POLYPHENOLS AND ACNE

Published research review of phytochemicals in preventing and treating skin disorders

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A literature search reveals multiple scientific publications that address the benefit of polyphenols for the treatment of acne and maintenance of healthy vibrant skin. Both topical applications and oral supplements containing polyphenols demonstrate a significant reduction in acne associated conditions, and in many cases complete elimination of facial blemishes. Polyphenols protect the skin against everyday damage resulting from exposure to UV and environmental pollutants. This protection helps slow down the aging process.

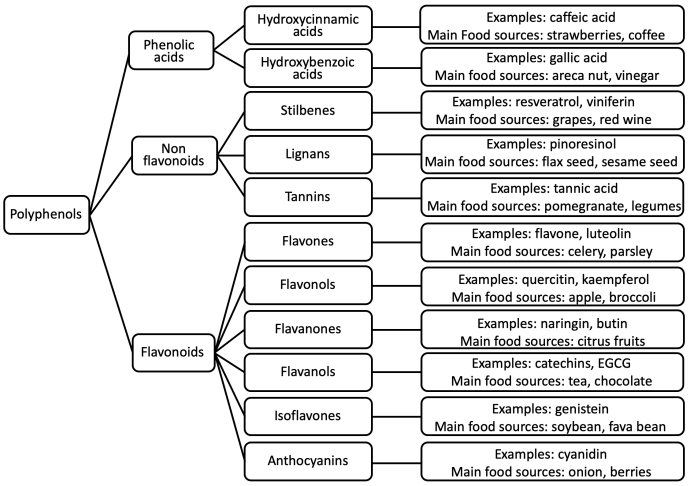

Figure 1 Classification of polyphenol groups under the broader class of phytochemicals known as phenols.

Plant Phenolics – Polyphenols – Their Potential Prevention and Therapy of Skin Disorders

Phenolic phytochemicals constitute a large group of organic compounds produced by plants and microorganisms. They are comprised of secondary metabolites (polyphenols) which act protectively to prevent and attenuate the progression of certain skin disorders, both minor problems (e.g., wrinkles, acne) and serious, potentially life-threatening diseases such as cancer. They work both ingested as a supplement and *via* topical applications.

Recently, many reports have been published on the potential effectiveness of phenolic compounds to prevent or reduce symptoms and shorten the healing time of skin disorders like acne [2-5].

Phenolic compounds are found to be one of the most important groups of plant secondary metabolites, due to their great participation in morphological development, physiological processes, and reproduction. These phytochemicals are synthesized through the pentose phosphate, shikimate and phenylpropanoid pathways.

MLG-50™ contains an abundance of natural polyphenols including flavonoids, non-flavonoids, and phenolic acids. Phenolics are mostly known for their broad spectrum of biological properties, which are due to their molecular structure. The main core of phenolic compounds is formed by at least one phenol ring, in which the hydrogen is usually replaced by a more active residue, such as hydroxyl, methyl or acetyl. The variable biological properties of

the phenolics result from the pattern and the degree of the substitutes. Usually in plants these compounds contain more phenolic rings, and thus they are called polyphenols [6-9]. They have strong intermolecular hydrogen bonds, which enhance their water solubility [1]. As figure 1 shows the classification breakdown of polyphenols, they are ubiquitous in nature and throughout our food supply from fruits and vegetables, nuts and seeds, and whole grains.

MLG-50™ is a molecular complex of polyphenols extracted by water from a prehistoric deposit versus from specific food groups.

Antioxidant Activity

Free Radicals, also known as ROS (Reactive oxygen species) negatively influence some immunological processes and aging, as well as pathophysiological mechanisms leading to skin inflammatory disorders [10]. Oxidative stress is understood as the disturbance of the homeostasis between reactive oxygen forms and the antioxidative defense system in the organism [11].

Antioxidant activity of phenolic compounds is associated with the annular structure of the molecule, conjugated double bonds and the presence of functional groups in the ring. The antioxidant activity of phenolics is possible through three mechanisms of action [12-15]:

1. Phenolics can inhibit free-radical formation, trap free-radicals (ROS) and neutralize singlet oxygen molecules.
2. Reduce the chelated metal ions (which are the catalysts for reactions leading to the formation of ROS).
3. Phenolic compounds interrupt the cascade of free radical reactions that cause lipid degradation and they protect the other compounds in cells with their antioxidant activity [12-15].

Our skin is well equipped with two crucial means of defense against oxidative stress: antioxidant enzymes (catalase, glutathione peroxidase and peroxide dismutase) and non-enzymatic molecules (vitamins, ubiquinone, glutathione) [16]. However, often our endogenous defense system against ROS is insufficient. Thus it is recommended to increase the amount of natural antioxidants through the diet, taking supplements, or by topical application. A great benefit of MLG-50™ is that it can be taken both as a supplement or can be applied topically to the skin, remaining colloidal in a wide pH range and miscible in both water-base and lipid-base formulas.

Examples of natural exogenous antioxidants, (effective topical ingredients for healthy skin) are the antioxidant vitamins (especially C and E), lipoic acid, coenzyme Q10, melatonin, resveratrol, curcumin and other polyphenols such as those contained in MLG-50™[17]. These compounds are safe and more biologically active than synthetic antioxidants [10].

Anti-Inflammatory Properties -- Fighting Cytokines and Interleukins

Every day, our body is exposed to external factors which cause various types of cell damage, irritation or allergies. The body's reaction is inflammation. During the complex process of inflammation an excess of free radicals are produced. The formation of free radicals -- reactive oxygen (ROS) and nitrogen species (RNS) -- are associated with the triggering of biological responses to activation of the transcription factor AP-1 and nuclear transcription factor kappa B (NF-κB) [18].

These factors regulate secretion of signaling molecules, such as pro-inflammatory cytokines and interleukins, which lead to skin inflammation, and swelling. The crucial functions of polyphenols are inhibition of pro-inflammatory mediators, neutralization of free radicals, ROS, RNS, and thus inhibition of lipid peroxidation [19].

During inflammation, arachidonic acid is released from the cell membrane phospholipids. The enzyme involved in this reaction is phospholipase A2 (PLA2), which is stimulated by oxidative stress. The released arachidonic acid is transformed by either the cyclooxygenase or lipoxygenase pathway. Eicosanoids are potent biologically active arachidonic acid-derived lipid mediators that are intimately involved in inflammation and cancer. Cyclooxygenase (COX), the key enzyme in prostaglandin (PG) biosynthesis, controls one of the major pathways of arachidonic acid metabolism and is the main target for non-steroidal anti-inflammatory drugs (NSAIDs) [20]. Polyphenols may inhibit both reactions, mostly due to the interruption of substrate binding to the enzyme by disruption of the hydrogen bonding system or due to the chelation of metal ions located in the active center of the enzyme resulting in significant alleviation of inflammation [21].

Antimicrobial Antibacterial Action

Phenolic compounds possess potent antifungal, antiviral and antibacterial activity [22]. Many types of infections, diseases, and conditions including acne, are often treated with a broad activity spectrum antibiotic which may kill the natural healthy microflora of the skin and contribute to creating resistant bacterial strains [23].

Recently over 90% of staphylococci, pneumococci and enterococci isolated from serious infections were found to be resistant to antibiotics.

The antibacterial properties of phenolics may result from the mechanism of their action on cell membranes [24]. Recently, it was reported that methanol extracts from *C. mucronatum* leaves have antibacterial properties against five prevalent bacteria: *Streptococcus pyogenes*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus cereus* and *Bacillus subtilis*. Regarding the phytochemical composition of *C. mucronatum* leaves, the presence of plant flavones: vitexin, isovitexin and tannins was confirmed. It was also shown that an ethanol extract from these leaves could potentially be used to treat wounds [25].

Thus the activity of polyphenols has special significance in the case of strains resistant to antibiotics and may be used for multi-strain bacterial infections, **without causing a simultaneous toxic effect on human tissues** [27,29]. MLG-50™ ™is comprised of a variety of organic acids, flavonoids and terpenoids many of which have proven antimicrobial activity.

Anti-Aging Properties of Plant Phenolics

The main mechanism of aging skin -- loss of elasticity, dryness, wrinkles, hyperpigmentation, age spots, inflammation – is based on the reaction to oxidative stress [30]. The condition of our skin is the result of many aspects, such as genetics, environmental factors, nutrition, exercise, alcohol abuse and smoking.

Indeed, the aging process can be slowed down by proper diet, good sleep, exercising, and therapeutic cosmetics. Phenolic compounds possess a broad spectrum of biological activities which influence the internal organs, as well as the human skin [26, 27]. Cosmeceuticals containing plant extracts, lipids, phenolic compounds, vitamins, and trace minerals work together to protect against UV and environmental chemical damage. They can aid collagen production, support healthy skin cell renewal, hydration, improve skin tone, texture, preserve healthy connective tissue, remove debris, reduce wrinkles, and inhibit excessive melanin synthesis (Figure1) [33].

The Complex Development of Acne vulgaris

Acne vulgaris is a very common chronic skin disease which causes many physical and psychological problems. Usually it occurs during adolescence, but often it can persist throughout life and leave permanent scarring on the face. The reasons for acne development are complex, but the main factors include:

1. Hormonal stimulation of sebaceous gland activity.
2. Excessive development of the protective protein keratin – which prevents normal shedding of dead skin cells (hyperkeratinization).
3. The development of anaerobic bacteria (*Propionibacterium acnes*) build-up in clogged skin follicles and subsequent inflammation.

Typical treatment of acne is based on five treatments:

1. Local medicines
2. Oral antibiotics
3. Oral retinoids
4. Oral hormonal therapies
5. Medicinal plants (phytochemical-based cosmeceuticals) and supplements.

The following properties in medicinal plants are valued [34]:

1. Anti-bacterial
2. Anti-inflammatory
3. Antioxidant
4. Anti-androgenic

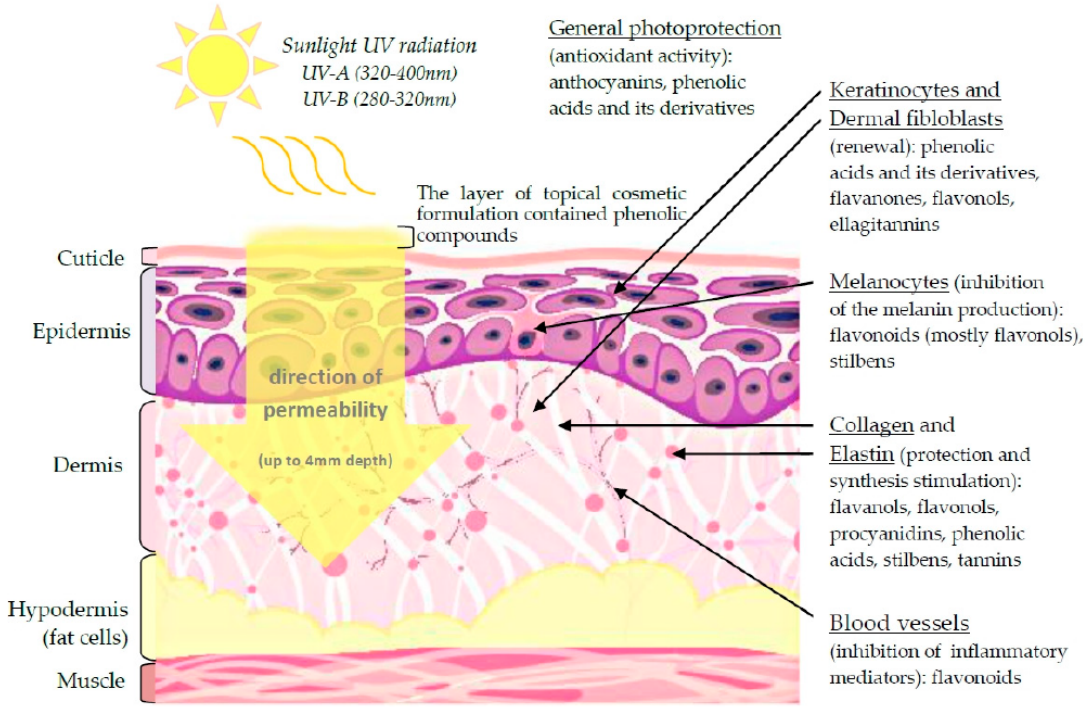

Figure 2. The scheme presents the cross-section of the skin structure and the specific influence phenolic compounds (such as those delivered in MLG-50™ based cosmetic formulations) on dermal tissue components. Black arrows indicate the particular component of skin tissue, according to which are listed the main classes of phenolic, effective in prevention or treatment signs of skin-aging. The yellow arrow indicates the direction and the depth of the cosmetic formulation permeability through the skin. The various layers of the skin structure are indicated on the left.

Polyphenol Action Against Acne vulgaris

It has been discovered there is a strong antimicrobial effect against *P. acnes* strains attributed to flavonoids isolated from *Eucalyptus maculate* [35-37], honokiol and magnolol, isolated from Magnolia sp., organic acids such as gallic, chlorogenic, caffeic, ferulic, and cinnamic acids, and flavonoids: myricetin, quercetin, luteolin, apigenin, and thymol – a monoterpenoid found in oil of Thyme [38]. Many of these plant phenols are found in MLG-50™.

Moreover, phenolic compounds have anti-inflammatory effects by reducing the secretion of serum inflammatory factors IL-8 and TNF-α induced by the bacteria *P. acnes*. [28]. The effect of mixtures of phenolic compounds and other drugs on *P. acnes* was also studied. Mixed formulations of antibiotics and phenolic compounds (kaempferol and either erythromycin or clindamycin; quercetin and either erythromycin or clindamycin) resulted in a synergic action that inhibited antibiotic resistant *P. acnes* growth. The combination of clindamycin with kaempferol or quercetin showed a greater effect than other formulations [29].

For acne lesions, the secretion of sebum has a significant negative effect. To reduce its secretion isotretinoin, a synthetic derivative of vitamin A, and hormonal therapy is most commonly used. Yoon *et al.* reported that the main phenolic component in green tea may be used for this purpose. They demonstrated that epigallocatechin-3-gallate (EGCG) reduced sebum excretion by modulating the AMPK–SREBP-1 signaling pathway. Moreover, the effect of EGCG extends also to reducing inflammation by suppressing the NF-κB and AP-1 pathways, induction of sebocytes cytotoxicity *via* apoptosis and reduction in the viability of *P. acnes*, *thus having a positive influence on almost all the pathogenic features of acne*. In clinical trials, this compound improved the appearance of acne lesions and was well tolerated [30]. Cosmeceutical preparations of MLG-50™ would be expected to produce a similar effect.

Conclusion

Phenolic compounds could be potentially effective in the treatment of various skin conditions, including acne, signs of aging, diseases and injury. They may be efficient in the treatment of both serious life-threatening dermal diseases (cancer) and minor skin conditions (acne). Numerous studies have shown the potent biological activity of polyphenols such as those present in MLG-50™ to possess a significant potential to inhibit or even reverse wrinkles, sagging, acne, hyperpigmentation marks, and inflammation; hence they are promising molecules for development of new cosmetic formulations.

Phytochemicals, phenolics, and polyphenols are versatile molecules for developing effective skin formulations in a variety of delivery products – cream, paste, oil, lotion, spray, and as an oral supplement. They can augment cleansers, astringents, toners, moisturizers, collagen and elastin stimulators, and antibiotics.

Particular phenolic compounds may act in a specific ways. MLG-50™ supplies over thirty organic acids, over seventy trace minerals, and over twenty flavonoid antioxidants. It is a highly stable water extract of prehistoric marine and terrestrial compost mined in the United States.

The following section spotlights selected scientific research articles that focuses on phytochemical-based cosmeceuticals (e.g. MLG-50™) for treating acne and associated skin conditions.

Study 1: Resveratrol, a component of MLG-50™, was incorporated in a carboxymethylcellulose-based gel. Clinical evaluation showed a 53.75% mean reduction in the GAGS score (reduction of acne associated lesions) on the resveratrol-treated sides of the face compared with 6.10% on the vehicle-treated sides of the face. These data were supported by histologic analysis, which showed a 66.7% mean reduction in the average area of acne lesions on the resveratrol-treated sides of the face [31].

Study 2: The grape seed extract (GSE) and its main active polyphenol, resveratrol (RES) a component of MLG-50™, have shown considerable antioxidant activities, besides possessed protective and therapeutic effects against various skin complications (including acne). This study demonstrates the favorable effects of RES, GSE and their nanoformulations for dermatological approaches, with specific emphasis on clinical interventions [32].

Study 3: The skin is directly exposed to the polluted atmospheric environment, and skin diseases, such as atopic dermatitis and acne vulgaris, can be induced or exacerbated by airborne particulate matter (PM). PM can also promote premature skin aging with its accompanying functional and morphological changes. PM-induced skin diseases and premature skin aging are largely mediated by reactive oxygen species (ROS), and the harmful effects of PM may be ameliorated by safe and effective natural antioxidants, an abundance which are found in MLG-50™ . Experimental studies have shown that the extracts and phenolic compounds derived from many plants, such as cocoa, green tea, grape, pomegranate, and some marine algae, have antioxidant and anti-inflammatory effects on PM-exposed cells. The phenolic compounds can decrease the levels of ROS in cells and/or enhance cellular antioxidant capacity and, thereby, can attenuate PM-induced oxidative damage to nucleic acids, proteins, and lipids [33].

Study 4: Resveratrol, present in MLG-50™, is a naturally occurring polyphenolic antioxidant that has received massive attention for its potential health benefits, including anticarcinogenesis, anti-aging and antimicrobial properties. The compound is well tolerated by humans and in recent years has been widely used as a nutraceutical. Its common use makes it interesting to investigate with respect to antimicrobial properties both as a single agent and in combination with conventional antibiotics. Resveratrol displays antimicrobial activity against a surprisingly wide range of bacterial, viral and fungal species. Following topical application resveratrol, a component of MLG-50™, has alleviated acne lesions caused by the bacterium *Propionibacterium acnes* [34].

Study 5: Acne vulgaris affects most people at some point in their lives. Due to unclear etiology, likely with multiple factors, targeted and low-risk treatments have yet to be developed. There is an emerging body of work on the human gut microbiome and how it mediates feedback between the foods we eat and our bodies. The gut microbiome is also an important mediator of inflammation in the gut and systemically. This research article explores the multiple causes of acne and how plant-based foods and supplements can control these. Collectively, the evidence suggests that approaches such as plant-based foods and supplements, such as MLG-50™, may be a viable alternative to the current first line standard of care for moderate acne, which typically includes antibiotics [35].

Study 6: Acne vulgaris is the most common skin condition associated with inflammation of pilosebaceous unit (composed of a hair follicle, arrector pili muscle, and sebaceous gland). Since conventional therapies have not demonstrated desirable effectiveness and possess remarkable side effects, there is a growing interest in the use of herbal medicines and isolated plant flavonoids, for the management of acne vulgaris. In this study, plant-derived molecules investigated in acne vulgaris have been reviewed and their possible underlying mechanisms of action were discussed. Most of the phytochemicals investigated in acne were from the category of polyphenols including resveratrol (a component of MLG-50™), myricitrin, schisandrin, terchebulin, alpha-mangotin, curcumin, ellagic acid and epigallocatechin 3-gallate. Moreover, alkaloids and terpenoids such as berberine, ursolic acid, lupeol were evaluated in acne vulgaris with less abundance. Various molecular mechanisms were involved in effects of phytochemicals including antioxidant (through down-regulation of H_2O_2, MDA (malondialdehyde level is commonly known as a marker of oxidative stress and the antioxidant status in cancerous patients), ROS and upregulation of SOD), anti-inflammatory (through reduction of proinflammatory cytokines, i.e., IL-1ß, IL-6, IL-8, TGF-β, TNF-α, NF-κB), immunomodulatory, antibacterial (against *Propionibacterium acnes* and *Propionibacterium granulosum*), antiandrogenic, reducing sebum production, and lipogenesis inhibitory activities. Therefore, phytochemicals, including those constituting MLG-50™, seem to be a precious source for identifying new medicines for treatment of acne vulgaris [36].

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