Review Article

A promising alternative for mature skin: the effects of phytoestrogens on human skin and its topical use

Alternativa promissora para peles maduras: os efeitos dos fitoestrógenos na pele humana e seu uso tópico

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■ **ABSTRACT**

Skin quality deteriorates with age for various reasons, including hormone deficiencies. In women, the decline in estrogen levels during menopause plays an important role in skin degeneration, with consequent atrophy, collagen reduction, loss of elasticity, and impaired wound healing. Research has demonstrated the beneficial effects of topical phytoestrogen in preventing and repairing skin aging, with localized action and without side effects. The objective of this study was to review the relevant literature, demonstrating that this can be a safe and effective alternative for treating the skin of perimenopausal women.

Keywords: Phytoestrogens; Genistein; Estrogens; Skin aging; Collagen; Administration, topical.

■ **RESUMO**

A qualidade da pele deteriora-se com a idade por vários motivos, incluindo as deficiências hormonais. Nas mulheres, o declínio dos níveis de estrógeno, durante a menopausa, tem papel importante na degeneração cutânea, com consequente atrofia, redução do colágeno, perda de elasticidade e deficiência da cicatrização de feridas. Pesquisas têm demonstrado efeitos benéficos do fitoestrogênio tópico na prevenção e reparação do envelhecimento cutâneo, com ação localizada e sem efeitos colaterais. O objetivo deste estudo foi revisar a literatura pertinente ao assunto, demonstrando que esta pode ser uma alternativa segura e eficaz para o tratamento da pele de mulheres na perimenopausa.

Descritores: Fitoestrógenos; Genisteína; Estrogênios; Envelhecimento da pele; Colágeno; Administração tópica.

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INTRODUCTION

The life expectancy of women has increased significantly in the last century. In the United States, it was approximately 50 years in 1900 and currently exceeds 80 years, according to the World Health Organization[1]. In Brazil, according to the IBGE (Brazilian Institute of Geography and Statistics, in portuguese: *Instituto Brasileiro de Geografia e Estatística*), in 1940, it was 48.3 years, and in 2015 it reached 79.1 years[2]. Thus, today it is expected that women spend more than a third of their lives after menopause, which leads to greater concern about health care in this period[3].

Skin quality deteriorates with age due to chronological aging, photoaging, environmental factors, and hormone deficiencies. Menopause is a milestone in a woman's life, accompanied by a significant drop in hormone levels. This change causes numerous climacteric symptoms, including the accelerated decline of skin conditions. The drop in estrogen levels that occurs during this period plays an important role in skin atrophy, in the reduction of collagen

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and water content, in the reduction of sebaceous secretions, in the loss of elasticity and wrinkling of the skin, and, in addition, in the impairment of wound healing.[4]

Studies show evidence that changes in estrogen levels are associated with the perception of aging. According to Lephart, in his study, a positive correspondence was demonstrated between estrogen levels and perceived age, facial attractiveness, skin color, and health[5].

Consequently, careful study of the molecular effects of estrogen on the skin and the corresponding cutaneous manifestations is important.

The important role of estrogen in skin integrity was demonstrated with the discovery of estrogen receptors in dermal fibroblasts and epidermal keratinocytes[4,6-8]. It acts through two distinct mechanisms: the classic pathway, with estrogen receptors ERa and ERb, which involves the nuclear location of the hormone-receptor complex, by which the expression of target genes is altered, and the non-classical pathway, which initiates a rapid cascade of intracellular signaling by coupling the hormone to estrogen receptors on the cell membrane, including the G-protein coupled estradiol receptor (GPER or GPR30). Thus, estrogen can exert its physiological effects through a combination of genomic and non-genomic pathways[9].

Estrogens generally improve collagen content and quality and increase dermal thickness and vascularity. In addition, they improve the migration of keratinocytes and, consequently, accelerate the wound healing process[7].

Studies have shown that 17 b-estradiol and genistein can combat skin aging, protecting fibroblasts and keratinocytes against peroxidation. They act by modulating the oxidant/antioxidant system and the mitochondrial membrane potential through mechanisms related to estrogen receptors (classical and non-classical) and to the activation of kinases[6,8,10].

The topical use of estrogens and phytoestrogens has demonstrated beneficial effects on preventing and repairing skin aging in postmenopausal women[11-16]. The importance of estrogen in maintaining human skin homeostasis is evidenced by the sudden acceleration of skin aging observed in women during the climacteric[9,11].

Phytoestrogens represent promising alternatives for treating skin aging, especially genistein, which has anti-photocarcinogenic and anti-photoaging properties by modulating the oxidant/antioxidant balance[8]. Phytoestrogens are substances plants produce with structural and functional properties similar to estrogens. Thus, they bind directly to estrogen receptors, exerting agonist and antagonist effects. Isoflavones have been shown to promote beneficial effects on aging skin regarding photoprotection, elasticity, hydration, and wrinkle prevention[9].

In recent years, much research has been carried out to elucidate the effects of topical estrogens and phytoestrogens, which would have a more localized action on the skin without the side effects of systemic hormone replacement. Studies have concluded that phytoestrogens have comparable efficacy to estrogen in skin aging. In addition, because they are plant-derived compounds with fewer possible side effects, they could be safer for topical use[17].

Thus, the localized use of these hormones in small areas, such as the face, neck, and decollete, is a safe and effective alternative for treating the skin of perimenopausal women.

OBJECTIVE

To review national and international scientific production through a narrative review of the literature to assess the role of topical phytoestrogens in human skin and their effect on skin rejuvenation.

METHOD

This is a narrative literature review of articles in journals in Portuguese and English published from 1996 to 2021. Bibliographical research was carried out from January to March 2021 through the search sources constituted by electronic resources in the following databases data: Latin American and Caribbean Literature on Health Sciences (LILACS), Health Information from the National Library of Medicine (Medline), Web of Science, Scopus and the Scientific Electronic Library Online (SciELO).

The descriptors (DeCS) used were: *Fitoestrógenos*/Phytoestrogens, *Genisteína*/Genistein, Estrogênios/Estrogens, *Envelhecimento da pele*/Skin aging, *Colágeno*/Collagen, *Administração tópica*/Topical Administration.

Additionally, a detailed manual search of the references of selected articles was performed to find studies not identified in the online search.

RESULTS

After identifying the articles, in the search mentioned above sources, the following selection criteria were used (Chart 1).

In all, 15 clinical studies and 7 literature reviews were selected.

DISCUSSION

In women, chronological aging is accompanied by a significant drop in hormone levels during climacteric and menopause. These changes lead to numerous symptoms, including the accelerated decline of skin conditions. With the increase in women's life expectancy

Chart 1. Article selection criteria.

Inclusion criteria	• Clinical studies in perimenopausal women treated with topical estrogen or phytoestrogen • Literature reviews on the effects of topical estrogen and phytoestrogen on human skin and skin aging • Clinical studies with histological sections and cultures of human cells and the effects of estrogens and phytoestrogens in vitro • Clinical studies evaluating the effects of estrogens and phytoestrogens on the skin of animals and the molecular mechanisms of action of these hormones
Non-inclusion criteria	• Clinical Studies with systemic hormone replacement • Case reports
Exclusion criteria	• Duplicate articles • Articles with conflict of interest

Source: Authors (2021).

and, consequently, the interest in skin care after menopause, studies on the beneficial effects of estrogens and phytoestrogens on skin in aging have increased a lot.

Long-term systemic hormone replacement therapy has been associated with unwanted systemic effects, according to the Women's Health Initiative (WHI) Study, Heart and Estrogen Replacement Study (HERS), and Million Women Study[18-20]. Thus, in the search for safe and effective alternatives, the more localized effects of topical estrogens and phytoestrogens on the skin have been explored.

Phytoestrogens are substances plants produce with structural and functional properties similar to estrogens. There are three main classes: isoflavones, lignans, and coumestans[21]. Among these, isoflavones, especially genistein, are the best studied. These bind directly to estrogen receptors, exerting both agonist and antagonist effects. Numerous studies have shown that isoflavones promote beneficial effects on aging skin regarding photoprotection, elasticity, hydration, and wrinkle prevention[11,22].

Bayerl & Keil[12], in a European multicenter controlled clinical study, in 2002, examined the effect of a cosmetic cream preparation, including isoflavone, in 234 women with a maximum age of 65 years, at least three years after menopause, with no replacement therapy hormone (HRT) or other substances that affect the skin's aging process. The duration of therapy was 12 weeks. The isoflavone cream was applied twice daily (in the morning at a concentration of 0.0075% and night at 0.015%) on the face, neck, and one arm. The other arm was not treated and served as a control.

Skin hydration and texture significantly improved in treated areas by 32.9% and 22%, respectively, compared to untreated areas. Facial wrinkles were significantly reduced by 22%, and skin sagging was significantly reduced by 24%[12].

Genistein has a molecular structure very similar to that of estradiol, has significant effects on the skin due to its ability to bind to estrogen receptors, and has been shown to provide protective effects against photoaging and photocarcinogenesis in human and animal skin when applied topically[23-25].

In a double-blind, randomized study by Moraes et al.[14], in 2009, 4% genistein gel was applied topically to the facial skin of postmenopausal women for 24 weeks, with improvement in dermal vascularization and an increase in epidermal thickness.

Patriarca et al.[15], in a prospective, randomized, double-blind study, in 2013, with 30 postmenopausal women, demonstrated an increase in the concentration of hyaluronic acid and fibroblasts in the dermis after topical treatment for 24 weeks with 4% genistein and 0.01% 17β-estradiol.

In a randomized, double-blind study, in 2017, with 30 patients aged between 45 and 55 years, Silva et al.[16] compared the effects of topical estrogen and topical genistein on the skin collagen of postmenopausal women. Patients were divided into three groups: topical estradiol, topical genistein, and control. A statistically significant increase in collagen type I and III was observed in both estradiol and genistein groups. The possibility of systemic absorption of topical estrogen was also a variable studied, with vaginal smears and transvaginal ultrasound being performed to measure the thickness of the endometrium before and after treatment.

In addition, serum estradiol dosage was performed before and 24 weeks after treatment. Initially, all selected women had vaginal and endometrial atrophy, with serum estradiol levels below 20pg/ml. None of these parameters changed after treatment. Based on these results, it can be inferred that topical therapy with estrogen and genistein does not produce significant systemic side effects[16].

Desmawati & Sulastri[26], in 2019, carried out a review study on phytoestrogens and their effects. It has been described that phytoestrogens are structurally similar compounds to 17β-estradiol. Among phytoestrogens, isoflavones are the most studied and are found in soy and other legumes. The amount of isoflavones needed to produce health effects is 40 to 70 mg daily. The main phytoestrogens, in the form of isoflavones, are genistein, daidzein, glycitein, formononetin, and biochanin.

The authors described that phytoestrogens could act with an anti-aging effect on the skin through estrogen receptors. They lead to increased hyaluronic acid, collagen, and extracellular protein matrix production. In addition, phytoestrogens can also increase vascularity and cell proliferation in the skin and prevent oxidative stress and apoptosis. Studies analyzed by the authors showed a reduction in cell death induced by ultraviolet radiation in cultured keratinocytes, an improvement in skin elasticity and thickness, and an increase in the production of procollagen type 126.

Rzepecki et al.[27], in 2019, carried out a review study aiming to provide an overview of the role of estrogen in the skin and the changes associated with its deficiency. Specifically, clinical studies using topical estrogens and topical isoflavones were analyzed. Improvement was observed in several parameters analyzed in the studies, both with estrogens and isoflavones. There was an increase in skin elasticity, epidermal thickness, hyaluronic acid concentration, and collagen concentration. Improvements in facial wrinkles, skin texture, hydration, sebum production, and wound healing have been observed. There were no significant systemic changes. The effects described were more noticeable in the estrogen-treated groups.

However, studies have shown that topically applied phytoestrogens have comparable efficacy to estrogens. In addition, some isoflavones (especially genistein) stand out for having a high affinity for ER-β (found more frequently in the skin, bones, and cardiovascular system) and low affinity for ER-α (more often found in the uterus and boobs). Thus, due to their ability to be tissue-selective, isoflavones are also considered selective estrogen receptor modulators (SERMs/SERMs)[27].

Therefore, although larger, well-controlled studies are needed, isoflavones are potential candidates for treating the skin without the negative aspects of systemic estrogen. Topical estrogens have low systemic absorption and thus low associated risks; however, genistein is believed to pose an even lower risk due to receptor selectivity. At the end of the study, the authors concluded that the effects of estrogen deficiency on the skin are an important endogenous cause of skin aging in women. However, treatment strategies that aim to act on the underlying hormonal deficiency and not on the resulting symptoms are limited[27].

Liu et al.[17], in a narrative review of the literature, in 2020, evaluated the effects of phytoestrogens on human skin and the mechanisms by which they can alleviate the signs of aging. The authors described that phytoestrogens could increase collagen and water content in the skin and protect against oxidative stress. Thus, they can significantly delay skin aging. The authors discussed the topical application of both estrogen and phytoestrogens. Both are possible; however, concerning estrogen, they deemed necessary a qualified specialist doctor who could accompany and monitor the concentration and areas of application, avoiding any adverse effects.

As for phytoestrogens, they considered them safer because they are compounds derived from plants with fewer side effects. Finally, this review demonstrates that phytoestrogens have comparable efficacy to estrogen concerning skin aging. Thus, in recent years, they have become an important research point in the fight against skin aging[17].

Lephart & Naftolin[28] did a recent review in 2021 on menopause, its effects on the skin, and innovations in cosmeceuticals for estrogen-deficient skin. The authors reported that this estrogen-deficient condition dramatically reduces skin health and well-being, negatively impacting dermal and homeostatic cellular mechanisms and other important biological functions. Changes include loss of collagen, elastin, fibroblast function, and vascularity. In addition, cellular and extracellular degradation occurs, leading to skin dehydration, wrinkling, atrophy, impaired wound healing, and barrier function. Such factors lead to a decrease in attractiveness and psychological health, with an increase in the perception of aging.

The authors report that based on their studies, topical estrogen or phytoestrogen can reverse these changes. Finally, the authors emphasize the need for a more concentrated local administration of hormones or innovative cosmeceutical agents, such as selective estrogen receptor modulators (SERMs/SERMs), including phytoestrogens are promising actives, for skin care products, especially when it comes to estrogen-deficient skin[28].

This study also reported that the plant kingdom is one of the greatest sources of new cosmeceutical ingredients. Plants are rich in antioxidants as they need to survive continuous exposure to ultraviolet radiation. The botanicals are considered safe and meet Food and Drug Administration (FDA) criteria for substances that can be placed in over-the-counter topical formulations. Thus, many studies have examined phytochemicals of the polyphenolic class, also known as phytoestrogens, which act as SERMs[28].

CONCLUSION

The drop in serum estrogen levels in the climacteric and menopause is an important contributor to the decline in skin functions. In turn, hormone replacement with estrogens or phytoestrogens favorably influences the quality of the skin and its functions in several aspects, promoting anti-aging action due to its ability to prevent the decrease in collagen concentration, restore skin elasticity and increase hydration of the skin, in addition to its important role in improving wound healing. However, despite the numerous positive effects of estrogen action on the skin, systemic hormone replacement should not be considered solely to combat skin aging.

On the other hand, studies show that topical treatment with phytoestrogens, especially genistein, improves skin quality and does not significantly increase the systemic dosage of these hormones. Thus, topical phytoestrogenic compounds represent a new, promising, and safe therapeutic approach for skin aging in perimenopausal women.

COLLABORATIONS

JLC Analysis and/or data interpretation, Conception and design study, Conceptualization, Data Curation, Investigation, Methodology, Visualization, Writing - Original Draft Preparation, Writing - Review & Editing.

IBR Data collection, Investigation

AH Final manuscript approval, Supervision, Validation.

LMF Supervision, Validation.

REFERENCES

1. World Health Organization (WHO). Life expectancy at birth (years) [Internet]. Geneva: World Health Organization; 2021 [acesso 2021 Abr 5]. Disponível em: https://www.who.int/data/gho/data/indicators/indicator-details/GHO/life- expectancy-at-birth-(years)
2. Brasil. Instituto Brasileiro de Geografia e Estatística (IBGE). Em 2019, expectativa de vida era de 76,6 anos [Internet]. Rio de Janeiro: IBGE; 2021 [acesso 2021 Mar 5]. Disponível em: https://www.ibge.gov.br/busca.html?searchword=expectativa%20de%20vida&searchphrase=all
3. Shah MG, Maibach HI. Estrogen and skin: An overview. Am J Clin Dermatol. 2001;2(3):143-50.
4. Brincat MP, Baron YM, Galea R. Estrogens and the skin. Climacteric. 2005;8(2):110-23.
5. Lephart ED. A review of the role of estrogen in dermal aging and facial attractiveness in women. J Cosmet Dermatol. 2018;17(3):282-8.
6. Carnesecchi J, Malbouyres M, de Mets R, Balland M, Beauchef G, Vié K, et al. Estrogens induce rapid cytoskeleton re-organization in human dermal fibroblasts via the non-classical receptor GPR30. PLoS One. 2015;10(3):e0120672.
7. Zhou T, Yang Z, Chen Y, Chen Y, Huang Z, You B, et al. Estrogen Accelerates Cutaneous Wound Healing by Promoting Proliferation of Epidermal Keratinocytes via Erk/Akt Signaling Pathway. Cell Physiol Biochem. 2016;38(3):959-68.
8. Savoia P, Raina G, Camillo L, Farruggio S, Mary D, Veronese F, et al. Anti-oxidative effects of 17 β-estradiol and genistein in human skin fibroblasts and keratinocytes. J Dermatol Sci. 2018;92(1):62-77.
9. Shu YY, Maibach HI. Estrogen and skin: therapeutic options. Am J Clin Dermatol. 2011;12(5):297-311.
10. Richardson TE, Yu AE, Wen Y, Yang SH, Simpkins JW. Estrogen prevents oxidative damage to the mitochondria in Friedreich's ataxia skin fibroblasts. PLoS One. 2012;7(4):e34600.
11. Schmidt JB, Binder M, Demschik G, Bieglmayer C, Reiner A. Treatment of skin aging with topical estrogens. Int J Dermatol. 1996;35(9):669-74.
12. Bayerl C, Keil D. Isoflavonoids in the Treatment of Skin Aging in Postmenopausal Women. Isoflavonoide der Behandlung der Hautalterung postmenopausaler Frauen. Aktuelle Derm. 2002;28(Suppl 1):S14-8. DOI: 10.1055/s-2002-35407
13. Son ED, Lee JY, Lee S, Kim MS, Lee BG, Chang IS, et al. Topical application of 17beta-estradiol increases extracellular matrix protein synthesis by stimulating tgf-Beta signaling in aged human skin in vivo. J Invest Dermatol. 2005;124(6):1149-61.
14. Moraes AB, Haidar MA, Soares Júnior JM, Simões MJ, Baracat EC, Patriarca MT. The effects of topical isoflavones on postmenopausal skin: double-blind and randomized clinical trial of efficacy. Eur J Obstet Gynecol Reprod Biol. 2009;146(2):188-92.
15. Patriarca MT, Barbosa de Moraes AR, Nader HB, Petri V, Martins JR, Gomes RC, et al. Hyaluronic acid concentration in postmenopausal facial skin after topical estradiol and genistein treatment: a double-blind, randomized clinical trial of efficacy. Menopause. 2013;20(3):336-41.
16. Silva LA, Ferraz Carbonel AA, de Moraes ARB, Simões RS, Sasso GRDS, Goes L, et al. Collagen concentration on the facial skin of postmenopausal women after topical treatment with estradiol and genistein: a randomized double-blind controlled trial. Gynecol Endocrinol. 2017;33(11):845-8.
17. Liu T, Li N, Yan YQ, Liu Y, Xiong K, Liu Y, et al. Recent advances in the anti-aging effects of phytoestrogens on collagen, water content, and oxidative stress. Phytother Res. 2020;34(3):435-47.
18. Grady D, Applegate W, Bush T, Furberg C, Riggs B, Hulley SB. Heart and Estrogen/progestin Replacement Study (HERS): design, methods, and baseline characteristics. Control Clin Trials. 1998;19(4):314-35.
19. Pardini D. Terapia de reposição hormonal na menopausa. Arq Bras Endocrinol Metab. 2014;58(2):172-81.
20. Speroff L. The Million Women Study and breast cancer. Maturitas. 2003;46(1):1-6.
21. Jacobs A, Wegewitz U, Sommerfeld C, Grossklaus R, Lampen A. Efficacy of isoflavones in relieving vasomotor menopausal symptoms - A systematic review. Mol Nutr Food Res. 2009; 53(9):1084-97.
22. Sator PG, Schmidt JB, Rabe T, Zouboulis CC. Skin aging and sex hormones in women -- clinical perspectives for intervention by hormone replacement therapy. Exp Dermatol. 2004;13(Suppl 4):36-40.
23. Wei H, Saladi R, Lu Y, Wang Y, Palep SR, Moore J, et al. Isoflavone genistein: photoprotection and clinical implications in dermatology. J Nutr. 2003;133(11 Suppl 1):3811S-9S.
24. Moore JO, Wang Y, Stebbins WG, Gao D, Zhou X, Phelps R, et al. Photoprotective effect of isoflavone genistein on ultraviolet B-induced pyrimidine dimer formation and PCNA expression in human reconstituted skin and its implications in dermatology and prevention of cutaneous carcinogenesis. Carcinogenesis. 2006;27(8):1627-35.

25. Accorsi-Neto A, Haidar M, Simões R, Simões M, Soares J Jr, Baracat E. Effects of isoflavones on the skin of postmenopausal women: a pilot study. Clinics (Sao Paulo). 2009;64(6):505-10.
26. Desmawati D, Sulastri D. Phytoestrogens and their health effect. Open Access Maced J Med Sci. 2019;7(3):495-9.
27. Rzepecki AK, Murase JE, Juran R, Fabi SG, McLellan BN. Estrogen-deficient skin: The role of topical therapy. Int J Womens Dermatol. 2019;5(2):85-90.
28. Lephart ED, Naftolin F. Menopause and the Skin: Old Favorites and New Innovations in Cosmeceuticals for Estrogen-Deficient Skin. Dermatol Ther (Heidelb). 2021;11(1):53-69.

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