Plant Flavonoids as Potential Natural Antioxidants in Phytocosmetics

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ABSTRACT
Phytocosmetics, the sub-discipline of cosmetology which primarily uses plant and plant extracts in beauty treatments, has been endorsed for thousands of years. After a period of time being pushed aside by an enormous wave of interest in synthetic products, phytocosmetics is slowly but surely returning to its propitious moment. Botanical compounds, among which flavonoids are highlighted, are being recognized for their biological activities – namely antioxidant, anti-aging, anti-inflammatory, antimicrobial and photoprotective activities. The purpose of this paper is to review updates in the extensive research into the potential of flavonoids in cosmetic applications, in order to demonstrate the newest achievement and encourage more interest into the field.

A literature search was performed in PubMed in February and March 2022 with key terms including “phytocosmetics”, “flavonoids” and “antioxidant”. To keep the search topical, the publication years were limited to after 2010. The results were screened with the exclusion criteria of duplicate papers, irrelevant research, and non-English articles. The antioxidant activity of flavonoids have been widely established in a variety of plant sources. Their potential in cosmetics is also evident and has been attributed to their chemical structures, with their biological mechanisms starting to be better understood.

In conclusion, flavonoids have been shown to be a viable alternative to synthetic antioxidants for cosmetic applications. However, there is still a need to evaluate effective delivery aids and formulations.

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1. Introduction

1.1. Phytocosmetics – drawing from the natural fountain of well-being

Nature has always been a fundamental part of human’s life and health. Folk medicine from any cultures around the globe have its roots in natural products, and more particularly, in plant-based products. Modern medicine could also be seen as having its basis on nature, as drug discovery and a great deal of research into novel medicinal and bioactive compounds have been inspired by botanicals and other natural products, ever since the first active chemical, morphine, was extracted from poppy opium [1, 2].

Unfortunately, this humble origin is sometimes forgotten, as synthetic compounds make their way into medical practices and pharmaceuticals, as stated by chemist Justus von Liebig: “The production of all organic substances no longer belongs just to living organisms [3].” However, natural products still hold profound advantages over synthetic ones in pharmaceutical chemistry, as they are essentially the tried-and-true solutions through the vigorous process of evolution, which translates to high stereosechemistry definition and high degree of activity and bioavailability. More than ever, technological advances and more open communication among different fields of study, there has been brimming excitement and potential in natural products exploitation [4].

The aforementioned prospects of natural medicines and phytomedicine can also be applied to phytocosmetics. Thanks to a shift in modern concept of health, which does not only mean the absence
of diseases, but also a state of well-being, botanical products have gained considerable interest in the market of self care and beauty treatment. The global market for plant-based organic cosmetic products was priced at 8.26 billion dollars in 2020 and is continuing to rise, especially in developed area such as North America and Europe, and emerging economies such as Asia [5].

It is clear that from both scientific and economic standpoint, phytocosmetics is rising in demand for serious study and dedicated attention.

1.2. Oxidative stress and its concern in cosmetics

Oxidative stress is a term referring to the excessive presence of reactive oxygen species (ROS) often called free radicals, occurring when the biological system fails to detoxify the ROS before they create damage, and/or when the body fails to repair such damage [6].

Free radicals, or oxidants, are highly reactive molecules that carry unpaired electrons that readily oxidize cellular structures such as cell and organelles membrane, proteins, and DNA. They include ROS, reactive nitrogen species (RNS), reactive sulfur species, and reactive carbon species. Some examples of these species are superoxide anion (O$_2^-$), hydroxyl radicals (•OH), singlet oxygen (‘O$_2$), hydrogen peroxide (H$_2$O$_2$), nitric oxide (NO), and peroxynitrite (ONOO$^-$). The damages caused by free radicals lead to a loss of functions, dysregulation of homeostasis, or even cell death, and are associated with aging and diseases. Free radicals are also involved in some allergic diseases and cancers [7, 8].

Free radicals can occur naturally inside the cells as by-products of metabolism. In fact, mitochondria are a prominent source of free radicals due to their respiratory reactions, which can produce superoxide in the matrix and intermembrane space. In the presence of superoxide dismutase, hydrogen peroxide can form, or peroxynitrite can form as a result of direct reaction with nitric oxide. These free radicals can induce membrane permeability, creating pores which allows them to leak out into the cytosol and continue their havoc [9].

However, free radicals load can be multiplied by many external stresses as well. These include pollution, sunlight, particularly UV, visible and infrared light, or psychological stress. As the outer protective layer of the body, skin is the organ experiencing the most stresses and expressing most detrimental effects. Within only 15 minutes of sun exposure, considerable increases in hydrogen peroxide and hydroxyl are detected [10]. Sunlight with UVA and UVB could so effectively induce free radicals formation because the normal functions of cells rely a lot on photosensitizer molecules, such as cytochromes, riboflavin, heme and porphyrin, which can be excited by the absorption of photons and react with oxygen to form superoxide or singlet oxygen [11].

2. Flavonoids as natural antioxidants

Plants and plant extracts have long been an abundant and reliable source of antioxidants, among which flavonoids have been an outstanding candidate.

Flavonoids are an abundant group of secondary metabolites in plants with a variety of functions. Up to 10,000 flavonoids have been found all plant parts while up to 1,000,000 metabolites are predicted in the entire plant kingdom [12, 13], and they are believed to hold essential tasks in plant biology, including development control, plant-microbe and plant-animal interactions, pigmentation, as well as defense against environmental stresses [14]. The latter function of flavonoids is significant, since it means that flavonoids have many desirable properties for human use as medicines, supplementary food and personal care.

Structurally speaking, flavonoids refer to compounds derived from a phenyl-substituted propyl benzene with a C15 skeleton, a C16 skeleton, or C6-C3 lignan precursor. Flavonoids are further classified into flavones, flanols, flavanones, anthocyanidins, and isoflavones. In a broader sense, chalcones, dihydrochalcones, and aurores are also considered flavonoids [15-17]. The chemical structure of these sub-classes are depicted in figure 1, and some most common compounds are shown in figure 2.
Figure 1. Basic structures of the main types of flavonoids found in plant materials. (a) backbone, (b) Flavones, (c) Flavonols, (d) Flavanones, (e) Flavanols, (f) Anthocyanins, and (g) Isoflavones

Figure 2. Common flavonoids that have been used in commercial products

The antioxidant activity of flavonoids have been linked to how many hydroxyl groups they have and where they are, as well as the aromatic rings in their chemical structure [18].

Many scientific evidences have suggested the tremendous health benefits of a plant-based diet, which could be explained by the abundance of antioxidants, especially flavonoids, in plants and vegetables. Naphatsorn K. and Chaiyavat C. investigated 17 local vegetables in Northern Thailand for their tannin and flavonoid contents. The results showed a clear correspondence between flavonoid contents and antioxidant activities of the vegetables. Hog plum (*Spondias pinnata*) was found to be the richest in flavonoids and established high antioxidant activities in the ABTS scavenging and ferric reducing assays [19].

An emerging approach in botanical research is to focus on the local species, which is good practice for the movement of organic personal care products, since locally sourced ingredients are much more sustainable. Nizar Y. *et al.* reported a comparison among the antioxidant activity and chemical
composition of the peel and pulp of two local Tunisian prickly pear species. The results showed higher antioxidant activity in the peel compared to the pulp, and in the thornless variants compared to the spiny ones. This observation corresponds highly with the same pattern for flavonoid contents in peel/pulp and thornless/spiny variants, suggesting that the extract’s antioxidant capacity primarily comes from its flavonoids [20].

Paulina M. tested the flavonoids contents and their correspondence with antioxidant capacity of 10 on-the-market plant extracts used in commercial cosmetic products. A highly correlated relationship was found, and the most potent extracts were found to be from arnica flowers, hawthorn flowers and lungwort herb. These extracts also established a numerous properties suitable for cosmetic use, such as moisturizing, anti-inflammatory, anti-irritant and UV protection [21].

3. Cosmetic applications of flavonoid antioxidants

The potent antioxidant activity of flavonoids is a great asset to exploit for cosmetic purposes. As discussed above, oxidative stress is the main culprit of most cosmetic and dermatological problems, and so supplementing the skin and body with antioxidants is considered the best approach for both preventative and therapeutic treatments.

3.1. Sun protection

A valuable characteristic of flavonoids that make them a candidate for protection against sun exposure is the presence of chromophores in their structure since one of their function in plant is for pigmentation. A chromophore is a molecular region that can absorb light energy in particular wavelengths to confer the perceived color. Interestingly, many flavonoids have been shown to absorb light in the UV range and blue light range, the most damaging ranges of sunlight [15, 22-24] (See Table 1). Besides, the antioxidant nature of flavonoids help neutralize the oxidative stress induced by sun exposure.

<table>
<thead>
<tr>
<th>No.</th>
<th>Flavonoids</th>
<th>Absorption band</th>
<th>Corresponding region</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kaempferol</td>
<td>367 nm</td>
<td>Benzene rings decorated with 3,5,7,4’-hydroxyl groups</td>
</tr>
<tr>
<td>2</td>
<td>Quercetin</td>
<td>371 nm</td>
<td>Benzene rings decorated with 3,5,7,3’,4’-hydroxyl groups</td>
</tr>
<tr>
<td>3</td>
<td>Myricetin</td>
<td>374 nm</td>
<td>Benzene rings decorated with 3,5,7,3’,4’,5’-hydroxyl groups</td>
</tr>
<tr>
<td>4</td>
<td>Crysín</td>
<td>313 nm</td>
<td>Benzene ring decorated with 5,7-hydroxyl groups</td>
</tr>
<tr>
<td>5</td>
<td>Apigenin</td>
<td>337 nm</td>
<td>Benzene rings decorated with 5,7,4’-hydroxyl groups</td>
</tr>
<tr>
<td>6</td>
<td>Naringenin</td>
<td>389 nm</td>
<td>Benzene rings decorated with 5,7,4’-hydroxyl groups</td>
</tr>
<tr>
<td>7</td>
<td>Taxifolin</td>
<td>290 nm</td>
<td>Benzene rings decorated with 3,5,7,3’,4’-hydroxyl groups</td>
</tr>
<tr>
<td>8</td>
<td>Anthocyanins</td>
<td>240-280 nm</td>
<td>Benzene rings with different hydroxyl positions</td>
</tr>
</tbody>
</table>

Several studies have worked into the photoprotective property of flavonoids. Silymarin, a flavonoid extracted from *Silybum marianum* has been tested for its photoprotection in several different formulations. A stand-alone ethanolic solution of silymarin (50 μmol/L) had a sun protection factor (SPF) of 5.5 [25]. An oil-in-water cream with 10% (w/w) silymarin exhibited an SPF close to 9, and combination of silymarin with other physical sunblock agents such as titanium dioxide and zinc oxide...
boosted the SPF to 16 and 18, respectively [26]. Most recently, a study applying nanoparticles technology reported an SPF 14.1 in vivo [27].

Two active compounds from *Buddleja scordioides*, one of which is a flavone called linarin, were tested on guinea pig and shown to have an SPF value of 9. It was also shown to have remarkable protection from UV damage [28]. Another report on *Moringa oleifera* extract enriched in quercetin and rutin established a consistent SPF of 2 regardless of extract solvents (hydroalcoholic, methanolic and water) [29]. Raspberry and blackberry are known for their high contents of antioxidants, especially flavonoids. A 2018 study was able to extract almost 3 and 7 mg of anthocyanin from 10 g of raspberry and blackberry, respectively. The authors used the extracts in an oil-in-water formulation, and achieved high values of SPF, 55 for blackberry and 37 for raspberry [30]. Anthocyanins are also one of the most abundant flavonoids in plants, especially in berries. There have also been evidence that anthocyanins are highly compatible with human natural flora, and can actually work together with the flora to increase their natural antioxidant activity. It has been shown that anthocyanins contribute to the production of other phenolic compounds that can activate Nrf2, which is responsible for antioxidant enzymes and proteins. They are also involved in reducing inflammation and oxidative stress by working on the TAK1-mediated MAKP and SphK/S1P mediated NF-κB pathways [31, 32].

Acacetin is a major flavonoid found in safflower seed. It has been shown to establish a photoprotective effect, and more significantly, an ability to inhibit UV-induced skin wrinkles. A study 2019 looked into the possible mechanism and found that acetin could regulate metalloproteinase-1 expression by inhibiting EGF-induced AKT phosphorylation in HaCaT cells and human dermal fibroblasts [33].

Letícia C. et al. reported a new sunscreen formulated from flavonoid-enriched plant-extract-loaded emulsion. The authors used a combination of extracts from *Ginkgo biloba* L., *Dimorphandra mollis* Benth, *Ruta graveolens* and *Vitis vinifera* L. leaves in a sucrose palmitate glyceryl stearate based emulsion, enriched with quercetin and rutin. The resulting formulation presented capacity for UVA/UVB protection, while also having promising antioxidant activity [34].

### 3.2. Anti-aging effects

Flavonoids have long been proposed as one of the most potent natural compounds to protect against signs of aging, especially on skin. Studies on anti-aging effects of plant extract often focus on the inhibitory ability to enzymes associated with skin structure compromising, such as collagenase and elastase, and the protection from damages caused by oxidative stress, which has been known as a cause of aging.

Taxifolin is a flavonoid with outstanding antioxidant activity isolated from the plant *Stizolophus balsamita*. Iwona M. et al. published a study in 2021 investigating its effects on mature skin. The investigation was performed on 97 Caucasian women who had clinically shown aging signs on their skin. The cream formulation of 3% *S. balsamita* extract was able to significantly reduce hyperpigmentation and erythema without causing irritant. More importantly, 3% taxifolin cream had the ability to improve viscoelasticity of aging skin with better penetration rate [35].

*Nymphaea lotus* L. is also a popular traditional medicinal plant that has been well-associated with beautification and skin care. In fact, water or ethanolic extracts from various parts of the plants, such as root, leaves and flowers, are commonly incorporated in local people’s homemade self care products such as toner and perfume. Much of this plant’s cosmetic potentials have been attributed to its high flavonoids contents, mostly in flower parts. Researchers have proposed the use of water lily extracts in anti-aging products, thanks to their flavonoids involvement in the inhibition of matrix metalloproteinase-1, which causes the breakdown of the extracellular matrix leading to skin aging. Also, stamen extracts have been shown to activate silent information regulator 2 gene, helping to retain cell longevity and regulate aging [36, 37].

Mariacaterina L. et al. carried out a screening of ninety herbal products to evaluate their potential in phytocosmetics. The criteria include the extracts activity against elastase and tyrosinase, which are two enzymes associated with aging, causing loss of skin elasticity and senile lentiginies, respectively. Among the ninety extracts, four candidates were active against both enzymes – *Ginkgo biloba* L.
(leaves), *Rhodiola rosea* L. (roots), *Vitis vinifera* L. (leaves), and *Camellia sinensis* Kuntze (leaves). The authors also determined the flavonoids content of the extracts, and drew a well-correlated relationship between them and the extracts potency [38].

### 3.3. Anti-inflammatory effects

Flavonoids anti-inflammatory effects are attributed to their ability to inhibit phospholipases and cyclooxygenase expression, as well as regulate immune cells migration and cytokines production.

The skin protective effects of polymethoxyflavones from the plant *Kaempferia parviflora* were investigated Hung M.P. research group. The authors showed how the flavonoids protected human dermal fibroblasts from oxidative stress and inflammatory damage brought about by tumor necrosis factor-α (TNF-α). They could suppress an array of pro-inflammatory mediators induced by TNF-α, including cyclooxygenase-2 (COX-2), interleukin (IL)-1β, and IL-6, as well as some transcription factors that play a role in oxidative stress damage, such as mitogen-activated protein kinase (MAPK), activator protein 1 (AP-1) and nuclear factor-kappa B (NF-κB). They also had an inhibitory effect on matrix metalloproteinase-1 (MMP-1) production, and interestingly, a stimulating effect on collagen production [39].

*Alpinia galanga* (L.) Willd. is a native flowering medicinal herb in Southeast Asian which has a rich flavonoids profile in many parts of the plant. In fact, the herb has been used extensively in many recipes in folk medicines, both for therapeutic purposes and beautification, especially anti-aging. The science behind such potent efficacy of the plant has been studied, and mostly associated with its flavonoids content. Galangin, a specific flavonoid found in the species was found to have protective properties to human dermal fibroblasts, with outstanding anti-inflammation effect via the inhibition of nuclear factor (NF)-κB and upregulation of heme oxygenase-1 [40, 41].

Fang F. and colleagues investigated into the ability of baicalin, a flavonoid found in *Radix Scutellariae* in suppressing acne-induced skin inflammation. The activities of the flavonoid against inflammation was well documented, with a clear decrease in pro-inflammatory cytokines (IL-1β, -6, -8, and TNF-α) in vivo, a down-regulation of JNK, ERK1/2, and κBα phosphorylation, inhibition of p65 nuclear translocation and NLRP3 inflammasome activation [42].

### 3.4. Hair care

Hair is also an aspect of cosmetics that can benefit from the antioxidant activity of flavonoids and flavonoids-rich plant extract, since oxidative stress has been linked to the aging of hair, including the worsening hair fibers condition, hair loss and greying [6].

Deeksha S. research group proposed a herbal shampoo formulations with *Cyclea peltata* extract, which was rich in biologically active compounds, especially flavonoids. The plant extract was shown to be a very potential candidate for shampoo since the fermentation of it naturally produce lactic acid, which is highly regarded for shampoo base due to sunlight protection and hair texture and strength improvement [43].

Silvia M.P. et al. reported a novel remedy for hair loss, which was phospholipid vesicles loaded with finasteride and baicalin, which is flavonoid from *Scutellaria baicalensis* Georgie, that has attracted a lot of scientific attention for its ability to promote hair growth. The formulation showed potential results, with the proliferation of hair follicle dermal papilla cells, acceleration of hair growth, and the increase in number of follicles in treated mice [44].

Another potential plant extract for hair growth promotion is *Pinus thunbergii*, the Korean maritime pine bark. The extract was found to be rich in flavonoids (48.82 mg QE/g). 2% was the optimal concentration of extract for hair growth speed, and following assessment showed evidence that the pine bark extract significantly weakened TNF-α and IL-1β, two pro-inflammatory cytokines, immunoreactivity, while increased the potency of anti-inflammatory cytokines such as IL-4 and IL-13. Moreover, various growth factors were also enhanced by the extraction, including insulin-like growth factor-1 and VEGF [45].

Jeayoon Kim et al. investigated quercitrin, a flavonoid found in *Hottuynia cordata* extract, which has an enhancement activity for hair growth. The researchers unveiled the molecular mechanism behind its
activity, and showed an increase in Bcl2 expression – an important marker for anagen hair follicle and cell survival, as well as an increase in Ki67 – a cell proliferation marker. They also found both mRNA- and protein-levels enhancement in various growth factors, such as bFGF, KGF, PDGF-AA, and VEGF. What is more, quercetin was also found to induce phosphorylation of Akt, Erk, and CREB, which suggested that the flavonoid can promote hair growth by boosting cellular energy metabolism [46].

4. Conclusions

The antioxidant activity of flavonoid-rich plant extracts have been proven by numerous scientific research. The chemical structures of flavonoids contribute greatly to this activity and their potential in cosmetic applications. Increasing interests in organic and plant-based natural cosmetics demand more effort in the field’s research to provide more concrete evidences, determining mechanisms, and evaluate better formulations or delivery methods to enhance their efficacy.

REFERENCES


Enhanced Expression of Growth Factors via Activation of MAPK/CREB Signaling


Le Hong Phu currently works at International University _ Vietnam National University Ho Chi Minh City as a role as an associate professor for Food Technology Field. He received his bachelor’s degree in biology from University of Science _ Vietnam National University, Ho Chi Minh City in 2000. He received his master and Ph. D degrees in Biochemistry from University of Science _ Vietnam National University, Ho Chi Minh City in 2003, 2012, respectively. He was promoted to associate professor in 2017. His research areas cover applied biochemistry, applied microbiology, as well as functional food. He is the author of nearly 50 international and national articles and the leader of 4 transfer research projects. He has successfully guided more than 100 students and graduates in Food Technology and Biotechnology. The articles are focused on objects such as coffee, pepper, cocoa, and others such as ginseng and algae that are being cultivated in the central provinces and the Central Highlands in Vietnam. Other research is aimed at producing convenient functional products that can be used immediately, such as instant tea. He focuses on research on fermentation conditions for the production of fermented coffee with microbes, using a combination of enzymes to process the extraction with high efficiency, as well as peel off the skins in the production of white pepper, honey coffees.

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