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The Benefit of Copper oxide Skin

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Abstract

Copper is essential to the creation and regeneration of the skin. In the recent decade, copper has been used in consumer and medical device products because of two fundamental qualities. Copper is an essential mineral for angiogenesis, skin formation and expression, and extracellular skin protein stability are just a few of the physiological and metabolic processes. On the other hand, copper is a potent biocide. Copper oxide is vital for a variety of physiological functions in the skin. Copper increases collagen, integrin, and fibronectin formation in the skin. Along with a rise in wrinkles and drooping skin on the face, there is a significant loss of skin elasticity and shrinking. Skin ageing symptoms include wrinkles, loss of suppleness, laxity, and a rough-textured appearance. It is frequently induced by sun exposure, although it can also be caused by pollution and smoking. Ageing is characterised by gradual changes in the majority of physiological systems. Thus, copper is required to develop and regenerate various skin processes, including skin ageing, skin development, and wound healing. Copper is considered safe for humans, as indicated by the widespread use of copper intrauterine devices and over-the-counter wound care medications containing copper. Copper has considerable biocidal properties and has been used as a biocide by numerous civilisations. As a result, it is not unexpected that copper and copper compounds have been utilised to cure skin illnesses and other ailments.

Keywords: Copper oxide; Skin aging; Free radical; Cu/Zn Superoxide Dismutase (SOD)

Introduction:

Copper is required for a variety of physiological processes occurring in the skin. Fibroblasts and massive, dynamic extracellular matrix (ECM) structures make up the majority of the skin's dermal layer (1, 2). These ECM structures, primarily composed of collagens I and III, elastin and fibrillin fibres, and glycosaminoglycan-rich proteoglycans, interact strongly, imparting strength, extensibility, and elasticity to the skin (3). As humans age, the amount and size of fibroblasts in the dermis diminishes, as does the amount of ECM produced by the skin's remaining fibroblasts (3). This results in structural and cosmetic changes to the skin, including a significant loss of skin elasticity and recoil, an increase in the look of wrinkles and sagging skin on the face, particularly around the eyes (4, 5). Reduced skin elasticity, wrinkles, and sagging can be caused by external factors such as UV radiation, which causes sunspots and uneven skin tone (3, 6). Copper is a critical mineral that has a role in a variety of physiological processes in humans (7). Copper boosts collagen, integrin, and fibronectin formation in the skin (7). Copper induces the expression of lysyl oxidase, metalloproteinases, glycosaminoglycans, and small proteoglycans involved in matrix remodelling, cell proliferation, and re-epithelization (8). Additionally, copper helps stabilize the ECM after it is formed (9, 10). This review aims to identify the roles of copper oxide and the mechanism by which it benefits the skin.

Skin aging:

The skin is the human body's biggest organ, covering the whole surface. Its primary function is to separate and shield the body's internal organs from the external environment and receive sensory stimuli, assist in temperature regulation, and excrete undesirable substances (11, 12). Over time, the changes of the skin are much more closely related to the skin's interaction with its environment than they are to genetic predisposition. Thus, skin ageing can be attributed to one's personal lifestyle in humans (13). Smoking, excessive exposure to sun radiation, and low air humidity, for example, are all known to contribute to the appearance of wrinkles (14). Additionally, a poor diet, excessive alcohol consumption, and certain diseases such as diabetes mellitus significantly accelerate skin ageing. People must arm themselves to prevent two different mechanisms that increase the aging of the skin (15). intrinsic and environmental, when facing the ravages of time.In the first around the age of 30, chronological signs of aging begin to appear, when cell renewal slows and hormone production changes, visible on the skin (16, 17). When exposed to external elements, particularly UV rays that are not protected, extrinsic agents accelerate the rate of normal skin ageing by forming free radicals that damage the skin's structural components, destroying collagen and elastin fibres while dehydrating the skin, resulting in symptoms such as dyschromia, changes in skin relief, and wrinkles among other things (18-20). The observed causal connection between oxidative stress and numerous degenerative processes has spurred interest in the efficiency of various antioxidants for topical use (21). Antioxidants are substances that prevent or inhibit the formation of free radicals (21). Consumer acceptability of a cosmetic product is mostly determined by its fragrance and color (21, 22). Thus, protection against lipid oxidation is critical, since many products have a short shelf life due to oxidation of the excipients, which can alter their fragrance and colour (23). Antioxidants can also be considered critical for formulation stability (24). The most prevalent form of oxidation is lipid oxidation, which occurs in fats and oils (24, 25). Thus, using catalysts, fats and oils are converted to free radicals, which are then transformed into peroxides and hydroperoxides by the action of oxygen, resulting in the formation of breakdown products (rancidity) (23, 26, 27). The skin covers the entire body's surface and is exposed to a range of environmental insults on a regular basis, including pathogens, injuries, and ultraviolet radiation (UV) (28). Temperature regulation, defense, sensing, and vitamin D generation are all important functions (13, 29). The skin's structural organization is one of its many defense systems against environmental insults: both the dermis and epidermis include enzymes, cells, and other chemicals that contribute considerably to protection (30). Various enzyme families especially contribute to skin defense by scavenging free radicals. molecules derived from pathogens, injuries, and UV radiation. Only enzymes like catalase, superoxide dismutase and peroxidase have antioxidant activity, and a few supporting enzymes can neutralise the harmful molecules called free radicals (31).

Lipid oxidation, interestingly enough, cannot be completely avoided or stopped (24, 32). It can be reduced to significantly improve the final product's stability and valuable life. Thus, while some antioxidants are deployed to defend the product itself, others shield the skin, scalp, and mucous membranes from the application site (33).

Free radical: skin damage:

The outer orbit of a free radical contains a single unpaired electron (34). Chemical reactions with other molecules release the energy produced by their unstable structure like as proteins, lipids, and carbohydrates, as well as membrane-specific membrane compounds and nucleic acids (34).The amino acids in proteins are altered by oxygen radicals and other reactive species, Enzymatic proteins often endure structural or functional changes as a result of this (22). Reactive oxygen species (ROS), also known as oxygen-derived products, are produced in endoplasmic reticulum, mitochondria, and peroxisomes during normal aerobic respiration and are involved in various biochemical activities that control cell growth proliferation, apoptosis, and autophagy, as well as other processes (35). It is a keratinocyte cytoplasmic protein called Kelch-like ECH-associated protein 1 (Keap1) (36). It is frequently associated to the nuclear factor erythroid 2-related factor 2 (Nrf2), which, according to Dinkova-Kostova et al, performs a role in the production of erythroid 2 breaks away from Keap1

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and it eventually goes to the nucleus and functions as a transcription factor, causing antioxidant enzymes such as copper/zinc SOD (Cu/Zn SOD) to be produced (37, 38). Additionally, autocatalytic processes can be triggered by the production of ROS. which generate additional free radicals, propagating the damage chain (39). These are intrinsically unstable and will typically degrade spontaneously (40). For instance, the superoxide anion is unstable and degrades on its own into oxygen and hydrogen peroxide in the presence of water (40). Numerous other exogenous factors can induce ROS production, such as pollutants and ultraviolet light (41). Excessive ROS production can lead to premature skin aging and the development of skin cancer (11). The human skin is constantly exposed to three types of ultraviolet radiation (13, 42). On the other hand, Cornification occurs in the epidermis via the self-protecting cells of keratinocytes (43). Furthermore, proline -rich proteins, also known as stress-inducible proteins, are tiny proteins with a lot of proline, expressed in the thickened cell envelope to protect keratinocytes from ROS (42).

Cu/Zn Superoxide Dismutase (SOD):

SOD is a highly conserved enzyme that is extensively produced in aerobic species' cytoplasm and is essential for cellular defense against oxidative stress (44). It belongs to a group of enzymes that catalyze superoxide radical dismutation (25). These radicals are created as a result of a variety of biological processes, including normal respiration products and immune cell oxidative bursts (45). SOD comes in multiple forms (Mn, Zn, Cu, Fe) and is capable of inactivating both intra- and extracellular superoxides (32). Copper and zinc SOD (SOD1), which is found in the nucleus, cytoplasm, peroxisomal and lysosomal compartments, and mitochondrial intermembrane space, has been studied in hepatocytes (32). Manganese SOD (SOD2) is found primarily in the mitochondrial matrix (46). The third, Cu/Zn extracellular SOD (SOD3) is a copper and zinc-containing extracellular SOD that is released. Anions of the superoxide radical are highly unstable molecules that are frequently generated during aerobic metabolism (47). It has been suggested that oxidative stress, which is caused by superoxide, is a factor in the beginning of a variety of diseases, including neurological illnesses, cancer, diabetes, premature aging, and dermatitis, due to the uncontrolled generation of superoxide and its reaction products (48). After UV exposure, the skin produces more ROS. Antioxidant enzymes can be released by epithelial cells and thymus-derived fibroblasts, particularly during times of stress (48). Mn SOD and cytosolic Cu/Zn SOD are found in all mammalian cells (48). Still, the extracellular only the high-molecular-weight isoform of SOD appears to be expressed. in a subpopulation of cells (49). There was a study found that an increase in extracellular SOD caused by ROS may act as a cancer suppressor, which supports Marklund's discovery of extracellular SOD's location both in fluid and in the extracellular matrix of tissues. In connective tissue, immunohistochemistry revealed the presence of EC SOD (50). The thymus, stomach, and skeletal muscle, on the other hand, lack it. Although extracellular SOD has been shown to protect the extracellular space and endothelial cell surface, its activity is relatively low (31, 51). These findings imply that the enzyme can act as paracrine and distant cells. SOD activity generates hydrogen peroxide, which inhibits the enzyme. This case, the superoxide radical is not neutralized and inhibits subsequent enzymes (for example, catalase) (48, 52).

Cu/Zn SOD is a homodimeric protein with a molecular weight of 15.9 kDa (32). Hydrophobic contacts stabilize the dimerization by increasing the stability of the solvent while lowering its accessibility (49). Each monomer is formed by two metal ions, a copper ion and a zinc ion, which perform structural or catalytic functions when combined. Cu/Zn SOD was initially detected in the cytosol, the outer membrane, and/or the intramembranous space, where superoxide radicals are formed between mitochondria and peroxisomes. Cu/Zn SOD seems to be a peroxisome-localized enzyme in fibroblasts (53). Cu/Zn SOD has recently been shown to have a significant novel function in yeast and humans (53). High levels of H_2O_2 promote the nuclear translocation of Cu/Zn SOD in response to oxidative stress, and the enzyme acts as a transcription factor, regulating the expression of genes involved in oxidative resistance and repair (44, 54). Additionally, it was demonstrated that only a small amount of Cu/Zn SOD scavenges superoxides in yeast, whereas the majority of Cu/Zn SOD is involved in peroxide signalling (53). On vertebrate cells, including human ones, few similar studies have been conducted, so it

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would be helpful if the results in Saccharomyces cerevisiae could be replicated. Indeed, 25% of genes associated with human degenerative pathologies are nearly identical to those associated with yeast, allowing for the research of identical antioxidant response genes in eukaryotic species that are substantially simpler (55). In a recent study, researchers used immunocytochemistry to locate Cu/Zn-SOD in human skin under various conditions (22). In some studies, in the skin, SOD activity remains constant due to natural ageing and photoaging (56). The activity increases in the epidermis and decreases significantly in the dermis (57). Antioxidant enzyme activity appears to vary between cell types; for example, fibroblasts have higher catalase levels, glutathione peroxidase, and superoxide dismutase than keratinocytes (58). Environmental direct contact-induced ROS production in the skin can result in premature ageing, skin diseases, and cancer (58, 59). The amount of exposure and the type of skin determine the rate of photoaging. People who live in hot climates, for example, are more exposed to light and thus more susceptible to photoaging (58). However, another study reported that SOD in the stratum corneum during the seasonal activity appears to be constant (58, 60, 61).

Copper oxide to improve skin characteristic:

Copper is a critical trace element that is involved in a variety of physiological and metabolic processes functions in humans, including skin formation and wound repair (62). Copper is required for a variety of skin development and regeneration processes (62). It has been demonstrated that copper is absorbed through intact skin. Copper should be included in a daily allowance of 0.9 mg (63). Copper is safe for humans, as evidenced that copper intrauterine devices have been used widely for a long time and copper-containing over-the-counter wound healing products (64). Dermal contact with copper poses an extremely low risk of adverse reactions (64). Copper is one of the nine minerals, humans require some vitamins, which are recognized as essential as it is involved in a variety of normal physiological mechanisms that occur in almost every human tissue, as well as the skin (64). Copper is found in approximately 110 mg per kilogram of body weight in the bones and muscles, 15% in the skin, 15% in the bone marrow, 10% in the liver, and 8% in the brain (64). Uptake of copper, distribution of copper to various organs, excretion of excess copper, and metabolism are all highly coordinated events. Copper is naturally occurring in various foods, including vegetables, grains, and meat, and for adults, a daily copper intake of 1 mg is suggested (62, 64). Because copper increases angiogenesis, it is necessary for wound healing and stabilises the skin's ECM (62). Copper stimulates the proliferation of dermal fibroblasts; b) increases the production of collagen (types I, II, and V) and elastin fibre components (elastin, fibrillins) by fibroblasts, presumably via the induction of TGF stimulates HSp-47, which is required for collagen fibril formation; d) acts as a cofactor for LOX, which is required According to the above, Cu-GHK, a copper-binding peptide detected in people serum and cerebral fluid stimulates collagen and elastin protein production (62). Additionally, Cu-GHK increases integrin expression and enables epidermal basal stem cells to proliferate and survive (9, 64). As a result, it has been discovered that this peptide promotes wound healing (62). Additionally, patients with a deficiency in copper metabolism (Menkes patients) exhibit decreased LOX activity and collagen formation (62, 64).

Copper as a biocidal properties:

Copper also has potent biocidal properties and has been used as a biocide by numerous civilizations for centuries (65). Both gram-positive and gram-negative bacteria, including antibiotic-resistant bacteria, as well as bacterial spores, fungi, and viruses, are difficult to kill when exposed to high copper concentrations (66). They are sometimes killed within minutes of being exposed to copper or copper compounds (65). As a result, copper biocides have become indispensable, with thousands of tons used annually in agriculture, wood preservation, and antifouling paints worldwide (65). Copper compounds have been incorporated into textiles and solid surfaces in recent years for odour and microbial control, including reducing microbial bioburden in medical institutions (65, 66). Copper is toxic to microorganisms via several distinct mechanisms. These include death from direct contact and harm from copper ions released during the process (66). The damage is nonspecific and may include phospholipids found on the microorganisms' envelopes, microbial envelope or intracellular proteins, and nucleic acid (67). Numerous bacteria

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and fungi, except viruses, deal with excess copper via intra- and extracellular sequestration via cell envelopes and efflux pumps on the membrane. Additionally, tolerance and adaptation occur when necessary genes are upregulated in the presence of copper and when secreted metabolites precipitate copper (68). On the other hand, microorganisms are incapable of dealing with copper overload (69). As a result, when they are exposed to high copper concentrations, they are irreversibly damaged and killed (70). Copper exists in a variety of oxidation states, including metallic copper (CuO), monovalent copper (Cu^{+}), and divalent copper (Cu^{2+}) (71). While Cu^{+} ions are more cytotoxic to bacteria than Cu^{2+} ions, cuprous ions are more cytotoxic to fungi (72). Notably, redox cycling between Cu^{2+} and Cu^{+} can catalyze the formation of short-lived hydroxyl radicals, which may contribute to the combined activity of cuprous and cupric ions being more cytocidal as compared to either oxidation state on its own (72). Under a wide range of environmental conditions, metallic copper emits noticeably more copper ions than Cu_2O and CuO layers. In the oxygen present and the external metallic copper layer oxidizes under ambient conditions to Cu_2O (72). At extremely high temperatures (>200°C), the Cu_2O layer further oxidizes to CuO. Cu_2O is just as impactful at contact killing as metallic copper (72).

UV rays stimulate the production of matrix metalloproteinases (MMPs) in the skin, resulting in collagen degradation (62). The most remarkable effect is seen in photoaging, where increased MMP activity increases hydrogen peroxide accumulation due to decreased dermal catalase (62). Hydrogen peroxide accumulation alters the activity of mitogen-activated protein (MAP) kinases involved in the pro-collagen synthesis, thereby accelerating the ageing process (62). SOD's effect on cellular antioxidant metabolism has been demonstrated in vitro, as has interaction with MMP and the regulation of extracellular matrix destruction that results as a result (73). Later, these findings were confirmed in an in vivo study using a pig model. Clinical studies on radiation-induced fibrosis have revealed some evidence that Cu/Zn SOD may be developed into an anti-fibrotic agent, with its therapeutic effect being attributed to the down-regulation of transforming growth factor-beta 1 (TGF-beta1). Indeed, SOD significantly inhibits TGF-beta1 expression, whereas increased TGF-beta1 expression is associated with fibrotic diseases (73). To maintain a favourable oxidant balance, direct exposure of murine skin to various oxidative stresses necessitates a high antioxidant capacity (73, 74). In both young and ageing skin, enzymes and antioxidant substances measurements revealed that SOD activity was more significant in the epidermis than in the dermis. Histo-densitometry confirmed these findings, revealing a negative connection between cutaneous Cu/Zn SOD and aging in humans and a higher level in males than females. Additionally, exposed skin expressed the enzyme at a higher level than non-exposed skin (74). Interestingly, carbazole has been shown to induce the production of ROS in the human keratinocyte cell line HaCaT (74). Carbazole is an aromatic heterocyclic compound, so named due to its structure containing one or more aromatic rings (74). When carbazole is present in human skin, such as in tattoo ink, extended exposure to sunlight can cause it to break down resulting in downregulation of antioxidant genes (hmox-1, keap-1, nrf-2, and bcl2) in HaCaT cells, as well as an increase in ROS, resulting in apoptotic cell death (75, 76). Experiments in vitro with HaCaT shed light on the physiology of SOD and oxidative stress-related skin diseases (75). Additionally, HaCaT cell lines were used to decipher an unexpected relationship between the NO/NOS system and Cu/Zn SOD (77). NO is thought to increase the expression of Cu/Zn SOD, thereby inhibiting the mechanism of keratinocyte proliferation (77). As a result, SOD defends human keratinocytes against UV damage, collagen and elastic fibre fragmentation, as well as metalloproteinase activation, cause ageing (77). A study published natural antioxidants derived primarily from plants for human skin: vitamin C, vitamin E, green tea, coenzyme Q10, and hydroxytyrosol are antioxidants that have been proved to mitigate the effects of UV radiation (78). A single UV rays exposure in human skin results in a transient decrease in SOD activity; however, chronic UVB irradiation results in an increase in epidermal SOD activity (78). UVB reduces the Cu/Zn SOD level in mouse skin, whereas UVA affects Mn-SOD (23, 78). On the other hand, seasonal variation has no effect on the SOD concentration in exposed or unexposed skin (18, 41, 78).

Conclusion :

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Copper is a necessary mineral for angiogenesis, skin creation and expression, and extracellular skin protein stabilization are just a few of the physiological and metabolic processes that it plays a role in. Additionally, copper possesses potent broad-spectrum biocidal properties. Copper's combination of these two unique characteristics results in it a stunning active ingredient for improving skin health. Thus, it is unsurprising that numerous civilisations have used copper and copper compounds to treat skin diseases and other maladies for more than two millennia. Furthermore, the function of copper, zinc, and superoxide dismutase in human keratinocyte protection cell line HaCaT against UV-B-induced harm may be crucial.

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