

## GANODERMA LUCIDUM AND CORDYCEPS SINENSIS IN ANTI-AGING MEDICINE

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### Abstract

Several studies have shown how to counter the unpleasant effect of the oxidative stress. In fact, as we know biological age depends on the combination of different factors: mental, hormonal, immune and genetic, but also on lifestyle factors. The condition known as "Oxidative Stress" is established when there is an imbalance between the production of oxidizing molecules (ROS) and antioxidant defenses in the body; it is an important pathogenetic mechanism of functional alterations that can lead to the most common degenerative pathologies. Monitoring "Oxidative Stress" is a good indicator of the general state of well-being and health of people and it can be useful to understand the mechanisms of aging. Anti-aging medicine aims to find out ways to slow down the aging process, reducing the likelihood of degenerative diseases and combining in a preventative way, an integrated approach that involves nutrition, nutraceuticals, nutritional substances in the form of supplements, vitamin complexes, phytotherapeutic and homeopathic products, and cosmeceutical products able to correct skin imperfections in an active and rapid manner. Starting from the description of the phenomenon of oxidative stress, the aim of this article is to explain the best that can be done to prevent it by using "miraculous mushrooms": Ganoderma Lucidum and Cordyceps Sinensis used both as a source of integration and in cosmeceuticals of last generation.

**Keywords:** *Oxidative stress, ganoderma lucidum, cordiceps sinensis, antiaging.*

## Introduction

In nature, everything follows a very precise logic determining a perfect balance, above all in biological phenomena it is possible to contrast mechanisms that are often present within the same living organism. Together they permit the perfect functioning in basal conditions and represent their adaptive capacity to vary the conditions of the environment in which it lives. Oxygen and its interactions with the biological systems has certainly placed us in front of one of the most striking paradoxes. On one hand oxygen is essential for vital phenomena but on the other hand it contributes to the formation of so called free radicals. These radicals, in their electronic configuration, have a not coupled electron, that is, an electron that exclusively occupies a specific orbital without sharing it with a second electron with an opposite spin. This condition represents a state of great thermodynamic instability, whereby oxygen tends to reach a stable situation by capturing an electron from nearby structures. It is clear that this behavior will lead to a cascade mechanism because the structures without an electron will be in turn in a situation of instability, so they too will tend to capture electrons from neighboring molecules, leading to an amplification of the phenomenon.

Free radicals cause serious and irreparable damage to proteins (1), DNA (2) and biological membranes by increasing lipid peroxidation and the establishment of pathological processes (3). In physiological conditions the production of oxygen free radicals does not exceed 5% of the oxygen introduced with respiration; these concentrations do not constitute a particular pathogenetic element. Oxidative stress occurs when the production of these substances increase and exceeds the capacity of antioxidant defenses naturally present in our body (4). The cell has different kind of defense mechanisms that protect it from the oxidative damage of radicals and allow their disposal or neutralization (5).

The antioxidant defense system is regularly distributed in the body, both extracellular and intracellularly. As regard plasma, food may supply

both all the proteins like albumin, bilirubin, uric acid, cholesterol, and various exogenous antioxidants like ascorbate, tocopherol, polyphenols.

Within the cell, the antioxidant defense system has its own precise compartment (6). In fact, the antioxidant system includes some enzymes (superoxide dismutase, catalase and peroxidase) and a series of substances taken from outside (vitamins and substances similar to antioxidant activity, such as polyphenols, trace elements, etc.). Some of these agents are liposoluble (e. g. tocopherols) and, entering the biomembrane structure, constitute the first line of defense against the attack of free radicals. Others are water-soluble (e. g. ascorbate) and intervene mainly in the context of the soluble matrix of the cytoplasm and the cellular organelles. All elements aim to protect the balance of antioxidant defenses. In fact, a reduction in antioxidant defenses is essentially caused by an absolute or relative deficiency of antioxidants.

In this work, it has been evaluated the role of innovative natural substances that could significantly contrast oxidative stress. In particular, two mushrooms have been considered: *Ganoderma Lucidum* and *Cordyceps sinensis*. The aim of this review is to demonstrate the mechanism of action of these two mushrooms on anti-aging issues.

## Methods

The oxidative damage caused by these free radicals may be related to ageing and diseases, such as atherosclerosis, diabetes and cancer.

Antioxidant supplements or food containing antioxidants may be used both to reduce oxidative damage, not only providing essential vitamins and minerals, and including important chemo-protective agent capable of protecting against some forms of cancer.

In this work two mushrooms have been considered, known for their antioxidant properties in Chinese medicine: *Ganoderma Lucidum* and *Cordyceps sinensis*.

## **Ganoderma Lucidum**

*Ganoderma Lucidum* (Reishi) is an inedible

mushroom with a bitter taste and woody consistency.

This fungus is constituted of about 90% of water. The remaining 10% consists of 10–40% protein, 2–8% fat, 3–28% carbohydrate, 3–32% fiber, 8–10% ash and some vitamins and minerals, with potassium, calcium, phosphorus, magnesium, selenium, iron, zinc and copper (7; 8).

Approximately 4,000 bioactive compounds have been isolated from the fruiting body of *Ganoderma lucidum*, including about 140 triterpenes / terpenoids, over 200 types of polysaccharides and glycoproteins, nucleotides, cerebrosides, ergosterols, fatty acids, proteins with specific activities, peptides and trace elements. Among the minerals it is important to note the presence of germanium in high quantities, which explains many of its effects on health.

Many scientific studies have been carried out about Reishi, both preclinical and clinical, recognizing its multiple pharmacological effects which are to be attributed to the variety of polysaccharides contained in the body of the fruit and in the spores (6).

Polysaccharides extracted from *Ganoderma lucidum* show a wide range of bioactivity, including anti-inflammatory, hypoglycemic, antiulcer, antitumorigenic and immunostimulant effects (9).

Polysaccharides are normally obtained from the fungus by extraction with hot water followed by precipitation with ethanol or methanol. It is also possible their extraction with water and alkalis. Structural analysis of GL-PS indicate that glucose is their main sugar component (10; 11). However, GL-PSs are heteropolymers and may also contain xylose, mannose, galactose and fucose in different conformations, including 1–3, 1–4 and 1-6-linked  $\beta$  and  $\alpha$ -D (or L)-substitutions (12; 13).

It seems that the characteristics of branched conformation and solubility influence the anticancer properties of these polysaccharides (14).

Terpenes and in particular triterpenes have also

been extracted from *G. lucidum*. They are based on lanostan, which is a metabolite of lanosterol, whose biosynthesis is based on squalene cycling (15).

The first triterpenes isolated from *G. lucidum* are the ganoderic acids A and B, which have been identified by Kubota et al. (16; 17).

Since then, more than 100 triterpenes have been reported in *G. lucidum* with known chemical compositions and molecular configurations. Among these, over 50 have been exclusively found in this mushroom. Majority are ganoderic and lucidenic acids, but other triterpenes have also been identified as ganoderal, ganoderiols and ganodermic acids (18; 19; 20). The analysis of the cultivated fruiting bodies of the *Ganoderma lucidum* revealed the presence of phosphorus, silica, sulfur, potassium, calcium and magnesium. Although in smaller quantities other elements have also been determined such as iron, sodium, zinc, copper, manganese and strontium (21).

*G. lucidum* can also contain up to 72  $\mu\text{g} / \text{g}$  dry weight of selenium (22) and can biotransform 20–30% of the inorganic selenium present in the growth substrate in selenium-containing proteins (22).

Other compounds that have been isolated from *G. lucidum* include enzymes such as metalloproteases, which delay clotting time; ergosterol (provitamin D<sub>2</sub>); nucleosides; and nucleotides such as adenosine and guanosine (23). Kim and Nho (24) also described the isolation and physicochemical properties of a highly specific and effective reversible inhibitor of  $\alpha$ -glucosidase, SKG-3, from the bodies of the fruits of *G. lucidum*. Furthermore, spores of *G. lucidum* have been reported to contain a mixture of several long-chain fatty acids that may contribute to the fungus's anti-tumor activity (25).

### **Cordiceps Sinensis**

Similarly, *Cordiceps sinensis* also known as "caterpillar fungus" or "Dong Chong Xia Cao" is a rare and expensive mushroom which was fortunately possible to cultivate.

In oriental tradition it is the mushroom of power, it gives vigor, strength and willpower. *Cordyceps* helps regenerate the body after debilitating

diseases, bringing energy to the body and mind.

Cordyceps contains a great variability of biologically active substances, considered important from a nutritional point of view; it contains all essential amino acids, vitamins E, K, B1, B2 and B12, mono-, di- and oligosaccharides, polysaccharides, proteins, sterols, nucleosides and nucleoside analogues, macro and microelements (K, Na, Ca, Mg, Fe, Cu, Mn, Zn, Pi, Se, Al, Si, Ni, Sr, Ti, Cr, Ga, V and Zr).

Among the most powerful bioactive components there are the analogous of nucleosides, absent in other natural remedies: cordicepine (3'-deoxyadenosine), cordicepic acid, 2'-deoxyadenosine and other analogues of deoxygenated nucleotides (uridine, deoxyuridine, adenosine, dideoxiadenosine).

Then there are polysaccharides, cyclo-furans, beta-glucans, beta-mannans. From the anamorphic form (*Tolypocladium inflatum*) of a species of *Cordyceps* (*Cordyceps subsessilis*), cyclosporine was isolated. This is an immunosuppressive substance that allowed post-transplant therapy aimed at avoiding rejection.

A number of sterols have also been identified in cordyceps: ergosterol, beta-3 ergosterol, ergosterol peroxide, 3-sitosterol, daucosterol, campesterol and others.

As well as the *Ganoderma succidum*, also the *Cordiceps sinensis* has multiple pharmacological properties. In 2015 the Pharmacopoeia Commission of the People's Republic of China recognized it for the treatment of chronic fatigue, cough, asthenia, dysfunction and renal failure. It has been investigated about *Cordyceps* antioxidant activity and its role in antiaging, anticancer, anti-inflammatory, anti-atherosclerosis and immunomodulatory activity (26).

Studies have shown that both the extract in water (27, 28, 29) and in ethanol (30, 31) of *Cordyceps* showed a significant antioxidant activity *in vitro*. However, the water extract showed a stronger inhibitory effect on superoxide anions and on hydroxyl radicals compared to ethanol extract (32).

Many active ingredients, such as cordycepin, polysaccharides and ergosterol, have been isolated from various *Cordyceps* species and represent a wide range of bioactivity. Nucleosides are one of the main ingredients in *Cordyceps*. More than 10 nucleosides and their related components (adenine, adenosine, cytidine, cytosine, guanine, guanosine, uracil, uridine, hypoxanthine, inosine, thymine, thymidine, 2'-desoxyuridine, 2'-deoxyadenine, cordycepin, N6-methyladenosine and 6-hydroxyethyladenosine) were isolated and / or identified in cordyceps (33).

Adenosine A1, A2A, A2B and A3 receptors are distributed in the brain, lungs, heart, liver, and kidneys and they are involved in mechanisms of the central nervous system (CNS) such as sleep, immunological response, respiratory regulation, cardiovascular function and hepatic and renal activity (34).

It is emphasized that the pharmacological effects of *Cordyceps* well combines with the distribution and physiological roles of adenosine receptors, including anticancer, antiaging, antithrombosis, anti-arrhythmias and antihypertension, immunomodulatory activity; and protective effects on kidneys, liver and lungs (34).

Cordycepin was isolated from *C. militaris* in culture in 1950 (35), and it was identified as 3'-deoxyadenosine in 1964 (36). It can be found mainly in cultivated *C. Militaris* (37). Cordycepin has shown antitumor, immunomodulatory and antioxidant properties. In particularly one study confirmed the cytotoxic effect on cancer cells of the cordycepin. Both in natural cordycepin *sinensis* and in cultivated *c.*, ten free fatty acids (FFA), called lauric acid, myristic acid, pentadecanoic acid, palmitoleic acid, palmitic acid, linoleic acid, oleic acid, stearic acid, docosanoic acid and lignoceric acid, have been found.

Natural *Cordyceps* contains more palmitic acid and oleic acid than cultivated (38).

FFAs are not only essential nutritional compounds but also modulators of many cellular functions through their receptors. FFA receptors are G protein-coupled receptors, including G (GPR) 40, GPR41, GPR43, GPR120 and GPR84 (39, 40) protein receptors. Activation of FFA receptors has

numerous physiological effects; it is therefore assumed that they are new therapeutic targets for diabetes, dyslipidemia and immunomodulation, in particular type 2 diabetes. Pentadecanoic acid (C15) and palmitic acid (C16) are the most powerful FFAs on GPR40 and can activate the GPR40 receptor and stimulate the release of calcium (41). This in turn triggers the release of insulin from pancreatic  $\beta$  cells, thus producing a hypoglycemic effect.

Recently, a particular interest on the potential of Cordyceps in slowing the growth of tumors is underlined. In fact, researchers believe that fungi can exert antitumor effects in different ways. Tests in vitro has been shown that *C.* is able to inhibit the growth of many types of human cancer cells, including lung, colon, skin and liver tumors (42, 43, 44, 45).

Studies conducted with mice have also shown that Cordyceps has antitumor effects on lymphoma, melanoma and lung cancer (45, 46, 47).

Cordyceps can also have benefits on the side effects associated with many forms of cancer therapy. One of these side effects is leukopenia. One study tested the effects of Cordyceps on mice that developed leukopenia after radiation and treatments with Taxol, a common chemotherapy drug (48). However, it is important to note that these studies have been conducted on animals and test tubes, not on humans. Some components of the polysaccharide and cordycepin (3'-deoxyadenosine) have been isolated from *C. sinensis* and *C. militaris*, which acted as potent anticancer components. In the future also humans could use these miraculous mushrooms to contrast the negative effects of the chemotherapy drugs.

## Results

Oxidative stress induced by reactive oxygen species (ROS) plays an important role in the process of human skin aging (49; 50). The skin is an interface between the body and the environment and it is constantly exposed to atmospheric oxygen, ultraviolet (UV) irradiation,

pollutants and xenobiotics.

Moreover, excessive alcohol consumption, poor nutrition, physical inactivity and stress can contribute to oxidative skin damage (51; 52). Endogenous defense systems against ROS are often insufficient to contrast oxidative processes in mature skin. ROS that are not neutralized can affect biomolecules and lead to cellular dysfunction or death and accelerated aging (53).

ROS can also induce MMP overexpression, which increases collagen fragmentation and can influence TGF- $\beta$  regulation (54).

ROS can also increase the activity of elastase, triggering wrinkle formation due to elastin flaking; as well, it can cause degradation of collagen fibrils in ECM (53).

It can also be a primary cause for hyperpigmentation or even carcinogenic processes in the skin (55).

As described, both *Ganoderma lucidum* and *Cordyceps sinensis* are medicinal mushrooms with a great variety of bioactive components, having both nutraceutical and pharmacological benefits (56). For these reasons they have been useful for topical applications in the last generation of cosmeceuticals (57; 58; 59; 60).

Modern trends in the cosmetic sector give priority to ingredients or extracts from natural sources with non-toxic effects and with the ability to delay the aging process (58; 59; 60), like, for example, the use of Aloe Vera compounds to protect the balance of antioxidant defenses in the body.

And, if we think that the aging is an intrinsic, natural mechanism that affects not only the skin but also other organs of the body due to changes in hormonal secretion that occur with age, we may understand why these natural compounds are so important. In fact collagen, dryness, deterioration of elastic fiber networks and development of sagging skin and wrinkles (61) may lead to the degradation of the skin.

The extrinsic mechanism derives from exposure to external factors, mainly solar radiation, often

known as photo-aging. Reactive oxygen species (ROS), deriving from oxidative cellular metabolism, cause damage to cellular components such as cell walls, lipid membranes, mitochondria and DNA, playing a crucial role in both processes. It induces the protein-1 activator (AP-1), a transcription factor that promotes the breakdown of collagen by regulating enzymatic matrix metalloproteinases (MMPs). The overexpression of matrix metalloproteinases (MMP-1, MMP-3 and MMP-9) leads to high levels of degraded collagen (62). Furthermore, UV radiation causes the downregulation of the transforming growth factor  $\beta$  (TGF- $\beta$ ), a cytokine that promotes the production of pro-collagen causing a reduced synthesis of collagen (Figure 1). Although elastin and collagen are the main components of the extracellular matrix, it also contains hyaluronic acid, a key molecule that is responsible for hydrating the skin and protecting it from oxidative stress (61).

Therefore, inhibitors of the enzyme elastase, hyaluronidase, tyrosinase and MMP-1 can be potential cosmetic ingredients in the treatment of skin aging, thus restoring the elasticity of the skin, increasing the moisture content, stimulating collagen synthesis and the skin lightening effect.

Natural phenolic compounds have been reported to possess anti-ROS properties, making them attractive candidates for the production of anti-aging creams or lotions in the cosmetic industry (63).

We have reported the wide range of bioactive metabolites such as polyphenols, terpenoids, polysaccharides, lectins, steroids, glycoproteins and various lipid components, extracts of fungi, as well as their secondary metabolites, to show how important are their biological functions as antioxidants, anticancer, antimicrobial, anti-inflammatory, immunomodulatory, antiatherogenic and hypoglycemic agents (64; 65; 66; 67).

In the following paragraphs are reported results of different studies on anti-tyrosinase, anti-collagenase, anti-elastase and anti-hyaluronidase activities of mushrooms extracts.

### Anti-tyrosinase activity

Melanin is a black pigment synthesized by tyrosine from epidermal melanocytes. It determines hair and skin color. Tyrosinase (EC 1.14.18.1), a multifunctional oxidase containing copper, is considered the key enzyme that allows melanogenesis in melanocytes.

This key enzyme catalyzes both the hydroxylation of L-tyrosine and the oxidation of L-3,4-dihydroxyphenylalanine (L-DOPA) to-quinone (dopaquinone) (68). To treat hyperpigmentation conditions, different tyrosinase inhibitors have been used.

In the cosmetic industry, the bioactive compounds available for skin bleaching include hydroquinone (HQ) (69), retinol (70), azelaic acid (71), kojic acid (72), vitamin C (73), arbutin (74) and other botanical products. HQ, the most popular depigmenting agent, inhibits the conversion of melanin DOPA by inhibiting the activity of tyrosinase (75). However, the cytotoxic and mutagenic effects of HQ on melanocytes and mammalian cells have been highlighted in several studies (74, 76). For this reason, the use of HQ in cosmetics has been forbidden in many countries due to health concerns.

Alternative agents such as kojic acid and arbutin have been developed, but their potential use in cosmetic products seems to be limited due to their adverse effects and poor capacity (77).

Various plants like also Aloe Vera have been the main source of all cosmetics before the availability of synthesized substances with similar properties.

The extracts of *Ganoderma lucidum* have been used as a raw material for their beneficial properties in the manufacture of cosmetic products, an interesting and innovative approach for the cosmetic industry. The name *Ganoderma* itself derives from the Greek *ganos* (meaning "brightness" and "shine") and *derma* (meaning "skin"). A large number of whitening face masks available on market contain extracts of *Ganoderma*. This is because *G.* extract has low cytotoxicity and a strong bleaching effect (78). *Ganodermanondiol* significantly inhibits the activity of tyrosinase, the expression of proteins related to tyrosinase and the

expression of the transcription factor associated with microphthalmia (MITF) in melanomacells B16F10. These results suggest that *G. lucidum* ganodermanondiol may be a potential candidate for development as an anti-pigmentation agent (79).

### Anti-Hyaluronosidase activity

It's the aging to determine the deterioration of the skin because the skin's extracellular matrix provides structural and mechanical support to the skin and also preserves its integrity (80).

In fact, collagen and elastin are structural proteins necessary for healthy skin but insufficient for a healthy skin matrix. The skin also needs adequate components to support regeneration, proliferation and repair (81). Hyaluronic acid (HA) is a natural glucose polymer that plays an important role as it rejuvenates skin, retains moisture, increases viscosity and reduces the permeability of extracellular fluid (82). HA is uniformly distributed in both prokaryotic and eukaryotic cells. In humans, it is more abundant in the skin, followed by vitreous eye, umbilical cord, synovial fluid, skeletal tissues, heart valves, lung, aorta and erectile tissues of the penis (83). The level of hyaluronic acid present in the skin decreases with age, with consequent loss of moisture and the inability of the skin to repair and rejuvenate itself.

Creams and lotions for the topical application of HA are solutions provided by the cosmetic industry, but face enormous challenges due to their tendency to cause an inflammatory response (84). The inhibition of HA degradation is fundamental to protect the connective tissues of the skin and this is possible if the action of the enzyme hyaluronidase that is able to degrade the extracellular matrix (ECM) is interrupted. Nowadays, researchers have shown that substances extracted from mushroom are capable of carrying out anti-hyaluronidase activity (85).

### Anti-inflammatory activity

Inflammation is a physiological response to the lesion, generally manifested by loss of function and pain, heat, redness and swelling. Overproduction of inflammatory mediators such as interleukins (IL 1 $\beta$ , IL-6, IL-8), tumor necrosis factor (TNF- $\alpha$ ), nuclear factor- $\kappa$ B (NF- $\kappa$ B), intercellular adhesion molecule 1 (ICAM-1), Inducible type cyclooxygenase-2 (COX-2), prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), 5-lipoxygenase (5-LOX) and nitric oxide synthesis can lead to inflammatory diseases and cancer (67).

Various cosmetic studies have reported that mushrooms, as well as their compounds: polysaccharides, terpenes, phenolic compounds, sterols, fatty acids, polysaccharide-protein complexes and other bioactive metabolites have anti-inflammatory abilities based on their ability to reduce the production of inflammation mediators. Regarding this aspect, Taofiq et al. (67) reviewed the anti-inflammatory activity of mushrooms and associated bioactive metabolites responsible for this phenomenon.

The anti-inflammatory mechanism has been attributed to the reduced level of release of inflammatory mediators such as NO and other inflammatory mediators such as interleukins (IL 1 $\beta$ , IL-6, IL-8), TNF- $\alpha$  and PGE<sub>2</sub> from inflammatory cells. NF- $\kappa$ B is a transcription factor that regulates the expression of several cytokines and pro-inflammatory enzymes such as IL-1 $\beta$ , TNF- $\alpha$ , iNOS and COX-2.

Therefore finding natural inhibitors of one or two passages of the NF- $\kappa$ B pathway is crucial in the prevention of inflammation (67).

Atopic dermatitis is a chronic inflammatory disease of the skin which is usually associated with redness, rash and severe itching caused by various environmental and physiological factors (86). This disease has been reported in recent years to affect 10–20% of children and 1-2% of adults. Although the physiological mechanism of the disease is not entirely clear, the overproduction of inflammatory mediators such as IL 1 $\beta$ , IL-6, IL-8, TNF- $\alpha$  of pro-inflammatory cells, such as macrophages, are known to be the main cause (86;87).

### Antimicrobial activity

With regard to the antimicrobial properties of mushroom extracts, a double effect must be kept in mind:

- ✓ the skin is constantly colonized by non-pathogenic micro-organisms such as mould, staphylococcus aureus and streptococcus species, and the distribution of this bacterial flora depends on the age of the individual, on environmental factors (88);
- ✓ the concern of the cosmetic industry in reducing the presence of synthetic ingredients with an antimicrobial and preservation function, and its progressive replacement with natural substances, due to the growing awareness of the negative effects reported for some artificial antimicrobial agents.

In fact, in this industrial field natural bioactive compounds with foreign spectrum of antimicrobial properties are slowly introduced, also justified by their multifunctional properties (89). Alves et al. (67) reviewed the antimicrobial activity of mushroom extracts and their bioactive compounds and reported that both edible mushrooms and inedible mushrooms showed activity against pathogenic microorganisms. Ganoderma has been shown to be the most interesting species both against gram-positive and gram-negative. Phenolic compounds it has been reported that they exhibit antibacterial activity interfering with cell membrane and cell wall of the invading pathogen and consequently carrying at the death of the pathogen (90). Alves et al. (74) revealed that phenolic acids such as 2,4-dihydroxybenzoic, protocatechuic, vanillic and p-coumaric acids showed an antimicrobial potential against Gram-positive and Gram-negative bacteria.

### Anti-collagenase and anti-elastase activity

Collagen is the most important component of the extracellular matrix of the skin responsible for restoring skin elasticity, flexibility and resistance and, as such, the degradation of collagen by UV

rays is responsible for the aging process (85). During the aging process, the components of the extracellular matrix of the skin (collagen, elastin and hyaluronic acid) decline, with consequent loss of strength and flexibility, and subsequently in the formation of wrinkles (91).

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 name just a few (92). MMP-1 is anchored to the membrane, being the main metalloproteinase that degrades collagen. Metalloproteinase (TIMP) tissue inhibitors are natural inhibitors reported to control undesired expression of MMPs and further protect ECM.

Skin aging is generally the result of high ROS generation due to overexposure of UV radiation. These generated ROS stimulate the mitogen-activated protein kinases, which stimulate the factor 1 of the activating protein (AP-1) causing an uncontrolled expression of MMP, responsible for the degradation of collagen and skin wrinkles.

Thereby, several studies were conducted to find natural inhibitors of AP-1 as a cosmeceutical ingredient to inhibit the expression of MMPs (92). So far 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 the literature for the anti-elastase activity of plant extracts (93; 94; 95).

Kim et al. (2014) reported the anti-collagenase and anti-elastase activity of the mycelial extract from *Tricholoma matsutake* (83).

L-ergothioneine (EGT) is a natural sulfur amino acid derived from histidine, which is supplied to mammals mainly from food sources. EGT is usually found in cells and tissues that are constantly exposed to oxidative stress and antioxidant properties have been reported in vitro (96, 97). Scientific studies have demonstrated its ability to neutralize hydroxyl radicals and hypochlorous acid, inhibit the production of oxidants by metal ions (98; 99) and participate in the transport of metal ions and in the regulation of metal enzymes (99).



Although ergotionein cannot be produced in human cells, it is present in some tissues at high levels as it is absorbed through diet (100); in humans it is absorbed by the intestine and concentrated in some tissues by a specific transporter called ETT (SLC22A4 gene), but even today its role in human metabolism is not fully known (101; 102).

Obayashi et al. (103) while studying the ability of EGT to inhibit the expression of the MMP-1 protein in skin fibroblasts has also seen its antiradical effect and its anti-inflammatory potential based on its ability to suppress TNF expression. These results suggest that EGT may be an important ingredient in the development of anti-aging cosmetics.

### Antioxidant activity

As already extensively described, various biological reactions, necessary for the normal functioning of the organism, take place in the body's cells and tissues. These reactions often cause the generation of species called free radicals. These free radicals include ROS, reactive nitrogen species (RNS) and reactive sulfur species (RSS). The body usually is able to balance the production and neutralization of ROS by its intrinsic antioxidant activity (glutathione peroxidase, catalase and superoxide dismutase), but often it can be depleted due to the excessive production of ROS that leads to the so-called oxidative stress (104). The body usually needs endogenous sources to satisfy its antioxidant needs and mushrooms, used as a dietary source, can help overcome this lack because they contain high amounts of bioactive compounds that exhibit antioxidant activity.

Moreover, these are sources of antioxidants such as vitamin C (ascorbic acid), vitamin E (tocopherol),  $\beta$ -carotene, vitamin K, flavonoids, phenolic acids, selenium and zinc tend to maintain an equilibrium to control oxidative stress (104).

Dermal exposure to high UV radiation causes the generation of ROS which usually leads to a combined effect of DNA damage, skin

inflammation, hyperpigmentation, stimulation of the skin fibroblast by expression of the matrix metalloproteinase 1 (MMP-1) responsible for degradation and the decrease in collagen synthesis resulting in the photo-aging effect on the skin (105). The important role of antioxidants in skin health drives the continuous search for compounds of natural origin that can eliminate ROS, inhibit the tyrosinase enzyme and suppress the expression of MMP-1. Ascorbic acid is usually used in skin care products but controversies in its effectiveness have been raised because of its inability to penetrate the skin together with its poor stability in cosmetic formulations. Tocopherol is also an important antioxidant reported to lower the expression of MMP-1 by suppressing AP1 and also inhibiting the enzyme tyrosinase making it an important anti-wrinkle and anti-hyperpigmentation agent (105).

Several publications have reported the antioxidant activity of mushroom extracts mainly as a radical scavenger (DPPH 2,2-diphenyl-1-picrylhydrazyl; ABTS 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid; Elimination of H<sub>2</sub>O<sub>2</sub> activity and O<sub>2</sub>), reduction of potency (ferric FRAP which reduces the antioxidant power) and inhibitors of lipid peroxidation (reactive substances of the thiobarbituric acid TBARS; degradation of the peroxide peroxide and FOX ferrous oxidation-xylenol)(105, 106).

### Conclusion

Aging is a complex and multifactorial process and therefore it has always had a main role in determining the senescence of the cell overlap at different levels: the molecular changes that occur during aging lead to cellular alterations which, in turn, contribute to the senescence of the organ and to the insufficiency of the system to which it belongs.

One of the most accredited theories of aging is the "oxidative" theories. In recent years, considerable progress has been made in the understanding of diseases associated with aging, such as diabetes, cardiovascular and neurodegenerative diseases, and the association

with functional alterations of the mitochondria. Mitochondria play a central role in cell survival. They are essential for the production of energy used in metabolic processes and, at the same time, they are the regulators of cell death by apoptosis. Furthermore, mitochondria are the main source of production of free oxygen radicals (ROS). ROS, a chemical species with an unpaired electron in their outermost orbit, are endowed with high reactivity and chemical instability; they have the ability to react with various molecules with which they come into contact and from which they subtract or to which they give off an electron in an attempt to acquire stability, thus producing other radicals according to reactions that often propagate in a chain. The oxygen free radicals ROS are physiologically produced by cells as a "waste product" of the activity of the mitochondrial electron transport chain.

Their accumulation involves the so-called "oxidative stress", ie the existence of an imbalance between the production of oxygen free radicals (ROS) and the defense activity of antioxidant systems.

Among the causes external to the body, we recall some physical agents (eg ultraviolet radiation), numerous chemical agents (eg hydrocarbons, herbicides, food contaminants, drugs) and certain infectious agents (eg viruses and bacteria).

Among the internal causes of the organism are the exaggerated acceleration of cellular metabolism (which occurs, for example, after an intense and prolonged physical effort, without adequate training) and numerous diseases (eg obesity, diabetes, etc.).

In conditions of good health, our body is able to prevent free radical damage thanks to natural defense systems that are referred to as antioxidants, precisely because they counteract the oxidizing action of free radicals.

Antioxidants, therefore, are agents capable of neutralizing the damaging action of free radicals.

Some incredible research has been done on the benefits of mushrooms.

The study focuses on fungi and their metabolites as important nutraceutical and cosmetic ingredients. These biotechnology engineering doctors have discovered that a variety of mushroom extracts and their bioactive metabolites have shown these promising benefits for the skin:

- ✓ Anti-tyrosinase;
- ✓ Anti-hyaluronidase;
- ✓ Anti-collagenase;
- ✓ Anti-elastase;
- ✓ Antioxidant protection;
- ✓ Antimicrobial;
- ✓ Anti-inflammatory;
- ✓ Anti-aging.

In the fight against oxidative stress, the mushrooms of "immortality" according to Chinese medicine, and in particular *Ganoderma Lucidum* and *Cordiceps Sinensis* can certainly be of primary importance and can be used for their known anti-aging properties with a combined action: from inside and outside. From the inside in the form of nutraceuticals and from the outside in cosmeceutical preparations.

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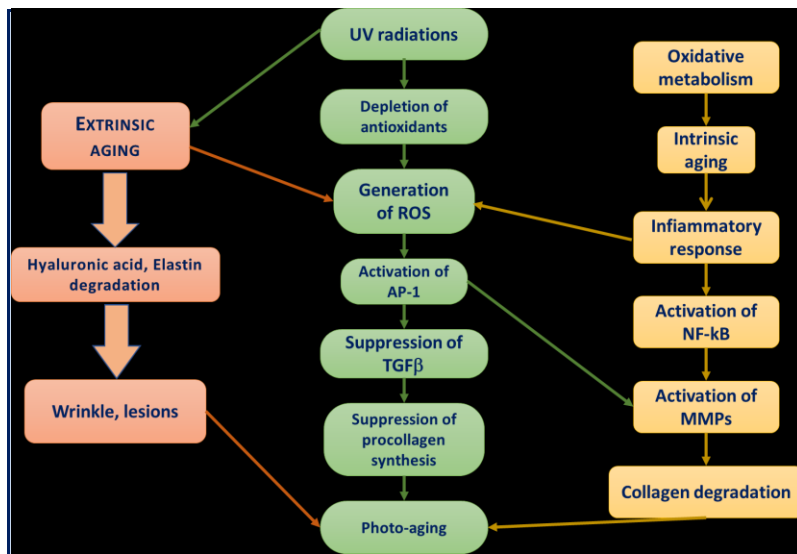


Figure 1. Skin aging process (UV: ultraviolet radiation; AP-1: activator factor protein; ROS: reactive oxygen species; MMP: matrix metalloproteinase; NF-kB: nuclear factor kB; TGF: transformation of the growth factor).