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MANAGING ESTROGEN-DEFICIENT SKIN: A NARRATIVE REVIEW ON THE ROLE OF HRT AND EMERGING ESTROGEN-MODULATING THERAPIES

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ABSTRACT

Estrogen plays a critical role in maintaining skin structure and function, influencing collagen synthesis, elasticity, hydration, barrier integrity, and wound healing. Menopause-related estrogen deficiency accelerates cutaneous aging, leading to increased dryness, laxity, thinning, and impaired repair. This review synthesizes current evidence on the effects of systemic hormone replacement therapy (HRT), topical estrogen treatments, and emerging estrogen-modulating compounds on estrogen-deficient skin. Systemic HRT has demonstrated improvements in dermal thickness, collagen content, elasticity, and hydration; however, study outcomes remain heterogeneous and clinical use is limited by systemic risks, including venous thromboembolism and breast cancer. Transdermal administration of HRT appears to offer a more favorable safety profile. Because systemic therapy cannot currently be recommended solely for dermatologic benefit, interest has shifted toward localized and selective approaches. Early data suggest that topical estrogen, SERMs and phytoestrogens, may enhance skin quality while minimizing systemic exposure, though long-term safety and efficacy remain insufficiently studied. Future research should focus on dedicated dermatologic trials, optimized dosing strategies, and tissue-selective therapies to support more personalized and safe treatment options. Also, scientists should consider external factors that may influence the results. Collectively, these findings underscore the potential of estrogen-targeted therapies to mitigate cutaneous aging in postmenopausal women while highlighting the need for more robust clinical evidence.

KEYWORDS

Skin, HRT, Estrogen, Menopause, SERMs, Phytoestrogens

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1. Introduction

1.1 Menopause and Its Impact on Skin Health

Menopause is a natural process that women experience around the age of 50. Declining estrogen levels are responsible for many of the body changes that impact health and quality of life. Connective tissue is strongly influenced by hormone levels; climacteric changes lead to bone density loss, muscle atrophy, and skin aging. (Davis et al., 2023) Skin is not one of the most frequently discussed organs in relation to menopause, yet it is significantly impacted by these hormonal shifts, leading to symptoms that affect quality of life (Zouboulis et al., 2022).

Skin changes associated with menopause are directly related to declining estrogen levels. Features such as elasticity, dermal thinning, wrinkles, skin dryness, slower wound healing, alterations in skin barrier function, reduced thermoregulation and decreased vitamin D production are direct consequences of reduced estrogen bioavailability all of which have a profound impact on overall skin structure and function, making it crucial to understand the complex mechanisms through which estrogens influence dermal health and to explore treatment options. Significant loss of collagen, around 30%, occurs within the first five years of menopause. (Lephart, 2018; Lephart & Naftolin, 2022)

Hormone replacement therapy is the most common and effective treatment for various menopausal symptoms. It works by replacing hormones, primarily estrogen, that a woman's body no longer produces sufficiently during menopause. For women who have not had a hysterectomy, estrogen is combined with a progestogen to protect against endometrial hyperplasia. (Davis et al., 2023)

In this review, we focus on HRT's effects on skin structure and function and explore the potential benefits of systemic and topical hormone treatments and other estrogen modulators in reducing age-related skin deterioration.

1.2 Estrogens role in skin structure and function

Estrogens play an important role in maintaining healthy skin by interacting with receptors in keratinocytes and fibroblasts. When estrogen binds to estrogen receptor alpha and beta, it triggers a series of events. These receptors form pairs and then move into the cell's nucleus, where they regulate gene activity. This leads to the production of proteins and peptides crucial for skin health. Specifically, estrogens stimulate the production of collagen and elastin, which provide skin strength, integrity, and elasticity. They also help keep skin moisturized and hydrated by increasing levels of hyaluronic acid, mucopolysaccharides, and sebum. Estrogens also encourage the growth of new skin cells (keratinocytes and fibroblasts), boost cell survival, and positively impact other components of the skin's support structure, such as fibrillin. Estrogens also act as powerful antioxidants, protecting skin from damage caused by harmful reactive oxygen species and oxidative stress. However, after menopause, beneficial estrogen levels decline, and the expression of ERβ in dermal cells decreases. This leads to reduced collagen and elastin, contributing to skin thinning and other signs of aging (Kamp et al., 2022; Lephart & Naftolin, 2022).

Estrogen deficiency is a major factor in the degradation of the skin's structure over time. This hormone's effects extend beyond direct nuclear receptor activation, as it can also have indirect impacts on skin cells through other pathways, such as membrane-bound G protein-coupled receptors. Skin aging is considered more affected by hormonal deficiency than chronological aging. Moreover, the greatest changes in skin structure are observed during first five years of menopause. (Wilkinson & Hardman, 2017, 2021)

2. Methodology

This narrative review synthesizes evidence on HRT and estrogen-modulating therapies for estrogen-deficient skin. We searched PubMed and Google Scholar using combinations of keywords related to “HRT,” “estrogen,” “skin,” “menopause,” “safety,” “phytoestrogens” and “SERMs”, For the section on *Systemic HRT - influence on skin*, priority was given to original clinical and experimental studies, while for HRT safety and alternative therapies we focused on recent literature (2017–2025), including systematic reviews, narrative reviews, and meta-analyses. Titles, abstracts, and full texts were screened for relevance, and data were extracted on study design, population of postmenopausal woman, interventions, and key outcomes. Findings were integrated narratively, with attention to methodological strengths, limitations, and consistency across studies.

All citations were managed according to APA 7th Edition guidelines. This review is limited by the heterogeneity of available studies, variation in hormone formulations and administration routes, and the scarcity of trials specifically designed to evaluate dermatologic outcomes as primary endpoints.

3. Results

3.1 Systemic HRT - influence on skin

3.1.1 HRT and skin thickness

Estrogen is responsible for many processes that impact general skin health, there are some studies that observe skin changes in women taking HRT and those who did not take them. HRT has been shown to significantly increase skin and dermis thickness. This has been confirmed by ultrasonography - skin ($p < 0.01$), and by skin biopsy - dermis ($p < 0.05$) (Maheux et al., 1994). Other research using non-invasive techniques has similarly shown an increase in skin thickness in treated menopausal women, with variations ranging from 7% to 15% depending on the body area. The breast skin and application areas exhibited the most significant increases, approximately 15%. This research suggests that the primary effect of HRT on skin is within the dermis, with observed differences in skin thickness of about 0.15 mm attributed to hormonal status. These findings collectively indicate that HRT can help prevent cutaneous atrophy, particularly dermal atrophy, often associated with hormonal aging (Caliens et al., 1996).

3.1.2 HRT and skin collagen changes

Various clinical studies, including randomized and double-blind, placebo-controlled studies, have shown that hormone replacement therapy positively influences skin collagen content in postmenopausal women. A comparative study measured skin collagen content in 52 postmenopausal women treated with estradiol and testosterone implants for 2 to 10 years and 66 untreated women. The treated group had a significantly higher mean skin collagen content of 221.12 (12.1) μg/mm², which was 34% greater than the 164.8 (8.4) μg/mm² found in untreated patients (P<0.001). This study also noted that treated women had a 30% greater skin thickness (1.19 mm vs. 0.93 mm, P<0.001), indicating that HRT helps prevent or reverse the

postmenopausal decline in skin collagen and thickness (Brincat et al., 1985). A randomized study involving 118 postmenopausal women observed that while skin collagen content naturally decreased with age and after menopause, all HRT regimens significantly increased it over 12 months, whereas a control group experienced a 3.2% decrease ($P < 0.05$). Specifically, women receiving continuous conjugated equine estrogens showed a 3.0% increase, while those on transdermal 17-estradiol exhibited the most substantial rise at 5.1% (5.8 µg collagen/mg protein, $P < 0.01$), representing a 7.0 µg collagen/mg protein greater difference than untreated patients (Castelo-Branco et al., 1992). Further supporting these findings in a randomized, double-blind, placebo-controlled study with 41 postmenopausal women, the hormonal treatment group (valerate estradiol and cyproterone acetate) demonstrated a significant increase in skin collagen content by 6.49% ($P=0.05$) over six months. The mean collagen content in the hormone group increased from 21897.4 ± 1635.3 at baseline to 23318.2 ± 2027.6 after treatment ($P \leq 0.05$), which is considered clinically relevant given that skin collagen can deplete by 30% during the first five years post-menopause (Sauerbronn et al., 2000).

3.1.3 HRT and skin elasticity

Skin elasticity and recoil were also examined. A pilot investigation in 2001 initiated the exploration into the influence of hormone replacement therapy on skin aging in postmenopausal women. This study found that HRT could significantly improve skin parameters. Specifically, a mean increase of 0.17 mm in skin thickness was observed after six months of HRT in hormonally treated groups ($P=0.0002$) (Sator et al., 2001). This improvement in skin thickness was linked to an increase in collagen and water content, contributing to better skin firmness and reduced slackness (Sator et al., 2001).

Building upon these findings, a prospective, randomized, double-blind, placebo-controlled study published in 2007 provided further detailed insights into skin elasticity changes. This research demonstrated that after seven months of oral sequential treatment with 2 mg 17β-estradiol/10 mg dydrogesterone, skin elasticity significantly increased at the right ramus of the mandible (Sator et al., 2007). For instance, the median gross elasticity at this specific site improved from a baseline of 0.580 to 0.640 after seven months ($p=0.006$) (Sator et al., 2007). An earlier segment of this research also indicated a 5.2% increase in skin elasticity at the right forearm after 12 months of HRT (Sator et al., 2007).

More recently, a 2014 study investigated skin viscoelasticity during hormone replacement therapy for climacteric aging, offering a deeper understanding of skin recoil. This research indicated that while skin distensibility and hysteresis generally increase during menopause, biological elasticity tends to significantly decrease in women not receiving HRT (Piérard et al., 2014). For women on HRT, 58.7% (44 out of 75) exhibited hysteresis values above the 90th percentile of non-climacteric aging women (Piérard et al., 2014). The study concluded that HRT primarily helps in preventing the decline of biological elasticity associated with aging, rather than substantially altering maximum deformation or hysteresis (Piérard et al., 2014). Together, these chronological studies underscore the positive impact of HRT on enhancing skin elasticity, thickness, and maintaining dermal structure, thereby influencing the skin's overall mechanical response and resilience in postmenopausal women.

3.1.4 HRT and skin hydration

Another skin feature that was investigated is hydration. Estrogens are known to contribute significantly to maintaining healthy skin by stimulating the production of hyaluronic acid, mucopolysaccharides, and sebum, which are essential for skin moisturization and hydration. The study, which examined postmenopausal women for at least 5 years, found that those undergoing HRT exhibited quantitatively higher skin hydration levels compared to their untreated counterparts. Specifically, on the forehead, the mean capacitance (measured in arbitrary units, a.u.) for the HRT group was 79.3 ± 10.3 a.u., compared to 75.2 ± 10.4 a.u. for the "Never HRT" group (Guinot et al., 2005). Similarly, on the cheek, the HRT group demonstrated a mean capacitance of 84.9 ± 7.4 a.u., while the "Never HRT" group had a mean of 81.1 ± 6.3 a.u. (Guinot et al., 2005). These differences were statistically significant.

Furthermore, the study also observed higher casual sebum levels in the HRT group, which contributes to the skin's moisture barrier. On the forehead, the HRT group showed a casual sebum level of 105.5 ± 58.8 mg/cm², significantly higher than the 75.3 ± 61.8 mg/cm² in the untreated group. For the cheek, the HRT group also had a higher sebum casual level of 43.5 ± 40.0 mg/cm², compared to 30.5 ± 36.9 mg/cm² in the group not receiving HRT (Guinot et al., 2005). These findings indicate that HRT can positively influence skin hydration parameters by increasing capacitance and sebum production in postmenopausal women.

3.1.5 HRT and wound healing

Wound healing and skin's capability to repair itself was also studied. A clinical research study investigated the effects of age and hormone replacement therapy on wound healing in healthy human females, alongside an animal model. This study demonstrated that intrinsic aging in women was associated with a delayed rate of cutaneous wound healing, characterized by reduced reepithelialization at day 7 post-wounding and decreased matrix collagen deposition at days 7 and 84. Specifically, mRNA levels for TGF-β1 were significantly lower in the aged group (87 ± 6 copies per picogram total RNA) at day 7 after wounding compared to young females (5656 ± 74 copies/pg) and the HRT group (6216 ± 97 copies/pg), with a highly significant difference ($P = 0.0006$) (Ashcroft et al., 1997). HRT reversed this age-related decline, significantly accelerating the rate of reepithelialization at day 7 ($P < 0.0001$) and markedly increasing collagen deposition to levels approaching those observed in young women. Systemic HRT, even when administered for as little as 3 months, was found to be sufficient to alter the wound-healing phenotype. However, while HRT improved healing rates, it was associated with adverse scarring profiles, both microscopically and macroscopically, resembling those of young females, contrasting with the superior quality of scarring (pale and flat) observed in the aged group without HRT (Ashcroft et al., 1997). Further in vitro findings showed estrogen treatment increased total TGF-β1 levels secreted by fibroblasts, with a 4-fold mean increase in young cells and a 12-fold increase for cells from aged subjects at a millimolar estrogen dose (Ashcroft et al., 1997).

More recently, another clinical research study explored how HRT impacts the skin barrier and immune system in postmenopausal women following an irritant challenge. The study found that HRT generally had a minimal effect on skin structure or resident immune cells under normal conditions. However, after a 48-hour challenge with 1.25% sodium lauryl sulfate, women on HRT (HRT+) displayed an enhanced epidermal barrier response (Kiss et al., 2024). This was evidenced by increased transepidermal water loss, measuring 49.7 (±5.4) g h–1 m–2 in the HRT+ group compared to 31.3 (±5) g h–1 m–2 in the HRT– group ($P < 0.05$) (Kiss et al., 2024). The HRT+ group also exhibited a thicker layer of cells in the top section of their skin, producing more filaggrin and showing increased cytokeratin 10 (K10)+ cell layers ($P < 0.01$) (Kiss et al., 2024). Following the irritant challenge, HRT users had a significant ($P < 0.01$) reduction in CD207+ cells in the epidermis, accompanied by an increase in CD207+ cells (migrating Langerhans cells) in the dermis. Furthermore, the numbers of dermal dendritic cells, macrophages, and specific macrophage subsets (CD11c+CD206– and CD68+CD206–) were significantly higher ($P < 0.05$) in the HRT+ individuals after SLS challenge (Kiss et al., 2024). These findings suggest that HRT may not only enhance the physical epidermal barrier function but also promote the accumulation of inflammatory macrophages and dendritic cells in the dermis under proinflammatory conditions, potentially leading to a more robust immune response and increased capacity for skin repair (Kiss et al., 2024).

3.1.6 HRT and ceramide profile of stratum corneum

A targeted lipidomic study, complemented by an in vitro investigation, was conducted to examine the ceramide profile and stratum corneum structure in pre-menopausal, post-menopausal, and post-menopausal women receiving hormone replacement therapy (Kendall et al., 2022). Post-menopausal women demonstrated a distinct perturbation in their ceramide profile and SC structure. Specifically, their stratum corneum exhibited lower levels of ceramides with a shorter average length and shorter sphingoid bases, indicative of altered *de novo* ceramide biosynthesis (Kendall et al., 2022). A significant reduction in ceramide abundance was observed compared to pre-menopausal women, with individual ceramide species across all classes showing notable decreases. For example, the ceramide classes CER[NH], CER[AH], and CER[EOH] achieved statistical significance with P-values of 0.0008, 0.0002, and 0.007, respectively (Kendall et al., 2022). Additionally, post-menopausal women displayed higher sphingomyelin levels (Kendall et al., 2022), and the average total carbon number of sphingomyelin species was lower in those not undergoing HRT ($P = 0.0082$) (Kendall et al., 2022). These alterations, particularly the presence of shorter ceramides, are associated with an impaired SC barrier function (Kendall et al., 2022). Importantly, these menopause-induced changes in ceramide abundance and quality were largely prevented or reduced in post-menopausal women on HRT, whose ceramide levels were similar to those of pre-menopausal women (Kendall et al., 2022). Further supporting this, an in vitro study showed that oestradiol at a concentration of 10 nM augmented the production of CER[NS] and CER[NDS] ceramides, with consistent upregulation of CER[NS] containing a C18 base. These findings underscore a direct role for oestrogen in regulating epidermal barrier ceramides and mitigating the structural transformations within the stratum corneum that are linked to menopause (Kendall et al., 2022).

3.1.7 Inconsistent Effects of HRT on Skin

We also found studies that imply that HRT may not induce significant changes in skin characteristics. For example, an open, non-randomized parallel-groups study involving 43 early postmenopausal women demonstrated no histological or immunohistological changes in skin specimens over a 12-month treatment period with systemic estrogen alone or combined with progestin (Haapasaari et al., 1997). Similarly, a randomized, double-blind, double-dummy, placebo-controlled multicentre study, which enrolled a larger cohort of 485 subjects for 48 weeks, found that low-dose HRT did not significantly alter mild to moderate age-related facial skin changes, nor did it show statistically significant benefits in clinically assessed skin laxity, texture, or dryness (Phillips et al., 2008).

Despite these findings, a critical examination of such studies often reveals inherent weaknesses that can limit the generalizability and robustness of their conclusions. One prevalent weakness lies in the study group size and design; while the latter study included a substantial number of participants (165 in the placebo group, 162 in the 1 mg NA/5 µg EE group, and 158 in the 1 mg NA/10 µg EE group), earlier research, such as a controlled trial involving only 60 postmenopausal nuns, yielded differing results, reporting an increase in skin thickness with estrogen therapy without commenting on clinically observable parameters (Phillips et al., 2008). The discrepancies across studies can also be attributed to varying methodologies, different measurement tools, and the use of diverse forms, dosages (e.g., 5 to 10 µg versus 50 mg estradiol in different studies), and administration routes of estrogen (Phillips et al., 2008). Furthermore, confounding factors, such as baseline estradiol levels, the number of years post-menopause (with some studies including women 5 to 7 years post-menopause, and others examining those less than 2 years post-menopause), sun exposure, and smoking status, are not always adequately controlled or accounted for, further complicating the interpretation of findings regarding HRT's true impact on skin aging (Phillips et al., 2008).

3.2 Safety Considerations of Hormone Replacement Therapy

The historical perspective on hormone replacement therapy has been complex, with early findings from the Women's Health Initiative significantly altering clinical practice by suggesting that systemic HRT posed more risks than benefits for many women, leading to a dramatic decline in its use (Viscomi et al., 2025). More recently, however, a nuanced understanding has emerged, indicating that HRT offers a favourable benefit-risk ratio for alleviating various menopausal symptoms in women under 60 years of age or within 10 years of menopause onset (Viscomi et al., 2025). A systematic review published in 2025 highlights that oral Menopause Hormone Therapy, particularly oral estrogen combined with a synthetic progestogen, increases the relative risk of certain complications (Hicks et al., 2025). Historically, the Women's Health Initiative trial significantly impacted prescribing practices due to its findings on risks such as breast cancer (with combined therapy, dependent on progestogen type), myocardial infarction, stroke, and venous thromboembolic events like pulmonary embolism and deep vein thrombosis (Hicks et al., 2025).

Regarding venous thromboembolism, it is well-established that the use of oral estrogens, with or without a synthetic progestogen, can significantly elevate the risk of VTE, especially in women with pre-existing risk factors (Hicks et al., 2025). Opposite to earlier findings, transdermal estrogen use has been associated with no increased risk of VTE in the postmenopausal population and may not confer additional risk even in women with VTE risk factors (Hicks et al., 2025; Vigneswaran & Hamoda, 2022). In women aged 50-59 years, there is an estimated additional 2 thromboembolic events per 1000 women with 5 years of unopposed oral estrogen, it hasn’t been noted in women on transdermal HRT, probably due to avoiding first-pass liver effect. (Vigneswaran & Hamoda, 2022). For women with prothrombotic mutations, oral HRT can lead to a 25-fold increased risk for VTE compared to non-users, whereas transdermal estrogens show a lower fourfold increased risk (Goldštajn et al., 2022). Specific progestogens in transdermal preparations also exhibit varying risks; transdermal estradiol with micronized progesterone or dydrogesterone is unlikely to increase VTE risk (Relative Risk 0.93; 95% Confidence Interval 0.65-1.33) compared to non-users, while norpregnane derivatives (RR 2.42; 95% CI 1.84-3.18) and medroxyprogesterone acetate (RR 2.77; 95% CI 2.33-3.30) are associated with higher VTE risks (Vigneswaran & Hamoda, 2022).

For cardiovascular disease, initial concerns from the WHI trial have been re-evaluated, with subsequent analyses suggesting that the impact of HRT on acute coronary disease risk is related to the woman's age at the commencement of HRT (Goldštajn et al., 2022; Rosenthal et al., 2020). HRT has been shown to decrease acute coronary disease risk by 44% in women younger than 60 years (Goldštajn et al., 2022). The Danish Osteoporosis trial, involving over 1000 women aged 45-58, reported a 50% reduction in a composite outcome measure (including heart failure, coronary events, cardiovascular mortality, and overall mortality) when HRT

was initiated within 10 years of menopause (Vigneswaran & Hamoda, 2022). Data from placebo-controlled randomized controlled trials indicate a significant reduction in all-cause mortality (6 fewer deaths per 1000 women) and coronary heart disease-related deaths (8 fewer deaths per 1000 women) for those who started HRT within 10 years of menopause (RR 0.70; 95% CI 0.52-0.95 and RR 0.52; 95% CI 0.29-0.96, respectively) (Vigneswaran & Hamoda, 2022). However, combined continuous HT, administered by oral, transdermal, subcutaneous or intranasal routes, increased the risk of a coronary event after 1 year's use from 2 per 1000 to between 3 and 7 per 1000 in relatively healthy postmenopausal women (Marjoribanks et al., 2017).

The risk of stroke with HRT also varies based on factors like age and administration route. The initial WHI study reported an increased risk of ischemic stroke by about one-third for both estrogen-only (RR 1.31; 95% CI 1.02-1.68) and estrogen plus progestogen (RR 1.37; 95% CI 1.09-1.73) across all age groups (Vigneswaran & Hamoda, 2022). Long-term follow-up from WHI indicated an increased risk of stroke for combined estrogen and progestogen (Hazard Ratio 1.16; 95% CI 1.00-1.35) and estrogen-alone (HR 1.15; 95% CI 0.97-1.37) in women aged 50-79 years, with the most significant risk observed in those aged 60-69 (Vigneswaran & Hamoda, 2022). A Cochrane review found a statistically significant increase in stroke risk (RR 1.21; 95% CI 1.06-1.38) for women who commenced HRT more than 10 years after menopause (Vigneswaran & Hamoda, 2022). Transdermal administration of estradiol is generally considered unlikely to increase stroke risk beyond that of non-users (Vigneswaran & Hamoda, 2022).

Regarding breast cancer, the risk is dependent on the type of therapy and progestogen used (Hicks et al., 2025). Combined continuous HT increased breast cancer risk after 5.6 years of use from 19 per 1000 to between 20 and 30 per 1000 (Marjoribanks et al., 2017). Conversely, estrogen-only HRT reduced breast cancer risk after 7 years of use from 25 per 1000 to between 15 and 25 per 1000 (Marjoribanks et al., 2017). Long-term WHI data from 2020 demonstrated a significant decrease in breast cancer diagnosis and mortality with estrogen-only HRT compared to placebo, while combined estrogen and progestogen HRT showed an increased risk of breast cancer but no significant difference in breast cancer mortality (Vigneswaran & Hamoda, 2022). Studies suggest that bioidentical estrogens may decrease breast cancer risk (HR: 0.65), whereas conjugated equine estrogens may increase it (HR: 1.49) (Rosenthal et al., 2020). The breast cancer risk with combined HRT may not differ based on progestogen type, but some studies indicate a higher risk with norethisterone acetate and a lower risk for dydrogesterone (Goldštajn et al., 2022). A cohort study showed that HRT used for less than 5 years was not associated with an increased breast cancer risk (Odds Ratio 0.93; 95% CI 0.80-1.04) but use for over 5 years was associated with an increased risk (OR 1.44; 95% CI 1.29-1.59) (Goldštajn et al., 2022).

Other complications include endometrial cancer, for which estrogen-only replacement therapy in women with a uterus is a primary risk factor (Goldštajn et al., 2022). However, the risk of endometrial hyperplasia and cancer with transdermal HRT is comparable to or lower than with oral HRT (Goldštajn et al., 2022). Gallbladder disease risk is also increased by combined continuous HT, from 27 per 1000 to between 38 and 60 per 1000 after 5.6 years of use (Marjoribanks et al., 2017). Combined continuous HT has also been linked to an increased risk of death from lung cancer, from 5 per 1000 to between 6 and 13 per 1000 after 5.6 years of use plus 2.4 years of follow-up (Marjoribanks et al., 2017). For women over 65 years of age taking continuous combined HT, an increased incidence of dementia was observed, rising from 9 per 1000 to between 11 and 30 per 1000 after 4 years of use (Marjoribanks et al., 2017). The Kronos Early Estrogen Prevention Study and the Early versus Late Intervention Trial with Estradiol were conducted to specifically evaluate HRT safety in early postmenopausal women, with KEEPS showing no increased risk for breast cancer (Rosenthal et al., 2020). A meta-analysis published in 2025 concluded that HRT can enhance the quality of life, improve hormonal balance, alleviate symptoms, and increase bone density, demonstrating a favourable safety profile with no significant increase in adverse events or dyslipidemia risk (Tang, 2025).

3.3 Non-HRT Estrogenic Treatment Strategies

HRT cannot currently be prescribed specifically as a therapy for estrogen-deficient skin due to the lack of high-quality research focused on its dermatological effects (Viscomi et al., 2025). Therefore, other forms of estrogen-based treatment will be outlined.

3.3.1 Estrogen topical therapy

Estrogen topical therapy seems worth exploring for its potential localized benefits on skin health, minimizing systemic exposure and associated risks. Regarding the safety profile, topical estrogen therapy generally presents a more favorable safety profile compared to systemic hormone replacement therapy, particularly concerning systemic risks. Topical formulations are designed to elicit localized effects on skin receptors with minimal systemic absorption (Rosset et al., 2025). Studies have rarely reported adverse effects,

and those observed were typically mild, such as temporary breast tenderness or localized reddening at the application site (Rzepecki et al., 2019). Most reports indicate no systemic symptoms attributable to the topical estrogens (Rzepecki et al., 2019). Topical estrogen preparations, such as commercial estradiol gels and compounded formulations, achieve measurable but generally lower systemic estradiol levels compared to oral or transdermal systemic therapy (Rosset et al., 2025). Therefore, topical hormone therapy offers a favorable safety profile for treating localized skin changes associated with hormonal decline (Rosset et al., 2025). However, concerns remain regarding possible systemic overdose via topical administration, which is considered an unstudied issue, and long-term safety data for topical hormone therapy are limited, necessitating careful product selection and monitoring for absorption variability (Lephart & Naftolin, 2021; Merzel Šabović et al., 2024; Rosset et al., 2025).

3.3.2 Selective estrogen receptor modulators (SERMs)

Selective estrogen receptor modulators (SERMs), such as raloxifene and tamoxifen, have shown promise as anti-aging therapies for estrogen-deficient skin, particularly in postmenopausal women where collagen content declines by 2% per year for up to 15 years without hormone replacement, and local aromatase enzyme activity drops to 30 times lower than premenopausal levels.(Lephart & Naftolin, 2022) These compounds exert tissue-selective estrogenic effects by preferentially activating estrogen receptor beta in skin keratinocytes and fibroblasts, promoting collagen synthesis—as demonstrated in vitro with raloxifene—increasing skin elasticity in vivo, enhancing thickness, hydration, and wound healing while mitigating systemic risks like endometrial hyperplasia associated with traditional estrogens.(Lephart & Naftolin, 2021; Merzel Šabović et al., 2024; Rosset et al., 2025) Methods of use include systemic oral administration (e.g., raloxifene approved for osteoporosis at doses preserving estrogen benefits without full agonist activity) or emerging topical formulations to localize effects and bypass long-term systemic concerns, with preclinical data supporting improved dermal parameters without significant adverse events in short-term studies.(Lephart & Naftolin, 2022; Merzel Šabović et al., 2024; Rosset et al., 2025) Safety profiles indicate a lower thromboembolic and oncogenic risk compared to unselective estrogens, as SERMs antagonize ERα in breast and uterus while agonizing ERβ in skin; however, robust human clinical trials for dermatological anti-aging remain limited, with no large-scale long-term data on exact incidences of side effects like hot flashes or venous thromboembolism, and further research is essential to establish efficacy thresholds, optimal dosing (e.g., 12–24 week topical regimens mirroring phytoSERM analogs), and contraindications in cancer-prone individuals.(Lephart & Naftolin, 2021, 2022; Rosset et al., 2025)

3.3.3 Phytoestrogens

Phytoestrogens are naturally occurring plant compounds that function as selective estrogen receptor modulators (SERMs), exerting tissue-specific estrogenic and anti-estrogenic effects. They have gained significant attention as a potential alternative to traditional hormone replacement therapy (HRT). While they are not identical to human estrogen, their ability to interact with estrogen receptors allows them to influence various biological processes, including those related to skin health (Lephart, 2021). Clinical and in vitro evidence supports the role of phytoestrogens as a beneficial anti-aging skin therapy, particularly for estrogen-deficient skin. Phytoestrogens, such as resveratrol and equol, function as Selective Estrogen Receptor Modulators, primarily binding to estrogen receptor beta, which is highly expressed in dermal cells like keratinocytes and fibroblasts (Lephart, 2021; Lephart & Naftolin, 2021). Their mechanism of action also involves potent antioxidant and anti-inflammatory properties, promoting skin health by increasing the production of hyaluronic acid, collagen (specifically type I and III), and extracellular protein matrix, while also enhancing skin vascularization and cell proliferation (Desmawati & Sulastri, 2019; Lephart & Naftolin, 2021).

For method of use, phytoestrogens can be applied topically or consumed orally. A randomized, 12-week single-center study demonstrated that a 0.3% equol lotion applied to the face and neck twice daily significantly improved skin parameters in women aged 40–70 with mild to moderate photo-aging. Improvements ranged from 51% for firmness to 78% for hydration over baseline values, with significant enhancements in smoothness, even skin tone/discoloration, lines/wrinkles, and pore size (Lephart, 2021). Other 12-24 week clinical studies using topical isoflavones also noted improvements in skin dryness, thickness, and facial wrinkles (Lephart & Naftolin, 2021). Oral supplementation of equol for 12 weeks has been shown to reduce wrinkles, such as crow's feet (Lephart & Naftolin, 2021). Furthermore, dietary intake recommendations for isoflavones average between 20 and 50 mg/day in regions like East and Southeast Asia, while the U.S. FDA considers 25 mg/day a safe intake (Desmawati & Sulastri, 2019; Lephart, 2021).

Regarding the safety profile, topical applications of phytoestrogens and isoflavones have generally not resulted in significant adverse effects in clinical studies (Lephart & Naftolin, 2021). Phytoestrogens are considered to have weaker effects than endogenous estrogens and are not typically stored in tissues, suggesting a low risk of hormone-related cancers (Merzel Šabović et al., 2024). They are regarded as a safe alternative to hormone replacement therapy, as they have not been shown to induce adverse changes in estrogen-sensitive organs like the uterus, ovary, or cervix at therapeutic doses, unlike certain external estrogens (Desmawati & Sulastri, 2019). Additionally, phytoestrogens do not appear to increase the risk of clotting in postmenopausal women (Desmawati & Sulastri, 2019). However, some research indicates that high dietary genistein (1000 or 1500 ppm) may decrease cell-mediated immunity, suggesting that the full impact of phytoestrogens on the immune system requires further investigation (Desmawati & Sulastri, 2019). It's also recognized that phytoestrogens can be classified as endocrine disruptors due to their binding to estrogen receptors, which is a point of ongoing discussion and perspective (Lephart, 2021).

3.3.4 Bioidentical hormone replacement therapy

Bioidentical hormone replacement therapy, utilizing estradiol and micronized progesterone, emerges as alternative to HRT anti-aging intervention for estrogen-deficient postmenopausal skin, mirroring yet potentially surpassing the benefits of classic hormone replacement therapy with conjugated equine estrogens and synthetic progestins like medroxyprogesterone acetate, while probably offering a superior safety profile.(Majidian et al., 2021; Rosenthal et al., 2020) Although superiority of bHRT is questioned, because there is no robust evidence about it.(Kauffman et al., 2024)

4. Discussion

4.1 HRT and Skin - Promise and Limitations

This narrative review highlights the significant impact of estrogen deficiency on skin structure and function and synthesizes current evidence on systemic HRT and emerging estrogen-modulating therapies. Collectively, findings confirm that estrogen plays a crucial biological role in maintaining dermal integrity through its influence on collagen production, extracellular matrix turnover, hydration, elasticity, and immune responses. Understanding how hormonal decline affects skin biology is therefore essential for evaluating therapeutic options aimed at mitigating climacteric skin deterioration.

The literature on hormone replacement therapy and its effects on postmenopausal skin quality remains heterogenous and seems to struggle with methodology that often varies a lot. There is a lack of standardisation in accessible search. Some studies report marked improvements in key parameters such as dermal thickness, elasticity, collagen content, and hydration. Vulnerabilities of those are small number of articles, small sample sizes. A lot of original publications that report remarkable skin quality effects was conducted in years 1980-2000 and often administered estrogen doses that were several-fold higher than current therapeutic standards. Because estrogenic stimulation of fibroblasts and neocollagenesis is dose dependent, these higher levels were more likely to produce measurable and sometimes striking improvements in dermal parameters. Yelding robust effects on dermal structure via sensitive, objective tools like skin biopsies for collagen quantification and high-resolution ultrasonography for thickness.(Majidian et al., 2021; Viscomi et al., 2025) Menopause age during start of hormonal therapy plays an important role in effectiveness, highlighting the significance of the "window of opportunity" concept, where earlier - preferably up to 10 years after menopause - intervention often yields more profound and lasting benefits and the risks associated with hormone replacement therapy are minimized, especially when considering the recent clinical position on the timing of intervention (Wilkinson & Hardman, 2021). Results are further complicated by confounding variables that are often inadequately controlled. Extrinsic factors, such as chronic sun exposure, smoking, and ethnicity (which involves pigmentation protective against wrinkles), exert a greater influence than HRT, yet are infrequently quantified (Brincat & Pollacco, 2024; Lephart & Naftolin, 2021; Viscomi et al., 2025). Study designs vary widely: non-randomized/open-label trials risk selection bias, while placebo-controlled RCTs differ in blinding rigor and progestogen inclusion, which may modulate estrogenic skin effects. (Lephart & Naftolin, 2021; Phillips et al., 2008).

Despite inconsistencies, meta-evidence tilts toward net benefits, validating HRT's mechanistic rationale via estrogen receptors in fibroblasts/keratinocytes promoting collagen/elastin synthesis.(Pivazyan et al., 2023) Guidelines withhold skin-specific endorsement due to sparse high-quality, skin-focused trials, prioritizing symptom relief.(Merzel Šabović et al., 2024; Viscomi et al., 2025) Future research demands standardized, adequately powered RCTs with early postmenopausal cohorts, multimodal objective measures (e.g., cutometry, optical coherence tomography), confounder adjustment, and diverse formulations. Integrating HRT with cosmeceuticals, lifestyle interventions, or aesthetics (e.g., fillers) could optimize rejuvenation. (Lephart & Naftolin, 2021; Viscomi et al., 2025)

4.2 Safety of HRT

The safety profile of Hormone Replacement Therapy has undergone significant re-evaluation, moving from initial broad concerns, largely influenced by the Women's Health Initiative findings, to a more nuanced understanding that supports a favourable benefit-risk ratio for women under 60 or within 10 years of menopause onset (Viscomi et al., 2025). While oral HRT, especially when combined with a synthetic progestogen, can increase the risk of venous thromboembolism, stroke, and certain cardiovascular events, transdermal estrogen application generally shows no increased VTE risk and may even reduce cardiovascular disease risk in younger women (Goldštajn et al., 2022; Hicks et al., 2025; Vigneswaran & Hamoda, 2022). Breast cancer risk also varies significantly by HRT type, with estrogen-only therapy potentially decreasing risk, whereas combined estrogen and progestogen therapies may increase it, particularly with long-term use (Goldštajn et al., 2022; Marjoribanks et al., 2017; Vigneswaran & Hamoda, 2022). Discrepancies in research findings highlight the heterogeneity of HRT regimens (oral vs. transdermal, different estrogen and progestogen types) and the importance of the "window of opportunity" for initiation, where earlier intervention (up to 10 years post-menopause) is associated with minimized risks and greater benefits (Brincat & Pollacco, 2024; Wilkinson & Hardman, 2021). These variations necessitate personalized treatment approaches, factoring in individual risk profiles, menopausal timing, and the specific formulation of HRT. Safety considerations remain a central factor limiting the broader clinical use of systemic HRT for dermatological purposes.

4.3 Topical estrogen therapy

Given that much work remains to be done in the field of systemic HRT and its safety concerns, researchers have begun to explore alternative approaches that may offer anti-aging benefits for the skin. One such option is the use of topical formulations containing estrogen, applied directly to the skin to target local estrogen deficiency. Topical estrogen therapy emerges as a promising avenue, primarily due to its potential for localized benefits on skin health while minimizing systemic exposure and associated risks (Rosset et al., 2025). Compared to systemic HRT, topical formulations generally present a more favourable safety profile, as they are designed to elicit effects on skin receptors with minimal systemic absorption (Rosset et al., 2025). Studies have rarely reported adverse effects, typically noting only mild, localized reactions such as temporary breast tenderness or reddening at the application site, with most reports indicating an absence of systemic symptoms (Rzepecki et al., 2019). While topical preparations do achieve measurable systemic estradiol levels, these are generally lower than those from oral or transdermal systemic therapy (Rosset et al., 2025). Consequently, topical hormone therapy appears to offer a favourable safety profile for addressing localized skin changes linked to hormonal decline (Rosset et al., 2025). However, concerns persist regarding the potential for systemic overdose via topical administration, which remains an understudied issue, and the availability of long-term safety data for topical hormone therapy is limited (Lephart & Naftolin, 2021; Merzel Šabović et al., 2024; Rosset et al., 2025). This necessitates careful product selection and vigilant monitoring for variability in absorption, highlighting the need for more robust, long-term studies to fully ascertain its efficacy and safety as a targeted treatment for estrogen-deficient skin.

4.4 Selective estrogen receptor modulators

SERMs represent another promising avenue. Their capacity to exert tissue-specific agonistic and antagonistic actions provides a theoretical advantage over classical estrogens. In particular, their preferential activation of ERβ in dermal cells could enable targeted anti-aging benefits while avoiding proliferative effects in breast and endometrial tissue. Early in vitro and short-term clinical data support improvements in collagen synthesis, elasticity, wound healing, and hydration (Lephart & Naftolin, 2022); however, robust long-term clinical trials in dermatology are lacking. Similarly, although SERMs generally carry a lower risk of thromboembolic events than traditional estrogens, systemic administration is not without risk, underscoring the need for topical SERM formulations and pharmacokinetic studies.

4.5 Phytoestrogens

Phytoestrogens provide an additional category of estrogen-modulating agents. Their weak but selective estrogen receptor activity, antioxidant capacity, and favorable safety profile make them attractive as both oral supplements and topical ingredients. They have shown potential to improve dermal thickness, collagen content, hydration, and elasticity, and their multimodal mechanisms—including modulation of ERβ, reduction of oxidative stress, and enhancement of lipid synthesis—align closely with cutaneous needs during menopause. (Desmawati & Sulastri, 2019; Lephart, 2021; Lephart & Naftolin, 2021). However, much of the evidence

remains preclinical or limited to small-scale human studies, and variability among phytochemical sources complicates direct comparisons. Some research suggests that high dietary intake of genistein, a type of phytoestrogen, might suppress cell-mediated immunity, indicating that their full impact on the immune system is still not completely understood and requires further investigation (Desmawati & Sulastri, 2019). More broadly, phytoestrogens are recognized as endocrine disruptors due to their ability to bind to estrogen receptors, a characteristic that continues to be a subject of ongoing debate and scrutiny (Lephart, 2021). Standardization of extracts, dose-response trials, and long-term safety data are crucial before phytoestrogens can be considered reliable therapeutic alternatives.

4.6 Menopausal skin changes and quality of life

Beyond the physiological changes, the impact of menopausal skin aging significantly affects women's quality of life. Visible signs such as dryness, wrinkles, and sagging can contribute to a decreased perception of attractiveness and self-image, leading to a considerable psychological burden (Bravo et al., 2024; Viscomi et al., 2025; Zouboulis et al., 2022). Surveys indicate that all women attending a menopause clinic experienced at least one skin symptom, with some even reaching scores on the Dermatology Quality of Life Index that signify a severe impact on quality of life (DeGiovanni, 2025). Despite this, skin and hair symptoms often receive less attention from healthcare professionals compared to other menopausal symptoms. Many women also report being insufficiently informed about the dermatological effects of menopause, highlighting a gap in patient education and the need for a shift in clinical priorities to address skin health with the same importance as other menopause-related issues (Bravo et al., 2024; Viscomi et al., 2025; Zouboulis et al., 2022). These changes can negatively affect emotional well-being, life satisfaction, and social interactions, emphasizing the broader subjective impact of skin aging during menopause (Viscomi et al., 2025).

5. Conclusions

Estrogen plays a central role in maintaining skin integrity, influencing dermal thickness, collagen synthesis, hydration, elasticity, and immune function. The decline in estrogen associated with menopause accelerates cutaneous aging and contributes to visible structural and functional deterioration. Overall, while systemic HRT remains the most thoroughly studied and biologically potent intervention for estrogen-deficient skin, its risk profile limits its dermatologic use. Topical estrogens, SERMs, and phytoestrogens offer promising targeted strategies with potentially safer profiles, but each requires further investigation. High-quality randomized controlled trials focusing specifically on skin outcomes, using standardized assessment tools and evaluating both systemic and local pharmacokinetics, are critically needed. Future research should also explore combinational approaches—such as pairing topical estrogenic agents with non-hormonal dermal therapies—to optimize efficacy while minimizing systemic exposure.

In conclusion, the management of estrogen-deficient skin is entering a period of therapeutic diversification. As our understanding of estrogen signalling in skin deepens, and as alternative hormone-modulating therapies advance, personalized treatment strategies may allow women to benefit from estrogen’s dermatologic advantages without incurring systemic risks. It is also worth considering the effects on the skin as an additional benefit when deciding on initiating HRT in a patient. Continued research will be essential to translate these promising avenues into evidence-based clinical practice. Ultimately, by effectively addressing the dermatological challenges of menopause, these advancements hold the potential to significantly enhance women's skin health and quality of life.

Conflict of Interest: Authors declare no conflict of interest.

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