Mushrooms extracts and compounds in cosmetics, cosmeceuticals and nutricosmetics - A review

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Abstract

The cosmetic industry is constantly in search of ingredients from natural sources because of their competitive effectiveness and lower toxicity effects. Mushrooms have been an important part of our diet for years and are now finding their way as cosmetic ingredients, either as cosmeceutical or as nutricosmetics. The present review focuses on the most relevant activities of mushroom extracts, as well as on their bioactive compounds, which make them interesting ingredients for cosmetic formulations. Mushroom extracts, as well as their bioactive metabolites, revealed anti-tyrosinase, anti-hyaluronidase, anti-collagenase and anti-elastase activity. Emphasis was also given to their important anti-oxidant, antimicrobial and anti-inflammatory potential, topics largely studied by numerous authors, making them very versatile and multi-functional cosmetic ingredients. Some of the bioactive compounds and the mechanism responsible for the activities ascribed to mushrooms were highlighted. Other activities were identified as needing to be further studied in order to identify the major compounds contributing to the target activity, as well as their mechanisms of action. Based on the above findings, mushroom extracts, as well as their bioactive metabolites, constitute important ingredients that can help to combat aging, reduce the severity of inflammatory skin disease and correct hyperpigmentation disorders. These findings and claims must be correctly supported by clinical trials and *in vivo* studies.

Keywords: Mushrooms; Cosmetic; Nutricosmetic; Bioactive; Aging

Contents

1. Cosmetics, Cosmeceuticals and Nutricosmetics

A "cosmetic product" is any substance with soft action that is either rubbed or sprinkled on the various parts of the human body with the sole aim to clean, beautify, increase the attractiveness, protect them and keeping them in good condition (Luque de Castro, 2011). The world's cosmetic industry is worth tens of billions of US dollars, and is in a constant search for new and improved natural products to serve as suitable raw-materials, able to compete with the artificial synthetic counterparts or add new bioactivities. In Asia, mushrooms have been used as medicinal ingredients for thousands of years and in China and Japan for example, they were kept in reserve for royalty because of their potency and efficacy (Hyde et al., 2010).

Cosmeceuticals can be defined as the combination of cosmetics and pharmaceuticals. They consist of products which are applied topically and comprise creams, lotions and ointments with biologically active compounds with medical drug-like benefits (Sharma, 2011). These products are known to contain ingredients that influence the biological function of the skin by supplying the needed nutrients for healthy skin while improving the appearance, the radiance, texture and anti-ageing activity (Hyde et al., 2010). The application of natural ingredients such as phytonutrients, microbial metabolites, dairy products (Haruta-Ono et al., 2012; Keller et al., 2014), minerals and animal protein components (Rodrigues et al., 2015) for skin care is very popular today. Extracts of coconut, jasmine, lemon grass, longan and several medicinal plants have been known to play an important role in the treatment of various skin diseases; being for this reason extensively studied and used in many countries around the world, including Africa (De Wet et al., 2013), where they play an important role in skin health care. Fungi, especially mushrooms and their products, are now finding their way into cosmetics and used extensively as crude material or as pure

compounds for treating various diseases usually associated with the skin (Hyde et al., 2010).

Nutricosmetics are the newest trend in skin care and involve combining food, cosmetic and pharmaceutical being still unknown to some dermatologists and consumers. This involves the consumption of dietary and nutritional supplements to produce a visual appearance benefit and improve the health of the skin (Luque de Castro, 2011). The focused primary action areas are: skin, hair and well being. Many micronutrients can provide these effects (e.g. vitamin C has an antioxidant potential and tends to reduce free radicals generation when the skin is exposed to UV radiation). Following these trends, cosmetic industries are now putting more efforts to develop nutricosmetics with high contents of several ingredients, such as collagen, hyaluronic acid, elastin and ceramide, known to maintain skin structure and function (Haruta-Ono et al., 2012). These authors reported that oral ingestion of dietary products improves the water-holding capacity of the skin and the barrier function. Hong et al. (2014) also reported the beneficial effect of green tea ingestion due to the presence of numerous phenolic compounds responsible for significant inhibition of enzymes such as collagenase, elastase and tyrosinase, thereby maintaining the structural stability, elasticity and blocking melanogenesis, respectively.

2. Skin aging

The skin is the largest organ of the body, accounting for about 15% of the whole weight. It acts as a barrier against physical, chemical and biologic attacks, while it prevents water loss from the body (Kendall and Nicolaou, 2013). Skin aging is known to be caused by an intrinsic, natural or cellular mechanism that affects not only the skin but also other organs of the body due to changes in hormonal secretion occurring with age, which often result in

collagen degradation, dryness, degeneration of elastic fibre networks, and development of laxative and wrinkle skin (Papakonstantinou et al., 2012). The extrinsic mechanism results from the exposure to external factors, mainly over exposure to solar radiation often known as photo aging. Reactive oxygen species (ROS), arising from oxidative cell metabolism causes damage to cellular components like cell walls, lipid membranes, mitochondria, and DNA, playing a major role in both processes. It induces activator protein-1 (AP-1), a transcription factor that promotes collagen breakdown by up regulating enzymes called matrix metalloproteinases (MMPs). Overexpression of matrix metalloproteinase (MMP-1, MMP-3 and MMP-9) leads to elevated levels of degraded collagen (Leem, 2015). Also, UV radiation causes downregulation of transforming growth factor β (TGF-β), a cytokine that promotes pro-collagen production thus causing reduced collagen synthesis (**Figure 1**). Even though elastin and collagen are the main components of the extracellular matrix, it also contains hyaluronic acid, a key molecule which is responsible for moisturizing the skin and making it less prone to oxidative stress (Papakonstantinou et al., 2012).

Therefore, the inhibitors of elastase, hyaluronidase, tyrosinase and MMP-1 enzymes can be potential cosmetic ingredients in the treatment of skin aging thereby restoring the skin elasticity, increase moisture content, stimulate collagen synthesis and skin lightening effect. Hence, cosmetic industry is searching for natural compounds, supplements or extracts with the ability to delay the aging process. Natural phenolic compounds have been reported to possess scavenging properties against ROS making them interesting candidates for production of antiaging creams or lotions in the cosmetic industry (Soto et al., 2015).

3. Mushroom extracts and individual compounds as cosmetic ingredients

Mushrooms are an important part of our diet and have been consumed for years because of their nutritional composition, taste and flavour. They have been extensively studied and several research publications have reported the presence of a wide range of bioactive metabolites, e.g. phenolic compounds, terpenoids, polysaccharides, lectins, steroids, glycoproteins and several lipid components. Several mushroom extracts, as well as their secondary metabolites, have been reported to display important biological functions such as antioxidant, antitumor, antimicrobial, anti-inflammatory, immunomodulator, antiatherogenic, and hypoglycemic activities (Ferreira et al., 2009; Ferreira et al., 2010; Alves et al., 2012; Taofiq et al., 2016). On the contrary, only very studies have been reported for the anti-tyrosinase, anti-collagenase, anti-elastase and anti-hyaluronidase activities of mushroom extracts and individual compounds (References cited in **Tables 1** and **2**, respectively). Even less explored, these studies and the discussed bioctivities, lead to dermatologists and researchers with interest in cosmetics to be optimistic about the future of mushrooms and their compounds in the cosmetic industry.

3.1. Antioxidant activity

Several biological reactions, required for normal functioning of the organism, take place in body cells and tissues. These reactions often cause generation of species with unpaired electrons called free radicals. These free radicals include ROS, reactive nitrogen species (RNS) and reactive sulphur species (RSS). The body usually has mechanisms to balance ROS production and neutralization by means of its intrinsic antioxidant pool (glutathione peroxidase, catalase and superoxide dismutase), but most of the times it can become depleted due to excessive ROS production allowing the body cells to suffer from oxidative stress (Carocho and Ferreira, 2013). The body usually needs endogenous sources to fulfil

its antioxidant requirements and mushrooms, used as dietary source, can help to surpass this lack since they contain high amounts of bioactive compounds displaying antioxidant activity. These dietary sources of antioxidants such as vitamin C (ascorbic acid), vitamin E (tocopherol), β-carotene, vitamin K, flavonoids, phenolic acids, selenium and zinc tend to maintain a balance to control oxidative stress (Carocho and Ferreira, 2013). Skin exposure to high UV radiation causes ROS generation which usually leads to a combined effect of DNA damage, skin inflammation, hyperpigmentation, stimulation of dermal fibroblast for expression of matrix metalloproteinase 1 (MMP-1) responsible for collagen degradation and decrease in collagen synthesis thus resulting into a photo-aged skin effect (Masaki, 2010).

The important role of antioxidants in the skin health drives the continuous search for compounds of natural origin capable to scavenge ROS, inhibit tyrosinase enzyme as well as suppress MMP-1 expression. Ascorbic acid is usually used in skin care products but controversy in its efficacy has been raised due to its inability to penetrate the skin together with its poor stability in cosmetic formulations. α-Tocopherol is also an important antioxidant that is reported to down regulate MMP-1 expression by suppressing AP-1 and also inhibiting tyrosinase enzyme making it an important anti-wrinkle and hyperpigmentation agent (Masaki, 2010).

Several publications have reported the antioxidant activity of mushroom extracts mainly as radical scavengers (DPPH 2,2-diphenyl-1-picrylhydrazyl; ABTS 2,20-azinobis 3-ethylbenzothiazoline-6-sulfonic acid; H_2O_2 and O_2 scavenging activity), reducing power (FRAP ferric reducing antioxidant power) and lipid peroxidation inhibitors (TBARS thiobarbituric acid reactive substances; Heme degradation of peroxides and FOX ferrous oxidation-xylenol) (Carocho and Ferreira, 2013).

3.2. Anti-inflammatory activity

Inflammation is a physiological response to injury, usually manifested by loss of function and pain, heat, redness and swelling. Overproduction of inflammatory mediators such as interleukins (IL 1β, IL-6, IL-8), tumor necrosis factor (TNF-α), nuclear factor-κB (NF-κB), intercellular adhesion molecule-1 (ICAM-1), inducible type cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE2), 5-lipoxygenase (5-LOX), and inducible nitric oxide synthase (iNOS) may lead to inflammatory diseases and cancer (Taofiq et al., 2016).

Numerous investigations have reported that mushrooms, as well as their isolated compounds such as polysaccharides, terpenes, phenolic compounds, sterols, fatty acids, polysaccharide–protein complexes and other bioactive metabolites exhibit anti-inflammatory potential based on their ability to reduce the production of inflammatory mediators. Regarding this aspect, Taofiq et al. (2016) reviewed the anti-inflammatory activity of mushrooms as well as the associated bioactive metabolites responsible for this activity. *Agaricus bisporus (*J.E.Lange) Imbach, *Phellinus linteus* (Berk. & M. A.Curtis) Teng, *Cordyceps* species, *Antrodia camphorata* (M.Zang & C.H.Su) Sheng H.Wu, Ryvarden & T.T.Chang, *Pleurotus* species and *Ganoderma lucidum* (Curtis) P. Karst., were the most studied species, and polysaccharides, terpenes and phenolic derivatives the compounds reported as the most responsible for the anti-inflammatory activity.

The mechanism of anti-inflammation has been attributed to reduced level of inflammatory mediator release such as NO and other inflammatory mediators such as interleukins (IL 1β, IL-6, IL-8), TNF-α and PGE2 from inflammatory cells. NF-κB is a transcription factor that regulates the expression of several pro-inflammatory cytokines and enzymes such as

IL-1β, TNF-α, iNOS, and COX-2. Hence finding natural inhibitors of one or two steps in the NF-κB pathway is crucial in the inflammation prevention (Taofiq et al., 2016).

Atopic dermatitis is a chronic inflammatory skin disease that is usually associated with redness, rash and severe itching caused by various environmental and physiological factors (Park et al., 2015a). This disease, in recent years, has been reported to be affecting 10–20% of children and 1–2% of adults. Although the physiological mechanism of the disease is not fully understood, the overproduction of inflammatory mediators such as IL 1β, IL-6, IL-8, TNF-α by pro-inflammatory cells, like the macrophages, have been known to be the major cause (Wu et al., 2011). Ukawa et al. (2007) reported that *Lyophyllum decastes* (Fr.) Singer extract suppressed the development of atopic dermatitis induced by repeated application of picryl chloride in mice, where results were compared with a control based on lesions severity. The extract was known to suppress production of IL-4 and serum IgE level. Park et al. (2015a) isolated a polysaccharides (GFP) from *Grifola frondosa* (Dicks.) Gray, and evaluated the ability of the isolated compound to suppress 2,4-dinitrochlorobenzene-induced atopic dermatitis-like skin lesion in NC/ Nga mice. GFP treatment was found to significantly suppress the skin lesion and when administered together with dexamethasone, an anti-inflammatory drug, a synergistic effect in AD-like skin lesion caused by reduced level of serum IgE and cytokines expression was observed. Other mushroom extracts with reported anti-inflammatory potential on skin induced dermatitis are butanol extract of *Cordyceps bassiana* Z.Z. Li, C.R. Li, B. Huang & M.Z. Fan (Wu et al., 2011) and ethanol extract of *Pleurotus eryngii* (DC.) Quél. (Choi et al., 2013).

3.3. Anti-tyrosinase activity

Melanin is the major pigment responsible for the skin colour. Human skin is constantly exposed to UV radiation that influences both skin function and structure. Body overexposure to UV radiation causes overproduction of melanin in the skin, due to the enhanced activity of tyrosinase enzyme. Tyrosinase is the rate-limiting enzyme in melanin biosynthesis pathway; it converts tyrosine to dihydroxyphenylalanine (DOPA) and then oxidizes it to dopaquinone (Meng et al., 2012). Subsequently, dopaquinone is converted to dopachrome through auto-oxidation, and finally to eumelanin (brown-black pigment) in the presence of dopachrome tautomerase (**Figure 2**). Alternatively, dopaquinone can also be converted to cysteinyl DOPA in the presence of cysteine or glutathione to form pheomelanin (yellow red pigment) (Jung et al., 2009).

The main causes of skin hyper pigmentation include auto-immune conditions, exposure to UV radiation, hormonal changes causing release of α-melanocyte-stimulating hormone, genetic factors, hormonal therapy or birth control pills and medication causing drug reaction. All these factors trigger over secretion of melanin from melanocytes causing hyper pigmentation (Ali et al., 2015). There are several signal transduction pathways responsible for increased melanin production by regulating mRNA expression of tyrosinase and tyrosinase-related protein (TRP1 and TRP2) (Chang, 2012). Melanin biosynthesis is initiated by several hormonal and chemical mediators and the most common is the cAMP-mediated pathway (Meng et al., 2012). cAMP is known to increase the expression of micropthalmia-associated transcription factor (MITF) via activation of the cAMP-dependent protein kinase A (PKA) and the cAMP-response element binding protein (CREB) transcription factor. The complex process of melanogenesis is regulated by MITF by binding to the promoter region of tyrosinase related protein, TRP-1, and TRP-2 thereby causing increase expression of tyrosinase enzyme responsible for melanin

biosynthesis (Park et al., 2011). Hence, compounds that tend to cause inhibition of MITF expression will be an inhibitor to the whole process of melanogenesis.

Hyper pigmentation disorders are unfavourable abnormalities usually characterized by darker skin appearance, light to dark brown spots, irregular grey patches on the face, neck and trunk, and pale brown to dark brown spots on the skin motivating researchers to find new ingredients or combinations of ingredients; among them the ones of natural origin can be effective solutions. The mechanism of depigmentation involves the inhibition of one or more steps in the melanogenic pathway or melanosome transfer resulting in lower melanin release and finally combating melanogenesis (Ali et al., 2015). Hydroquinone has been used to treat hyperpigmentation disorders; nevertheless it raises safety concerns namely the reported carcinogenic potential, exogenous ochronosis effect, cell irritants and exudation of offensive fish odour from the skin (Sarkar et al., 2013). Others consider the use of corticosteroids and kojic acid that, nevertheless their high effectiveness, have been reported to cause local or systemic negative effect upon long term exposure. Because of the negative effect associated with the above depigmenting agents, the search of alternative natural products rich in bioactive chemicals with ability to treat these disorders, such as the ones obtained from plants, mushrooms, rhizomes or marine algae, have become important fields of research. Several compounds especially phenolics such as arbutin, resveratrol, ellagic acid and gentisic acid have been isolated from plants and have been reported to inhibit one or more steps in the melanogenic pathway (Ali et al., 2015). These phytochemicals do not only combat melanogenesis but have also been reported to play additional functions such as acting as moisturizers, provide support and stability to the skin and have antiaging effect, thereby preserving the skin health. Studies reporting the anti-tyrosinase inhibitory activity of mushroom extracts and individual bioactive metabolites are described in **Table 1**.

Pleurotus species are among the most cultivated edible mushrooms in the world. They present high nutritional value and have been reported to show medicinal properties such as anti-inflammatory effect, antioxidant, immunomodulatory and antimicrobial activity. These medicinal properties have made scientists to be optimistic about their future as possible cosmetic ingredients. Meng et al. (2011) studied extracts from the fruiting bodies of *P. citrinopileatus* Singer for their tyrosinase inhibition potential and inhibition of melanin production. Kojic acid was used as positive control and results showed that they significantly inhibited tyrosinase activity by 100.0% at a concentration of 100 µg/mL. At the same conditions, *n*-hexane-, ethyl acetate-, and *n*-butanol-soluble extracts showed up to 28.8%, 27.4%, and 41.0% inhibitory activity, respectively. The depigmentation mechanism caused by the extracts was reported to be associated with the inhibition of signals involved in the melanogenesis pathway. Also B16 melanoma cells exposed to *P. citrinopileatus* extract, namely the *n*-hexane- (50 µg/mL), diethyl ether-e (75 µg/mL), and ethyl acetate-soluble (100 µg/mL) fractions showed melanin inhibition production by 63.1%, 64.0%, and 58.8%, respectively. Other *Pleurotus* species with reported anti-tyrosinase activity are *Pleurotus ferulae* Quél. (Alam et al 2012); *Pleurotus nebrodensis* (Inzenga) Quél. (Alam et al., 2011a); *Pleurotus ostreatus* (Jacq. ex Fr.) P.Kumm. (Alam et al., 2010; Hapsari et al., 2012) and *Pleurotus salmoneostramineus* Vassil (Alam et al 2011b). Although *Pleurotus species* are the most studied mushroom species with reported anti-tyrosinase potential, none of those studies were able to identify the bioactive metabolites responsible for this activity.

Park et al. (2015b) recently studied the tyrosinase inhibitory activity of several ethanolic mycelium extracts in the presence of arbutin and ascorbic acid as positive controls. Among the studied extracts, *Inonotus mikadoi* (Lloyd) Gilb. & Ryvarden, at 10 mg/mL, significantly inhibited tyrosinase activity by up to 46.0±7.5%. *Coriolus versicolor* (L.:Fr.)

Quél., and *Fomitopsis* sp., also at the same concentration, inhibited tyrosinase activity by 26.3±8.3% and 23.9±2.5% respectively. The authors concluded that some of these extracts with tyrosinase inhibitory effect can further be developed as functional additives for the cosmetic industry.

Inonotus obliquus (Ach. ex Pers.) Pilát, also known as "chaga mushroom" is a medicinal mushroom commonly used in Russia and other North-European countries with reported anti-tumour and immunomodulatory properties (Taofiq et al., 2016). Studies were conducted by Yan et al. (2014) who investigated the tyrosinase inhibitory activity of petroleum ether and *n*-butanol extracts of *Inonotus obliquus*. At 10 μg/mL, petroleum ether and n-butanol extracts showed tyrosinase inhibitory activity with IC_{50} value of 3.81 and 6.32 μg/mL, respectively. The bioactive compounds responsible for the activity were reported to be betulin and trametenolic acid, which were described as capable to reduce melanin content and to display a noncompetitive type of tyrosinase inhibition. Betulin (**Figure 3**) inhibited effectively tyrosinase activity with an IC_{50} of 5.13 μM, even more effective than kojic acid (6.43 μM) used as positive control. The reported results suggest that these compounds can be further studied in view of potential cosmetic ingredients development for treatment of hyperpigmentation.

Some phenolic compounds (**Figure 3**) and their derivatives have been reported to display anti-tyrosinase activity. Recently, Chaiprasongsuk et al. (2016) studied the anti-melanogenesis effect of dietary phenolic compounds (caffeic acid (CA), ferulic acid (FA), quercetin (QU), rutin (RU) and avobenzone (AV)) shortly after exposure of B16F10 melanoma cells to UVA radiation. Inhibition of melanin content, as well as inhibition of tyrosinase activity, was evaluated. The results were expressed in terms of IC_{30} values, and the ability of the compounds to inhibit UVA-mediated melanin content and tyrosinase activitiy were ranked as QU>RU≈CA≈AV>FA. The results suggest that CA produced a

higher tyrosinase inhibition effect than FA. The results are also in agreement with the ones reported by Thangboonjit et al. (2014) that described IC_{30} values (μM) for the tyrosinase inhibition activity of *p*-coumaric acid, caffeic acid and ferulic acid as 22.86±2.1, 43.09±2.3 and 51.85±1.7, respectively. The mechanism of anti-melanogenesis of the compounds were reported to be due to suppression of tyrosinase protein expression in UVA-irradiated B16F10 cells.

3.4. Anti-hyaluronidase activity

The skin extracellular matrix provides structural and mechanical support to the skin while it also preserves its integrity (Muiznieks and Keeley, 2013). The degradation of the skin matrix plays a vital role in the skin aging development. Collagen and elastin are structural proteins that are necessary for skin health but insufficient for a healthy skin matrix. The skin also needs appropriate components to support dermal regeneration, proliferation and migration (Ito, 2014). Hyaluronic acid (HA), is a naturally occurring glucose-based polymer that plays an important role as skin rejuvenant, holds moisture, increases viscosity and reduces permeability of extracellular fluid (Saranraj and Naidu, 2013). HA is evenly distributed in both prokaryotic and eukaryotic cells. In humans, it is most abundant in the skin, followed by the vitreous of the eye, the umbilical cord, synovial fluid, skeletal tissues, heart valves, the lung, the aorta and erectile tissues of the penis (Papakonstantinou et al., 2012).

The level of hyaluronic acid present in the skin decreases with age thus, leading to loss of moisture and the inability of the skin to repair and rejuvenate itself. Creams and lotions for topical application of HA are solutions provided by the cosmetic industry, but they are faced with enormous challenges because of their tendency to cause an inflammatory response (Saranraj and Naidu, 2013). Inhibition of HA degradation is central to protecting

the connective tissues of the skin and some natural compounds such as saponins and flavones (β-aescin) from horse chestnut seeds (*Aesculus hippocastanum* L.) have been reported to have non-competitive anti-hyaluronidase activity (Dudek-Makuch and Studzińska-Sroka, 2015). Studies reporting the anti-hyaluronidase activity of mushroom extracts and individual bioactive metabolites are described in **Table 1**.

Pleurotus citrinopileatus is an edible mushroom also known as golden oyster mushroom. Several studies have reported its antigenotoxicity, angiotensin-converting enzyme (ACE) inhibition, anti-hyperlipidemic, anti-atopic dermatitis, antioxidant and anticancer activity (Meng et al., 2011). These authors reported the anti-hyaluronidase activities of *n*-butanol soluble fraction, aqueous-soluble fraction, and methanol extract of *P. citrinopileatus*. These extracts were found to inhibit hyaluroridase activity by 9.7%, 10.8%, and 25.4%, at concentrations of 2.0, 1.1, and 4.1 mg/mL, respectively, which makes it an important material for cosmetic products.

Trametes lactinea (Berk.) Sacc is a macrofungi belonging to the family of Polyporaceae with reported ability to inhibit hyaluronidase enzyme in the presence of hyaluronic acid as substrate (Yahaya et al., 2012). The activity was evaluated using two different extraction solvents both at 100 µg/mL; aqueous extract displayed the highest hyaluronidase inhibition by up to 88.6±0.11% followed by acetone extract with 88.3±0.14% inhibition. The positive control (apigenin) inhibited hyaluronidase activity by up to 87.4±0.03% but the authors were not able to correlate the phenolic composition of the extract with the inhibition of hyaluronidase activity displayed by the extract.

The hyaluronidase enzyme is among the enzymes that are responsible for degrading the extracellular matrix (ECM) and only very few studies have reported the anti-hyaluronidase activity of mushroom extracts. These enzymes activate several signal transduction

pathways that hydrolyse the ECM and have become important target compounds in the development of anti-aging cosmetic agents (Piwowarski et al., 2011).

3.5. Anti-collagenase and anti-elastase activity

The human skin is composed of the epidermis, which is firmly attached and supported by connective tissue to the underlying dermis. Dermal fibroblasts in the extracellular matrix (ECM) generate two structural proteins; collagen and elastin that are necessary for several protective roles in the skin (Kim et al., 2014). Elastin is an ECM protein that provides elasticity to connective tissues such as the aorta, lung, cartilage, elastic ligaments and skin. Elastase is a metalloproteinase enzyme that is capable of degrading elastin, even though it is quite resistant against proteolytic degradation, continuous exposure to elastases leads to damage of elastic fibres thus leading to declined skin resilience and wrinkles. Elastase activity has been reported to increase significantly with age and as a result, interest to screen natural matrices such as plants, mushrooms, rhizomes and marine algae for production of active cosmetic ingredients able to reduce skin aging and wrinkles have increased (Onar et al., 2012).

Collagen is the most important component of the extracellular matrix of the skin responsible for restoring the skin's elasticity, flexibility and strength and as such, degradation of collagen by UV irradiation is responsible for the aging process (Piwowarski et al., 2011). During the process of aging, the components of the extracellular matrix of the skin (collagen, elastin and hyaluronic acid) levels decrease thereby resulting into loss of strength and flexibility, and subsequently into the formation of wrinkle (Ndlovu et al., 2013).

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases that degrade the extracellular matrix associated with some pathological and physiological conditions such as inflammatory and vascular diseases, carcinogenesis, wound healing and bone resorption to mention but a few (Thomas et al., 2014). MMP-1 is membrane anchored, being the main metalloproteinase that degrades collagen. Tissue inhibitors of metalloproteinases (TIMPs) are natural inhibitors reported to control undesired expression of MMPs and further protect the ECM. Skin aging is generally a result of high generation of ROS due to overexposure to UV radiations. These generated ROS stimulate the mitogen-activated protein kinases, which stimulate the activator protein factor 1 (AP-1) causing uncontrolled expression of MMPs, responsible for collagen degradation and skin wrinkling. Hence, several studies are being conducted in order to find natural inhibitors of AP-1 as cosmeceutical ingredient to inhibit the expression of MMPs (Thomas et al., 2014). Until now very few reports are available on the anti-elastase and anti-collagenase activity of mushroom extracts or their metabolites, but several studies are available in literature for the anti-elastase activity of plant extracts (Thring et al., 2009; Moon et al., 2010; Piwowarski et al., 2011), earthworm extract (Azmi et al., 2014) and marine algae extracts (Thomas et al., 2014). Kim et al. (2014) reported the anti-collagenase and anti-elastase activity of mycelial extract from *Tricholoma matsutake* (S. Ito & S. Imai) Singer by treating dermal fibroblast cells with *T. matsutake* extract at concentrations of 1-100 µg/mL for 72 h followed by analysis of elastase, MMPs and type 1 collagen expression. The extract was found to decrease elastase mRNA and protein expression of MMP-1 and MMP-3 in a dose-independent manner by up to 81.4±3.92% at a concentration of 100 µg/mL, while phophoramidon, used as positive control, had a decreasing effect by up to 89.6±7.74% at a concentration of 10 µM. Although the extract could not inhibit collagen expression, the results suggest that *T. matsutake* extract has anti-aging potential with ability to prevent degradation of the ECM.

Kim et al. (2007a) studied the antioxidant, anti-tyrosinase and anti-collagenase activity of the mycelial extract of *Grifola fondosa* (GF-M) as well as an exopolysaccharide (EPS) isolated from it. The anti-collagenase activity was evaluated based on the ability of the studied sample to inhibit the expression level of MMP-1 in UVA-irradiated human dermal fibroblasts. EPS and GF-M at 100 µg/mL significantly inhibited the expression of MMP-1 by 20 and 40%, respectively, while also mentioning that EPS showed a potent inhibition even higher than trans-retinoic acid (tRA), a widely known inhibitor of UVA-induced MMPs. The extract also caused 53% increase in the biosynthesis of collagen. Treatment of B16 mouse melanoma cells with EPS and GFM significantly inhibited melanogenesis by 25 and 17%, respectively. These results suggest that the mushrooms as well as the isolated polysaccharides are potential ingredients to reduce skin aging as well as hyperpigmentation.

Bae et al. (2005) isolated an exopolysaccharide from the submerged mycelial culture of *Grifola frondosa*. The exopolysaccharide (EXP) was analysed for its ability to inhibit expression of matrix metalloproteinase 1 (MMP-1) protein in dermal fibroblast after UVA exposure. There was a significant decrease in the expression level of MMP-1 mRNA by up to 61.1% at 250 µg/mL concentration of exopolysaccharide, suggesting that EXP can be an important ingredient contributing to the photo-aging potential of the mushroom extract.

L-Ergothioneine (EGT) is a sulphur-containing derivative of the amino acid, histidine, which is supplied to mammals mainly by dietary sources. EGT is usually found in cells and tissues that are constantly exposed to oxidative stress and several reports about its antioxidant and cytoprotective effects are available in numerous publications (Bazela et al., 2014). Obayashi et al. (2005) studied the ability of EGT to inhibit expression of MMP-1 protein in dermal fibroblasts while also studying its radical scavenging effect as well as its anti-inflammatory potential based on its ability to suppress TNF-α expression. Among the

results (**Table 2**), it can be observed that EGT at 2 mg/mL, down-regulated the expression of MMP-1 protein by 52% after exposure of dermal fibroblasts to UVA, also showing an excellent scavenging ability against ROS as well as inhibition of TNF-α. These findings suggest that EGT can be an important ingredient in the development of anti-aging cosmetic products.

L-Ascorbic acid (AA) is an important antioxidant that is common in some cosmetic formulations. Recently, Kwak et al. (2015) prepared two hybrid compounds containing AA and *p*-coumaric acid as multifunctional cosmeceutical agents forming ascorbyl-3-*p*-coumarate (A-3-*p*-C) and ascorbyl-2-*p*-coumarate (A-2-*p*-C). These compounds were tested for their ability to increase collagen synthesis from human dermal fibroblasts. The results suggest that at 100–300 μM, A-3-*p*-C and A-2-*p*-C augmented collagen release from human dermal fibroblasts by 120–144% and 125–191%, respectively. Moreover, they also decreased MMP-1 expression. These authors also reported a potent inhibition of melanin content by the compounds suggesting that A-3-*p*-C and A-2-*p*-C could be used as multifunctional ingredients for anti-aging as well against hyperpigmentation.

3.6. Anti-microbial activity

The skin is constantly colonised by non-pathogenic microorganisms such as fungi, *Staphylococcus aureus* and *Streptococcus* species. The distribution and density of the skin micro flora depends on the individual's age, environmental factors such as sebum secretion, temperature and humidity (Elsner, 2006). The presence of these microorganisms is known to cause inflammatory skin diseases such as atopic dermatitis, seborrhoeic dermatitis, cellulitis, erysipelas, impetigo, folliculitis, furuncle, carbuncle abscess and psoriasis (Alsterholm et al., 2010). Among the common skin diseases mentioned above, atopic dermatitis have been known to be associated with increased colonisation of the skin

by microbes such as *Staphylococcus aureus* and these organisms tend to worsen the state of the disease (Salah and Faergemann, 2014). Cosmetic industries are constantly searching for interesting bioactive compounds from natural origin to replace synthetic anti-microbial agents coupled with the fact that these microorganisms also develop resistance against conventional topical antimicrobials (Ribeiro et al., 2015). External application of medicinal plants in the form of paste and infusions for treatment of skin inflammatory diseases has been practiced for many decades (Nesy and Mathew, 2014).

Numerous research studies have reported the anti-microbial potential of mushroom as well as their bioactive compounds. Alves et al. (2012) reviewed the anti-microbial activity of mushroom extracts as well as their bioactive compounds and reported that both edible and non-edible mushroom displayed activity against pathogenic microorganisms. *Lentinula edodes* was indicated to be the most interesting species against both gram-positive and gram-negative bacteria followed by species from the genera *Boletus*, *Ganoderma*, and *Lepista*. Phenolic compounds are secondary metabolites found in mushrooms and other natural sources for protection against UV light, insects, viruses and bacteria (Heleno et al., 2015). They have been reported to display antibacterial activity by interfering with the cell membrane and cell wall of invading pathogen and subsequently leading to the death of the pathogen (Ribeiro et al., 2015). Alves et al. (2013) revealed that phenolic acids such as 2,4-dihydroxybenzoic, protocatechuic, vanillic and *p*-coumaric acids showed higher antimicrobial potential against both Gram-positive and Gram-negative bacteria, while ferulic, caffeic, syringic, ellagic and chlorogenic acids also displayed interesting results. These authors went on to conclude that despite the recognized antimicrobial activity of some of the enumerated compounds, their mechanism of action needs to be fully understood and before the problem of the multiple resistance of bacteria to antibiotics is solved.

4. Commercially available cosmetics with mushroom-based ingredients

Dr. Andrew Weil For Origins™ Mega-Mushroom (https://www.origins.com/dr-weil-mega-mushroom) was among the first premium Western brands to exploit fungi in skin care. Launched in 2006, the product is a skin relief face mask used to calm, soothe, and defend skin against visible signs of aging. In its formulation it includes *Hypsizygus ulmarius* mycelium, *Ganoderma lucidum* and *Cordyceps sinensis* (Berk.) Sacc. extracts. Recently added by Dr. Weil For Origins product catalogue is Plantidote Mega-Mushroom Body Cream, a moisturizing cream containing the three-mushroom's complex as well as other ingredients like as ginger, turmeric and holy basil (*Ocimum sanctum* L.).

Menard is a brand of cosmetic product with mushroom ingredients (www.menard-cosmetic.com). It employs the use of *Ganoderma lucidum* extract in its Embellir range, not only to give an appearance benefit but to eliminate toxins and help repair skin damage associated with over exposure to UV radiation and free radicals.

Estée Lauder employed the *Ganoderma lucidum*, wolfberry and ginsengin along with other antioxidants, moisturizers, some cell-communicating ingredients and some mixtures of common skin ingredients in a new Re-Nutriv sun care product (www.esteelauder.com). This product claims to defend, revive the skin radiance, and help reduce the aging effects of everyday exposure to UV radiation, including the formation of age spots, uneven skin tone and other imperfections.

Aveeno Positively Ageless is a moisturizing eye cream that contains natural Shiitake Complex, a clinically proven antioxidant that works with the skin's natural renewal process (http://www.aveeno.com). This formula intends to brighten the appearance of the skin around the eyes and reduce the appearance of dark circles. Positively Ageless

collection launched in October 2007 have been developed to improve the appearance of skin and fight the signs of aging.

Dr. Patricia Wexler owns Wexler Dermatology in New York City (www.wexlerdermatology.com). The Instant De-Puff Eye Gel was reformulated with *Agaricus bisporus* L. and other important ingredients. This antiaging product contains ingredients that improve the skin surface and boost elastin level in the skin necessary for preventing wrinkling.

5. Concluding remarks

The present review focuses mainly on the anti-tyrosinase, anti-hyaluronidase, anti-elastase and anti-collagenase activity of mushrooms, as well as on their bioactive metabolites, while also mentioning their antioxidant, anti-inflammatory and antimicrobial activity. Mushrooms are important sources of natural bioactive compounds with the potential to be used as cosmetic ingredients to treat several disorders associated with the skin. Tyrosinase inhibitors have been known to reduce melanin content and inhibit tyrosinase activity. Among mushroom species, *Pleurotus* species seem to be the most reported even though the bioactive compounds responsible for this activity have not been identified yet. Other mushrooms with anti-tyrosinase activity are *Agaricus* species, *Inonotus* species, *Lentinula* species and *Ganoderma* species. Bioactive compounds such as 2-amino-3H- phenoxazin-3-one, 2-hydroxytyrosol, *p*-coumaric, botulin, trametenolic acid and some dietary phenolic acids were reported to display tyrosinase inhibitory activity. Hyaluronic acid is as important component of the extracellular matrix that helps to moisturize, repair and rejuvenate the skin. Hyaluronidase enzyme has been found to inhibit this component and thus finding a natural agent with anti-hyaluronidase activity can lead to the discovery of an

important anti-wrinkle agent to protect the connective tissue. In this context, only *Pleurotus citrinopileatus, Pleurotus tuber-regium* and *Trametes lactinea* have been reported so far to display anti-hyaluronidase activity while the identification of the bioactive compounds responsible for this activity was not reported. Collagen and elastin, the most important component of the ECM, suffer a drop with age and several signal transduction pathway are activated during the aging process. Few mushrooms have so far been studied for this activity whose mechanism of action has been attributed to suppression of the matrix metalloproteinases activity. *p*-Coumaric acid seems to be a very interesting cosmetic ingredient because of its reported anti-collagenase, anti tyrosinase and anti-inflammatory activity. Hence further clinical and *in vivo* studies should be conducted on the potential of this compound as a cosmetic material.

Some mushroom species such as *Lyophyllum decastes*, were reported to combat atopic dermatitis by oral ingestion of the fruiting bodies resulting in the disease improvement, suggesting that oral ingestion of mushroom can also exert an appearance benefit. *Cordyceps bassiana*, *Pleurotus eryngii*, and *Grifola frondosa* also caused improvement of induced atopic dermatitis *in vivo* in animal models.

The antioxidant, anti-inflammatory and the antimicrobial activity of mushroom extracts have been reported in several papers, though further studies need to be conducted in order to determine the mechanism of action as well as the bioactive metabolites responsible for ascribed activities. This may be a key issue for the successful development of cosmetic ingredients that will be able to protect and defend the skin against free radicals, reduce production of inflammatory mediators, inhibit collagenase, elastase and tyrosinase associated with inflammatory diseases, wrinkle, aging and hyperpigmentation.

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Table 1. Mushrooms extracts with reported cosmeceutical potential.

Mushroom species	Bioactivity	Bioactives	Effects	Reference
Agaricus bisporus (J.E.Lange) Imbach	Anti-tyrosinase	2-Amino-3H-phenoxazin-3-one	At 0.5 µM, 1 µM and 2 µM inhibited melanin production by 80%, 54.1% and 39.4%, respectively.	Miyake et al 2010
Agaricus brasiliensis Fr.	Anti-tyrosinase	Extract	Methanolic extract at 10 mg/mL inhibited tyrosinase activity up to 49.82±0.51% relative to 48.95±0.35% for kojic acid.	Huang et al., 2014
Coriolus versicolor (L.:Fr.) Quél.	Anti-tyrosinase	Extract	At 10 mg/mL, inhibited tyrosinase activity up to 26.3±8.3%.	Park et al., 2015b
Ganoderma lucidum (Curtis) P. Karst.	Anti-tyrosinase	Extract	At 1 mg/mL, the extract inhibited tyrosinase activity up to 80%.	Chien et al., 2008
Grifola frondosa (Dicks.) Gray	Anti-collagenase	Exopolysaccharide	At 250µg/mL, it decreased expression of MMP-1 mRNA by 61.1%.	Bae et al 2005
	Anti-collagenase, Anti-tyrosinase	Mycelia extract (GF-M), Exopolysaccharide (EPS)	At 100 µg/mL EPS and GF-M inhibit expression of MMP-1 by 20 and 40 %, GF-M caused 53 % increase in collagen synthesis, EPS and GFM inhibited melanogenesis by 25 and 17 % respectively.	Kim et al., 2007a
Inonotus mikadoi (Lloyd) Gilb. & Ryvarden	Anti-tyrosinase	Extract	At 10 mg/mL, it showed tyrosinase inhibitory activity up to 46.0 ± 7.5%.	Park et al., 2015b
Inonotus obliquus (Ach. ex Pers.) Pilát	Anti-tyrosinase	Extract	At 10 μg/mL petroleum ether and n-butanol extract showed tyrosinase inhibitory activity with IC_{50} value of 3.81 and 6.32 μg/mL respectively.	Yan et al., 2014
	Anti-tyrosinase	Betulin and trametenolic acid	Betulin tyrosinase activity showed an IC_{50} of 5.13 μM, trametenolic acid 7.25 μM while kojic acid (6.43 μM) was used as control.	Yan et al., 2014
Lentinus edodes (Berk.) Pegler	Anti-tyrosinase	Extract	At 0.125–1.0 mg/mL, acetonic, methanolic, and hot water extracts inhibited tyrosinase enzyme by 11.94–54.22, 15.12–54.61 and 3.09–47.32% respectively	Yoon et al., 2011b
Lentinus lepideus (Fr.) Redhead & Ginns	Anti-tyrosinase	Extract	Acetonic, methanolic, and hot water extracts at 0.125–1.0 mg/mL inhibited tyrosinase enzyme by 9.71–58.84, 11.23–56.22 and6.97–51.52% respectively	Yoon et al., 2011a
Metarhizium anisopliae (Metschn.) Sorokīn	Anti-tyrosinase	2-Hydroxytyrosol (2-HT)	2-HT inhibited tyrosinase activity with an IC_{50} value of 13.0 mmol/L compared to 14.8 mmol/L for kojic acid.	Uchida, Ishikawa, & Tomoda, 2014
Pleurotus citrinopileatus Singer	Anti-tyrosinase	Extract	At 100 µg/mL *n*-butanol soluble, *n*-hexane soluble and ethyl acetate soluble extract caused 41.0, 27.4 and 28.8% tyrosinase inhibition respectively.	Meng et al 2011
	Anti-hyaluronidase	Extract	At 2.0, 1.1, and 4.1 mg/mL, extract inhibited hyaluronidase activity by 9.7%, 10.8%, and 25.4% respectively.	Meng et al 2011

Pleurotus ostreatus (Jacq. ex Fr.) P.Kumm.	Anti-tyrosinase	Extract	At 0.125-1.0 mg/mL, acetone, methanol, and hot water extracts inhibited tyrosinase activity by 11.37-52.05%, 11.36-59.56%, and 9.60-49.60% respectively.	Alam et al., 2010
	Anti-tyrosinase	Extract	Ethanolic and aqueous extracts inhibited tyrosinase activity with EC_{50} value of 1.125 mg/mL and 2.350 mg/mL respectively.	Hapsari et al., 2012
Pleurotus tuber-regium (Rumph. ex Fr.) Singer	Anti-hyaluronidase	Extract	Aqueous and methanolic extract at 100 µg/mL significantly inhibited hyaluronidase activity by 22.19 and 3.94% respectively.	Dandapat, & Sinha, 2015
Trametes lactinea (Berk.) Sacc.	Anti-hyaluronidase	Extract	Aqueous and acetonic extract inhibited hyaluronidase activity by 88.6 ± 0.11% and 88.3 ± 0.14% inhibition for respectively	Yahaya et al 2012
Tricholoma matsutake (S. Ito & S. Imai) Singer	Anti-elastase, anti-collagenase	Extract	At 100 µg/mL, it decreased expression of MMP-3 and inhibited elastase activity by 81.4 ± 3.92%	Kim et al., 2014
Volvariella volvacea (Bulliard ex Fries) Singer	Anti-collagenase	Phenolic compounds, polysaccharide	Sonicated aqueous extracts stimulate collagen biosynthesis up to 146.77±13.20 %	Ruksiriwanich et al., 2014

MMP-1 : matrix metalloproteinase-1; MMP-3 : matrix metalloproteinase-3.

Table 2. Commercial compounds found in mushrooms with reported cosmeceutical potential.

Compounds	Bioactivity	Effects	Reference
p-Coumaric acid	Anti-tyrosinase	At 10 µg/mL showed a higher tyrosinase activity inhibition than arbutin, but comparable to kojic acid.	An, Koh, & Boo 2010
	Anti-tyrosinase	Reduced MITF and tyrosinase mRNA expression by 73 and 82 %, respectively.	Jun et al., 2012
	Anti-tyrosinase	Inhibited hyperpigmentation up to 77% in human skin.	Seo et al., 2011
	Anti-collagenase	At 30 µg/mL inhibited MMP-1 expression from dermal fibroblasts.	Seok, & Boo, 2015
p-Coumaric acid, methyl *p*-coumarate	Anti-tyrosinase	Inhibited tyrosinase activity with an IC_{50} of 3 mM compared to methyl *p*-coumarate IC_{50} 30 mM.	Song et al., 2011
Ascorbyl-3-*p*-coumarate, Ascorbyl-2-*p*-coumarate	Anti-tyrosinase	At 100 µM, A-3-*p*-C and A-2-*p*-C decreased melanin content by 65 and 59 %, respectively.	Kwak et al., 2015
Ascorbyl-3-*p*-coumarate, Ascorbyl-2-*p*-coumarate	Anti-collagenase	At 100–300 µM, A-3-*p*-C and A-2-*p*-C promote collagen release by 120–144 % and 125–191 %, respectively.	Kwak et al., 2015
Ergothioneine	Anti-collagenase	EGT at 2 mg/mL suppressed expression of MMP-1 protein by 52%.	Obayashi et al., 2005
Dietary phenolic acids	Anti-tyrosinase	The IC_{30} (µM) values for the tyrosinase inhibition activity was *p*-coumaric acid 22.86 ± 2.1, Caffeic acid 43.09 ± 2.3 and Ferulic acid 51.85 ± 1.7.	Thangboonjit et al., 2014
Dietary phenolic acids	Anti-tyrosinase	The IC_{30} (µM) values for the tyrosinase inhibition activity was caffeic acid 24.1 + 6.2 and ferulic acid >30 µM.	Chaiprasongsuk, et al. 2016
Ellagic acid	Anti-collagenase	At 5µM suppressed expression of MMP-1 and at 1-10µM up regulated collagen levels	Bae et al., 2010
Gallic acid	Anti-tyrosinase	At 2.5-100 µM inhibited melanin content with an IC_{50} of 18.3 µM.	Kumar et al., 2013
Gallic acid	Anti-tyrosinase	At 0–400 µM reduces melanin synthesis via down-regulation of MITF.	Su et al., 2013
	Anti-tyrosinase	At 200 µM inhibited tyrosinase activity up to 85% and suppress melanin content in B16 melanoma cells.	Kim, 2007b
N-nicotinoyl tyramine (NNT)	Anti-tyrosinase	Suppressed expression of MITF and tyrosinase in a dose dependent manner.	Kim et al., 2015
Hispolon	Anti-tyrosinase	At < 2 µM inhibited the expression of tyrosinase and MITF up to 58.9-61.7%.	Chen et al., 2014

MMP-1: matrix metalloproteinase-1; MITF: microphthalmia-associated transcription factor

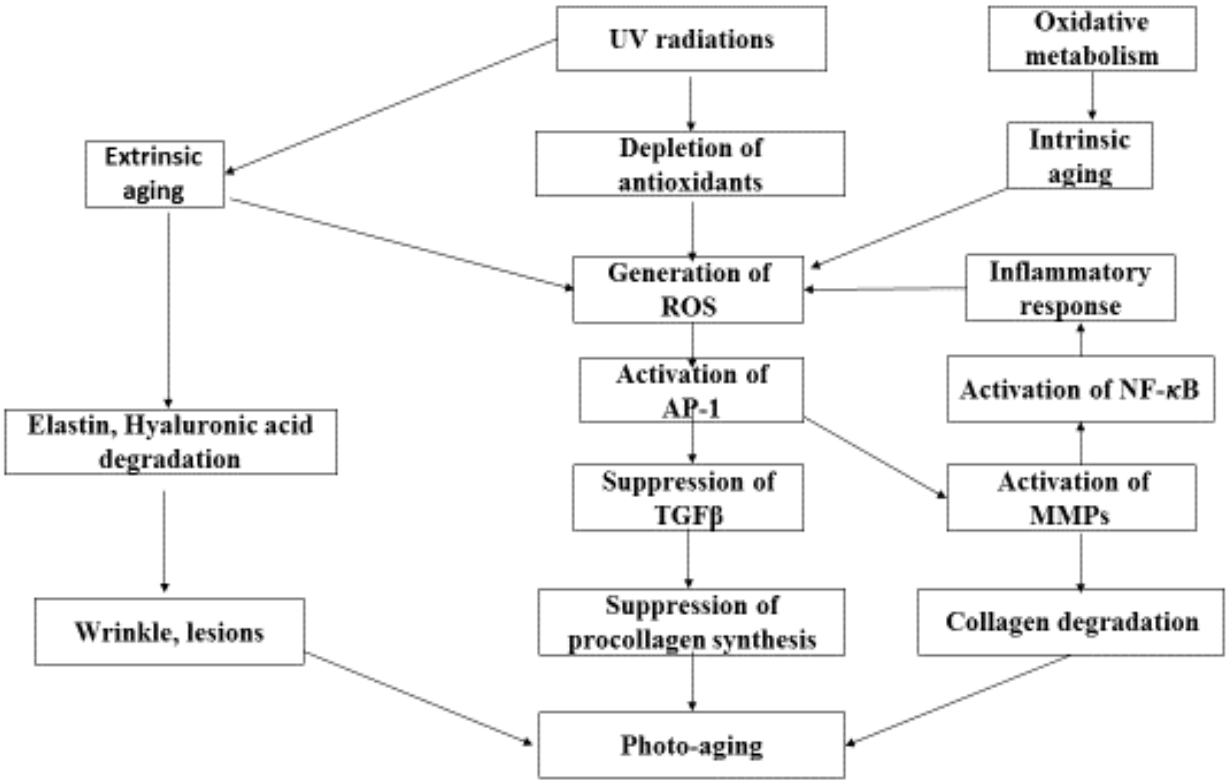

Figure 1. Overview of skin aging process. (UV: ultraviolet radiation; AP-1: activator factor protein; ROS: reactive oxygen species; MMPs: matrix metalloproteinases; NF-κB: nuclear factor κB; TGFβ: transforming growth factor β)

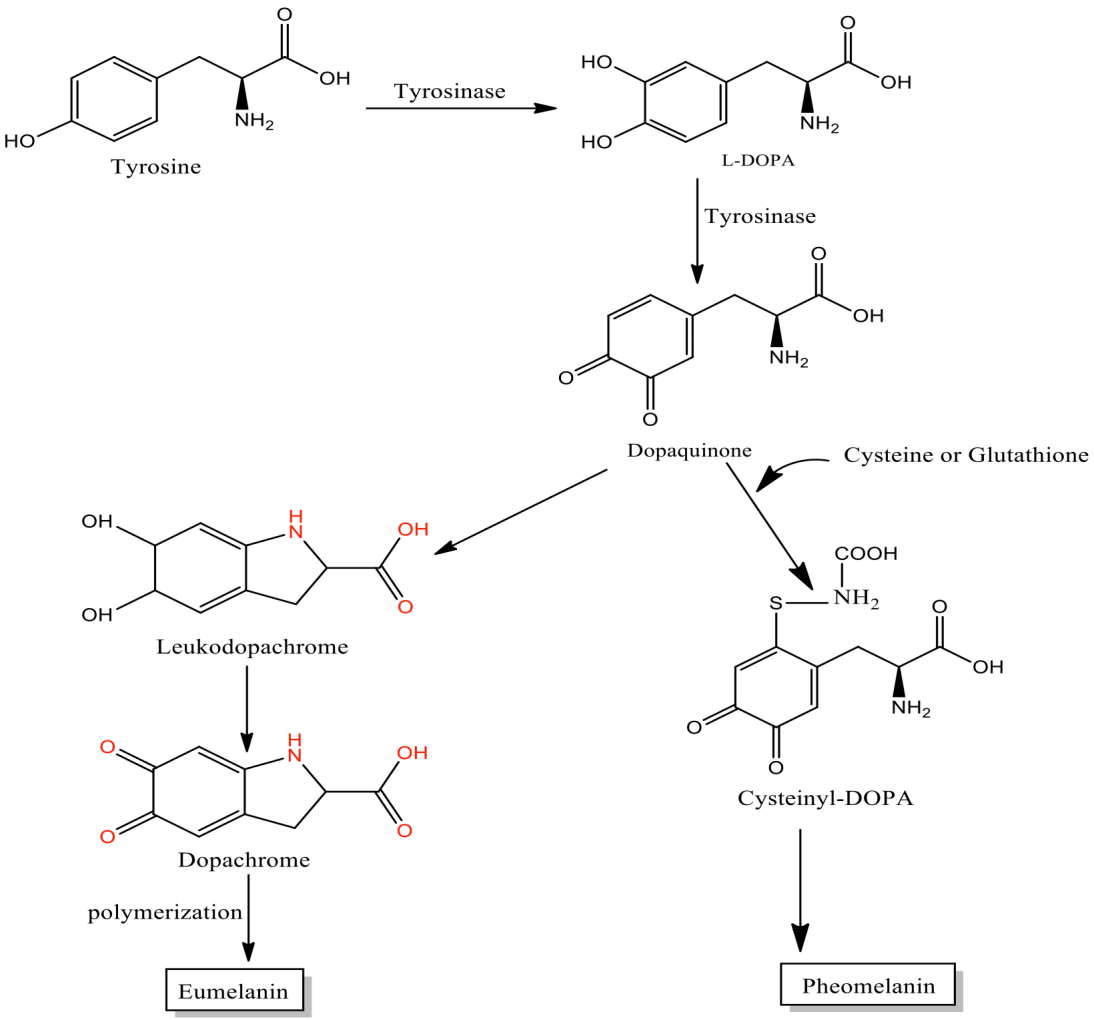

Figure 2. Melanin biosynthesis pathway.

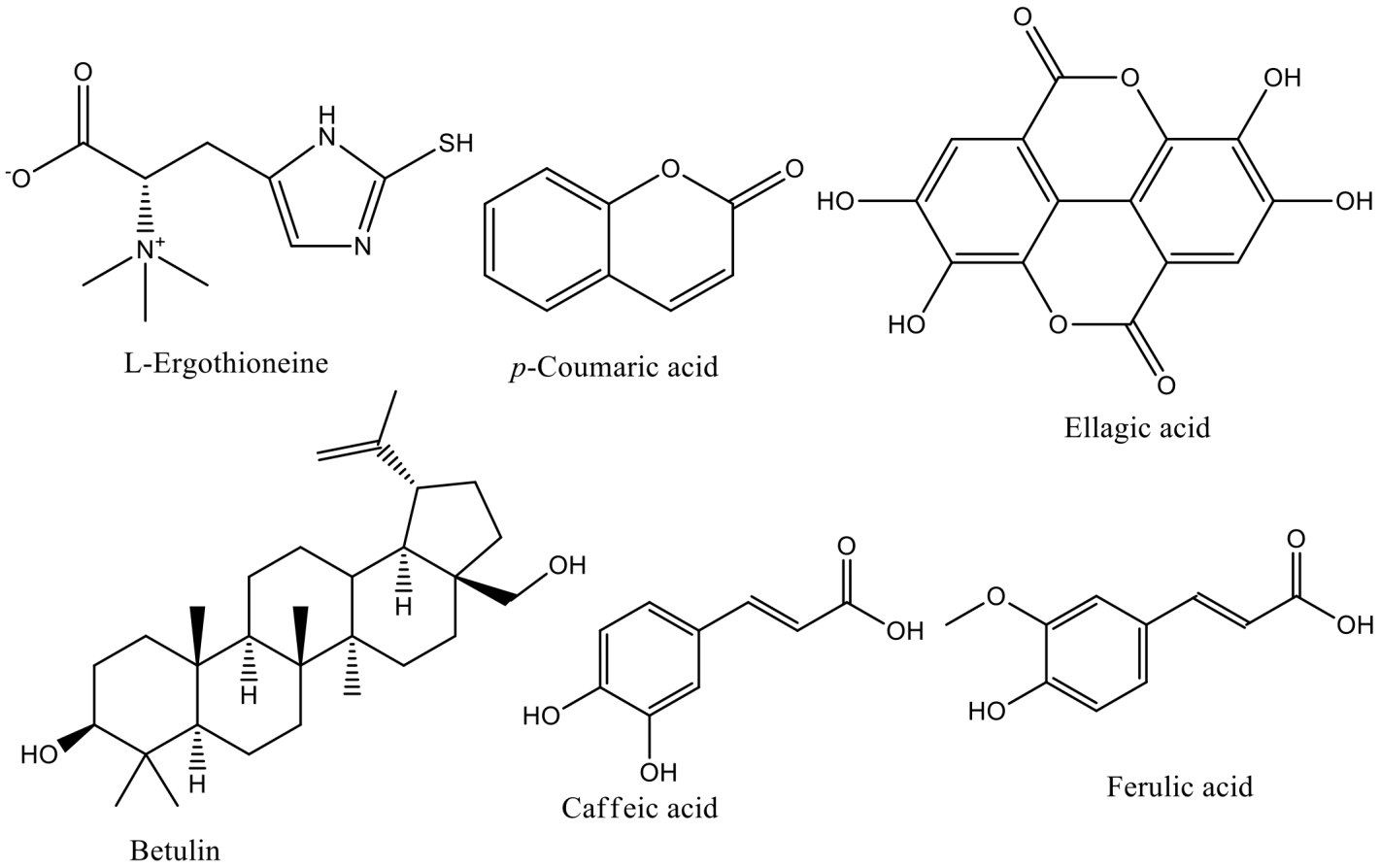

Figure 3. Compounds from mushrooms with reported anti-tyrosinase activity.