapy: Challenges and

5.2. Future Directions

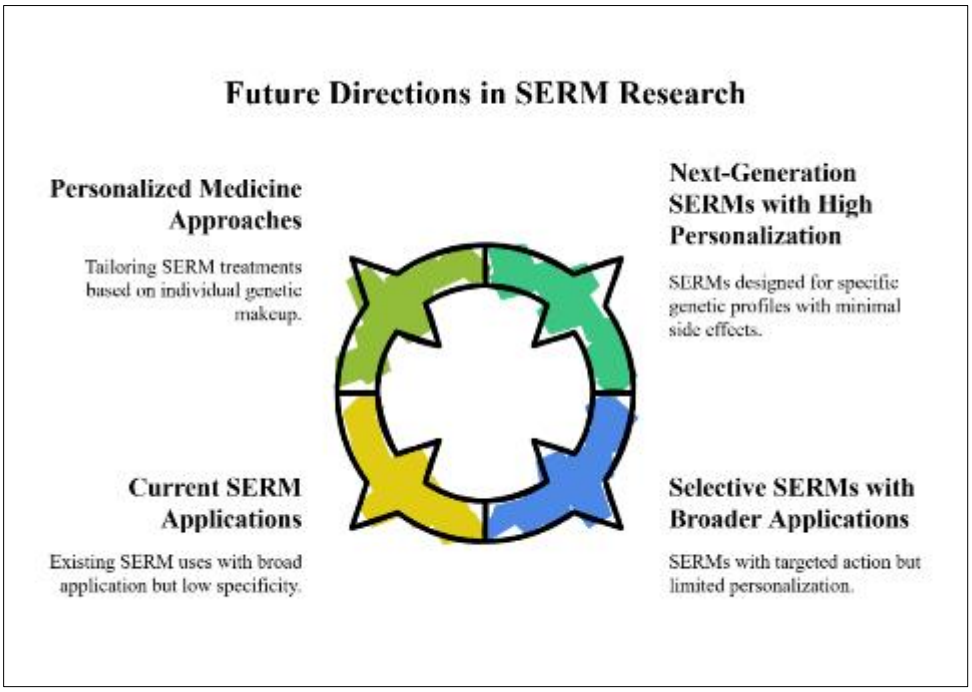

Figure 3 Future Directions in SERM Research

The future of SERM research should focus on developing more selective and safer next-generation compounds. Enhancing the ability of SERMs to act as targeted agonists or antagonists in specific tissues, while minimising undesirable off-target effects, could significantly broaden their therapeutic applications[18]. This would involve a deeper understanding of the underlying pharmacological mechanisms and tissue-specific signalling pathways.

Personalized medicine approaches hold great promise for optimising SERM therapy. Advances in pharmacogenomics may enable clinicians to tailor SERM treatments based on individuals' unique genetic and molecular profiles, thereby improving the efficacy of these therapies and reducing the risk of adverse effects[74, 75]. This personalized approach could account for factors such as variations in drug metabolism and receptor expression, leading to more targeted and effective interventions.

Ongoing and future clinical trials are expected to provide invaluable insights into the expanded use of SERMs beyond cancer treatment, exploring their potential in autoimmune disorders, metabolic syndrome, neurodegenerative diseases, and other non-cancer conditions[38, 76]. These trials will likely shape future clinical practice by identifying new therapeutic indications for SERMs and refining existing treatment protocols, ultimately expanding the arsenal of tools available to clinicians for managing a wide range of estrogen-responsive conditions[77].

The field of Selective Estrogen Receptor Modulator research and development remains an active and promising area of investigation. While the current applications of SERMs are well-established, their potential for addressing non-cancer conditions continues to be explored, with the promise of improved safety and efficacy profiles in the future[78].

6. Conclusion

Selective Estrogen Receptor Modulators have emerged as a versatile and promising class of agents in the field of non-cancer therapeutics. They have demonstrated significant potential in managing a range of conditions, including osteoporosis, cardiovascular health, cognitive function, and menopausal symptoms. The tissue-selective actions of SERMs allow them to deliver targeted benefits while minimising the risks often associated with traditional hormone therapies.

Despite the promising outcomes observed in various studies, the clinical use of SERMs is not without its challenges. Concerns around thromboembolic risks and patient-specific variability in response highlight the need for careful patient selection, close monitoring, and further research to optimise their use. The development of next-generation SERMs with enhanced tissue selectivity and the application of personalised medicine approaches offer a promising pathway to unlock the full therapeutic potential of these compounds and improve patient outcomes across diverse non-cancer conditions.

Continued investment in research, including well-designed clinical trials, will be crucial in expanding the clinical utility of SERMs and addressing the existing challenges. By pursuing these avenues, the medical community can strive to unlock the full potential of SERMs and deliver better, more tailored treatments for patients in need.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflict of interest.

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