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NEW DERMATOCOSMETIC FORMULATIONS USING BIOACTIVE COMPOUNDS FROM INDIGENOUS NATURAL SOURCES

BY

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Abstract. Along with the amazing development of the dermatocosmetic industry, there has also been a surge in the research, concerning the biologically active ingredients for these products. Significant growth has taken place both in the presentation forms of the dermatocosmetic products and in the production methods, which ensure the quality and performance of the bioactive compounds. At the same time, special attention is paid to those pathologies which affect the population more frequently. Among these, rosacea, venous leg ulcer and acne have been some of the most challenging diseases in recent years, due to the complexity of the etiology and difficult healing. Among the most recent components of therapeutic formulas of the above-mentioned diseases, scientific research has shown great interest in bioactive compounds with antioxidant activity, which contribute to combat the effects of free radicals. This paper aims to present several examples of a series of new dermatocosmetic formulations using bioactive compounds from indigenous natural sources, currently existing

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on the dermatocosmetics products market and also, some new development directions in this field.

Keywords: antioxidants; bioactive compounds; dermatocosmetics; indigenous flora; liquid-solid extraction.

1. Introduction

Bioactive compounds from natural extracts have been playing an important role in the pharmaceutical industry for decades. One of the major areas of therapeutic products is the dermatocosmetic industry. The dermatologic benefits of natural bioactive ingredients are numerous and they have led to the development of a special category of products, biocosmetics or cosmeceutics, an intermediate form between medicine and cosmetic. In other words, they contain biologically active ingredients and are considered similar to dermatologically topical products. Published literature offers the following synonyms: performance cosmetic products, functional cosmetic products, dermaceuticals, active cosmetics, phytocosmetics, skinceuticals, nutricosmetics, dermatocosmetics (Roncea *et al.*, 2016).

Natural active ingredients act as effective adjuvant with important activity of biorevitalisation, protection and trophic support, as they show significant pharmacological activity (Ramana *et al.*, 2014). Types of natural compounds found in dermatocosmetics are: hormones, vitamins, enzymes, alkaloids, aminoacids, antibiotics, antiseptics. Besides improving skin aspect by their antiaging role, biocosmetics or cosmeceuticals have proven efficacy as active agents in preventing or ameliorating various dermatological conditions (Tagami *et al.*, 2006). Some effects display simultaneously, such as antioxidant, anti-inflammatory, anticarcinogenic, modulating cellular proliferation, angiogenesis, melanogenesis, protein synthesis (Ndiaye *et al.*, 2011).

Oxidative stress is related to particular skin disorders such as inflammatory skin disease and non-melanoma skin cancer (Bickers and Athar, 2006; Kruk and Duchnik, 2014).

This article aims to present an analysis of bioactive compounds with antioxidant properties, from natural extracts and to make an incursion into indigenous extracts and various forms of formulations available on the market.

2. Bioactive Compounds with Antioxidant Properties

Some strong arguments justify developing an important number of studies related to oxidative stress, a theory born sixty years ago. Among these arguments are the following: achieving advanced information about reactive oxygen and nitrogen species generation and metabolism, identifying oxidative damage biomarkers, evidence of direct relation between oxidative stress and

some acute and chronic diseases, as well as finding the most effective natural antioxidants, as bioactive molecules (Chien-Hsing *et al.*, 2017).

Oxidative stress is generated when the homeostatic processes fail and free radical generation is higher than the capacity of the body's immune defences. During the production of ATP, a complex process using oxygen, free radicals are created, as reactive oxygen species (ROS) or reactive nitrogen species (RNS). These are molecules with one or more free electrons. At relatively low levels, ROS and RNS acts as molecular signals activating stress response. But at high levels, cellular injury and tissue damage occur, involving DNA, proteins, membranes lipid peroxidation, calcium influx, mitochondrial swelling, lysis. Furthermore, excessive free radicals often create more free radicals accelerating the damaging processes (Pham-Huy *et al.*, 2008).

Antioxidants scavenge free radicals, by preventing and repairing damages caused by free radicals and can be endogenous or exogenous (Pham-Huy *et al.*, 2008). Antioxidants have the major role of neutralizing excess free radicals, which leads to cell protection and disease prevention. The antioxidant donates an electron, stabilizing it. Although the antioxidant becomes a free radical, it is less reactive.

The major endogenous antioxidants are enzymatic or non-enzymatic. The enzymatic antioxidants are superoxide dismutaza (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductaza (GRx). The non-enzymatic antioxidants are lipoic acid, glutathione, L-arginine, coenzyme Q10, metal-chelating protein, melatonin, etc. When endogenous antioxidant system is overwhelmed, exogenous antioxidants help preventing oxidative stress (Pham-Huy *et al.*, 2008).

In terms of antioxidant activity, we can refer to the following groups of plant extract compounds: polyphenols (Table 1), vitamins, terpenes.

Table 1
Characterization of Some Common Polyphenols in Dermatocosmetic Preparations

Compound	Source	Biological Effect	Ref.
Resveratrol	Grapes, Berries, Nuts, Fallopia sp.	Antioxidant, Antiproliferative, Stimulating detoxification, Antimicrobial, Antiviral, Antifungal, Antiprotozoal Inhibiting keratinocyte proliferation	(Higdon <i>et al.</i> , 2015, Gambini <i>et al.</i> , 2015)
Ferulic Acid	Oat, Rice, Eggplant, Chinese medicinal plant (<i>Angelica sinensis</i> , <i>Cimicifuga Heracleifolia</i> , <i>Lignsticum chuangxiong</i>)	Antioxidant, Antimicrobial, Antiinflammatory, Anti-thrombosis, UV protection agent, Antitumoral, Vasculoprotector, Increase sperm viability, Lowers cholesterol	(Ou and Kwuok, 2004; Brenelli de Paiva <i>et al.</i> , 20013)

Table 1
Continuation

Compound	Source	Biological Effect	Ref.
Lycopene	Tomatoes, Watermelon, Pink-grapefruit, Apricots, Asparagus, Parsley	Antioxidant, Antitumoral, Prevents Atherosclerosis and Blindness	(Stoica <i>et al.</i> , 2018; Dasgupta and Klein 2014)
Vitamin C	Citrus fruits, Tomatoes, Potatoes, Green leafy vegetables	Antioxidant, Protection against UV-damage, Inhibits melanogenesis, Induce collagen synthesis, Support skin lipid production, Neuroprotector	(Pullar <i>et al.</i> , 2017)
Vitamin E	Sunflower oil, Grains, Avocado, Broccoli, Kiwi	Antioxidant, Cardioprotective, Antitumor, Prevent cataract, neurological diseases, arthritis	(Pham-Huy <i>et al.</i> , 2008)
Q10 Coenzyme	Rapeseed oil	Antioxidant, Promote regeneration, wound healing by supporting collagen and elastin synthesis	(Shegokar, 2016)

Based on multiple biological activities and health benefits, the following three antioxidants represent special compounds of major interest.

2.1. Polyphenols

Among the largest and the widespread groups of natural compounds, polyphenols are recognized as non-volatile secondary plant metabolites with impressive, numerous biological effects (Veskoukis *et al.*, 2012; Tulay *et al.*, 2014). According to their chemical structure, there are over 10 categories of more than 8000 phenolic molecules identified so far (De la Rosa *et al.*, 2019). Each category contains at least one well-known compound and many important biological effects such as antioxidant, anti-inflammatory, antimicrobial and protective activity are common to a large part of polyphenols. Phenolic compounds protect biomolecules like proteins, nucleic acids, polyunsaturated lipids, glucides from oxidative damage.

In their antioxidant activity, specific processes have been described: free radicals scavenging, metal ion chelating, induce cytokine production inductor in human monocytes and macrophages.

There are studies, which showing that the in vitro oxidative efficiency of some polyphenols is higher than that E or C vitamins, suggesting similar results in vivo (Rice-Evans *et al.*, 1997).

2.1.1. Resveratrol. Resveratrol is a natural stilbene, a non-flavonoid polyphenol (*trans*-3,4',5-trihydroxystilbene) with anti-inflammatory, antitumoral and antioxidant properties (Salehi *et al.*, 2018). Resveratrol is also a phytoalexine, a substance with low molecular weight and special role, which accumulates as a response to an infection, temperature or UV lesion and microorganisms, in order to protect the plant, a wide spread phenomenon called ISR (Induced Systemic Resistance).

Resveratrol was detected in more than 70 plant species but the most common sources are grapes (*Vitis vinifera* L.) red wine, berries, peanuts and some medicinal plants (*Fallopia* sp.) (Salehi *et al.*, 2018).

An impressively large number of studies reveal potential benefits of resveratrol in human body. The following mechanism of action is considered: increase expression of antioxidant enzymes, antimicrobial, antifungal, antiviral, and inhibiting keratinocyte proliferation (Ndiaye *et al.*, 2011; Wen *et al.*, 2020).

In detail, resveratrol is considered to have anticancer prevention effect through his "effects on enzymes biotransformation", "inhibition of proliferation and induction of apoptosis", "inhibition of tumor invasion and angiogenesis", "anti-inflammatory effects" (Wen *et al.*, 2020). Related to cardiovascular, neurodegenerative and metabolic disease prevention, resveratrol is considered to express specific biological activity with real benefits in preventing and treating the mentioned pathologies (Higdon *et al.*, 2015; Salehi *et al.*, 2018).

2.1.2. Ferulic acid. Another non-flavonoid polyphenol is ferulic acid, a major hydroxycinnamic acid. It is a widely spread compound in plants, especially in Chinese medicine plants but also in high concentration in rice, eggplant, oat, citrus, apple seeds, bananas, broccoli, spinach, cabbage, potatoes, carrots, tomatoes (Ou and Kwok, 2004; Brenelli de Paiva *et al.*, 2013).

Ferulic acid exhibits potent and antiradical antioxidant activities. It is also considered to express antimicrobial, anti-inflammatory, anti-thrombosis, antitumoral, vasculoprotector activity, to increase sperm viability and to lower cholesterol (Ou and Kwok, 2004; Brenelli de Paiva *et al.*, 2013).

In a study developed to show synergistic protection in skin of antioxidants, it has been discovered that ferulic acid improved chemical stability of the formula and doubled photoprotection as measured by erythema and sunburn cell protection (Lin *et al.*, 2005; Brenelli de Paiva *et al.*, 2013).

Even if ferulic acid is already known to have multiple pharmacological beneficial activities, there are additional promising biological effects which remain to be *in vivo* studied.

Based on its multiple biological effects but also on its low toxicity, ferulic acid is largely used in food and cosmetic industry.

2.2. Vitamins

2.2.1. *Vitamin E* is a fat-soluble vitamin with very active antioxidant properties. Its most bioactive form in human is α -tocopherol. In the same time the natural source vitamin E is nearly twice as effective as synthetic α -tocopherol. It is recommended in prevention of some kind of cancers, cardiovascular disease, cataract, neurological disorders and arthritis. Rich source of vitamin E are sunflower oil, grains, avocado, broccoli, kiwi fruit (Pham-Huy *et al.*, 2008).

2.2.2. *Vitamin C* is a water-soluble vitamin well-known for its antioxidant and immunomodulator properties. In the same time, vitamin C has powerful contribution in preventing colon and stomach cancer and atherosclerosis. Also known as ascorbic acid, vitamin C is essential in collagen and some neurotransmitter biosynthesis (Pham-Huy *et al.*, 2008). Its activity is synergic with vitamin's E activity. The most common sources of C vitamin are green vegetables, fruits, tomatoes. Vitamin C is considered the most effective antioxidant in plasma (Harisson, 2012). The role of vitamin C in maintaining skin's health is vital, as it contributes in collagen and elastin synthesis, keratinocyte differentiation, protection against UV-induced damage, inhibits melanogenesis, enhance the production of barrier lipids preventing dry skin conditions wound healing, delay signs of aging (Pullar *et al.*, 2017).

2.3. Terpenes –Lycopene

Lycopene is a tetraterpene known also as a carotenoid. It is extracted especially from tomatoes, but is also found in other food plants such as watermelon, pink-grapefruit, apricot and even white plants such as asparagus and parsley. It is known that the thermic processes tomatoes offer a higher bioavailability of lycopene than the raw tomatoes (Pham-Huy *et al.*, 2008). It is for great interest due to its biological role in preventing oxidative stress related disease, especially some types of cancer (skin, prostate, breast, lung, endometrial) and chronic disease such as atherosclerosis (Stoica *et al.*, 2018; Dasgupta and Klein, 2014). In skin damage, the lycopene has also a powerful effect as an anti-inflammatory agent and protector from UV rays (Stoica *et al.*, 2018).

Based on some studies it is considered that the scavenging free radical properties of lycopene is twice that of β -carotene and ten times higher than that of α -tocopherol (Rao and Shen, 2002; Erdman *et al.*, 2009).

3. Types of Bioactive Compounds Associations in Dermatocosmetic Products

The dermatocosmetic industry is continuously developing and has a direct impact on the society. The need for new effective products, with higher compliance for patients, leads the research to advanced formulas with associations of different active ingredients or similar ingredients in various concentrations. Moreover, these ingredients can be obtained in more favourable economic conditions from indigenous sources.

An amount of studies has shown the importance of antioxidants association for increasing the protective activities in the body cells and tissues, with strong evidence for preventing and ameliorating important diseases, either systemic or cutaneous. Additional advantages are related to higher bioavailability and preservation of the active ingredient.

The major advantage of combining specific bioactive compounds can be the increase of the basic action, with better therapeutic results and better satisfaction for patients and specialists, thus improving the attributes of the product and also substituting chemical compounds.

4. Types of Dermatocosmetic Products and Presentation Forms

For dermatocosmetic products the presentation form is of major importance. The user-friendliness of these products is crucial for correct and efficient administration. The interest in new application formulas and textures is continuously growing, whether we are talking about serums, gels, biofilms, emulsions or creams and is strongly influenced by the continuously growing exigent demand of consumers.

5. Conclusions

Many dermatological conditions are now associated with oxidative stress: rosacea, acne, pigmentation disorders, allergies, photoaging. Plant extracts have been a rich source of active ingredients. Studies and modern research reveal the potential of phytochemical antioxidants to prevent or ameliorate dermatological disease. Most of the natural compound are safer for health and for skin and have stronger biological effects than the synthetic ones. In order to obtain safe and performant bioactive compounds from plant matrix, “green” extraction technologies are continuously tested and developed. The dermatocosmetic industry is interested to find new formulas to enhance the product attributes and also economical and simple ways to obtain active ingredients from indigenous source.

An important topic for further research is discovering the right synergism and the optimum associations between antioxidant compounds but also advanced research on mechanism and biological effects of new antioxidants, such as lycopene and ferulic acid.

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NOI FORMULĂRI DERMATOCOSMETICE
UTILIZÂND COMPUȘI
BIOACTIVI DIN SURSE NATURALE INDIGENE

(Rezumat)

Pe fondul dezvoltării impresionante a industriei dermatocosmetice, a luat amploare și cercetarea privind ingredientele biologice active ce stau la baza formulării acestor produse. O dezvoltare semnificativă a avut loc atât în privința formelor de prezentare a produselor dermatocosmetice cât și a metodelor de obținere care să asigure calitatea și performanța compușilor respectivi.

În paralel, o atenție deosebită se acordă acelor patologii cu incidență crescândă în rândul populației. Dintre acestea, rozaceea, ulcerul venos și acnea reprezintă afecțiunile cele mai provocatoare ale ultimilor ani, prin complexitatea etiologiei și prin dificultățile terapeutice.

Printre cele mai noi componente ale formulelor terapeutice în afecțiunile amintite, cele mai studiate sunt ingredientele cu acțiune antioxidantă ce contribuie la contracararea efectelor radicalilor liberi ce se formează la nivelul țesuturilor.

Această lucrare își propune să prezinte câteva exemple de ingrediente dermatocosmetice din surse naturale prezente în mod curent în formule dermatocosmetice, dar și unele propuneri noi de cercetare în acest sens.