

The effects of estrogens and phytoestrogens on human skin and its topical use for prevention of skin aging - Literature Review

Os efeitos dos estrogênios e fitoestrogênios na pele humana e seu uso tópico para prevenção do envelhecimento cutâneo: revisão da literatura

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ABSTRACT

Skin quality and function drastically reduces with age due to chronological aging, photoaging, environmental factors and hormonal deficiencies. Decreased menopausal estrogen levels play a role in cutaneous atrophy, collagen and water content, loss of elasticity, skin wrinkling and deficiency of wound healing. Much research has been done to elucidate the beneficial effects of topical estrogen, which would have a more localized action on the skin without systemic side effects. The objective of this study was to review the relevant literature, demonstrating that this may be a safe and effective alternative for the treatment of women's skin in perimenopause.

Keywords: Estrogens; Phytoestrogens; Skin aging; Collagen; Antioxidants

RESUMO

A qualidade e a função da pele reduzem-se drasticamente com a idade devido ao envelhecimento cronológico, ao fotoenvelhecimento, aos fatores ambientais e às deficiências hormonais. O declínio dos níveis de estrogênio na menopausa tem papel importante na atrofia cutânea, redução do colágeno, perda de elasticidade e deficiência da cicatrização de feridas. Pesquisas têm demonstrado os efeitos benéficos do estrogênio tópico, que teria ação mais localizada na pele sem efeitos colaterais sistêmicos. O objetivo deste estudo foi revisar a literatura pertinente ao assunto, demonstrando que o uso do estrogênio tópico pode ser uma alternativa segura e eficaz para o tratamento da pele de mulheres na perimenopausa.

Palavras-Chave: Antioxidantes; Colágeno; Estrogênios; Envelhecimento da pele; Fitoestrogênios

Review

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INTRODUCTION

Life expectancy for women has increased significantly in the past century. In the United States, it was approximately 50 years in 1900, and currently, it exceeds 80 years.¹ In Brazil, according to the Instituto Brasileiro de Geografia e Estatística (IBGE), in 1940, the life expectancy was 48.3 years, and, in 2015, it reached 79.1 years.² Thus, today, women are expected to spend more than a third of their lives after menopause, which leads to greater concern about health care in this period.³

The quality of the skin deteriorates with age due to chronological aging, photoaging, environmental factors, and hormonal deficiencies. Menopause is a milestone in a woman's life, which is accompanied by a significant drop in hormone levels. This change causes numerous symptoms that constitute the climacteric, among them the accelerated decline in skin conditions. The drop in estrogen levels that occurs in this period plays an essential role in cutaneous atrophy, in the collagen and water content reduction, in sebaceous secretions decrease, in elasticity loss, and in skin wrinkling, as well as in the wound healing deficiency.⁴

Consequently, it is vital to carefully study the molecular effects of estrogen on the skin and its corresponding cutaneous manifestations.

The critical role of estrogen in skin integrity has been demonstrated with the discovery of estrogen receptors in dermal fibroblasts and epidermal keratinocytes.^{4,5,6,7} Studies have shown that 17 β -estradiol and genistein can combat skin aging through its protective effects related to modulating lipid peroxidation, as demonstrated in dermal fibroblasts extracted from patients with Friedreich's ataxia.⁸ They also act on the mitochondrial membrane potential through mechanisms related to estrogen receptors (classical and non-classical) and the activation of kinases.^{5,6} Thus, estrogen can exert its physiological effects through a combination of genomic and non-genomic pathways.⁹

The use of estrogens has shown beneficial effects in the prevention and repair of skin aging in postmenopausal women. The acceleration of skin aging observed in women during the climacteric evidences its importance in maintaining human skin homeostasis.^{8,9} In general, estrogens not only improve collagen content and quality but also increase dermal thickness and vascularity. Also, they contribute to enhancing the migration of keratinocytes and, consequently, accelerate the wound healing process.⁷ Phytoestrogens also represent promising alternatives for the treatment of skin aging, especially genistein, which has antiphotocarcinogenic and antiphototoaging properties by modulating the oxidant/ antioxidant balance.⁵

In recent years, much research has been conducted to elucidate the effects of topical estrogen, which would have a more localized action on the skin without the adverse events of systemic hormone replacement. Thus, topical estrogen can be a safe and effective alternative for skin treatment of women in perimenopause.

OBJECTIVES

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

METHODS

This is a narrative review of the literature of articles published in journals in Portuguese and English between 1993 and 2018. A bibliographic search was conducted from July to November 2018 using the search engines in the electronic resources of the following databases: Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), Health Information from the National Library of Medicine (Medline), Web of Science, Scopus, and in the electronic library Scientific Electronic Library Online (SciELO).

The descriptors (DeCS) used were: estrogênios/estrogens, fitoestrógenos/phytoestrogens, envelhecimento da pele/skin aging, colágeno/collagen, antioxidantes/antioxidants.

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

RESULTS

After identifying the articles in the mentioned search sources, we selected: clinical studies with women in perimenopause treated with topical estrogen or phytoestrogen; literature reviews on the effects of topical estrogen on human skin and skin aging; clinical studies with histological cuts and cultures of human cells and the effects of estrogens *in vitro*; and clinical studies with evaluation of the effects of estrogens and phytoestrogens on the skin of animals and the molecular mechanisms of the action of this hormone. Clinical studies with systemic hormone replacement and case reports were excluded. In total, we included 16 clinical studies and eight literature reviews.

DISCUSSION

Human skin is composed of a connective tissue highly rich in collagen, which provides essential structural, and functional support. Type I (80%) and type III (15%) collagens are prevalent.⁹ In the aging process, the dermal collagen fibers decrease in number and fragment, thinning and weakening the skin structure. These changes in collagen fibers create a microenvironment that promotes age-related skin diseases.^{10,11,12} In women, a significant drop in hormone levels that occurs in climacteric and menopause accompanies chronological aging. These changes cause numerous symptoms, among them, the accelerated decline of skin conditions.

As interest in skincare after menopause is increasing, studies on the beneficial effects of estrogens and phytoestrogens on the aging skin have also been significantly expanding.

According to Shu et al.,⁹ there are two predominant forms of estrogen receptors in the skin, called estrogen receptor α (ER α) and estrogen receptor β (ER β).^{9,13,14}

These receptors are distinct proteins encoded by different

genes;¹⁵ however, both bind to estradiol with similar affinity. Thus, estrogen acts through two distinct mechanisms: the classic pathway, with estrogen receptors ER α and ER β , involving the nuclear localization of the hormone-receptor complex, which alters the expression of target genes; and the non-classical pathway, which initiates a rapid cascade of intracellular signaling by coupling the hormone to estrogenic receptors on the cell membrane, including the G protein-coupled estrogen receptor (GPER or GPR30).

The molecular basis of the estrogen action on the skin has been gradually elucidated in recent studies. In 2018, Savoia et al.⁵ demonstrated in their research a protective effect of genistein and 17 β -estradiol against peroxidative damage in fibroblasts and keratinocytes by modulating the release of nitric oxide (NO) and reactive oxygen species (ROS), glutathione content (GSH) and mitochondrial function. The involvement of estrogen receptors (ERs), non-classical membrane G protein-related estrogen receptor (GPER30), and kinase activator (PI3K-Akt, p38 MAPK, ERK 1/2) has also been elucidated. Furthermore, it has been shown that estrogens induce remodeling of the actin cytoskeleton in isolated human dermal fibroblasts through the ER-independent, GPER30-dependent non-genomic mechanism.

Carnesecchi et al.⁶ showed that the lack of estrogens induces rapid reorganization of the cytoskeleton of human dermal fibroblasts, resulting in a significant change in the cell format. After the replacement of 17 β -estradiol, the cell morphology, and organization of the cytoskeleton were completely restored. The receptor involved would be the non-classic GPER-30. Richardson et al.⁸ demonstrated potent cytoprotective properties of estrogens in vitro. They can prevent lipid peroxidation and the collapse of mitochondrial membrane potential, increase oxidative phosphorylation, and maintain ATP levels and aconitase activity in fibroblasts in patients with Friedreich's ataxia (FRDA).

Another study, by Zhou et al.,⁷ observed that estrogen accelerates wound healing by inducing proliferation of epidermal keratinocytes via the intracellular Erk/Akt signaling pathway, both in vitro and in vivo. Phytoestrogens are substances produced by plants, with structural and functional properties similar to those of estrogens. There are three main classes: isoflavones, lignans, and coumestans.¹⁶ Among them, isoflavones, especially genistein, are the best studied. These bind directly to estrogen receptors, exerting both agonist and antagonist effects.^{17,18} Several studies have shown that isoflavones promote beneficial effects on aging skin in terms of photoprotection, elasticity, hydration, and wrinkle prevention.¹⁰ A study by Cicrosta et al.,¹⁹ published in 2006, with ovariectomized rats, conducted oral treatment with isoflavones (20 and 40 mg/day for 14 weeks). The results presented general improvement in skin morphology and a significant increase in skin collagen in the treated group compared to the control group. Therefore, phytoestrogens have been considered as potential alternatives to estrogen.

However, long-term hormone replacement therapy has been associated with unwanted systemic effects. Thus, in the search for safe and effective alternatives, the most localized ef-

fects on the skin of topical estrogens and phytoestrogens have been explored.

In 1996, Schmidt et al.¹⁰ compared the effects of estradiol cream 0.01% and estriol 0.3% in 59 patients in the peri and post-climacteric with signs of skin aging and who did not undergo hormone replacement. After six months, a significant improvement in skin aging symptoms was observed. Both estriol and estradiol, at the concentrations used, demonstrated comparable results. Fewer adverse events have been reported in the estriol group. Ten patients were biopsied, and there was a significant increase in type III collagen.¹⁰

In a randomized, double-blind study with 30 patients between 45 and 55 years old, Silva et al.²⁰ compared the effects of using topical estrogen and topical genistein on the skin collagen of postmenopausal women. The patients were divided into three groups: topical estradiol, topical genistein, and control. There was a statistically significant increase in both type I and type III collagen in the groups that used estradiol and genistein. The possibility of systemic absorption of topical estrogen was also a variable studied, with vaginal smears and transvaginal ultrasound performed to measure the thickness of the endometrium before and after treatment. Furthermore, serum estradiol was measured before and 24 weeks after the therapy. Initially, all selected women had vaginal and endometrial atrophy, with serum estradiol levels below 20 pg/ml. None of these parameters changed after the treatment. Based on these results, it can be inferred that topical therapy with estrogen and genistein doesn't cause significant systemic adverse events.

Genistein has a molecular structure very similar to that of estradiol, presenting significant effects on the skin due to its ease in binding to estrogen receptors^{21,22} and it has been shown to provide protective effects against photoaging and photocarcinogenesis in human and animal skin when applied topically.^{23,24} A double-blind, randomized study by Moraes et al.²⁵ (2009), applied topical genistein gel 4% to the facial skin of postmenopausal women for 24 weeks, with improved dermal vascularization and increased epidermal thickness. Patriarch et al.²⁶ demonstrated an increase in the concentration of hyaluronic acid and fibroblasts in the dermis after topical treatment with genistein and estrogen. Thus, phytoestrogens are also promising alternatives in the treatment of skin aging.

CONCLUSION

The drop in serum estrogen levels in climacteric and menopause contributes significantly to the decline in skin functions. In turn, hormone replacement with estrogen 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, restores skin elasticity, and increase skin hydration, in addition to the essential role in improving wound healing. However, despite the numerous positive effects of estrogen 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 estrogens or phytoestrogens, especially genistein, also im-

proves the quality of the skin and does not significantly increase the systemic dosage of these hormones. Thus, topical estrogenic

compounds represent a new, promising, and safe therapeutic approach for skin aging in women in perimenopause. ●

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