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REVIEW

The Pathogenesis of Oxidative Stress-Induced Chloasma and Its Therapeutic Implications

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Abstract: The majority of oral and topical skin-whitening products, as well as chemical peels, are commonly used to treat chloasma, a challenging skin pigmentation disorder. However, the therapeutic efficacy of these treatments often falls short of patients' expectations and is accompanied by notable side effects. Oxidative stress, characterized by an imbalance between oxidation and antioxidation, plays a crucial role in various clinical conditions and leads to oxidative damage, including cellular dysfunction, DNA damage, protein and lipid peroxidation, and even irreversible cell death. Recent research has shown that the onset of chloasma is closely associated with oxidative stress. This review explores the role of oxidative stress in the pathogenesis of chloasma and examines the related signaling pathways and biomarkers. Our findings suggest that antioxidant therapy can enhance the effectiveness of chloasma treatment by inhibiting tyrosinase activity and reducing melanin production. We hope this review will provide a theoretical foundation for future antioxidant-based treatments for chloasma.

Keywords: oxidative stress, chloasma, pathogenesis, antioxidant therapy, review

Introduction

Chloasma is a condition characterized by hyperpigmentation due to increased melanocyte activity, primarily affecting sun-exposed areas such as the neck and face. While it does not directly impact physical health, chloasma can cause significant psychological and social distress.[1,2]

Recent studies have shown that the complex interactions between epidermal melanocytes, keratinocytes, dermal fibroblasts, and vascular endothelial cells contribute to the development of chloasma. The main risk factors include ultraviolet exposure, pregnancy, oral contraceptives, hormonal changes, heredity, inflammatory dermatoses with hyperpigmentation, and the use of photosensitizing medications.[3] Additionally, air pollution is a significant factor influencing melanin production in human skin, which is closely associated with oxidative stress pathways.[4]

The primary goals of chloasma treatment are to inhibit melanin production, suppress hyperactive melanocytes, reduce inflammation, and address other related factors.[5] Treatments related to chloasma include photoprotection, chemical peels, oral and topical whitening agents, and laser therapy.[6] Among the primary medications used to target melanogenesis and hypermelanocytosis are hydroquinone (HQ) and azelaic acid. However, their use is associated with significant side effects, making them less safe options.[7] Consequently, an increasing number of scientists are focusing on oxidative stress to develop novel treatments for chloasma.

Numerous studies have shown a strong association between oxidative stress and the mechanisms underlying chloasma. The pathogenesis of chloasma is closely linked to cellular senescence, which is characterized by oxidative stress, DNA damage, and mitochondrial dysfunction.[8,9] Researchers have tested oxidative stress-related biomarkers and serum melatonin levels in both chloasma patients and healthy controls through clinical observation. The findings showed an imbalance between oxidants and antioxidants in the chloasma group, characterized by increased oxidative stress and decreased serum melatonin. In contrast, serum melatonin levels were low in the healthy control group.[10–13] Furthermore,

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studies have established a positive correlation between the severity of chloasma and oxidative stress-related indicators by assessing Melasma Area and Severity Index (MASI) scores in patients with varying degrees of the condition.[14]

This review aims to explore the potential role of antioxidant therapy in the treatment of chloasma, with a focus on the underlying mechanisms of oxidative stress and its clinical implications. The following sections will discuss the pathophysiology of chloasma, current treatment strategies, and the potential for antioxidant therapies to improve patient outcomes.

Mechanism of Oxidative Stress

Since its initial introduction thirty years ago, the idea of oxidative stress has garnered a lot of interest.[15] Redox homeostasis is an equilibrium state when cells continue to perform their regular physiological tasks,[16] comprising numerous other physiopathological processes, immunological response, antioxidant defense, cell communication, and preservation of cellular function.[17] Redox equilibrium is crucial for maintaining normal cellular structure and function; disruption of this balance leads to the onset of oxidative stress.

Oxidative stress is a process that leads to dysregulated redox balance, which in turn causes inflammation and cellular damage. The release of mitochondrial DNA (mtDNA), which can directly activate the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway, is facilitated by dysfunctional mitochondrial oxidative phosphorylation, which is characterized by increased formation of mitochondrial reactive oxygen species (mtROS) and restricted electron transport.[18] A small amount of electrons leak from Complex I and III of the electron transport chain (ETC), producing superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2), which generate hydroxyl radicals (·OH) via the Fenton reaction, which in turn generates water during mitochondrial respiration. Most electrons pass along the ETC to the end to combine with molecular oxygen. Oxidative stress results from an overload of the antioxidant system or too high amounts of mtROS, which breaks down the integrity of mtDNA and releases it into the cytoplasm.[19]

The mitochondria are the primary source of reactive oxygen species (ROS) production. ROS are a mixture of free radicals and oxygen derivatives that do not function as free radicals during normal cellular metabolism.[20] However, external stimuli like chemicals or UV radiation can also cause the skin to create ROS.[21] ROS are engaged in numerous critical physiological processes, including gene transcription, immunological response, signal transduction, and cell signaling.[22] Normal cells can maintain their oxidative homeostasis in the presence of several antioxidant systems that regulate ROS generation. The skin also needs a little quantity of ROS to strengthen the immune system.[23] On the other hand, oxidative over-oxidation occurs when there is an excess of ROS within the cell and an inadequate level of cellular antioxidant defense. This leads to an imbalance in redox homeostasis and consequent oxidative damage, including DNA damage, cellular dysfunction, and irreversible cellular damage and death.[24] Excess reactive oxygen species ROS cause tyrosinase to be activated and melanin synthesis to rise, upsetting the equilibrium of oxidants and antioxidants in the skin and resulting in chloasma, according to studies.[25,26]

The Value of the Current Oxidative Stress Indicators

An imbalance in the body's redox balance, known as oxidative stress, can cause tissue inflammation, cellular damage, and the emergence of illness. ROS, antioxidant enzyme activity, and other factors are frequently utilized as oxidative stress indicators in scientific and clinical research. The thorough assessment of oxidative stress levels in the body and the guidance of disease prevention and therapy can be achieved by the combined evaluation of various indicators. When these markers are measured together, it is possible to determine the total amount of oxidative stress inside the body, as well as the degree of oxidative damage to cells and tissues. This information may then be used to inform disease prevention and treatment strategies.[27–29]

Superoxide Dismutase (SOD)

An essential antioxidant enzyme present in all living things, including plants, animals, and microbes, is called superoxide dismutase (SOD). Its primary job is to convert superoxide anion into more stable forms of oxygen and hydrogen peroxide, thereby shielding cells from oxidative stress. The human body contains a variety of SOD forms, mostly categorized as iron SOD (Fe SOD), manganese SOD (Mn SOD), and copper-zinc SOD (Cu/Zn SOD).[30] Numerous

factors, such as genetic, environmental, and nutritional factors, affect the expression and activity of superoxide dismutase. Sufficient superoxide dismutase activity is necessary to preserve the intracellular redox balance, lessen the damage caused by oxidative stress, delay the aging process, and fend off disease.

Research has demonstrated that serum SOD activity reacts to the degree of oxidative stress response and is strongly correlated with redox metabolic capacity.[31,32] Research on inflammatory and pigment-altered dermatoses revealed evidence of dysregulated oxidative pathways and increased superoxide dismutase. Serum SOD levels can be evaluated to determine the state of oxidative stress, as it is suggested that variations in SOD levels are among the biochemical changes brought on by oxidative stress.[33,34] In certain animal studies, the expression of antioxidant genes like MnSOD has been used to measure the degree of oxidative stress in experimental mice exposed to UV light.[35] Additionally, patients with chloasma had significantly higher serum levels of SOD according to clinical investigations.[10,14] Nonetheless, giving tomato extract supplements to chloasma patients was able to raise their serum SOD levels, which in turn improved the condition's severity.[36]

Reactive Oxygen Species (ROS)

The primary byproducts of oxidative stress are ROS, which include hydrogen peroxide, hydroxyl radicals, and superoxide anion. The degree of oxidative stress can be inferred indirectly from measuring ROS. One of the first ROS to be formed is superoxide anion, which the intracellular antioxidant system can neutralize and preserve redox equilibrium under normal circumstances. ROS play crucial biological functions in apoptosis, immunological response, cell signaling, and other processes. However, by inducing lipid peroxidation, protein degradation, DNA breakage, and other processes that ultimately result in aberrant cellular activity and even cell death, high levels of superoxide anion can worsen the process of oxidative stress. Consequently, oxidative stress damage can be effectively prevented by managing the production and elimination of superoxide anion.[37]

Melanocyte survival and melanin synthesis are impacted by oxidative stress in chloasma, which is a multifactorial injury to melanocytes. ROS generated during melanogenesis makes melanocytes more vulnerable to oxidative stress.[38] ROS levels in the skin tissues or test mouse cells can be used to measure oxidative stress levels because external stimuli like UV irradiation or melanogenesis can cause excessive ROS generation, which activates Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) and sends it to the nucleus.[39,40] Nevertheless, it has been discovered that certain natural compounds (Maclurin and Hesperidin) may prevent melanogenesis by lowering ROS levels.[41] Furthermore, investigations have shown that ROS-mediated nuclear translocation of microphthalmia-associated transcription factor (MITF), a transcription factor that promotes melanogenesis, may be a mechanism for oxidative stress-induced chloasma.[42]

Malondialdehyde (MDA)

The generation of malondialdehyde (MDA) is typically brought on by oxidative stress or free radical activity-induced lipid peroxidation. Lipid molecules are oxidatively destroyed and lipid peroxidation happens when cells or tissues are under oxidative stress, which results in the production of MDA. As a result, the amount of oxidative damage to cells or tissues can be indicated by the MDA level.

MDA is a potent oxidant that is highly oxidizing. Elevated oxidative stress levels also lead to an increase in MDA synthesis, which may worsen chloasma. Patients with chloasma have been found to have significantly higher serum MDA levels, which are positively correlated with the severity of their condition.[12,14] However, it was found that chloasma could be effectively improved by reducing the expression of MDA when the antioxidant astaxanthin (AST) was given to patients with chloasma. This resulted in a decrease in serum MDA levels and an increase in antioxidant enzyme activity, which significantly ameliorated oxidative stress and immune damage.[43]

Glutathione (GSH), Glutathione Peroxidase (GSH-PX), Glutathione Reductase (GR)

The primary function of glutathione peroxidase is to convert peroxides, including organic and hydrogen peroxide (H_2O_2), into their alcohol and water equivalents. This process stops the peroxides from damaging cellular structures and

membranes. Together, glutathione, glutathione reductase, and glutathione peroxidase comprise a tightly interacting antioxidant system that guards cells from oxidative stress-related damage.[31]

Glutathione levels and glutathione peroxidase activity are two biochemical changes brought on by oxidative stress, and as a result, the status of oxidative stress can be determined by measuring the related blood levels.[33] Clinical observational studies have revealed that the group of patients with chloasma had considerably increased serum glutathione and glutathione peroxidase activity when compared to the healthy controls.[10,14] It has been shown that there is a strong negative association between serum glutathione levels and the severity of chloasma (MASI score), which is consistent with the possibility that there is a direct correlation between the two.[44]

Oxidative Stress and Chloasma

Tyrosinase, TYRP1, TYRP2, and MITF are the primary genes involved in melanogenesis, and studies have demonstrated that these genes are considerably up-regulated in lesional skin tissues of chloasma patients. Melanogenesis is still the primary pathological basis of chloasma.[5] Chloasma is characterized by increased helioelastic hyperplasia, disruption of the basement membrane, increased dermal vascularity, mast cell infiltration, and subclinical inflammation. Perivascular lymphohistiocyte infiltration is occasionally present, as well as excessive epidermal melanin deposition, which is primarily expressed as an increase in melanin content. However, there is no significant proliferation of melanocytes, only hypertrophy of melanocyte bodies and prominent dendrites.[45,46] Inhibiting its biological activity may be a more effective treatment for chloasma, as this shows that the reason of hyperpigmentation in chloasma is directly tied to UV exposure and the enhancement of its melanocyte activity rather than an increase in the number of cells.

One of the main reasons of hyperpigmentation is oxidative stress.[24] Melanocytes, which are highly susceptible to oxidative stress, and keratin-forming cells interact to determine skin pigmentation.[47] Oxidative stress causes unsaturated fatty acid levels to rise, lipid peroxidation, and oxidation of proteins and DNA. Additionally, the melanocytes in the skin produce more undesired melanin as a result of this stress. Long-term UV radiation exposure raises the amount of ROS in melanocytes and keratinocytes, which damage DNA by attacking unsaturated fatty acids, which in turn causes lipid peroxidation and activates the p53 protein. The skin's antioxidant system is further compromised by the buildup of lipid peroxides and DNA damage, which also causes the generation of melanin and hyperpigmentation, inflammation, aging, and the development of chloasma[42,48,49](Figure 1). Antioxidant therapy is suggested to have the ability to increase the efficacy of chloasma by preventing the formation and production of melanin.

Chloasma Is Also Impacted by Signaling Pathways Linked to Oxidative Stress

Numerous interconnected signaling pathways are involved in oxidative stress, and they cooperate to control physiological and pathological activities in cells (Figure 2).The following are some of the main signaling mechanisms connected to oxidative stress.

Kelch-Like ECH-Associated Protein 1 (KEAP1)-Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2)-Antioxidant Response Element (ARE) Signaling Pathway (KEAP1-Nrf2-ARE Signaling Pathway)

One significant intracellular signaling system that is primarily involved in controlling how cells respond to oxidative stress and harmful chemicals is the KEAP1-Nrf2-ARE signaling pathway.[50] By controlling the expression of detoxifying enzymes like glutathione S-transferase and sulphotransferase as well as antioxidant enzymes like catalase (CAT), superoxide dismutase, and glutathione reductase, it primarily serves to scavenge intracellular oxygen radicals and harmful substances, shielding cells from oxidative damage and toxic effects.[42,51,52]

An essential modulator of cellular responses to oxidative stress is KEAP1-Nrf2-ARE signaling. A transcription factor called Nrf2 (nuclear factor E2-related factor 2) controls the expression of several genes involved in detoxification and antioxidant defense. It is believed that Nrf2 is a pro-survival factor that is generated in such unfavorable circumstances to regulate cytoprotective processes. Its regulation is dependent on Nrf2, which serves as a master regulator.[50] Keap1

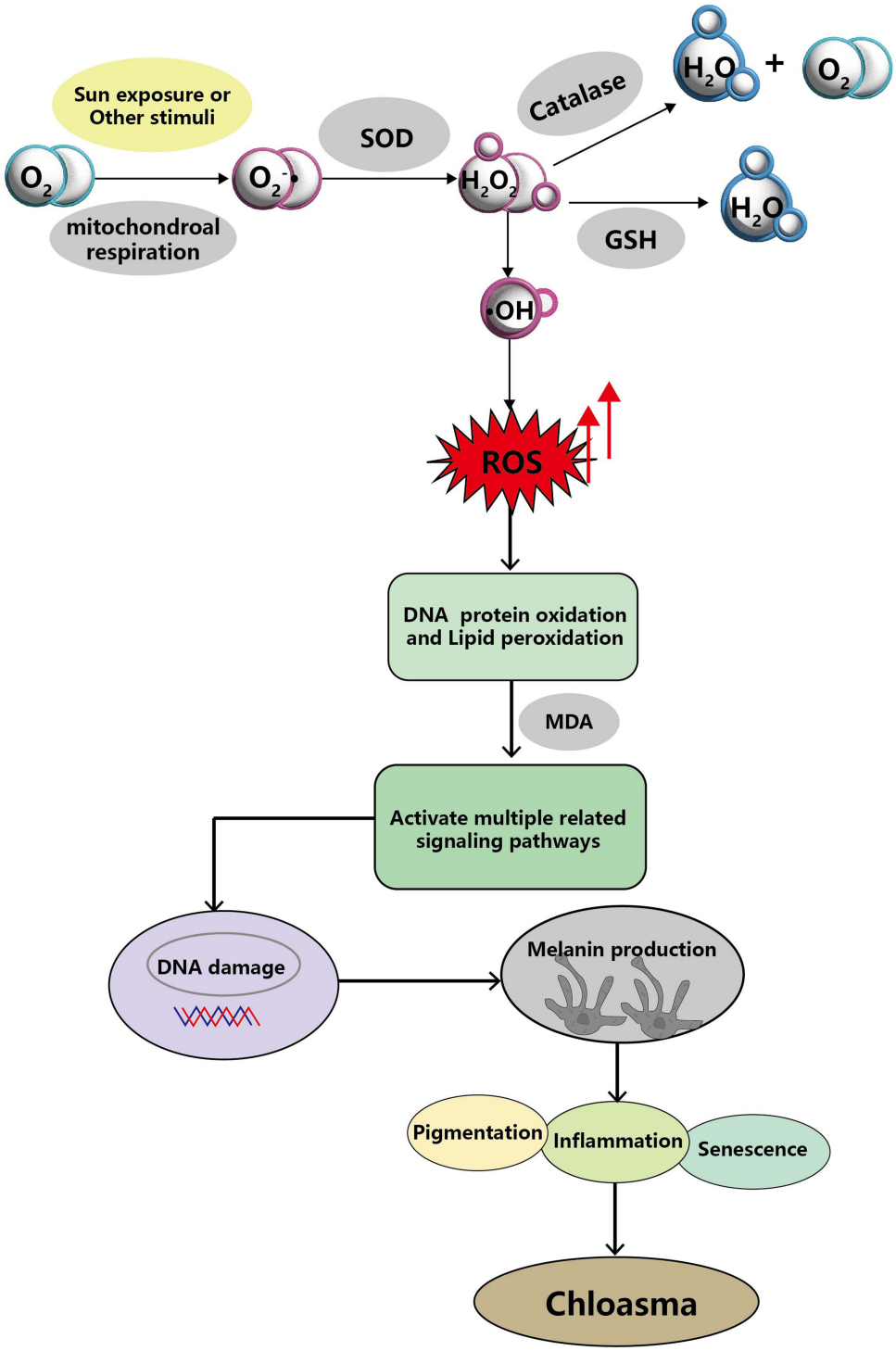

Figure 1 Oxidative stress and the formation mechanism of chloasma.

(Kelch-like protein 1) adversely regulates Nrf2 activity. Normal circumstances involve Nrf2 attaching to Keap1 and being targeted for destruction. On the other hand, oxidative stress prevented Keap1 from functioning, allowing Nrf2 to be liberated and go to the nucleus.[50] A particular DNA sequence known as an Antioxidant Response Element (ARE) is typically found in the promoter region of genes related to detoxification and antioxidants. The transcription of these genes is encouraged when Nrf2 attaches to the ARE in the nucleus, which increases the production of detoxifying and antioxidant enzymes. NRF2's target protein gene, NAD(P)H quinone dehydrogenase 1 (NQO1), is primarily engaged in

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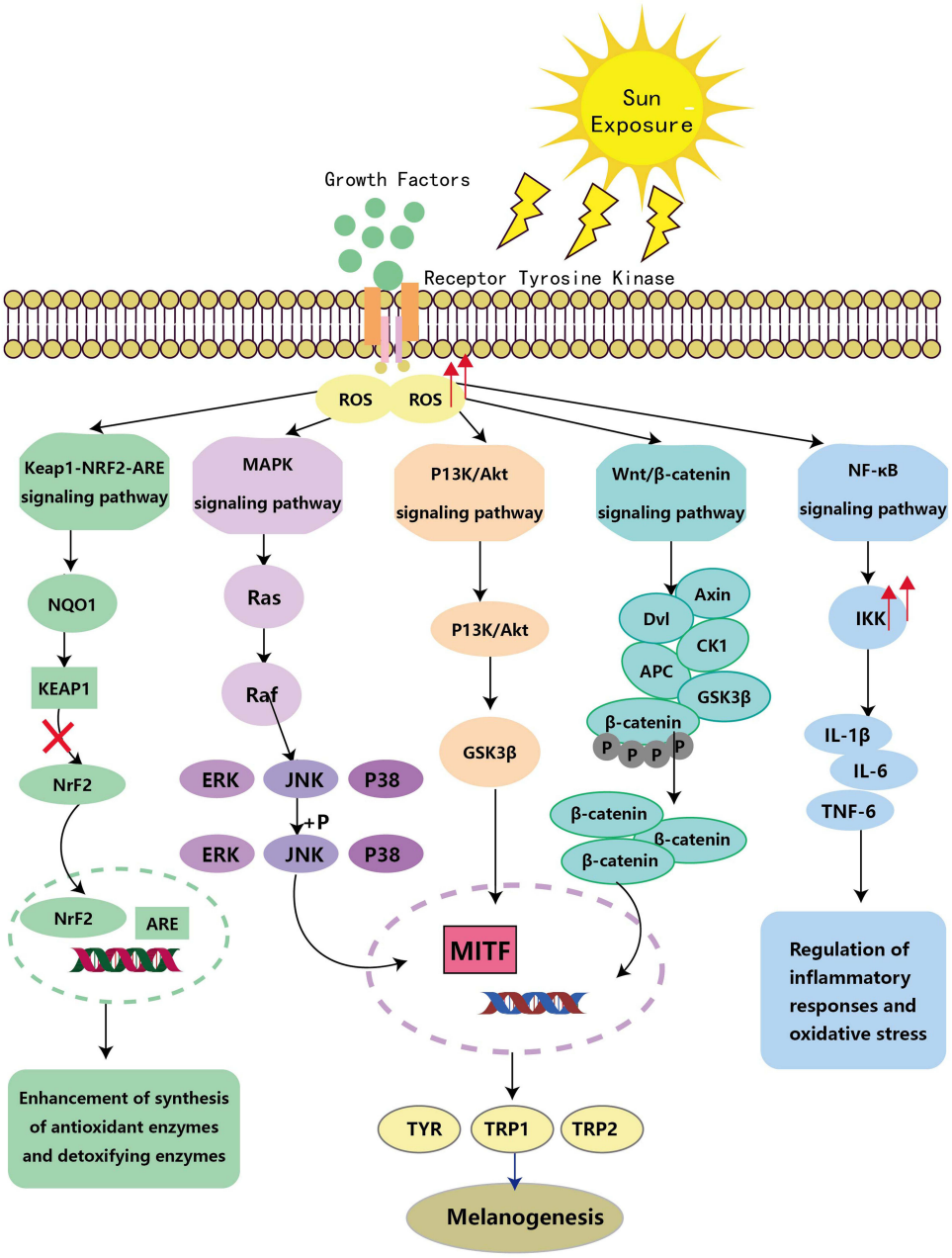

Figure 2 The relevant signaling pathways of oxidative stress also affect chloasma.

intracellular redox processes and metabolism related to detoxification. Overexposure to ROS causes the NQO1 gene to be upregulated, which in turn activates the KEAP1-Nrf2-ARE pathway, increases the production of melanin, and eventually results in the formation of chloasma.[53]

We believe that melanin anabolism is strongly related to the KEAP1-Nrf2-ARE signaling pathway, and that NRF2 signaling plays a role in the pathophysiology of UV-induced skin pigmentation.[47,54,55] Furthermore, some studies have demonstrated the efficacy of Nrf2 agonists in the management of conditions resembling hyperpigmentation.[54,56] Through stimulating the KEAP1-Nrf2-ARE pathway, a variety of natural substances and medications have been identified to improve cellular antioxidant capacity and toxic metabolism. It has been demonstrated that astaxanthin (AST) can act as an antioxidant to reduce oxidative stress and immunological damage in the skin via influencing the NF-κB and KEAP1-Nrf2 pathways.[43] Studies conducted in vitro and in vivo have demonstrated that flexin extract can activate NRF2 and up-

regulate the antioxidant enzymes CAT and Heme Oxygenase-1 (HO-1) to exert antioxidant effects in addition to its anti-inflammatory and antioxidant qualities.[40] Research has demonstrated that Paeonia lactiflora can protect melanocytes from Nrf2-mediated oxidative stress by promoting the production of Nrf2 nuclear translocation and its downstream-regulated antioxidant genes in response to oxidative stress.[57] Astragalus purpurascens decreased melanogenesis by initiating melanocyte autophagy and activating the Nrf2-mediated antioxidant pathway, according to the results of both in vitro and in vivo tests.[58]

Mitogen-Activated Protein Kinase Signaling Pathway (MAPK Signaling Pathway)

In addition to regulating cell division, apoptosis, proliferation, stress response, and other physiological activities, the MAPK signaling pathway is a crucial cellular signaling mechanism that works closely with oxidative stress.[59,60]

Oxidative stress and MAPK signaling pathways are mutually controlled. The major MAPK pathways, which are activated under oxidative stress circumstances, are the p38 MAPK pathway, the c-Jun N-terminal Kinase (JNK) pathway, and the extracellular signal-regulated kinase (ERK) pathway. Under oxidative stress, they become active, particularly when it comes to controlling the expression of MITF.[61,62] They are believed to be important modulators of the cellular response to oxidative stress, reducing oxidative damage by controlling the expression of genes (such as heat shock proteins and antioxidant enzymes) that are sensitive to oxidative stress. Furthermore, activation of the MAPK signaling pathway may decrease oxidative stress-induced apoptosis by modulating the expression or phosphorylation of apoptosis-related proteins. In contrast, the regulation of antioxidant enzyme expression, for instance, could have an impact on intracellular redox equilibrium when the MAPK signaling pathway is activated. This reciprocal control is essential to the survival and proper operation of cells and aids in the preservation of physiological homeostasis within the cell.[63]

Several signaling pathways control the manufacture of melanin, with the ERK-related MAPK signaling system playing a major role.[63] Chloasma has been the subject of numerous clinical investigations; biopsies taken from the affected and adjacent normal skin of patients with the condition have revealed aberrant expression of the P38 MAPK factor, indicating a possible link between the development of chloasma and the oxidative stress-induced modulation of the MAPK pathway by excess ROS.[39,40,64]

Furthermore, the MAPK pathway and melanin anabolism have been linked to a number of naturally occurring antioxidants and their derivatives. Chuanxiong ligustici extract of hyssop has been demonstrated to be an effective and safe antimelanogenic agent by regulating the MAPK signaling pathway and antimelanogenesis.[65] A lignan molecule found in Schisandra chinensis called Schisandrin B has anti-oxidant properties and decreases melanogenesis by down-regulating MITF and melanogenic enzymes through the activation of the MAPK pathway.[66] Red clover extract, purotol, has also been demonstrated to activate the synthesis of cAMP, upregulate the expression of MITF, and ultimately boost melanogenesis via increasing the expression of p-p38 and p-JNK in the MAPK pathway.[63] Swetiajaponin, a naturally occurring substance possessing antioxidant qualities, has demonstrated the ability to impede oxidative stress-induced MAPK/MITF signaling, therefore reducing the production of melanin in both cellular and human skin models.[67] It has been demonstrated that maclurin increases cellular tyrosinase activity and melanin levels; this effect is mostly due to an increase in MITF gene expression mediated by the MAPK signaling pathway. However, additional in vitro experimentation is required to confirm these findings.[68,69]

Phosphatase and Tensin Homolog (PTEN)/Phosphoinositide 3-Kinase (PI3K)/Protein Kinase B (AKT) Signaling Pathway (PTEN/PI3K/AKT Signaling Pathway)

Numerous physiological processes, including the cell cycle, growth, apoptosis, metabolism, and proliferation, are tightly regulated by the PTEN/PI3K/AKT signaling system, which also intricately interacts with oxidative stress.[70] Apoptosis is typically the result of oxidative stress, however the active AKT signaling pathway can delay the initiation of apoptosis by phosphorylating and controlling a number of anti-apoptotic proteins, including Caspase-9 and Bcl-2-associated death promoter (BAD). Thus, it lowers intracellular oxidative stress, prevents oxidative stress-induced cellular damage, and increases cell survival by promoting the development and activity of intracellular antioxidant enzymes (superoxide

dismutase, glutathione peroxidase, etc).Additionally, by controlling the activity of the AKT signaling pathway, oxidative stress may have an impact on the physiological condition of cells.[71]

Numerous investigations have demonstrated the strong relationship between melanogenesis and oxidative stress in the PTEN/PI3K/AKT signaling pathway. Numerous investigations on natural products have demonstrated their ability to prevent melanogenesis by elevating the activity of the AKT pathway. These items include decursin, fermented wild cherry berry (FA), and Pinostilbene Hydrate, a resveratrol derivative.[65,72,73] Furthermore, research has demonstrated that phosphorylation of FoxO6 is driven by activated Akt, which appears to be significant evidence that treatment with PI3K/AKT inhibitors reduces FoxO6 activity and increases melanogenesis.[35]

Wnt/β-Catenin Signaling Pathway

An crucial cell signaling system for embryonic development, cell proliferation, differentiation, apoptosis, and other biological activities is the Wnt/β-catenin signaling pathway.[74] Oxidative stress and the Wnt/β-catenin signaling pathway are mutually regulated.[75,76] On the one hand, Wnt/β-catenin signaling pathway activation can control intracellular antioxidant enzyme expression, increasing cellular antioxidant capacity and decreasing oxidative stress-induced damage.Conversely, oxidative stress can also impact the Wnt/β-catenin signaling pathway's activity, which can have an impact on cell survival, proliferation, and differentiation.[77]

Numerous investigations have demonstrated that the Wnt/β-catenin signaling system can affect intracellular redox balance by controlling the expression of genes linked to oxidative stress.[78] For instance, by controlling the expression of antioxidant enzymes, participants in the Wnt/β-catenin signaling system might shield cells from oxidative damage. An inhibitor of Wnt/β-catenin-cyclin leads to a significant reduction in inflammation and oxidative stress marker expression, according to a study.[79] Likewise, the activity of components linked to the Wnt/β-catenin signaling pathway can be impacted by oxidative stress.[64] For instance, oxidative stress can modify the activity of important proteins in the Wnt/β-catenin signaling pathway by altering their phosphorylation state.[80] We propose that pigmentation is significantly influenced by this signaling mechanism. Indeed, a number of studies have demonstrated the efficacy of Wnt/β-catenin signaling inhibitors in lowering hyperpigmentation.[81]

NF-κB Signaling Pathway

An essential transcription factor, the nuclear factor-κB (NF-κB) controls the expression of several genes and plays a role in biological processes like immune response, inflammation, cell development, and survival.[82] Oxidative stress and the NF-κB signaling pathway are closely regulated and interact.[83,84] The activation of the NF-κB signaling pathway can be regulated either directly or indirectly by oxidative stress. Reactive oxygen radicals, for instance, have the ability to directly influence the activity of important regulatory proteins in the NF-κB pathway. Alternatively, by controlling signaling molecules upstream of the NF-κB pathway like IκB kinase (IKK), oxidative stress can have an indirect impact on NF-κB activity.[85]

The expression of multiple antioxidant enzymes, including glutathione reductase and SOD, is regulated by NF-κB, which impacts the intracellular antioxidant capacity.[86] An inflammatory response is frequently present in conjunction with oxidative stress, and the NF-κB signaling pathway is essential for controlling both the immune system and inflammation. By controlling the expression of inflammatory factors including Interleukin-1 beta (IL-1β), Interleukin-6 (IL-6), and Tumor Necrosis Factor-alpha (TNF-α), NF-κB plays a role in controlling the relationship between the oxidative stress and the inflammatory response.[39]

Research has verified that baicalin, an extract derived from Scutellaria baicalensis, primarily impacts the liver and intestinal system by means of the NF-κB signaling pathway, which mediates the upstream oxidative stress and downstream apoptosis and immune response pathways generated by inflammation.[87]

Antioxidants Improve Chloasma

An increasing number of antioxidants, including tranexamic acid, vitamin C, azelaic acid, cysteamine, glutathione, carotenoids, and other antioxidants that have been demonstrated to be important in hyperpigmentation diseases, are currently being used in the clinical care of chloasma[86,88](Table 1).

Table 1 Application of Antioxidants in Chloasma

Antioxidant	Research design	Oral (O) /Topical (T) /Injection (I)	Sample size	Days	Outcome	Conclusion	References
Thiol Antioxidants							
cysteamine	RCT	T	40	120	I: reduction mMASI 24%; C: reduction mMASI 41% (P = 0.015) at 60 days. I: reduction mMASI 38%; C: reduction mMASI 53% (P = 0.017) at 120 days. (P = 0.087).	Cysteamine proved to be safe, well-tolerated, and effective.	[89]
cysteamine	RCT	T	14	112	I: reduction mMASI 1.52 ± 0.69 (21.3%); C: reduction mMASI2.96 ± 1.15 (32%) (P = 0.3).	Topical cysteamine may have comparable efficacy to topical HQ.	[90]
Tranexamic acid	Split face, prospective, randomized	T	40	56	I: improvement mMASI 65.92%; C: improvement mMASI 20.75%	Tranexamic acid is a promising treatment for melasma, and its topical solution with microneedling appears effective.	[91]
Tranexamic acid	RCT	I	120	84	MASI scores and VISIA brown spot and red zone ranking improved in all four groups (P < 0.05).	The effect of BBL combined with the intradermal injection of TA in the treatment of melasma is remarkable.	[92]
Tranexamic acid	Retrospective of clinical cases	O and T	75	1095	Mmasi score: from 6.92 to 3.84. VISIA shows: Spots (from 49.67 ± 3.43 to 56.09 ± 3.31), UV spots (from 41.39 ± 24.45 to 44.56 ± 25.86), and Brown spots (from 23.97 ± 17.89 to 28.16 ± 21.28) (P = 0.035, P = 0.018, P = 0.07).	The efficacy and safety profile of the combination of drug-laser-photon therapy systemic treatment in melasma patients has been proved.	[93]
Tranexamic acid	Multicentre prospective	O	98	84	Clinical photographs showed that all four doses of TA were effective in treating chloasma, and the efficacy correlated with treatment time and dosage.	Oral TA was safe and effective for the treatment of melasma.	[94]
Tranexamic acid	RCT	T	30	84	Statistically significant improvement of mMASI was reported in all studied groups with a significantly better improvement in patients of groups A and B than those of group C.	Topical TXA is a safe and fairly effective treatment modality for facial melasma.	[95]
Tranexamic acid	Split-Face	T and I	56	84	The mMASI score was significantly reduced compared with the baseline in both treated sides (P < 0.001).	Intradermal injection and microneedling of TXA could be safe and effective in melasma treatment.	[96]
Tranexamic acid	Molecular Experiment	/	/	/	Melanin contents, tyrosinase activity, protein and mRNA levels of TYR, MITF and TRP-1 were downregulated in NHEMs in the presence of TA-treated KCM.	TA can stimulate TGF-β1 expression in keratinocytes, inhibiting melanogenesis through paracrine signaling.	[97]
Tranexamic acid	Animal experiments	T	30	70	TSA treatment on the mice skin increased mitochondrial marker levels and epidermal thickness while decreasing dermal elastosis for all the treatment groups.	Topical TSA application significantly increased mitochondrial biogenesis, which may alter epidermal thickness and reduce dermal elastosis in mouse skin histology.	[98]
Natural antioxidants (Phenolic compounds)							
Paeonol	Molecular Experiment	/	/	/	Paeonol improved cell viability and melanogenesis in PIG1 cells treated with H2O2. Paeonol also alleviated oxidative stress by restoring the activities of superoxide dismutase, catalase, and glutathione peroxidase.	Paeonol protected melanocytes against H2 O2 -induced oxidative stress by Nrf2 mediated antioxidant pathways.	[57]
Licorice	Molecular Experiment	/	/	/	Heat treatment increased total phenolic content. In particular, isoliquiritigenin, an antioxidant and anti-melanogenic compound of licorice, was produced by heat treatment.	WH-130, with higher levels of bioactive phenolics like isoliquiritigenin, has potential as a novel skin whitening ingredient for cosmetics.	[99]
Pinostilbene hydrate	Molecular Experiment	/	/	/	Pinostilbene Hydrate (PH) downregulates melanogenesis via the inhibition of MITF expression, followed by the MAPK signaling pathways.	PH may be used to treat or prevent hyperpigmentation disorders and in functional cosmetic agents for skin whitening.	[73]

(*Continued*)

Table 1 (Continued).

Antioxidant	Research design	Oral (O) /Topical (T) /Injection (I)	Sample size	Days	Outcome	Conclusion	References
Propolises	Molecular Experiment	/	/	/	All tested propolis extracts strongly inhibited commercially available mushroom tyrosinase, with the four most active extracts showing inhibition ranging from 86.66% to 93.25%.	Tested propolis extracts could be used for skin cosmeceutical and medical applications.	[100]
Indian Ginseng	Molecular Experiment	/	/	/	WAD from W. somnifera suppresses intercellular ROS generation and inhibits IL-6 and IL-8 expression, potentially reducing inflammation in human skin.	WAD has protective effects against skin damage.	[101]
Natural antioxidants (Flavonoids compounds)							
Hesperidin	Molecular Experiment	/	/	/	Hesperidin reduced tyrosinase, TRP-1, and TRP-2 expression, while increasing p-Erk1/2 expression.	Hesperidin strongly inhibited melanin production and tyrosinase activity.	[41]
Maclurin	Molecular Experiment	/	/	/	Maclurin induced CREB phosphorylation via cAMP/PKA and p38 MAPK pathways, while suppressing p44/42 MAPK activation to enhance melanogenesis.	Maclurin's melanogenic effects depend on increased MITF expression, mediated by p38 MAPK/CREB and cAMP/PKA/CREB activation.	[68]
Maclurin	Molecular Experiment	/	/	/	Maclurin reduced melanin content in melan-a cells and significantly decreased UVB-induced melanin accumulation (~47%) in a concentration-dependent manner in a human skin model.	Maclurin may be applied as an anti-melanogenic agent.	[69]
Fraxin	Molecular and Animal experiments	/	/	/	Fraxin could activate NRF2 and upregulate antioxidase CAT and HO-1.	Fraxin could effectively combat melanogenesis and oxidative stress in hyperpigmentation disorders.	[40]
Decursin	Molecular Experiment	/	/	/	Decursin inhibited melanin synthesis by downregulating MITF through the PKA/CREB pathway.	Decursin's anti-melanogenic effects were confirmed in 3D human skin models, supporting its potential as a protective agent against hyperpigmentation.	[65]
Schisandrin B	Molecular Experiment	/	/	/	Schisandrin B reduced melanogenesis by downregulating MITF and melanogenic enzymes through MAPK and CREB pathways.	Schisandrin B has the potential use in whitening.	[66]
The ethanolic extract of mulberry twigs (EEMT)	Molecular Experiment	/	/	/	EEMT showed radical scavenging, reducing, and ferrous ion-chelating activities, and protected phospholipids from free radicals.	EEMT might serve as a natural antioxidant and tyrosinase inhibitor.	[102]
Extract of Sorghum bicolor(ESB)	Molecular Experiment	/	/	/	ESB inhibited melanogenesis by reducing the expression of MITF, tyrosinase, and TRP-1.	ESB may have physiological potential to be used skin whitening material.	[103]
Vitamins and trace elements antioxidants							
Ascorbic palmitate (AP)	Molecular and Animal experiments	/	/	/	AP-TFs can inhibit tyrosinase activity and melanogenesis.	AP-TFs is a safe and effective method to enhance the delivery of lipophilic drugs to the EP. treatment of melasma.	[104]
Magnesium ascorbyl phosphate (MAP)	Single blinded, split-face	/	20	90	A significant difference was found between the right side (MAP aspasomal cream) and left side (15% TCA) in mean hemi-MASI reduction, with the greatest improvement on the right side.	MAP aspasomal cream is a new, side-effect-free treatment for melasma.	[105]
Magnesium ascorbyl phosphate (MAP)	RCT	/	40	180	MAP ethosomal and niosomal gels both significantly improved chloasma, with ethosomes showing faster response and niosomes offering longer-lasting effects and minimal side effects.	Combining the two formulations might yield faster and more lasting results.	[106]

(*Continued*)

Table 1 (Continued).

Antioxidant	Research design	Oral (O) /Topical (T) /Injection (I)	Sample size	Days	Outcome	Conclusion	References
Retinoic Acid	RCT	/	42	60	Both Group A (microneedling and 5% retinoic acid) and Group B (5% retinoic acid alone) showed clinical improvement in chloasma within 60 days, reducing the MASI score by nearly 50%.	Retinoic acid is effective in the clinical treatment of melasma	[107]
Zinc and Selenium	Molecular Experiment	/	/	/	The trace elements Zn and Se showed no toxicity at the tested concentrations, and 100 μM Zn reduced melanin content.	The mechanism needs further exploration to advance new research for melasma treatment and therapeutic use.	[108]
Carotenoids antioxidants							
Tomato extract	RCT	/	62	84	The treatment group had higher serum SOD levels than the placebo control group ($P<0.05$). The MASI score decreased significantly in the treatment group compared to the control group ($P<0.05$).	Tomato extract supplementation can boost serum SOD levels and reduce melasma severity.	[36]
Astaxanthin (AST)	Molecular Experiment	/	/	/	AST significantly reduced MDA levels and increased antioxidant activity. Nrf2 expression was upregulated by 117.95%, while Keap1 expression decreased by 51.22%.	AST treatment ameliorated oxidative stress and immune impairment overall.	43]
Other antioxidants							
Laccase	Molecular Experiment	/	/	/	Laccase from Trametes versicolor combined with natural phenol redox mediators effectively degraded eumelanin from Sepia officinalis.	Offering an alternative procedure to traditional whitening agents	[109]
Bilirubin	/	/	100	/	The serum Bile concentration was significantly higher in the case group ($P < 0.05$) and positively correlated with chloasma severity (correlation coefficient, +0.3; $P < 0.05$).	Bilirubin could be involved in confronting the process of oxidative stress.	[110]
ZJ1	Molecular Experiment	/	/	/	Whole lysate (WL) and bacterial lysate (BL) of ZJ1 downregulate melanogenesis genes and indirectly inhibit intracellular tyrosinase activity.	ZJ1 fermentation lysates could be used as therapeutic agents for hyperpigmentation disorders and whitening agents in cosmetics.	[111]
Non-crosslinked hyaluronic acid	Retrospective	/	6	60	All six chloasma cases showed further improvement in chloasma clearance after hyaluronic acid injection. ANOVA analysis of the scores before, during, and after treatment revealed significant differences between the three groups.	Non-crosslinked hyaluronic acid with antioxidants may enhance the effectiveness of Nd:YAG laser toning for melasma treatment.	[112]
Sunscreen	Randomized in vivo	/	39	7	Human skin explants treated with the test product showed a 82% protection, with significantly lower levels of accumulated carbonylated proteins after exposure to 460 nm blue light.	The test product protects against oxidative stress and both immediate and long-term pigmentation caused by blue light.	[113]

Thiol Antioxidants

One of the most prevalent antioxidants in muscles is cyclamine, which also acts as an activator of glutathione reductase, reducing glutathione to reduced glutathione. Measuring mMASI and MELASQoL in clinical chloasma patients, the antioxidant 5% cysteamine and the skin-whitening agent phenylphenol were found to be helpful in treating chloasma. Although cysteamine is safer than benzophenol, it is more effective. Cysteine is anticipated to be used as an alternative to benzophenol in therapy.[89,90]

N-acetylcysteine (NAC) provides glutathione precursors (cysteine), directly scavenges free radicals, and promotes glutathione regeneration. These actions help to regulate intracellular oxidative stress, increase cellular antioxidant capacity, and shield cells from oxidative damage.[114] By reducing oxidative stress, tranexamic acid has been demonstrated in numerous studies to be a secure and successful treatment for facial chloasma. Topical tranexamic acid has

been shown to be useful in improving chloasma in a number of controlled clinical trials.[91,115] When tranexamic acid is used to treat chloasma, several studies comparing pre- and post-treatment efficacy utilizing MASI scores and VISIA (Canfield VISIA Skin Tone Analysis) have demonstrated notable outcomes.[92–94] According to certain research, topical tranexamic acid plus fractional carbon dioxide laser or microneedling is a much more effective treatment for chloasma than it is on its own.[95] Furthermore, the outcomes of tranexamic acid injections under the skin or by microneedles for the treatment of chloasma have verified that both administration techniques are secure and efficient.[96] In reference to refractory chloasma, a study examining the efficacy of topical tranexamic acid in combination with vitamin C in treating the condition demonstrated a noteworthy improvement in MASI scores and the chloasma Quality of Life Scale. However, the study was somewhat biased due to the absence of a control group and the testing of pertinent indexes.[116] Nevertheless, research has demonstrated that oral tranexamic acid can increase Transforming Growth Factor Beta 1(TGF-β1) expression in keratinocytes, which results in additional antioxidant suppression of melanogenesis through paracrine signaling.[97] Thus, by switching from topical to oral tranexamic acid administration, the researchers were able to verify that oral tranexamic acid is a secure and reliable treatment for refractory chloasma.[97,117] Furthermore, topical tranexamic acid was studied using an animal test to treat mice whose skin was exposed to UV-induced oxidative stress, which served as a model for chloasma. The outcomes demonstrated that application of tranexamic acid topically effectively reduced oxidative stress-induced mitochondrial impairment, which might decrease epidermal thickness while elevating the expression levels of the mitochondrial markers Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha (PGC1α), Translocase of Outer Mitochondrial Membrane 20 (Tom20), and Cytochrome c Oxidase Subunit IV (COX IV).[98]

Furthermore, it has been demonstrated that intracellular glutathione plays a significant role in limiting the escalation of oxidative stress. The comparative analysis of erythema and lesion counts in VISIA, conducted before and after antioxidant treatment, validates the efficaciousness of antioxidant therapy for dermatological ailments.[44,118]

Natural Antioxidants

Natural antioxidants are substances that the body can scavenge from free radicals and employ to lessen the damage caused by oxidative stress, herbal remedies, and other natural sources. These substances include meals, herbs, and other natural sources.[86,119,120] Phenolics and flavonoids are the most prevalent natural antioxidants and antimelanin chemicals.[103]

Phenolic Compound

The phenolic compound Paeonia lactiflora, which is present in the root bark of cortical wood sandalwood, has the ability to reduce oxidative stress by reestablishing the activities of glutathione peroxidase, catalase, and superoxide dismutase.[57] It also has the potential to treat a number of diseases by acting on the antioxidant pathway, which is mediated by nuclear factor Nrf2. Licorice is utilized as a natural antioxidant for skin whitening because of its anti-inflammatory, anti-tumor, anti-platelet, and immunomodulatory properties. By raising the amount of antioxidant phenolic compounds (like ISL), licorice can be heat-treated to produce Glycyrrhiza glabra extract WH-130, which can be further studied as a potential new material for the treatment of skin conditions like chloasma.[99] The resveratrol derivative PH suppresses the expression of melanogenic enzymes and inhibits MITF, which results in the downregulation of melanogenesis.[121] Polypodium leucotomos prevents UV radiation-induced apoptosis and lowers the generation of ROS and Nitric Oxide Synthase (NOS).[122] Tyrosinase activity testing, free radical scavenging testing, and ultra-high performance liquid chromatography were utilized to confirm the antioxidant activity of propolis extract, which can be used to treat chloasma.[100] Indian Ginseng Extract WAD has antioxidant properties that shield the skin by preventing the synthesis of intercellular ROS.[101]

Flavonoid

Citrus fruit peels naturally contain hesperidin, a flavonoid that functions as an antioxidant and inhibits melanogenesis by degrading MITF via the Erk1/2 pathway.[41] Maclurin is a naturally occurring flavonoid that can be found in the mulberry tree's roots and bark. It has been demonstrated to work as an antimelanogenic agent and possesses antioxidant and anti-

tyrosinase activity. It can also prevent melanogenesis.[68,69] A bioactive material called fraxin was isolated from Cortex fraxini. Experiments conducted both in vivo and in vitro have demonstrated that Fraxin can perform antioxidant effects by up-regulating the antioxidant enzymes CAT and HO-1, activating NRF2, and inhibiting the activation of ERK, which is strongly associated to melanogenesis. Additionally, through scavenging intracellular reactive oxygen radicals (ROS), fraxin shields Manganese Transporter 1 (MNT1) cells from H_2O_2-induced death.[40] A significant transcription factor in melanogenesis, MITF, is inhibited by an extract from Angelica sinensis, which has antimelanogenic properties.[65] It has also been demonstrated that Schisandrin B, an extract from Schisandra chinensis, has anti-inflammatory and melanin-lowering qualities.[66] Morus alba branch ethanolic extract (EEMT), a naturally occurring antioxidant with anti-tyrosinase and antioxidant properties.[102] It was shown that the ethanol extract of Sorghum bicolor exhibited both antioxidant action and antimelanogenesis. This suggests that it could be further explored as a potential skin-whitening agent.[103]

Vitamins and Trace Elements (Vitamin CEA and Zinc Selenium)

Researchers have encapsulated ascorbyl palmitate AP (a vitamin C derivative) within transferosomes (TFS) to generate AP-TF, which addresses the problem of AP's inability to pass directly through the stratum corneum. It has been demonstrated that AP inhibits complexinase activity and melanin synthesis. Experiments conducted in vitro and in vivo have verified that AP-TF can enter melanocytes via the stratum corneum, block the activity of Tyrosine enzyme and the synthesis of melanin, and successfully reduce skin inflammation and oxidative stress.Additionally, testing on animals' skin irritation verify its safety.[104] Additional research has revealed that Magnesium Ascorbyl Phosphate (MAP) is a derivative of ascorbic acid that shares the same anti-aging, brightening, and antioxidant properties as ascorbic acid but is more stable.[105,106,123] One of the most potent low molecular weight antioxidants, vitamin E protects against lipid peroxidation and lessens the negative consequences of oxidative stress.[86,124] Because retinoic acid plays a significant role in the production of retinal pigments, which have antioxidant qualities of their own, retinoic acid can also be partially regarded as one of the compounds linked to the antioxidant process that helps treat chloasma.[32,107] As components of significant antioxidant enzymes, zinc and selenium have antioxidant properties. In vitro tests utilizing these antioxidant compounds for antimelanotic activity have demonstrated their ability to lower melanin activity.[108]

Carotenoids

Tomato extract supplementation as an adjuvant therapy may raise serum SOD levels and lessen the severity of chloasma.[36] Potential antioxidant astaxanthin (AST) has been demonstrated to improve liver histopathological damage, raise antioxidant enzyme activity, dramatically lower malondialdehyde (MDA) levels, and lessen immunological and oxidative stress.[43]

Other Antioxidants

There is ample evidence of the antioxidant qualities of weaker antioxidant medicines, such as niacinamide, polypodophyllum leucocephala, angelica dahurica, grape seed extract, aminocarboxylic acid, phytic acid, zinc, silymarin, koji ginseng powder, botanical extracts, and parsley.[125] As an oxidative enzyme, laccase guards against oxidative stress-related damage to skin tissue. Combinations of laccase mediators are efficient at breaking down tan real melanin and may provide a better treatment option for chloasma than conventional whitening products. This has to be thoroughly studied.[109] Furthermore, bilirubin may be utilized to treat chloasma as a new antioxidant.[110] With potential for development, extracts of Bifidobacterium bifidum strain ZJ1, which was isolated from Chinese centenarians, exhibit antimelanin and antioxidant properties.[111] Antioxidant-rich non-cross-linked hyaluronic acid increases the effectiveness of Nd:YAG laser toning for the treatment of chloasma.[112] Additionally, novel sunscreens have demonstrated efficacy against oxidative stress and a strong protective impact against hyperpigmentation caused by blue light, both immediately and over time.[113]

Multicomponent, Multipathway Drug Combinations

Research has started to concentrate on multi-component, multi-pathway medication combinations to increase efficacy in the treatment of chloasma because single components and single routes have limited efficacy. Drug

combinations with low skin penetration, such as glabridin, 3-O-ethyl-L-ascorbic acid, and tranexamic acid, are loaded onto dissolving microneedles (MN) to improve drug penetration and absorption. These combinations are used as tyrosinase inhibitors, antioxidants, and melanin delivery inhibitors, respectively. Drug-laden microneedles (DMNs) loaded with active components demonstrated substantial antioxidant and inhibitory effects on the activity of the enzyme complex, as well as reduced melanin synthesis, according to the results of in vivo and in vitro investigations. Clinical research has attested to both its safety and efficacy in treating chloasma.[126] The most successful treatment for chloasma has been discovered to involve retinol, diosmin, and ferulic acid in combination, according to artificial intelligence mathematical modeling. In vitro cellular complexinase activity tests have revealed a synergistic decolorizing impact of these antioxidant-effecting components. Subsequent studies revealed that the combination up-regulated the gene expression of IL-1β, Tissue Inhibitor of Metalloproteinase 3 (TIMP3), and numerous endogenous antioxidant enzymes while down-regulating the production of ET-1 and COX-2 and IBMX-induced dendriticity in human melanocytes to inhibit important pathways of chloasma. The phototypic VI 3D epidermal model's melanin levels were likewise lowered by this combination.[127] Significant depigmenting, anti-oxidant, and anti-angiogenic effects were shown when a depigmenting formula (BLTX) for hyperpigmentation diseases was evaluated utilizing in vitro models of human cells and skin cultures.[128] Among the carotenoids formed from tomatoes, lycopene is one of the most effective oxygen neutralizers. Wheat can be used to extract hydro-quinone, a substance that inhibits tyrosinase and is used to treat hyperpigmentation. Making a cream with wheat bran extract and lycopene to treat patients with clinical chloasma, which has been demonstrated to be both safe and effective in relieving the condition.[129] Research has demonstrated that tannic acid can be used as a carbon source to create unique carbon quantum dots (CQDs) that are created from tannic acid (T-CQDs). Antioxidant, anti-aging, and low cytotoxic, this synthesized unique material can be further developed for the treatment of chloasma and other hyperpigmented skin illnesses.[130]

Outlook

The current state of chloasma treatment is expensive, with mediocre efficacy and a high rate of side responses that negatively impact patients' quality of life. It so compels us to come up with fresh, more effective therapy approaches. Oxidative stress is a popular topic in research right now and is closely related to the processes that lead to the development of chloasma.by becoming aware of the connections between oxidative stress and the signaling pathways that are involved in chloasma. This review was created in an effort to find more effective and targeted therapies for chloasma.

Based on the progress made in the field of oxidative stress research, including related indicators like superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH), glutathione peroxidase (GPx) (antioxidant), malondialde-hyde (MDA), tyrosine hydroxylase (TH), reactive oxygen species (ROS), and its related KEAP1-Nrf2-ARE pathway, MAPK pathway, PTEN/PI3K/AKT pathway, Wnt/β signaling pathway, NF-κB signaling pathway, and so forth. The findings of these studies all point to the potential benefits of antioxidant treatment in ameliorating the condition of chloasma, increasing patient safety and improving patient quality of life.

Conclusion

In conclusion, this review highlights the significant role of oxidative stress in the pathogenesis of chloasma. The evidence suggests that antioxidant therapy is a promising approach for the treatment of chloasma, showing positive effects in reducing pigmentation and improving skin condition. However, while the therapeutic potential is evident, further clinical studies are necessary to establish more definitive evidence regarding the optimal targets and mechanisms of action for antioxidant therapies. Future research should focus on elucidating these mechanisms to refine treatment strategies and improve the safety and efficacy of antioxidant-based therapies for chloasma.

Abbreviations

IL-1β, Interleukin-1 beta; IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-alpha; NF-κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells; TGF-β1, Transforming Growth Factor Beta 1; PTEN, Phosphatase and Tensin Homolog; PI3K,

Phosphoinositide 3-kinase; AKT, Protein Kinase B; PGC1α, Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha; Tom20, Translocase of Outer Mitochondrial Membrane 20; COX IV, Cytochrome c Oxidase Subunit IV; HO-1, Heme Oxygenase-1; NRF2, Nuclear factor erythroid 2–related factor 2; MNT1, Manganese Transporter 1; JNK, c-Jun N-terminal kinase; IKK, IκB kinase; ERK, Extracellular Signal-Regulated Kinase; TIMP3, Tissue Inhibitor of Metalloproteinase 3; KEAP1, Kelch-like ECH-associated protein 1; MAPK, Mitogen-Activated Protein Kinase; ARE, Antioxidant Response Element; BAD, Bcl-2-associated death promoter; MITF, Microphthalmia-associated Transcription Factor; NQO1, NAD(P)H quinone dehydrogenase 1; CAT, Catalase; ROS, Reactive oxygen species; NOS, Nitric Oxide Synthase; MDA, Malondialdehyde; SOD, Superoxide dismutase; GSH, Glutathione; GPx, Glutathione Peroxidase; GR, Glutathione reductase; TH, Tyrosine hydroxylase; MASI, Melasma Area and Severity Index; cGAS-STING, Cyclic GMP-AMP synthase-stimulator of interferon genes; ETC, Electron transport chain; HQ, Hydroquinone.

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Disclosure

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