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Review article

The Efficacy of Raloxifene in the Treatment of Psoriasis: A Comprehensive Review

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Abstract

Psoriasis The skin gets thick and irritated when. The epidermis, the outermost layer of skin, proliferates excessively and is populated by dangerous T-cells. Certain medications, such as cyclosporine, retinoids, and methotrexate, may not always be safe, Raloxifene is drug that belong to a selective estrogen receptor modulator (SERM) that using in prevent and treat bone loss in postmenopausal women, Raloxifene is a therapeutic agent used to treat osteoporosis and psoriasis by targeting immune responses and cellular pathways involved in the disease process. to investigate the efficacy and mechanism of action of raloxifene in the management of psoriasis, with a focus on how it affects the generation of cytokines and the regulation of immune cells. The role of raloxifene in the management of psoriasis is still under debate, raloxifene may be effective in treating autoimmune diseases such as Psoriasis due to its function is the regulation of cytokine production and immune cells. Therefore, the ability of SERMs to act on both estrogen receptors and immune systems is instigating news in the field of drug development that the specific mechanisms underlying the association between Raloxifene and VDR ligand activity in psoriasis remain unclear and require further investigation. Future research exploring the cross-link between estrogen receptors, VDRs, and their respective ligands in psoriatic skin cells could provide valuable insights into the therapeutic potential of Raloxifene and other SERMs in the management of psoriasis.

Keywords: ***Raloxifene, Psoriasis, immune modulation, cytokine regulation, VDR ligands.***

Introduction

Psoriasis is a skin disease where the skin becomes thick and inflamed. The top layer of the skin (epidermis) grows too much and is filled with harmful T-cells [1]. There are medicines like methotrexate, retinoids, and cyclosporine, but they can have safety issues [2]. Other treatments include creams, UV light, and specific drugs like glucocorticoids and vitamin D analogues [3]. Disease Characteristics About 2% of adults have psoriasis [4], and it gets more common with age, indicated that the prevalence of psoriasis increases in older individuals, with a peak incidence in patients between 57 and 62 years of age [5]. Study by Rosset *et al.*, 2023 have shown that psoriasis affects a significant percentage of individuals over the age of 60, with a prevalence of 14.5% among geriatrics attending dermatology clinics [6]. The disease Psoriasis is a chronic inflammatory skin disease characterized by thick skin scales and inflamed skin with increased blood vessels. The pathophysiology of psoriasis involves the activation and migration of T cells to the dermis, triggering the release of cytokines like tumor necrosis factor-alpha (TNF-alpha), leading to inflammation and rapid skin cell production [7].

New treatments focus on stopping T-cells to reduce the disease. Study by Kotb *et al.*, 2018b have shown that targeting specific pathways involved in T cell signaling transduction, such as Ca2+/CaN/NFAT, MAPK/JNK, PI3K/Akt/mTOR, and JAK/STAT, could be promising for managing psoriasis [8].

Raloxifene is a type of drug called a selective estrogen receptor modulator (SERM) [9]. It is being tested to help prevent and treat bone loss in postmenopausal women [10]. The way a specific part of the raloxifene molecule (the basic amine-containing side chain) is positioned is crucial for its effectiveness in targeting specific tissues [11]. Scientists have developed new analogues of raloxifene with the side chain positioned orthogonally to the stilbene plane, mimicking its low-energy conformation [12]. It is imperative that the side chain favors this orientation to ensure tissue selectivity in drugs such as SERMs like raloxifene [13]. When the structure of the ER with raloxifene in the crystalline state was analyzed by the X-ray crystallography, the importance of the alkylaminoethoxy side chain in the antiestrogenicity of raloxifene was demonstrated to reside in particular amino acids, namely aspartate in the position 351, situated in the ligand-binding domain of the ER [14]. Moreover, the Yeo *et al.*, 2013 have indicated that the basic side chain of raloxifene provides key information regarding its binding to bone tissue in structure-activity study including the ability to modify binding to the organic matrix as well as mechanical properties of the bone [15]. It has also been demonstrated that Raloxifene induced

TGF-beta 3 gene expression and supports IVD health through activation of estrogen pathway; while at the same time, protecting bones in rats with little to no impact on the uterus [16-18]. Increases estrogen receptor-α levels, promotes estrogenic responses and increases extracellular matrix anabolic processes which if translated to clinical practice can partially relieve painful IVD degeneration in postmenopausal women resulting from aging, sex and estrogen deficiency [19,20]. Moreover, Raloxifene has inhibitory effect on virus such as Ebola & Influenza A hence suggests possibility of using the drug to treat SARS-CoV-2 [21]. In other trials looking at the clinical effect of raloxifene in healthy middle-aged men, Serman et al have shown that the serum estradiol is to be raised and in subjects whose estrogen level was low, the marker of bone turnover was to be reduced [22]. In addition, Ferretti *et al.* 2017 have established that raloxifene treatment can reduce plasma Lp (a) and have a bearing in reducing SCM IL-18 and has influence over lipid profile also [23], In addition, this form of estrogen actually decreases the risks of CVDs, such as a lower carotid intima-media thickness as well as improved functionality of the endothelial layers [24]. Besides, raloxifene also showed to have a potential role in modulating the carotid IMT and endothelial function for the better [25,26]. These effects can be attributed to the increase in plasma adiponectin concentration which may help in explaining why atherosclerosis process slows down in post-menopausal women under the treatment with raloxifene [27]. Taken together, these findings indicate that given raloxifene's multiple pharmacological roles, it might be useful to investigate the role of this drug in treating different diseases other than breast cancer such as psoriasis.

Pathophysiology

Epidermal cells in psoriasis are also found to divide so that they go up to the more outer layer of the skin within second days instead of a normal 12 days. This is through effects of immune cytokine stimuli leading to red, scaly and well demarcated plaques in the skin [28]. According to Natoli *et al.* 2023 inside their performance they established that epidermal cell of complexity the keratinocytes are partly to blame for with psoriasis because they initiate inflammation cell and worsen skin disease [29]. Regarding the epidermis, cell cycle alteration, over proliferation and apoptotic death have been proposed to contribute to psoriasis [30]. indicating that the mechanisms governing keratinocyte biology in psoriasis should also be evaluated and probably targeted in experimental treatments. In the last phase of cornification, the transformations of the skin become fuller on both the structural and the genetic level. As these cells mature, then lose their cell organelles and become corneocytes, the outer skin layer becomes thicker and has disordered layering patterns [31,32]. The events occurring during this transition include: They lose the granular layer; They come out with fewer protein products such as filaggrin; They create new sorts of keratin especially the keratins 6 and 16 [33]. The downregulation of filaggrin and other FLG-like proteins in atopic dermatitis patients' skin, both lesional and nonlesional, is influenced not only by genetic mutations but also by proinflammatory cytokines, contributing to epidermal barrier dysfunction [34]. Additionally, the gene expression profile associated with age-related cell transformation reveals a post-senescence neoplastic emergence signature, highlighting metabolic pathways like xenobiotic metabolism as potential determinants of the switch from senescence to pre-transformation in normal keratinocytes [34]. Various growth factors and signaling molecules (cytokines) are increased, affecting skin cell behavior. Skin cells produce inflammatory molecules in response to signals like IL-1, TNF-R, and IFN-γ. There are interactions between skin cells and immune cells, leading to more skin cell growth and inflammation [35,36,37].

Psoriasis involves a complex interplay of various immune cells in the skin. Neutrophils, a type of white blood cell, accumulate in the outer skin layer, contributing to inflammation [38]. T-cells and macrophages are also crucial in psoriasis pathogenesis, with T-cells, including CD8 T-cells in the epidermis and CD4 T-cells in the dermis, playing significant roles in immune responses [39]. According to Fernández Domper *et al.*, 2022, the development of psoriasis involves innate immune cells such as dendritic cells, NK cells, and NKT lymphocyte and the further release of inflammatory cytokines inflaming the skin disease [40]. Vascular endothelial cells are involved in psoriasis where dysfunctions are shown to play a role in immune-mediated aspects of the skin condition [41].

Psoriasis involves imbalanced cytokines in the body, with type 1 cytokines Interferon Gamma and IL-2 being over produced encouraging cell mediated immunity [42,43]. On the other hand, the levels of type 2 cytokines like IL-4 and IL-10 are reduced in the plasma, which affects the antibody mediated immune response of the patient [44]. They further promote the inflammatory status in psoriasis since intracellular signaling pathways stimulate the release of pro-inflammatory cytokines such as TNF-α, IL-1 β, IL-6, IL-17 A, and IL-23, while a decrease in anti-inflammatory cytokines particularly TGF b as analyzed in various studies [45,46].

Other interventions such as UV light therapy, particularly narrow band UVB, is established to affect T-cell subsets where; it enhances only regulatory T cells (Tregs) but reduces Th 17 cells [47]. Moreover, there are some immunosuppressive drugs for example cyclosporin A that can inhibit the production of Il 2, which is useful in T cell proliferation [48]. Experimental treatments like DAB389IL-2 and CTLA4-Ig target active T-cells, highlighting their importance in psoriasis pathogenesis [49]. Moreover, high doses of UV light within a specific wavelength range have been effective in treating various skin disorders, including psoriasis, by targeting diseased tissue areas while minimizing damage to healthy skin [49].

The keratinocytes that make up the skin's outermost layer are the primary clinical findings in psoriasis. However, the interaction of keratinocytes with many cell types (innate and adaptive immune cells, vasculature) across the dermal layer of the skin shapes the formation of the psoriatic plaque instead of being limited to inflammation in the epidermal layer. Psoriasis may be thought of as having two phases: an initiation phase that may be brought on by medicines, infections, or trauma (Koebner phenomenon) and a maintenance phase that is defined by a persistent clinical progression [50] as showed in figure 1

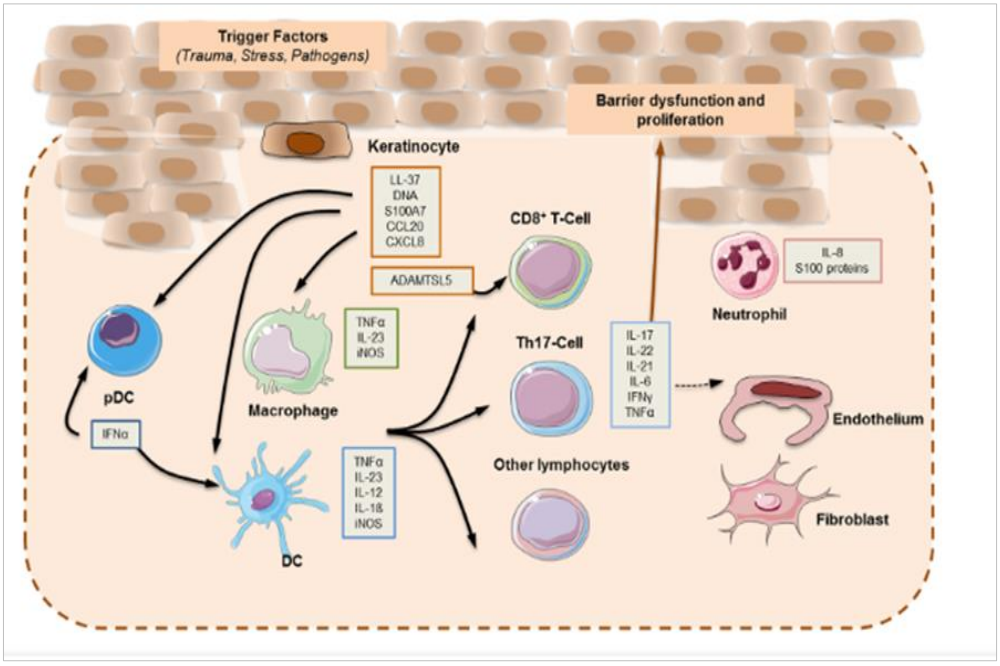

Figure 1: The psoriasis pathophysiology

Current Therapies for Psoriasis

Psoriasis treatment varies based on the extent of the condition, with creams suitable for small areas and stronger therapies for larger areas. Coal tar and anthralin are effective but underutilized treatments due to concerns about appearance and safety, despite their cost-effectiveness and long remission time [51]. The steroid superfamily, including glucocorticoids, vitamin D3 analogues like calcipotriol, and retinoids such as tazarotene, are commonly used and effective when topically applied, with new formulations like betamethasone dipropionate spray and halobetasol propionate foam showing improved absorption and ease of use [52,53]. Emerging treatments like tapinarof, a promising aryl hydrocarbon receptor inhibitor, and roflumilast, a phosphodiesterase type 4 inhibitor, have shown significant lesion improvement and notable pruritus management in phase III trials, offering new options for psoriasis management [54].

UVB light around 312 nm and UVA light in combination with psoralen (PUVA) are commonly used for treating larger skin areas [55]. Oral medications like retinoids, methotrexate, fumaric acid esters, and cyclosporine are also utilized in dermatological conditions [56]. The combination of UV therapy with retinoids has been shown to enhance efficacy and reduce risks [57]. While glucocorticoids can lead to skin thinning, retinoids promote skin growth and collagen production, potentially counteracting this effect [58]. Moreover, combining tazarotene with glucocorticoids or calcipotriol with glucocorticoids and UV light has demonstrated increased effectiveness in treatment [59].

Ligands for the Nuclear Hormone Receptors

Nuclear hormone receptors (NRs) play a crucial role in gene regulation and are targeted by various treatments for psoriasis, including glucocorticoids, retinoids, and vitamin D3 analogues [60,61]. These ligands bind to specific receptors like the glucocorticoid receptor (GR), retinoic acid receptor (RXR), and vitamin D receptor (VDR), which have domains for DNA and hormone binding, influencing gene expression [62-64].

Glucocorticoids exert their anti-inflammatory effects by inhibiting proteins like NF-κB and AP-1, but their long-term use can lead to skin thinning and drug resistance, potentially worsening psoriasis upon discontinuation [65,66]. Calcitriol, the active form of vitamin D3, binds to skin receptors, promoting skin cell maturation and reducing proliferation, with calcipotriol being a common effective topical form [67]. In a study conducted by Segaert *et al.*, 2017 involving 167 chronic plaque psoriasis patients, calcipotriol ointment (50 µg/g) applied twice daily resulted in complete clearance for 26% of patients and significant improvement for 50-70%, although 20% experienced skin irritation [68]. New synthetic analogues like tacalcitol and maxacalcitol have emerged, showing efficacy in cell differentiation and growth inhibition with reduced impact on calcium levels, making them promising alternatives for psoriasis treatment [69].

Advanced targeted biological medications have been developed in recent years as a consequence of a rapid development in psoriasis therapy. Conventional systemic treatments for psoriasis include retinoids, cyclosporin A, and methotrexate (MTX). With the exception of MTX, which may also be administered subcutaneously, all of the former are oral medications. An introduction to two more recent medications that have been licenced for the treatment of psoriasis, dimethyl fumarate and apremilast, concludes this in. VDR Ligand Activity in Psoriasis [50] drug that used in treatment of psorsis.

Table1: Drugs available for psoriasis therapy.

Drug Class	Generic Name	Administration	Mechanism of Action
Topical	Corticosteroids	Cream, Ointment	Anti-inflammatory
	Calcineurin Inhibitors	Cream, Ointment	Immunosuppressive
	Vitamin D Analogues	Cream, Ointment	Modulates keratinocyte proliferation and differentiation
	Coal Tar	Cream, Ointment	Anti-inflammatory, antipruritic
	Topical Retinoids	Cream, Gel	Normalizes keratinocyte differentiation, reduces inflammation

Systemic	Methotrexate	Oral	Inhibits dihydrofolate reductase, anti-inflammatory
	Cyclosporine	Oral	Calcineurin inhibitor, immunosuppressive
	Acitretin	Oral	Retinoid, regulates keratinocyte differentiation
Biologics	TNF-alpha Inhibitors	Subcutaneous injection	Blocks TNF-alpha, reduces inflammation
	IL-17 Inhibitors	Subcutaneous injection	Blocks IL-17A, reduces inflammation
	IL-23 Inhibitors	Subcutaneous injection	Blocks IL-23, reduces inflammation
	IL-12/23 Inhibitor	Subcutaneous injection	Blocks IL-12/23, reduces inflammation
Phototherapy	UVB	Light treatment	Suppresses immune response, reduces inflammation
	PUVA	Light treatment	Suppresses immune response, reduces inflammation

All of the conventional systemic medications are immunomodulators, with the exception of apremilast, which need thorough clinical supervision because of their frequent adverse effects, which mostly affect the kidney and liver. The only systemic treatments for psoriasis included on the World Health Organization's (WHO) Model List of Essential Medicines are methotrexate and cyclosporine, albeit they are only listed for the conditions of immunosuppression in the case of the latter and joint disease in the former. Although apremilast and FAE side effects are often not fatal, they may be significant enough to justify stopping the medication[70].

During more than ten years, TNF-α inhibitors have been accessible. They are useful for treating psoriatic arthritis and plaque psoriasis and are regarded as first-generation biologics. In psoriasis clinical research, TNF-α inhibitors continue to be the gold standard for assessing medication effectiveness. At present, this group comprises four medications: certolizumab, adalimumab, infliximab, and etanercept. Etanercept is distinct within the biologics category due to its nature as a recombinant human fusion protein, rather than a monoclonal antibody. The Fc region of an IgG1 antibody is linked to the receptor part of the TNF-α ligand. It was the first TNF-α inhibitor that the FDA (Food and Drug Administration) in the US has authorised for psoriasis. Adalimumab is a monoclonal IgG1 antibody that is completely human, while infliximab is a chimeric monoclonal antibody [71].

Vitamin D and its analogs, such as 1,25 (OH)2D3 and calcipotriol, exert their effects in psoriasis through the Vitamin D Receptor (VDR), which forms complexes with RXR to regulate gene activity via VDREs, impacting genes like osteocalcin, osteopontin, and p21 involved in calcium management and cell growth [72-74]. VDR agonists promote maturation and barrier formation in keratinocytes, slowing down skin cell growth and reducing immune cell infiltration, including neutrophils, while decreasing pro-inflammatory cytokines like IL-8 and increasing anti-inflammatory IL-10 [75,76]. Additionally, VDR agonists can suppress activated T-lymphocytes and modulate immune proteins like IL-2 and GM-CSF, contributing to immune system regulation in psoriasis treatment [77].

Retinoids, derived from Vitamin A, play a crucial role in embryonic development and maintaining healthy skin and tissues postnatally [78]. These compounds are utilized in skin treatments and cancer therapies, with all-trans-retinoic acid (RA) being a significant retinoid involved in gene activation through RAR-RXR pairs, where RXR is typically inactive [79]. While early tests with all-trans-RA for psoriasis showed skin irritation and poor efficacy, newer synthetic retinoids like tazarotene have been developed to target specific skin receptors, showing promising results in plaque psoriasis treatment with a 60-70% improvement rate over 12 weeks and lasting benefits post-treatment cessation, albeit with mainly local skin irritation as a side effect [80, 58,81].

Oestrogen as an immunomodulator in psoriasis

Estradiol (E2) is the primary estrogen before menopause and plays a crucial role in various body tissues [82]. Oestriol (E3), abundant during pregnancy, is not present in non-pregnant women and is assumed to have effects similar to E2 [83]. Oestrone (E1) is the predominant estrogen after menopause [84]. A study by Murase *et al.* found a strong correlation between the reduction in psoriasis during pregnancy and E2, with a lesser association with E3, but no significant link with E1, indicating the specific impact of E2 and E3 on this skin condition [85].

Estrogen, particularly E2, plays a crucial role in modulating immune responses in skin conditions like psoriasis and autoimmune diseases such as multiple sclerosis (MS). Studies indicates that E2 can reduce the production of inflammatory cytokines like IFN-c, TNF-a, IL-17, and IL-22 [86-88]. In murine models of psoriasis-like dermatitis, E2 has been shown to suppress inflammation by enhancing IL-10 production while also inducing the expression of pro-inflammatory cytokines like IL-22 and IL-23 [89]. In addition, it was demonstrated that E2 also can suppress the differentiation of Th1 and Th17 cells in lymph nodes, decreasing skin inflammation[90].

In the case of psoriasis, Th1, Th17, and Th2 are imbalanced and the inflammatory response increases by the reduced activity of Th2 cells which promotes the activity of Th1 and Th17 cells [91]. Pregnancy is associated with high levels of estrogen that are likely to up-regulate Th2 cells and create favorable conditions for immune modulation particularly by the suppression of inflammatory reactions and conversion of CD4+CD25- T cells to Tregs [92]. Regulatory T cells involve the immunosuppressive and anti-inflammatory processes, and there is a decrease in Tregs and the efficiency of Tregs in people with psoriasis [93]. Higher levels of E2 during pregnancy augments Tregs contributing to optimal immune function and minimizing inflammation All rights reserved thereby reducing IFN-c and TNF-a, and therefore reducing Th1 & Th17 while increasing Tregs & Th2 cells, which enhances amelioration of psoriasis of pregnancy [93,94].

One of the components contributing towards the establishment of psoriasis is oxidative stress. Researchers have observed that there is a disruption in the oxidant-antioxidant balance in skin affected with psoriasis such that the oxidant levels such as ROS are high while antioxidant levels such as glutathione, superoxide dismutase, and catalase are low. These disbalances resulted in higher concentrations of toxic substances, such as malondialdehyde, and thus elevated oxidative stress in psoriatics. Enzymes such as MAPK/AP-1, NF-kB and JAK-STAT when triggered by ROS inflammation heightens which is a critical part of psoriasis development and progression [95-99].

The dual roles of controlling the antioxidant gene and harmful free radicals have been attributed to estrogen E2. Based on rat research, it can be noted that E 2 supplementation after ovariectomies increases the activity of protective enzymes and improves the mitochondria's functional index, both of which contribute to a reduction in cellular damage. Additionally, E 2 has been connected to improving antioxidizing defense and minimizing oxidative damage, which may help improve the prognosis of a number of illnesses, including psoriasis [83,100-102].

Estrogen therefore influences traits such as psoriasis through promotion of skin cell proliferation and migration in multiplication to the base level of the skin. Niehues *et al.*, 2022, Luo *et al.*, 2020: As for the potent estrogen E2, it has been reported that it stimulates the proliferation of rat KCs in vitro [103,104], data basing on these studies reveal that E2 contributes to the worsening of psoriasis via promotion of skin cell [105]. Furthermore, E2 also participates in the synthesis of the proteins that are important in the firmness and functions of the skin barrier layer sufficient hydration and fatty skin layers that are important in the anti-psoriasis protection of the skin [106]. Thirdly, it has been noted that E2 stimulates the overexpression of epidermal growth factor in skins of patients suffering from psoriasis therefore promoting skin cell growth [107].

Immune Cell- Kcs are useful in attending to alarms from immune cells and they are somehow exacerbated in diseases like psoriasis, where there is an interplay balance between Kcs and immune cells [108]. Cytokines and chemokines are managed by Kcs and it is discrete among sections of the skin and diseases like atopic dermatitis and psoriasis [109]. Estrogen (E2) has a double-edged effect on KC behavior in psoriasis: while it can inhibit the production of inflammatory proteins and reduce immune cell attraction, it may also stimulate KC growth, potentially exacerbating psoriatic symptoms [110].

Higher oestrogen levels during pregnancy have been associated with improvements in psoriasis severity, potentially due to the calming effect of high oestrogen on the immune system [91]. Erlandson *et al.*, 2023 suggested that higher oestradiol levels, a form of oestrogen, in both women and men are linked to less severe psoriasis [111]. While Vessey *et al.*, 2000 indicated that high-dose oestrogen contraceptives improved psoriasis symptoms, another study by Vessey *et al.*, 2000 did not find a significant effect, possibly due to variations in oestrogen doses [112]. Oestrogen's positive effects on psoriasis treatment may stem from its ability to modulate immune responses, with high levels generally suppressing immune activity and low levels potentially stimulating it [113].

Selective Estrogen Receptor Modulators (SERMs) are synthetic compounds that interact with estrogen receptors in a tissue-specific manner, exhibiting either estrogenic or antiestrogenic effects [114]. Unlike estrogens, SERMs offer the advantage of providing beneficial estrogenic effects without some of the harmful side effects associated with traditional estrogen therapy. SERMs like tamoxifen and raloxifene have been extensively studied and utilized in clinical settings for conditions such as breast cancer treatment and prevention, as well as osteoporosis management [115,116]. Thus, SERMs are selective estrogen receptor modulators that mimic estrogen activity in some tissues but block it in others, which gives them an advantage over traditional estrogen-based drugs in combating estrogen-related diseases, and offers patients the chance at a better prognosis with fewer adverse effects [117].

Raloxifene, a drug in the class of SERM, was the first specifically approved for use to treat and prevent postmenopausal bone loss, and has fewer side effects than tamoxifen [10]. However, despite of able to prevent uterine cancer raloxifene might even help in preventing cancer while the above side effets of Evista include blood clots and eye problems [118]. Weger *et al.*, 2010 proposed that raloxifene may be useful in treatment of psoriasis through suppression of such cytokines of the disease as IL-12p40 and TNF-a, which in return may explain its immunomodulatory effect and provide a novel pathway to the disease treatment [119].

Ozgocmen *et al.*, 2007 and Ozbasar *et al.*, 2010 illustrated that raloxifene prevented formation and accumulation of toxic lipid peroxidation products like malondialdehyde and promoted uterine elevation of defense enzymes including catalase in red blood cells and blood samples from women with renal diseases [120,121]. Furthermore, Nishi *et al.* 2013 highlighted that raloxifene increases exercisory activity and promotes a stimulating effect in damaged kidney mice, thus supporting the prospect of such treatment to much mice conditions [122]. Collectively, these observations point to the fact that raloxifene has the potential to beneficially regulate the generation of undesirable molecules and protect beneficial molecules in the body, and therefore may be useful in the treatment of psoriasis due to its ability to help rebalance pathological changes in biochemical profiles in the body.

Conclusion

The role of raloxifene in the management of psoriasis is still under debate, regarding this consideration, raloxifene may be effective in treating autoimmune diseases such as Psoriasis due to its function is the regulation of cytokine production and immune cells. Therefore, the ability of SERMs to act on both estrogen receptors and immune systems is exciting news in the field of drug development for uses, which are besides cancer and osteoporosis.

Declarations

Ethics approval and consent to participate

Not Applicable

Data Availability

Data would be available upon reasonable request.

Conflicts of Interest

The author(s) declare(s) that there is no conflict of interest.

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