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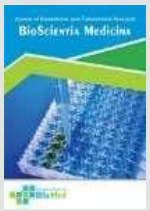

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The Effect of Free Radicals on Vitiligo

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A B S T R A C T

Vitiligo is a depigmentation disorder that is commonly found in the community. The causes of vitiligo are multifactorial such as genetic and environmental factors accompanied by the presence of non-specific and specific immune system factors. Melanocytes are the main target exposed by reactive oxygen species (ROS) during the process of melanogenesis. Such exposure can cause loss of homeostasis and cell death and has implications for vitiligo. Clinical manifestations of vitiligo are generally white depigmented macular lesions that are well demarcated. Based on its distribution, vitiligo can be divided into segmental and non-segmental vitiligo different in terms of prognosis, treatment and resolution of vitiligo.

1. Introduction

Vitiligo is a skin disorder characterized by depigmentation due to the selective loss of melanocytes, causing loss of pigment in the affected skin area. Vitiligo is a pigmentation disorder of the skin that is quite common, with a prevalence of 0.5-2% of the world's population. Population vitiligo in Denmark is reported to affect 0.38%, while in China, it affects 0.093% of the population, and in India, it is 8.8% of the population.[1] Research by Diana in 2017 reported the number of vitiligo patients at the dermatology and venereology polyclinic at Dr. Moewardi General Hospital in 2013-2016 as many as 108 people or 0.46% of all skin and genital polyclinic patients at Dr. Moewardi General Hospital with a frequency of 52.78% male and 47.22% female.[2] Vitiligo affects ethnic groups and people of all skin types. Vitiligo itself can be divided into two main subtypes, namely segmental vitiligo (SV) and non-segmental vitiligo (NSV).[3] Not only a cosmetic disorder, vitiligo is an autoimmune disease that can interfere with the sufferer's quality of life. Vitiligo has no racial or gender preference but is a complex disease associated with genetic and environmental factors accompanied by metabolic disorders, oxidative stress, and cellular abnormalities.[3,4]

The mechanism of loss of melanocytes in vitiligo is due to immune dysregulation and oxidative stress.[6] Oxidative stress is an imbalance in redox, which can ultimately damage cells and trigger cell death. The skin, as the largest organ in the human body, is very vulnerable to excessive exposure to free radicals, which triggers the emergence of oxidative stress. Damage and cell death will also trigger a widespread

inflammatory reaction. The main reason for the formation of free radicals in the body when there is inflammation of the skin, is to destroy microorganisms and or degrade damaged tissue structures. Excessive production of free radicals and not balanced with adequate neutralization can have an impact on cell death itself.[5,6]

The main clinical manifestation of vitiligo is the presence of milky white macules with fairly homogeneous and well-defined depigmentation.[7] Non-segmental vitiligo is characterized by a symmetrical distribution, unpredictable course, and association with autoimmune disease. Whereas in segmental vitiligo, generally found a unilateral distribution, autoimmune associations are not so strong, and stabilization is fast. Segmental vitiligo has an earlier age of onset compared to non-segmental vitiligo.[8]

Free radicals are unstable molecules and are formed by oxidation processes when the body's metabolism occurs. Most of the radicals originate from oxygen in the biological systems of the body and are known as reactive oxygen species (ROS). Many studies have stated that oxidative stress in vitiligo occurs due to a redox imbalance in the skin, which causes excessive ROS production. ROS accumulation results in toxic effects on cell components such as deoxyribonucleic acid (DNA), proteins, and lipids that cause degeneration and apoptosis of melanocytes, resulting in depigmented macular lesions. This literature review aimed to determine the effect of free radicals on vitiligo.[9]

Vitiligo

Definition

Vitiligo is a skin pigmentation disorder characterized by loss of melanocytes that mainly affect the skin, thus causing dilution of pigmentation in the area and causing white depigmented macules that are well demarcated. Occasionally, there is involvement of the mucosa and hair. Cases of vitiligo have been recorded as early as 1700-1100 BC in India. These cases were called "switra," derived from the Sanskrit word "sveta," meaning white spot. Switra has been mentioned in the ancient classical writings of Ayurveda and in Persian chronicles since 2200 BC.[10]

Etiology and risk factors

Vitiligo is a skin pigmentation disorder that is still common, with a prevalence of 0.5-2% of the world's population. As many as 5-16% of cases of vitiligo are cases of segmental vitiligo. Men and women have more or less the same prevalence of vitiligo, although women are generally more inclined to treat this pigmentation disorder. Vitiligo can occur at any age but generally appears between the ages of 10-30 years. As many as 50% of cases of vitiligo occur before the patient is 20 years old. Race and any skin type have the same risk for vitiligo. As many as 25% of NSV cases occur in patients before the age of 10 years, 50% occur in patients who are not yet 20 years old, and 70-80% occur in patients who are not yet 30 years old. Meanwhile, SV occurs in 5-16% of cases of vitiligo and is more common at a younger age than NSV.[1,4,11]

Risk factor in the occurrence of vitiligo is genetic (80%), with environmental factors (20%) also having an effect on the occurrence of vitiligo.[1,4,12] Genetic risk factors found in 20% of cases of vitiligo, which is first-degree descent, who also suffers from vitiligo, and risk vitiligo in patients who have first-degree descent with vitiligo increases 7-10x. Research by Bergqvist et al. in 2020 shows that there are at least 50 gene loci that have important factors in the occurrence of risk vitiligo.[1,4] Environmental factors such as excessive sun exposure, contact with bleaching chemicals, mechanical stress, and coebnerization have been reported in some patients as triggers for vitiligo.[13]

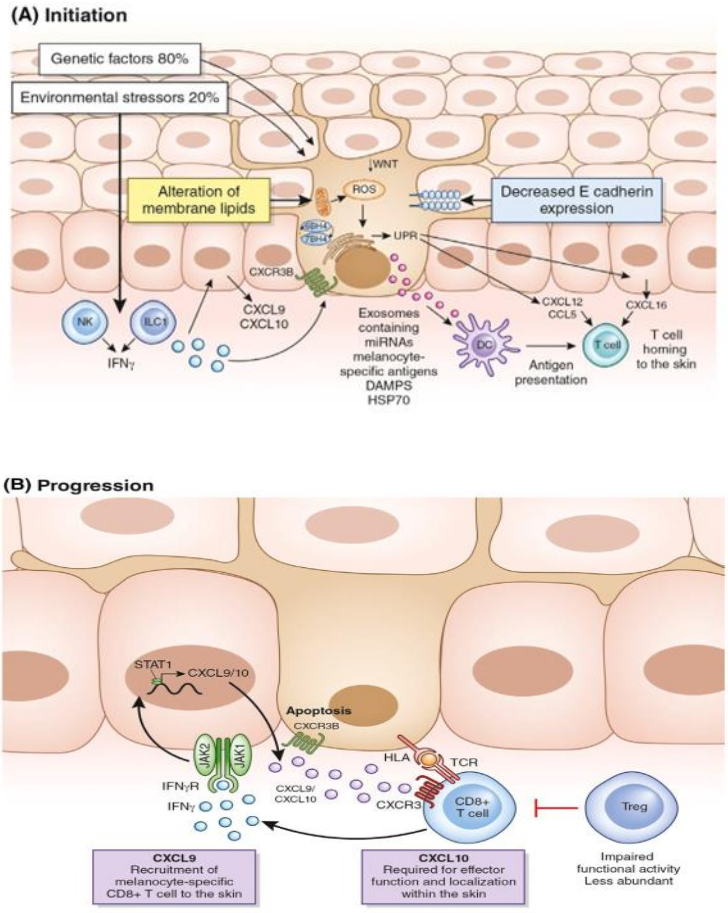
Pathogenesis

Pathogenesis vitiligo involves an intrinsic defect in the melanocytes and an autoimmune targeting of these melanocytes. So the production of melanin itself is toxic to melanocytes.[3] Melanocyte intrinsic defects make melanocytes more susceptible to damage due to oxidative stress. Factors that influence the pathogenesis of vitiligo are genetics, oxidative stress, inflammatory mediators and melanocyte release

mechanisms. The innate (non-specific) and adaptive immune systems are also said to play a role in the occurrence of vitiligo (Figure 1). Segmental and non-segmental vitiligo are believed to have different mechanisms of pathogenesis, with neuronal/somatic mosaicism more reliable in the occurrence of segmental vitiligo, although there are several pathogenesis that also affect the two types of vitiligo. Both vitiligo are believed to pass through several stages involving the release of proinflammatory cytokines and neuropeptides induced by internal and external trauma, resulting in vascular dilatation and an immune response.[4,8,12]

Vitiligo is influenced by several factors, one of which is genetics. Some of the genes that affect the non-specific immune system are IFIH1, CASP7, NLRP1, and TICAM1, and those that affect the immune system adaptive are CTLA4, CD80, HLA, GZMB, FOXP3, and others. In addition, certain alleles present in melanocytes (TYR, OCA2, and MC1R) initiate the occurrence of vitiligo. It was found that the XBP1 gene plays a role in initiating inflammation.[3,4,12]

stress oxidative is the result of an increase in the level of reactive oxygen species (ROS) and subsequent reduction of antioxidant enzymes and disrupting the function of cellular proteins and lipid membranes, thereby interfering with the activity of antioxidant systems in both lesional and normal skin. The theory of an imbalance in the antioxidant system in vitiligo is thought to cause an increase in the sensitivity of melanocytes to oxidative stress, which causes cell death. Increased ROS was reported in active lesions, suggesting oxidative stress as an acceptable cause of vitiligo pathogenesis.[4,12]



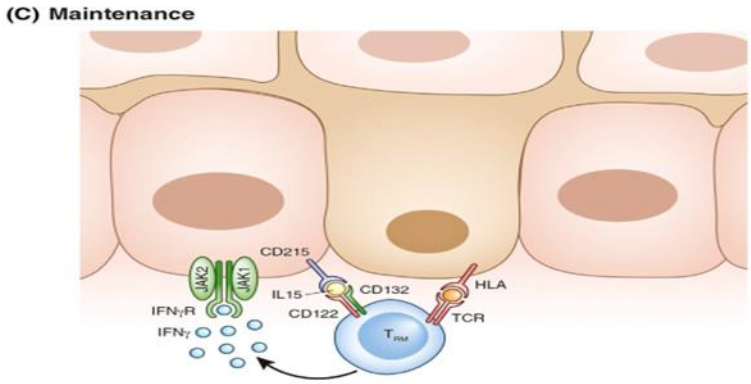


Figure 1. Pathogenesis of vitiligo.[4]

Information: NK = Natural killer, ILC = Innate lymphoid cells, IFN = Interferon, CXCR = Chemokine receptor, CXCL = Chemokine ligand, WNT = Wingless/Integrated, ROS = Reactive oxygen species, UPR = Unfolded protein release, CCL = Culture collection, STAT = Signal transducer and activator of transcription, HLA = Human leukocyte antigen, JAK = Janus kinase, TCR = T-cell receptor, CD = Cluster of differentiation, Treg = Regulatory T cells.

System immune non-specific to vitiligo is a system that bridges oxidative stress and the adaptive immune system. Non-specific immune system activation occurs early in vitiligo by detecting stress signals and damage-associated molecular patterns (DAMPs) from damaged melanocytes, such as DNA and high morbility group box 1 (HMGB1). Immune system adaptive like Humoral and cellular immune systems, have a role in the pathogenesis of vitiligo. In the serum of vitiligo patients, it is known to have antibodies against the surface and cytoplasm of melanocytes. These antibodies induce the destruction of melanocytes by means of lysis and cytotoxicity. ROS production from vitiligo skin lesions is associated with activation of the adaptive immune system, especially $CD8^+$ cells. CD8+ cytotoxic T cells are cells that specifically target the destruction of melanocytes. In patients with vitiligo, increased expression of IL-15 was found due to ROS, resulting in activation of T-cells via the JAK-STAT pathway.[4,7,12]

The pathogenesis of vitiligo can be divided into 3 stages, namely initiation, progression and maintenance. The initiation stage occurs due to an increase in ROS production, thus occurring unfolded protein response (UPR) and exosomes containing melanocyte antigen-specific mIRNAs, DAMPs by melanocyte cells. These exosomes deliver vitiligo target antigens to nearby dendritic cells and stimulate their maturation into antigen-presenting cells (APC) efficiently. In addition, UPR activation also induces CXCL16 by disrupting keratinocytes and causing recruitment of CXCR6+ CD8 T-cells. NK and ILC-1 cells produce interferon-gamma, which induces chemokine production by keratinocytes. The progression stage is the stage of existence of Cells CD8+ T in vitiligo lesions that produce several cytokines such as interferon-gamma, there is a meeting between IFN-γ to its receptor causes activation of the JAK-STAT pathway, and secretion of CXCL9 and CXCL10 occurs in the skin and through CXCR3, CXCL9 promotes recruitment of melanocyte-specific CD8+ T cells to the skin while CXCL10 promotes their localization in the epidermis and increase the inflammatory process that occurs. Activation of CXCR3B by CXCL10 induces apoptosis in melanocytes and is continued at the maintenance stage of vitiligo What has happened is maintained by the cell melanocyte-reactive T_{rm} (T-resident memory) which will continue to persist in the skin via IL-15 signaling.[4,6,12]

Clinical manifestations

Clinical manifestations vitiligo in the form of macular lesions or depigmented patches with well-

defined round, oval or irregular shapes of varying sizes, not scaly, without itching, spread segmentally or non-segmentally. Classification of vitiligo based on the Vitiligo Global Issues Consensus Conference (VGICC) in 2011 can be seen in Table 1.[4]

Table 1. Classification of vitiligo.[4]

Types of vitiligo	Subtype
Non-segmental (NSV)	Focal vitiligo refers to small, isolated, depigmented lesions that acquire no clear pattern of distribution and that do not progress after a period of 1-2 years.
	Mucosal vitiligo usually involves the oral and/or genital mucosa.
	Acrofacial vitiligo is characterized by depigmented macules confined to the face, head, hands, and feet.
	Lip tip variety is a subcategory of the acrofacial type in which the lesions are confined to the cutaneous lips and the distal tips of the fingers.
	Generalized vitiligo is the most common form of vitiligo
	Vitiligo universalis refers to complete or nearly complete skin depigmentation (80% - 90% of the body surface).
Segmental (SV)	Focal.
	Mucosa.
	Unisegmental.
	Bi- or multisegmental.
Mixed (NSV + SV)	Refers to the initial VS relationship followed by the occurrence of bilateral VNS lesions months or less frequently, years later.
Unclassified	Multifocal nonsegmental asymmetry.
	Mucosa (one location).
	Focus on onset
	Vitiligo punctate: The lesions appear as macules punctiform1-1.5 mm, well-defined to involve any area of the body.
	Hypochromic vitiligo or vitiligo minor refers to a partial defect in pigmentation and appears to be limited to individuals with darker skin types.
	Follicular vitiligo presents with prominent leukonychia and limited skin involvement.

Free radicals

A free radical is a chemical substance (atom, molecule, or ion) that has one or more unpaired electrons in its external orbitals. These conditions make free radicals unstable and very reactive towards other compounds. Free radicals will continue to try to achieve stability by capturing electrons from other compounds so that if they are not controlled, they can have a bad impact because of their nature, which can trigger a chain reaction and cause cell damage. Free radicals can come from inside or outside the body. The formation of free radicals in the body is a process that occurs continuously and cannot be avoided. These free radicals are formed during metabolism and energy production. In living cells, free radicals are formed in the plasma membrane, mitochondria, peroxisomes, endoplasmic reticulum, and cytosol through enzymatic reactions in metabolic processes.[12,14]

Free radicals in the body have several forms, such as lipid radicals, protein radicals, deoxyribonucleic acid (DNA) radicals, and reactive oxygen species (ROS). ROS itself is a metabolite or by-product produced from aerobic metabolic processes and is highly reactive. The main type of ROS is superoxide (O_2-), hydrogen peroxide (H_2O_2), hydroxyl radical (OH), singlet oxygen ($^1O_2$), nitrite oxide (·NO), and peroxynitrite ($ONOO^-$). Superoxide is produced by adding 1 electron molecule to an oxygen molecule. This process is mediated

primarily in the mitochondria. Under normal circumstances, the electrons are used to reduce oxygen to water in the mitochondria. About 1-3% of the electrons leak and form superoxide. Superoxide will later be changed to H_2O_2 by superoxide dismutase. H_2O_2 is more stable than superoxide. This compound will undergo 3 processes in the cell, namely neutralized by the enzymes catalase and glutathione peroxidase, forming more reactive free radicals, namely hydroxyl radicals, through the Fenton reaction and reacting with chloride ions to form hypochloric acid radicals, which play a role in the phagocytosis process. The hydroxyl radical itself has a powerful destructive effect, which is initiated when it attacks lipids, proteins, and cell DNA (Figure 2).[14,15,16]

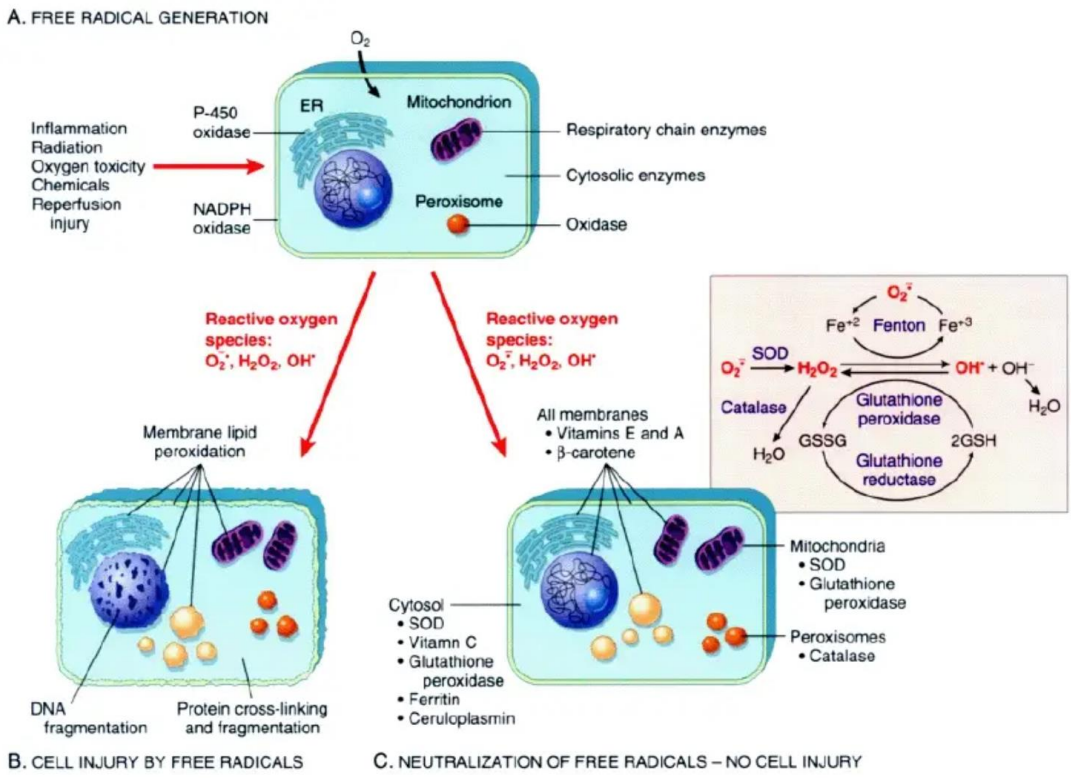


Figure 2. Formation of free radicals, cell damage due to free radicals, and neutralization of free radicals.[16]
Information: SOD = Superoxide dismutase, GSSG = Glutathione disulfide, GSH = Glutathione, NADPH = Nicotinamide adenine dinucleotide phosphate hydrogen.

The source of free radicals from outside the body can be in the form of environmental pollution, drugs, radiation, cigarette smoke, depletion of ozone, chemicals, toxins, alcohol, pathological microorganisms, anesthetics, pesticides, and solvents used in industry. Under normal conditions, the presence of free radicals is not always a bad thing. Free radicals have an important role in our body. Among them, they regulate blood flow in the arteries, become part of the immune system, and can function to kill cancer cells. Nitric oxide (NO) in blood vessels it is useful for regulating blood pressure, while in phagocytic cells, it functions to help eliminate parasites. Hydrogen peroxide also has the physiological function of killing bacteria along with lysosomes and chloride. If excess peroxide is found, it will be neutralized by the enzymes catalase or glutathione peroxidase.[14,16]

ROS production in the body will be balanced by the antioxidant defense system in normal conditions to

avoid an imbalance. There are two types of antioxidants in the body, which are enzymatic and non-enzymatic. Enzymatic antioxidants include superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), while non-enzymatic antioxidants include vitamin C, vitamin E, and glutathione (GSH) and beta carotene. This balance will reduce the oxidative damage that can be caused by ROS.[15,17]

An imbalance of increased production of free radicals that exceeds the capacity of antioxidants in the body will cause a condition called oxidative stress.[6] It is this oxidative stress that has been shown to contribute to the occurrence of various dermatological problems, including vitiligo.[15,18]

Influence free radicals in vitiligo

Vitiligo is currently still a pigmentation disorder that is often found, but the etiology of vitiligo is still not clearly known. Vitiligo is a skin depigmentation caused by the destruction of melanocytes. Many studies state that oxidative stress has an important role in the pathogenesis of vitiligo. The existence of the process of oxidative stress and autoimmunity, especially with the presence of genetic susceptibility, affects the occurrence of vitiligo. Elevated lipid peroxidase levels are a marker of oxidative stress in the early stages of vitiligo, indicating that ROS may be considered as an important early factor in inducing vitiligo and facilitating melanocyte loss.[14,19,20]

Melanocytes are the main target exposed to ROS during the process of melanogenesis. Such exposure can cause loss of homeostasis and cell death. Reactive oxygen species can interact with polyunsaturated fatty acid (PUFA) to initiate lipid peroxidase. The process will produce malondialdehyde (MDA) and trans-4-hydroxy-2 nonenal (4-NHE). Lipid peroxidase is the main manifestation and the first parameter of oxidative stress that can be used by many researchers to see the involvement of ROS in cell damage. Malondialdehyde itself is a metabolic product that can be used as a biomarker of oxidative stress. MDA levels were found to be significantly different in patients with vitiligo compared to patients without vitiligo. MDA levels positively correlated with the severity and activity of vitiligo. Patients with high serum MDA were found to be at risk of experiencing vitiligo 7.62 times higher than patients with normal MDA levels. This supports the large role of free radicals in the occurrence of vitiligo.[21]

Increase in ROS, especially H_2O_2, and peroxynitrite, in the patient's epidermis with vitiligo, followed by decreased levels of catalase, glutathione peroxidase, and glutathione reductase. This defect in antioxidant function increases the susceptibility of melanocytes to both immunological and ROS-induced toxicity.[20,22,23] up to hydrogen peroxide (H_2O_2) is said to occur due to the effect of increased SOD activity in vitiligo patients. SOD is the main antioxidant that works to counteract superoxide (O_2) so as to reduce its toxicity in cells. SOD will change O_2 to be H_2O_2. Under normal circumstances, H_2O_2 formed from this process will then be converted into H_2O from O_2 by the second antioxidant, namely catalase (CAT), whose levels decrease in vitiligo patients. This decrease in catalase levels eventually affects the accumulation of H_2O_2 toxic to melanocytes.[24,25]

The process of melanogenesis carried out by melanocytes also contributes to the increased levels of H_2O_2. Melanogenesis is a process that requires a large amount of energy to produce melanin pigment in large quantities.[21] This process can create a highly pro-oxidant environment in the epidermis. Some intermediate molecules such as 3,4-dihydroxyphenylalanine (DOPA), dopachrome, and 5,6-dihydroxyindole formed during melanin biosynthesis. The end result of this change is a continuous increase in H_2O_2, which restrains the activity of antioxidant enzymes that lead to the destruction of melanocytes. The high level of H_2O_2 will inactivate and reduce levels of methionine sulfoxide reductase A and B and levels of thioredoxin/thioredoxin reductase so that it will further impact on oxidative stress and death of melanocyte cells. H level$_2O_2$ which is high in the epidermis is also found to be able to oxidize adeno

corticotropic hormone (ACTH) and alpha-melanocyte-stimulating hormone (MSH), in which the two hormones normally function as antioxidants in human melanocytes. This condition eventually affects all cell components and causes the destruction of melanocytes (Figure 3).[24,25,27]

Continuous oxidative stress stimulus causes irreversible damage to melanocyte DNA, and the cell will then enter the aging process and experience irreversible proliferation inhibition. Aging melanocytes (senescence) will produce a phenotype senescence-associated secretory phenotype (SASP) and will secrete proinflammatory factors such as IL6, cyclooxygenase, extracellular matrix metalloproteinases (MMPs) and insulin-like growth factor binding protein. These excreted substances will later recruit immune cells to destroy the old melanocytes. This procedure can also affect the surrounding cells so that it will have a wider impact.[26]

Lipid peroxidation due to ROS will cause a decrease in mitochondrial function. Mitochondria are not only a source of ROS emergence but are also affected by the destructive effects of ROS itself. Mitochondria are very important for the survival of melanocyte cells. Mitochondrial damage is characterized by permeability of the mitochondrial outer membrane, loss of cell membrane potential, and apoptosis. Damage to mitochondria will contribute further to the damage to melanocytes.[21,26]

Research by Chen et al. in 2021 examined further compounds that are by-products of the process of destroying macromolecules due to ROS, such as advanced oxidative protein products (AOPP), advanced glycosylation end products (AGE), MDA and 8-hydroxy-2'-deoxyguanosine as diameters to evaluate the progress of vitiligo. These compounds have been shown to reflect the duration and activity of vitiligo.[26]

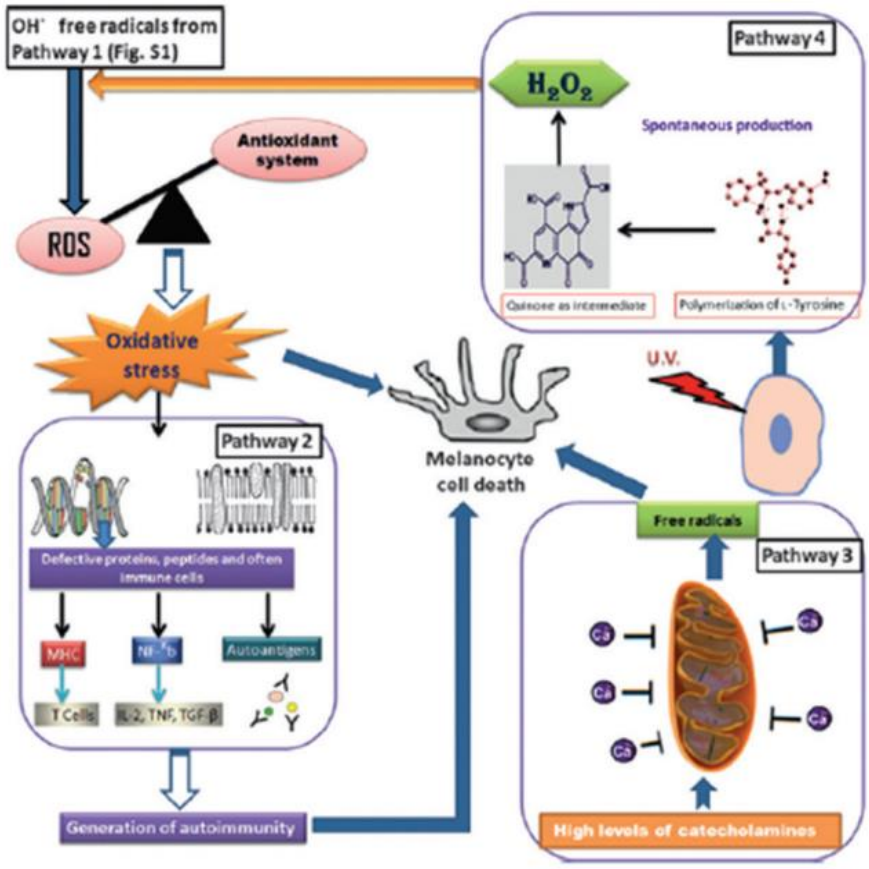


Figure 3. Oxidative stress and vitiligo.[27]

Information: ROS = Review of system, MHC = major histocompatibility complex, NF = Neurofibromatoses, THE =Interleukin, TNF = Tumor necrosis factor, TGF = Transforming growth factor.

2. Conclusion

Vitiligo is a depigmentation disorder that is commonly found in the community. The causes of vitiligo are multifactorial, such as genetic and environmental factors accompanied by the presence of non-specific and specific immune system factors. Melanocytes are the main target exposed by reactive oxygen species (ROS) during the process of melanogenesis. Such exposure can cause loss of homeostasis and cell death and has implications for vitiligo. Clinical manifestations of vitiligo are generally white depigmented macular lesions that are well demarcated. Based on its distribution, vitiligo can be divided into segmental and non-segmental vitiligo different in terms of prognosis, treatment and resolution of vitiligo.

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