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RESVERATROL IN THE PREVENTION AND TREATMENT OF OXIDATIVE STRESS

BY

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Abstract. The therapeutic approach of some of the most frequent diseases continues to bring about suggestions, studies and solutions regarding the mechanisms involved in their control and the best ingredients for the products in the treatment schemes. Among the bioactive ingredients, the antioxidants are impressively frequent for numerous pathologies. First ranking in this category are the diseases of the century: diabetes, oncology, metabolic, neurodegenerative, as well as certain dermatological diseases. Among these, rosacea, acne and venous ulcer have been most challenging lately as a result of their etiological complexity and the curing difficulties. As issues of great interest for scientific research, antioxidant bioactive compounds are the focus of numerous studies regarding solutions to optimise obtaining methods, successful associations and the best presentation forms in order to be as patient compliant as possible. Resveratrol is an acknowledged antioxidant, largely used both in internal and external usage aimed products. The present paper intends to draw a synthesis of the latest information about the role resveratrol plays in relieving oxidative stress and to suggest new research directions.

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Keywords: antioxidant; dermatocosmetics formulas; liquid-solid extraction; oxidative stress; resveratrol.

1. Introduction

Human society evolution has lead to an unprecedented technological development and the most urban and modern lifestyle but also, to higher level of pollution, natural resources depletion and exhausting daily life schedules. All these have a negative impact on human life, speeding up the rise of stress level and the damage in human body. Among consequences of stress damage the first mentioned are century's diseases (diabetes, cancer, neurodegenerative pathologies) and also a number of dermatological conditions including rosacea (Merticaru, 2017), acne, venous ulcer, already difficult and extremely highly prevalent pathologies.

Specialists in multidisciplinary teams are in continuous attempt to find new effective solutions to this phenomenon and one of the major ways of coping chronic stress in all its forms are pharmaceuticals.

In published literature there are named three forms of stress as phenomena impacting human body: eustress, distress and oxidative stress (Kupriyanov and Zhdanov, 2014). Eustress is the physiological response leading to an adaptative behavior or, based on others, is the lack of negative reaction to stressors (Kupriyanov and Zhdanov, 2014). Distress is the condition of overwhelming by endogenous or exogenous stressors, leading to different kind of damages. Oxidative stress is the imbalance between prooxidants and antioxidants in the body, which, in normal conditions should remain inoffensive.

Any alteration of homeostasis leads to an increasing in free radicals production, exceeding the capacity of neutralizing by the local tissue. Continuous accumulation of oxygen or nitrogen radical species is followed by multiple interactions with diverse molecules and cellules, generating damages in proteins, membranes and genes. These processes are accelerated in pathological conditions, amplifying the base problem.

Antioxidants are compounds which help the body to fight oxidative stress, to prevent or stop the production of free radical species, helping in removing them and ameliorate the oxidative damage in cells and tissues. According to Halliwell (2007), "any substance that delays, prevents or removes oxidative damage to a target molecule" can be considered an antioxidant. Natural or biosynthetic antioxidants manage to strike the balance between production and neutralize free radical species, on definite or indefinite time, according to the conditions (Veskoukis *et al.*, 2012).

There are a variety of exogenous antioxidants providing protection against oxidative damage and related pathologies. Based on this, antioxidants become some of the most tested and used today in various pharmaceuticals,

dermatocosmetics and food supplements. These products must meet strict quality requirements following specific standards, guides and Pharmacopoeia, in respect for consumer's safety. In this regard it is for general interest to reduce synthetic compounds quantity and use natural compounds from green extractions and resources, maintaining quality standard of final products.

The major focus is on plants (Pietta *et al*., 2003), respectively towards primary and secondary metabolites study, resulted in increased interest for economical development. The advantages of natural compounds are: most of them are non-proteic, can be obtained by steam distillation from vegetal material, using aqueous or organic solvent and have low molecular weight, under 2000 Da (except biopolymers, natural rubber, condensed tannins and some polysaccharides such as pectines and amidon).

This paper aims to synthesize information from published literature about the importance of antioxidants, fighting oxidative stress and ameliorate related damages. From a wide range of natural antioxidants, the presentation is focused on polyphenols with a special mention of resveratrol.

2. Phenolic Compounds from Natural Sources

Phenolic compounds are organic compounds recognized as one of the largest and widely spread non-volatile secondary plant metabolites, with proven significant antioxidant, anti-inflammatory and antimicrobial properties (Dai and Mumper, 2010). They have a specific aromatic ring with one or more hydroxyl groups attached. There are over 8000 different phenolic molecules identified, organized in more than 10 categories according to their chemical structures (Fig. 1).

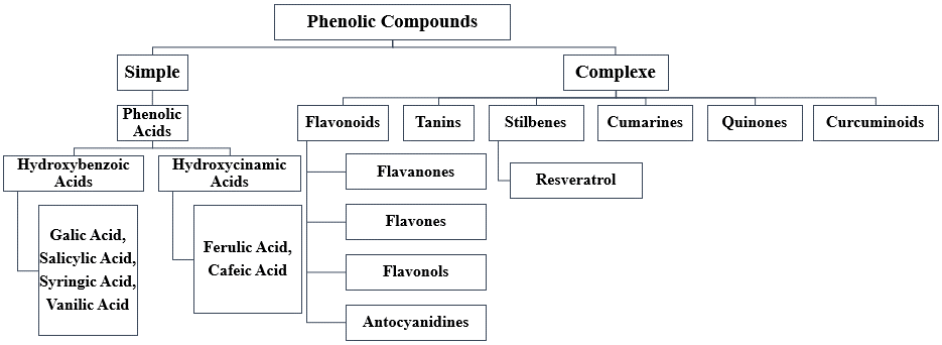

Fig. 1– The classification of phenolic compounds
(adapted from Dai and Mumper, 2010; Tulay *et al*., 2014).

The role polyphenols play in plant structure is complex, with contributions in reproduction and defense systems. Due to their organoleptic properties, polyphenols have also numerous applications in chemical, food and

pharmaceutical industries. In the past decades the interest for biological effects and the polyphenols potential in preserving the human health and ameliorate different pathologies, has strikingly increased (Pietta *et al*., 2003).

Polyphenols are considered to be the most active compounds to ameliorate metabolic syndrome, both in vitro and in vivo. Their beneficial contribution has been already proven in consistent research regarding some different damage related pathologies: cardio-vascular disease, cancer, neurological conditions, diabetes, dermatology (Hogervorst *et al.*, 2017).

The research on polyphenols biological effects in human body shows a variety of potential mechanisms of action which can prevent some diseases: (Fig. 2):

i) in **oncology**, by inhibiting bacterial enzymes replication, inducing apoptosis in tumor cells and inhibiting telomerase activity in tumor cells (Tulay *et al*., 2014);

ii) **anti oxidative damage**, neutralizing free radicals, chelating metal ions, monocytes/macrophages stimulation to produce cytokines (Veskoukis *et al*., 2010);

iii) **antihypertensive** (Halliwell, 2006), producing vasodilatation,

iv) **neuroprotective** (Tulay *et al*., 2014);

v) **anti-inflammatory** etc.

They also have the capacity of neutralizing bacterial toxins, indicating a new potential effective source of antimicrobial therapy against antibiotics resistant pathogens (Docherty *et al*., 2004; Spinei, 2015; Sun *et al*., 2018).

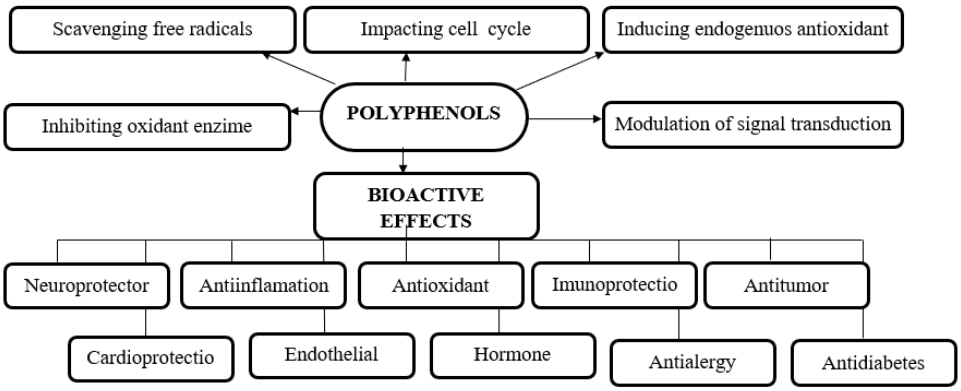

Fig. 2 - Bioactive effects of polyphenols (adapted from Spinei, 2015).

2.1. Methods of Polyphenols Obtaining and Characterization

Polyphenols obtaining technologies include methods of extraction using ultrasounds, microwaves, pressured liquid, pulsatile electric field, supercritical fluids and high hydrostatic pressure. Each method presents advantages and

weeknesses. The focus in improving obtaining techniques is on increasing specific parameters of polyphenols, such as: solubility, selectivity and sensibility, the permeability of cellular membranes (diffusibility) and purity level (Suwal and Marciniak, 2018).

Extraction performance and efficiency is depending on several factors:

- Technique
- Size of vegetal material particles
- Storage conditions
- Other interacting substances
- Covalent bonds of polyphenols in vegetal material

Phenolic compounds can be extracted from fresh, frozen or dried vegetal material. Before extraction, vegetal samples are dried, milled and homogenized (Fig. 3). Drying by freezing generally leads to a higher concentration of bioactive ingredients retained, compared to air drying.

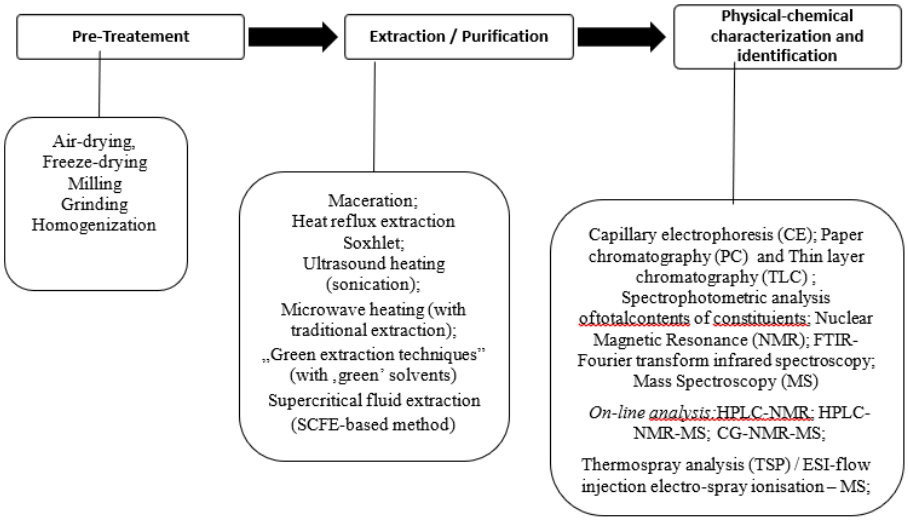

Fig. 3 – Extraction protocol of polyphenols from vegetal material (adapted from Dai and Mumper, 2010).

3. Resveratrol

Resveratrol is a natural polyphenol with a stilbene structure, named *trans*-3,4′,5-trihydroxystilbene, presenting anti-inflammatory, anticancer and antioxidant properties. The main sources of resveratrol are grapes (*Vitis vinifera* L.) and derived products like red wine, peanuts, berries and specific medicinal plants such as Fallopia sp. (Anastasiadi *et al*., 2012; Halliwell, 2007).

Potential mechanisms of action of resveratrol positively influencing health are numerous (Gambini *et al*., 2015; Ramirez-Garza *et al*., 2018).

Resveratrol induce a wide-range antioxidant enzyme expression, contributing in in oxidative stress decreasing. Additionally, a large number of receptors, kinases and different enzymes interact with resveratrol, influencing his biological effects (Gambini *et al*., 2015).

The best known is the antioxidant property of resveratrol, widely studied and generating a major interest aiming including it in food supplements and dermatocosmetic products. There are studies indicating other important biological effects of resveratrol, such as antiproliferative, stimulating detoxification, antimicrobial, antiviral, antifungal, antiprotozoal and inhibiting keratinocytes proliferation (Docherty *et al*., 2004; Fabbrocini *et al*., 2011; Ndiaye *et al*., 2011; Merticaru, 2017; Wen *et al*., 2020).

3.1. Extraction Methods of Resveratrol

In order to obtain biologically active ingredients from vegetal material, solid-liquid extraction method is often chosen, using different parts of the plant or plant mixtures according to the objective, or liquid-liquid extraction to separate specific components from solid-liquid extraction product obtained. Published literature offers abundant information about different methods of traditional solid-liquid extraction (using solvents and distilation), up to modern technologies, non-conventional (pulsator - electric field, enzyme digestion, ultrasounds (Sun *et al*., 2018), microwaves, heating or supercritical fluid extraction (Khaw *et al*., 2017) or so-called „green extraction techniques", using modern solvents /reagents for active ingredient extraction (Table 1) (Wang *et al*., 2013; Talmaciu *et al*., 2015; Zhang *et al*., 2015; Piyaratne, 2018; Averilla *et al*., 2019; Yang *et al*., 2019).

Choosing the right extraction method is related to the objective of the study, to the type and the part of the plant, the reagent/solvent chriteria (toxycity level for the vegetal material and environment, chemical profile of the extracted compounds) (Ballard *et al.*, 2010; Anastasiadi *et al*., 2012; Niedt, 2012; Garcia *et al*., 2016).

The efficiency in plant extracts obtaining is higher when combining techniques: extraction and identification.

Table 1
Extraction Methods of Resveratrol

Vegetal material	Extraction method / Analysis method	Pharmacological effects	Ref.
Polygonum cuspidatum dried roots powder combined with rice wine fermentation	Ultrafiltration (UF) / DPPH solution in ethanol	Enhanced antioxidant activity	(Yang *et al*., 2019)

Table 1
Continuation

Vegetal material	Extraction method / Analysis method	Pharmacological effects	Ref.
Vitis labrusca grape peel	Thermal heat and enzymatic treatments / ethanol-water extraction / HPLC/UPLC	Cytoprotective effect, prevention of excessive ROS accumulation	(Averilla *et al.*, 2019
90-year-old Picea mariana black spruce tree dried powder	Soxhlet liquid – liquid extraction with methanol / Borat complex extraction / silica gel column chromatography / Ion exchange chromatography /Column chromatography with Sephadex LH-20 / Acetylation-deacetylation reactions	Enhance E-resveratrol biosynthesis	(Piyaratne, 2018)
Arachis repens (peanut grass)	Conventional maceration (CM), Ultrasound assisted extraction (UAE), Microwave assisted extraction (MAE) / Folin-Ciocâlteu, DPPH method	New source of trans-resveratrol, optimized extraction through UAE and MAE	(Garcia *et al.*, 2016
Arachis hypogaea (Peanut sprouts)	Multistage countercurrent extraction (MSCE, alkaline extraction and acid precipitation method (AEAP)	Time, energy and cost saving technology	(Zhang *et al.*, 2015)
Vitis vinifera species	Solvent methanol mixture, HPLC/ DPPH, TPTZ, MDA, DMSO	Vinification bioproducts with important bioactive ingredients	(Anastasiadi *et al.*, 2012)

3.2. Methods of Resveratrol Characterization

As a result of extraction, there are complexe associations of vegetal extracts with chemical composition depending on the processed parts of the plant, growing and harvesting conditions, extraction techniques. Therefore, emphasis shall be placed on selectivity and accuracy of quantitative method of determination. Considering selectivity and accuracy as analitical performance chriteria, the following method of quantitative determination are chosen for vegetal extracts composition (Ignat *et al*., 2011) (Table 1):

- Spectrophotometric techniques
- Liquid chromatographic techniques (HPLC-high performance liquid chromatography, HSCCC-high speed counter current chromatography, SFC-supercritical fluid chromatography, TLC-thin layer chromatography)

For structural characterisation there are mentioned the followingmethods (Ignat *et al*., 2011; Talmaciu *et al*., 2015) (Table 1):

- Spectrometric methods based on nuclear magnetic resonance (NMR),
- Infrared radiations Fourier (FTIR),
- Mass spectroscopy (MS) (*i.e.* NMR spectroscopy, FTIR spectroscopy, MS mass spectroscopy).

3.3. Mechanism of Action of Resveratrol

Present studies demonstrate a complex activity of resveratrol with "multiple biological effects" (Gambini *et al.*, 2015) and numerous benefits upon human body. Resveratrol has a powerful influence on a wide range of antioxidant enzymes, thus resulting in decreasing of oxidative stress. In the same time, a large number of receptors, kinases and different enzymes interact with resveratrol and have a potential influence upon his biological effects (Gambini *et al*., 2015).

Resveratrol's antiproliferative and antioxidant effects are also of great interest (Athar *et al*., 2007). It has been demonstrated (Athar *et al*., 2007) that resveratrol has the potential to interact with ERalpha-associated PI3K pathway and has an agonist activity for the cAMP/kinase –A system. Resveratrol promotes apoptosis through several mechanism of action, among which is the stimulation of the increasing of a growth-inhibitory/pro-apoptotic ceramide level, the induction of a detoxification enzyme (Quinone reductase, QR) or Bcl-2 downregulation. Resveratrol is also considered to suppress Src tyrosine kinase activity and nitric oxide generation. Resveratrol can also interfere with an ERalpha-associated PI3K pathway, following a process that could be independent of the nuclear functions of the ERalpha and acts as an agonist for the cAMP/kinase-A system. It also promotes the accumulation of growth inhibitory/pro-apoptotic ceramide and induction of quinone reductase (QR, a phase II detoxification enzyme) and induces caspase-independent apoptosis through Bcl-2 down regulation. It has been shown to suppress Src tyrosine kinase activity, nitric oxide generation and the NFkappaB pathway

In foods supplements, resveratrol intakes is considered to be safe at up to 5 g (Ramirez-Garza *et al*., 2018).

An important list of biological effects such as anti-inflammatory, anti-proliferative, anti-microbial and antioxidant, leads to conclusion that resveratrol is an effective ingredient in the treatment of acne vulgaris (Fabroccini *et al*., 2011). Thus, it is already demonstrated that resveratrol has an antibacterial

activity against *Propionibacterium acnes*, has a reduced cytoxicity compared to benzoyl peroxide, inhibits inflammatory markers for acne lesions and demonstrates also an antiviral, antifungal and anti-protozoal activity (Docherty *et al*., 2004; Holian and Walter, 2001). Moreover, resveratrol has a demonstrated activity against keratynocite proliferation, an important phenomenon involved in acne.

In vitro, various assays show that resveratrol has a powerful antioxidant activity, especially compared to other standard antioxidants such as α-tocopherol. Among its actions are DPPH, DMPD and $-O_2$ radical scavenging, superoxide anion and hydrogen peroxide scavenging and metal chelating activity (İlhami, 2010).

4. Types of Resveratrol Based Dermatocosmetics Products

Based on the beneficial impact of resveratrol on human cells and tissues, it is for great interest practical attempts to incorporate this extremely active ingredient in various dermatocosmetics formulas, easy to use and with advanced therapeutic performance.

There is a wide range of resveratrol containing products, based on extracts usually standardized to deliver 8% resveratrol in food supplements (*PDR for Nutritional Supplements 2nd ed. Thomson Reuters, Montvale, NJ 2008, p. 545* Hazardous Substances Data Bank (HSDB)) and 5% in dermatocosmetics, products which can be categorized based on two criteria: formula and presentation form.

Table 2
Presentation forms of Resveratrol Based Dermatocosmetic Products

Secondary associated antioxidant	Presentation form	Indications
Vitamin C	Day/Night serum	Loss of firmness
Vitamin A	Dark spot corrector	Dark spots,PIH
Vitamin E	Peels	Dryness, dehydration
Baicalin	Cream	Redness, rosacea, acne
Catehine (flavanols)	Mask	Wrinkles, fine lines
Superoxide Dismutase	Lip balm	Lip lines, dehydration
Bisabolol	Gel	Mature skin, dull skin
Glutathione	Exfoliating products	Large pores, sebum excess, free radical damage
Q10 Coenzyme	Anti UV protection products	Sun damage
Associations of those mentioned above	After sun lotion	Anti-inflammatory, sensitive skin,

Upon formula, there are numerous products which combine resveratrol with other antioxidants, such as vitamin C, E, A, baicalin, catehine, superoxide dismutase, with hyaluronic acid, retinol, niacinamide, mandelic, glycolic, lactic, malic or salicylic acids, peptides, ceramides or essential oils.

Upon presentation form, there can be found food supplements and dermatocosmetic products such as serums, creams, masks, balms, exfoliants, antiUV protection products, peelings.

There is research that highlights a number of advanced performances of resveratrol-based products, offering through their results cutting-edge solutions for effective antioxidant combinations, the best recommended concentration, and improved bioavailability (Amiot *et al*., 2013).

5. Conclusions

Based on numerous studies which demonstrate its important potential to reduce the oxidative stress, resveratrol can be used as an effective ingredient for products with anti-tumor, anti-viral, neuroprotective, anti-aging and anti-inflammatory effects. Regarding dermatological pathology, several clinical studies suggest that resveratrol is a potential adjuvant in acne treatment. Additionally, resveratrol has a protective effect upon preserving the pharmaceuticals and cosmeceuticals, maintaining the therapeutic quality and prolonging the availability of the product, by minimizing or preventing lipid oxidation in the formulas.

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RESVERATROL ÎN PREVENȚIA ȘI TRATAMENTUL STRESULUI OXIDATIV

(Rezumat)

Abordarea terapeutică a unora dintre cele mai frecvente maladii (diabetul, bolile oncologice și afecțiunile neurodegenerative, dar și o serie de boli dermatologice) continuă să aducă propuneri, studii și soluții legate de mecanismele implicate în controlul acestora și ingredientele optime pentru produsele din schemele de tratament. Printre ingredientele bioactive, antioxidanții se regăsesc cu o frecvență impresionantă pentru numeroase afecțiuni. Compușii bioactivi cu acțiune antioxidantă reprezintă subiectul a numeroase studii care vizează soluții pentru optimizarea metodelor de obținere, asocierilor performante și celor mai bune forme de prezentare pentru complianța cât mai bună la pacient. Un antioxidant recunoscut și utilizat pe scară largă în produse deopotrivă pentru uz intern și extern este resveratrolul. Lucrarea își propune să sintetizeze informații de ultimă oră referitoare la rolul resveratrolului în combaterea stresului oxidativ și trasarea unor direcții noi de cercetare în acest sens.