REVIEW ARTICLE

Vitiligo and Diet: Searching for a Link

Manar Mohammad Aladwani,[1] Reem Saif Alrashidi,[1] Nawaf Almutairi[2]

[1]*Medical Students, Kuwait University, Jabriya, Kuwait*
[2]*Professor, department of Medicine, Kuwait University, Jabriya, Kuwait*

ABSTRACT

Vitiligo is a common form of localized depigmentation. An acquired condition caused by the gradual loss of melanocytes. Clinically it is is characterized by milky-white, sharply demarcated macules. Worldwide prevalence of vitiligo is estimated to be varying from 0.5% –1%. Age of onset in around half of the cases is less than 20 years of age, and it affects both the sexes equally. Histopathology of active vitiligo reveals perivascular lymphocytic infiltration, epidermal aggression, and basal layer vacuolar degeneration. Special stains for melanin reveal a lack of dopa-positive melanocytes in the basal layer of the epidermis. The etiology of vitiligo is not fully understood and there are various theories suggested. But, none of them seems to explain all the cases by its own. Hence, it is often purported to be multifactorial. Regarding management, there are number of safe and highly effective therapies approved in recent years. A combination of phototherapy, systemic and topical immunosuppressive agents, and surgical procedures may slow the progression of the condition, transform depigmented patches, and promote repigmentation. The ability of certain nutrients to modulate, promote, or interfere with pathophysiology and immune system activity is referred to as immunonutrition. We will discuss the food and food components that may affect the vitiligo.

INTRODUCTION

Vitiligo is a common form of localized depigmentation. An acquired condition caused by the gradual loss of melanocytes. This condition is characterized by milky-white, sharply demarcated macules.[1] Worldwide, vitiligo is estimated to be prevalent in 0.5%–1% of people. Vitiligo occurs in about 50% of patients under the age of 20, and it affects both sexes equally.[2] In active vitiligo, histopathology reveals perivascular lymphocytic infiltration, epidermal aggression, and basal layer vacuolar degeneration. In inflammatory vitiligo, there is an infiltrate of lymphocytes and histiocytes along the erythematous border. In some biopsies, mainly in the active stages of the disease, this infiltrate is also found in the marginal areas. There is a lack of dopa-positive melanocytes in the basal layer of the epidermis according to histochemical studies.[3]

Theories to explain the pathogenesis of Vitiligo:

In terms of vitiligo aetiology, there are a various theories; the same mechanism may not apply to every case.

Correspondence: *Prof. Nawaf AlMutairi, department of Medicine, Kuwait University, Jabriya, Kuwait*
E mail: nalmut@usa.net

The autoimmune/autoinflammatory theory:

There is strong evidence for the autoimmune/auto-inflammatory theory, which is currently the leading hypothesis. This theory is based on the clinical association between vitiligo and several autoimmune or auto-inflammatory diseases. Genetic susceptibility to other autoimmune diseases has been demonstrated in association with vitiligo. A number of circulating autoantibodies specific for pigment cells have been detected in the sera of patients with vitiligo. In about 10% of patients, anti-melanocyte antibodies are present at high levels, especially those against tyrosinase 1 and 2 (TRP-1 and TRP-2).[4] Cell-mediated immunity may be activated in vitiligo, according to studies revealing CD4+ and CD8+ lymphocytes in the dermal-epidermal junction.[5,6]

NEURAL THEORY

According to Lerner's "neural theory," dysfunction of the sympathetic nervous system (SNS) affects melanin production and causes depigmentation.[7] In vitiligo patients, nerve growth factor (NGF) levels & HVA and VMA levels are correlated with disease activity.[8] Moreover, stress can trigger the release of catecholamines by stimulating the hypothalamic-pituitary-adrenal axis. By releasing catecholamines, stressors cause vasoconstriction, hypoxia, and an overproduction of oxygen radicals that lead to melanocyte destruction.[9]

Integrated theory (convergence theory):

The convergence theory explains that vitiligo may be a syndrome with multi-factorial etiology rather than a single disease. As the pathophysiology of vitiligo cannot be adequately explained by immune or non immune mechanisms, the most accepted theory suggests that the pathophysiology of vitiligo is influenced by a combination of biochemical, environmental, and immunological factors.[10]

INTRINSIC THEORY

In the intrinsic theory, an intrinsic defect in melanocytes may cause melanocyte death. The abnormal rough endoplasmic reticulum, the lack of melanocyte growth factors such as basic fibroblast growth factor (bFGF) and the decrease in melanocytes expressing the c-kit receptor may contribute to melanocyte damage.[11]

Apoptosis and accelerated cell senescence:

The non-lesional skin of vitiligo patients shows some cytologic changes, including vacuolization of cytoplasm, marginalization of DNA in the nucleus, dendrite loss, and detachment.[12] Furthermore, degeneration of basal and suprabasal epidermal cells in the depigmented and normally pigmented skin due to swelling of the membrane-bound organelles, formation of vacuoles, and cytoplasm condensation are associated with the apoptotic changes.[13] The lower expression levels of the antiapoptotic Bcl-2 and FLIP proteins in vitiliginous skin, the high levels of the proapoptotic bax and p53 proteins, and the active forms of caspase-3, 8, and 9 contribute to the apoptotic process in vitiligo.[14]

BIOCHEMICAL THEORY

The biochemical hypothesis argues that biochemical abnormalities of melanocytes and keratinocytes leading to aberrant melanization are in vitiligo pathogenesis. Oxidative stress is implicated in the destruction of melanocytes.[15] It has been suggested that defective free radical

defense, excessive hydrogen peroxide (H_2O_2), and toxic intermediate melanin metabolites play a role in this process.[16] Danger signals named damage-associated molecular patterns (DAMPs), including reactive oxygen species (ROS) and iHSP70, are released from stressed melanocytes.[17] A rise in oxidative stress markers (superoxide dismutase, malondialdehyde, and ROS) and a reduction in antioxidative enzymes (catalase, glutathione peroxidase, glutathione reductase, thioredoxin reductase, thioredoxin, and superoxide dismutases) are caused by increased sensitivity of melanocytes to external prooxidant stimuli.[18] It has also been suggested that mitochondrial dysfunction, such as changes in mitochondrial transmembrane potential and electron transport chain, may play a role in vitiligo pathophysiology.[19] The recycling of tetrahydrobiopterin, which is an essential cofactor in tyrosinase synthesis from L-phenylalanine, is also affected by oxidative stress. Dihydropteridin reductase, a key enzyme involved in the recycling process of 6-tetrahydrobiopterin, is modified by oxidative stress by altering its active site.[18] Therefore, there is an increase in the production of hydrogen peroxide and a decrease in the level of catalase, resulting in the death of melanocytes.[20]

There are more theories about the cause of vitiligo, and they each have their own proof and respect. In fact, it appears that no one theory can stand alone as a cause of vitiligo. It may be a syndrome, as mentioned previously with most of the causes, or it may be a white patch manifesting different kinds of diseases, such as headaches. Vitiligo's pathogenesis requires more and more research in order to find out the exact cause and, subsequently, the proper treatment.

THERAPY

Currently, treating vitiligo is one of the most challenging dermatological concerns. Nevertheless, there have been a number of safe and largely effective therapies developed in recent years. A combination of phototherapy, systemic and topical immunosuppressive agents, and surgical procedures may slow the progression of the condition, transform depigmented patches, and promote repigmentation.[21] Treatment effectiveness is influenced by the type of vitiligo (segmental or non-segmental), severity, distribution, frequency, age of the patient, type of skin, and willingness to follow therapy consistently. Lips, hands, and feet are more resistant to treatment, while head, neck, face, abdominal regions, arms, and legs are more likely to recover.[22] Repigmentation begins at the edges of the lesions or in a pattern known as "perifollicular". It is important to evaluate the treatment's efficacy after at least two to three months. Vitiligo is most commonly treated with ultraviolet radiation, which, when combined with other therapies, has been shown to yield better results.[23]

Can oxidative stress umbrella cover all other theories?

Despite the lack of a clear pathogenesis for vitiligo, growing evidence points to oxidative stress as the initial trigger followed by immune dysregulation in patients with vulnerable genetic backgrounds. In the epidermis and blood of vitiligo patients, there was an obvious redox imbalance. In vitiligo patients, the increased production of reactive oxygen species (ROS) combined with a compromised antioxidant system produces a pro-oxidant milieu that challenges melanocytes

to oxidative stress, resulting in dysfunction or death.

Oxidative stress is characterized by an excess of ROS production and a dysfunctional antioxidant system. DNA, proteins, and lipids are oxidized in the resulting oxidative milieu, and the products of this oxidation are reliable markers of oxidative stress. The levels of 8-hydroxylated guanine (8-OH_2dG) and malondialdehyde (MDA) in patients with active vitiligo are significantly higher than those in healthy individuals.[24] Vitiligo patients produce excessive hydrogen peroxide (H_2O_2) in their epidermis. H_2O_2 can be generated by spontaneous dismutation of superoxide anion (O_2) in acidic pH conditions. This spontaneous dismutation is accelerated by 140-fold by the enzyme superoxide dismutase (SOD). It was found that vitiligo patients have an elevated level of SOD in their epidermis and blood. Finally, the enzyme NADPH oxidase 4 (NOX4) is known to produce directly H_2O_2 due to its third extracytosolic loop (E-loop) that performs SOD activity.[25] As a secondary messenger, H_2O_2 can penetrate the cellular membrane due to its molecular structure and has an extended lifetime compared to other ROS. It has been proposed that the mitochondrial electron transport chain is the main intracellular site of ROS overproduction in patients with vitiligo. An increase in mitochondrial DNA copy number was found in the blood of vitiligo patients, indicating that mitochondria play a role in the disease's pathogenesis.[26]

A human's antioxidant system consists of antioxidant enzymes that remove ROS at a controlled rate and low molecular weight antioxidants (LMWAs) that scavenge ROS. Catalase is an enzyme that catalyzes the decomposition of H_2O_2 into water and oxygen. Compared to healthy controls, vitiligo patients had lower levels of catalase in their epidermis and blood, as well as a genetic polymorphism in the catalase gene.[27] Glutathione peroxidase (GPx) is another enzyme important for reducing intracellular H_2O_2 to water. Vitiligo patients have decreased GPx expression and activity in their blood and skin,[28] and Mansuri *et al* have confirmed the genetic association between vitiligo and variations in the GPx gene.[29] Thioredoxin reductase (TxR) reduces the LMWA thioredoxin repristinating its ROS scavenging activity. It has been shown that vitiligo skin has a decreased level of TxR.[30]

According to the existing data, redox imbalance is strongly associated with vitiligo pathogenesis. In vitiligo patients, oxidative stress suppresses melanocyte function in three main ways. First, as was noted before, melanocytes of vitiligo patients are genetically susceptible to oxidative stress evoked by mechanical pressure (Koebner effect), chemical threats (e.g., the exposure to phenolic chemicals), and ultraviolet B (UVB) radiation.[18] Second, Wang *et al* demonstrated in vitro that oxidative stress can induce the morphological changes in melanocytes, namely, the loss of dendrites through which melanocytes transport the melanin to surrounding keratinocytes.[31] Third, ROS can directly affect the activity of tyrosinase, the enzyme that catalyzes the melanin synthesis from its precursor tyrosin. H_2O_2 can alter calcium homeostasis, disrupting the uptake of L-phenylalanine, an amino-acid precursor of tyrosine in melanocytes.[32] Moreover, H_2O_2 can directly regulate the activity of tyrosinase: low concentrations of H_2O_2 ($\leq$0.3 mM) activate the enzyme whereas high concentrations of H_2O_2

(≥0.3 mM) downregulate its activity.[33] High concentration of H_2O_2 (1 mM) was found in the skin of vitiligo patients, which can explain the low tyrosinase activity in vitiligo melanocytes.[34] Finally, oxidative stress has been found to be closely correlated with autoimmunity in vitiligo, where inflammasomes, which contain caspase-1 copies in their central part, can play a key role.[35] Oxidative stress was shown to induce the inflammasomes formation and, thus, activation of caspase-1 which performs the processing and maturation of IL-1β and IL-18 further released from the cells to attract other immune cells and start the immune reaction. Inflammasomes are components of native immunity that help the cell cope with viruses or bacteria it cannot handle alone. Moreover, the formation of inflammasomes is the initial step in chain events bringing to a programmed cell death called pyroptosis.[36] The three key events in pyroptosis include the formation of inflammasomes and the release of cytokines, the formation of pores in the plasmatic membrane that lead to cell swallowing, and a necrosis-like explosion of the cell's contents. In vitiligo skin, melanocytes that undergo this type of cell death may release products of protein oxidation formed by intracellular oxidative stress or abnormal protein folding caused by collapse of the endothelial reticulum (ER), which may lead to autoimmune disease.

As a result of the above information, topical and oral antioxidants for suppressing, respectively, local and systemic oxidative stress can be considered as adjuvant treatments for vitiligo, as they may interfere with the suspected pathogenesis of the disease.

FUNCTIONAL FOODS

The term "functional food" is defined as whole food, food supplement, enriched, or fortified food with beneficial health effects when consumed as part of a regular diet.[37] The ability of certain nutrients to modulate, promote, or interfere with pathophysiology and immune system activity is referred to as immunonutrition.[38] We will discuss below the food and food component that may affect the vitiligo.

VITAMIN B_{12} AND FOLIC ACID

Of the eight types of B vitamins, vitamin B_{12}, also called cobalamin, is one of the nine water-soluble vitamins. Among the most prevalent deficiencies, it may lead to blood and nerve disorders if untreated.[39] The best way to get vitamin B_{12} is through a non-vegetarian diet that includes dairy, meat, and eggs. Every day, 2 points-4 µg of B_{12} are typically consumed. Reabsorption is only between fifty and sixty percent.[40] Studies on vitiligo patients have demonstrated the benefit of vitamin B_{12} for repigmentation. Treatment for Vitiligo: Folic acid, also known as vitamin B_9, has been shown to be effective. The body cannot synthesize it, so it must be consumed through diet. Low levels of vitamins B_{12} and B_9 were found in 15 patients with vitiligo, according to an original study done at the University of Alabama's Birmingham Medical Center? Nine of these patients experienced repigmentation following a three-year course of vitamin B_{12} and B_9 administration.[41]

VITAMIN C

Vitamin C is one of the water-soluble vitamins that is found mostly in citrus fruits such as lemon, kiwi, oranges, and green leafy vegetables. It is

important to include vitamin C in a balanced because of its antioxidant properties and immune-modulating effects. However, its contraindicated to use vitamin C in treating vitiligo because it interferes with melanin production processes.[42]

VITAMIN D

Vitamin D, a fat-soluble vitamin, plays important role in absorbing substances like calcium and magnesium, and it act on skin receptors to affect the growth and development of melanocytes and keratinocytes. 25-hydroxyvitamin D_3 (calcifediol) work on Dihydroxy vitamin D_3 receptors on the melanocyte to stimulate melanin secretion.[43] Research found that vitamin D levels affect the immune system, since the immune system contain different enzymes/metabolites that play role in metabolizing vitamin D, suggesting that the immune system also plays role in the converting vitamin D from its inactive form into its active forms of calcitriol. This creates an association between the normal immune system in human's body and the levels of vitamin D in the circulation. Any imbalance in vitamin D levels would lead to impairment of immune system function. It's believed that this impairment in the immune system might increases the chances of developing autoimmune diseases. Therefore, administering adequate doses of vitamin D levels in patients who are deficient, could significantly improve treatment outcomes for autoimmune disorders.[44] Still, there is limited medical evidence support the fact that low vitamin D could lead to vitiligo. Because of relation to the immune system, its highly advised to include it in the therapy for managing vitiligo. Multiple studies have been done to understand the effect of vitamin D in patient with vitiligo. According to a previous study done by Finamor *et al*., which consist of 16 patients, 35000 IU (international unit) of vitamin D_3 was given daily for six months. Results showed that, out of 16, 14 patients showed 25% to 75% regimentation. This finding suggest that the fact vitamin D supplementation could lower disease progression.[45]

ZINC

Zinc is a cofactor that is essential for the normal functioning for multiple protein. Also, skin antioxidants such as superoxide dismutase, uses zinc as an enzyme cofactor.[46] Zinc also play a role in controlling gene expression. Also, it may inhibit melanocytes destruction since apoptotic caspases are activated when there is a decrease in the concentration of intercellular zinc.[47] It has been found that zinc have an advantage in treating vitiligo when combined with tropical steroids, but still, more investigations are needed. However, zinc supplementations have gastrointestinal adverse effect. A recent experiment done by Yaghoobu *et al.*, 13.3% of the participant who consumed zinc complained of gastric discomfort.[48]

GINKGO BILOBA

Ginkgo biloba (GB), an ancient Chinese plant, has previously showed a great role in the treatment of multiple ailments, mainly vitiligo, dementia, and macular degeneration, anxiety, and cardiovascular disease.[49] GB have anti-inflammatory effects. The mechanism of its anti-inflammatory effect is explained by a decrease in cyclooxygenase activity and Tumor Necrosis Factor alpha's role (TNF-a) in inducing the production of intereukin-8 and vascular endothelial growth factor (VEGF). These advantages of ginkgo have been used as therapeutic due its

vital rule of oxidative stress in the pathogenesis of vitiligo. Additionally, since emotional anxiety believed to worsen vitiligo, ginkgo's antioxidative properties could decrease the spread of the condition.[50]

POLYPODIUM LEUCOTOMOS

Polypodium leucotomos (PL), a species of fern, has been studied for its therapeutic role in multiple dermatological conditions, particularly vitiligo, psoriasis, atopic dermatitis, and in preventing UV-induced skin damage. Investigations have been done on the anti-inflammatory, antioxidant, photoprotective, and immunomodulatory properties of PL. ingesting PL can be used to improve the efficacy of narrowband UV-B in treating vitiligo once used with phototherapy.[51] It was also showed that combining PL with PUVA (psoralen plus ultraviolet-A radiation) treatment results in an increased regimentation. Participants undergoing PUVA along with PL, more than 50% of then had re-pigmentation than the group undergoing PUVA with placebo. All participants saw the successful treatment of their condition undergoing Anopsos therapy for five months, which is a hydro soluble lipid derivative of PL.[52]

KHELLIN

Khellin, a crystalline extract from the plant Ammi visnaga, has been used in traditional medicine throughout the Mediterranean. The oral type of khellin is being investigated as a promoter of melanogenesis and proliferation of cultured normal human melanocytes and Mel-1 melanoma cells. These have an important role in photosensitizing vitiligo therapy once combined with UV therapy. Combining of 4 percent of preparation of tropical khellin with monochromatic excimer laser (MEL) treatment at 308 nm, has been found to effectively decrease depigmented lesions compaired to no treatment.[53]

GLUTEN

Celiac disease (CD), an autoimmune disease that affects the intestines, is characterized by sensitivity to gluten. This disease can lead to multiple adverse reactions, including damage to intestinal mucosa causing diarrhea in most of the causes, abdominal discomfort, and other gastrointestinal symptoms. Studies showed that patients diagnosed with CD had higher prevalence of vitiligo compared to people without CD. Studies also showed that following glutenfree diet had improved symptoms of patients diagnosed with CD and autoimmune dermatological conditions like psoriasis, dermatitis hepatitis, and vitiligo. This is commonly known as GFD. A single case of 9 year old child with both CD and vitiligo showed huge improvement after following GFD for 1 year duration.[54] Moreover, there have been reports showing concurrent occurrence of DH and vitiligo. Two studies discussed this relationship, and in both of them, the DH lesions were significantly resolved after the patients followed a GFD. However, vitiligo lesions remained the same. A previous study about a 53 year old female showed a huge improvement in DH lesions after 5 months of following GFD, however the vitiligo lesions didn't change.[57] Another case of a 21 year old patient with vitiligo, DH and CD showed a significant resolution in DH lesions after following a strict GFD and tropical steroids. However, the vitiligo lesions remained the same.[58]

PHENYLALANINE

Phenylalanine (Phe), an amino acid, used as a treatment for vitiligo due to its essential role in controlling carecholamine, antibody synthesis, and melanin production. Phenylalanine is hydroxylated to tyrosine which play an important rule in melanin production. As per neural hypothesis, there was an association with the etiopathogenesis of vitiligo and catecholamines that is secreted but autonomic nerve terminals, either directly or indirectly.[9] The production of catecholamine is disturbed by PE or metabolite levels, and this may affects vitiligo onset or improvement. In a previous clinical study discussed the phenylalanine's effect on vitiligo, each participant participated as their own control. The study didn't show any improvement after four months of UV-A treatment for the subjects who received oral phenylalanine (50 mg/kg) twice a week for the first four months when the treatment was given separately. However, the study also showed that 94.7 percent of participants expressed follicular repigmentation and 26.3 percent had dense repigmentation after adding phenylalanine along with UV-A irradiation.[59]

PHYLLANTHUS EMBELICA

Libellula embelica Linn. known as "amla fruit" or Indian Gooseberry, is a tropical and subtropical fruit that is widely distributed throughout China, India, Indonesia, and Thailand. Studies have shown that *P. Embellica's* high vitamin C and polyphenolic content contribute to its potent antioxidant potential. A. P. A second study involving 130 participants looked at embelica fruit in relation to carotenoids and vitamin E, which are frequently used in the treatment of vitiligo. In the study, half of the subjects received only conventional treatments, such as topical drugs and phototherapy. Traditional therapy for the second group of patients involved topical medication or phototherapy in addition to a diet rich in antioxidants, vitamin E, and carotenoids taken three times a day. Based on these studies, a greater proportion of patients in the antioxidant-supplemented group experienced mild repigmentation in the head, neck, and truck area six months later. The group with higher erythema, more vitiligous patches, more inflammation, and a faster expansion of the vitiligous zone was not given antioxidants.[60]

PIPERINE

The primary alkaloid in black pepper, piperine, has been shown in vitro experiments to promote melanocyte replication and induce the formation of melanocytic dendrites. Numerous studies suggest using piperine when there is UV exposure. Studies reveal that piperin stimulates the effect of UV light on melanocytes. In the mouse cell line melan-a, piperine only increased melanocyte proliferation and dendritic production in the absence of UV-A. Mice treated with both piperine and UV radiation (UVR) exhibited a more noticeable pigmentation than those treated with either drug alone. Research has shown that when treating vitiligo, UVR and piperine should be used at different times to avoid photoisomerization of the former.[61,62]

NIGELLA SATIVA

Nigella sativa, a perennial plant species producing black cumin, is commonly used to treat different illnesses, particularly dermatological conditions. Thymoquinone, an essential component of *Nigella sativa,* is being investigated for

its potential benefits, especially for its anticancer, immunomodulatory, and anti-inflammatory properties.[63] Tropical application with *Nigella sativa* oil has been shown a huge improvement in the Vitiligo Area Scoring Index score within four months.[64]

PUNICA GRANATUM

Pomegranate (Punica granatum Linn.) is one of the initial fruit trees that have been planted. It is abundant in polyphenolic compounds and tannins. Thus, consuming three to six servings of commercially available pomegranate juice daily may have antioxidant advantages.[65]

GREEN TEA

Catechins are a type of polyphenolic compounds that are found in green tea and belongs to the flavonoid class. They are responsible green tea's antioxidant properties. Among these, Epigallocatechin-3-gallate (EGCG) is considered the most abundant and therapeutically significant component of green tea. It has a strong antioxidant activity, which can be explained by scavenging reactive oxygen and nitrogen species (ROS/RNS) and shows potent anti-inflammatory characteristics, which can modulate T-cell-mediated immune responses.[66] Previous In vitro studies have revealed that EGCG'S have a strong antioxidant effect on primary human melanocytes, including the reduction of ROS production, restoration of impaired mitochondrial function, and decreasing of apoptosis activated by hydrogen peroxide. Also, EGCG regulates oxidative stress pathways in melanocytes exposed to stress. Animal experimental studies showed depigmentation influenced by monobenzone.[67] Studies showed the immune-modulating and oxidative stress properties of 2, 5, and 10% EGCG cream. However, there is no data regards the effect of EGCG on humans. Furthermore, it is suggested to achieve its antioxidant potential by consume 5 to 16 cups of tea daily. EGCG extract supplementation appear might be easier option than tea infusion.[68]

CURCUMIN

Curcumin, scientifically referred to as diferuloylmethane, is a primary the primary lipophilic polyphenol that is naturally occurring in the rhizome of *Curcuma longa* (turmeric) and other Curcuma species. Multiple studies showed that curcumin showed strong and complex antioxidant properties, allowing it to influence antioxidant system both directly and indirectly, as well as inhibit the production of reactive oxygen species (ROS) and their intracellular origins. An in vivo study showed that combining narrowed UV-B (NB-UVB) and tetrahydro-curcuminoid topically in patients with vitiligo, result in higher rate of re-pigmentation compared with using (NB-UVB) alone.[69]

CONCLUSION

In summary, despite various theories about the pathogenesis of vitiligo, none of them can be perfectly used. Viewing vitiligo as a syndrome with of these theories doesn't align with the nature of the disease. Now, it's more accurate to consider vitiligo as a sign or symptoms of various diseases with different causes that lead to melanocyte damage.

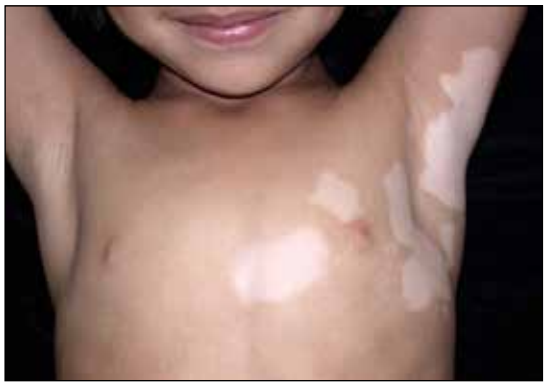

Fig. 1

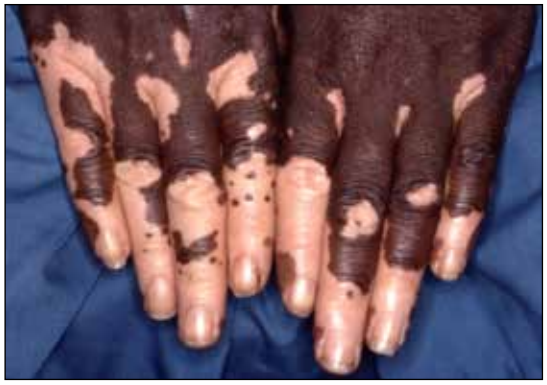

Fig. 2

REFERENCES

1. Bologna J, Pawelek JM. Biology of hypopigmentation. J Am Acad Dermatol 1988; 19:217-55.
2. Boniface K, Seneschal J, Picardo M, *et al.* Vitiligo: Focus on Clinical Aspects, Immunopathogenesis, and Therapy, Clinical reviews in allergy & immunology. Clin Rev Allergy Immunol. 2018; 54(1):52-67.
3. Montes LF, Abulafia J, Wilborn WH, Hyde BM, Montes CM. Value of histopathology in vitiligo. Int J Dermatol. 2003; 42:57-61.
4. Passeron T, Ortonne JP. Physiopathology and genetics of vitiligo. J Autoimmune. 2005; 25:63-68.
5. Zhou L, Li K, Shi YL, Hamzavi I, *et al*. Systemic analyses of immunophenotypes of peripheral T cells in non-segmental vitiligo: Implication of defective natural killer T cells. Pigment Cell & Melanoma Research. 2012; 25:602-11.
6. Palermo B, Campanelli R, Garbelli S, *et al*. Specific cytotoxic T lymphocyte responses againstMelan-A/MART1, tyrosinase and gp100 in vitiligo by the use of major histocompatibility complex/peptide tetramers: The role of cellular immunity in the etiopathogenesis of vitiligo. J Invest Dermatol. 2001; 117(2):326-32.
7. Lerner AB. Vitiligo. J Invest Dermatol. 1959; 32:285-310.
8. Rateb AAH, Azzam OA, Rashed LA, *et al*. The role of nerve growth factor in the pathogenesis of vitligo. Journal of the Egyp Wom Dermatol Soc. 2005; 1:18-2.
9. Morrone A, Picardo M, Luca CD, *et al*. Catecholamines and vitiligo. Pigment Cell Research. 1992; 5:65-69.
10. Le Poole IC, Das PK, Van Den Wijngaard RM, *et al*. Review of the etiopathomechanism of vitiligo: A convergence theory. Exp Dermatol. 1993; 2(4):145-53.
11. Norris A, Todd C, Graham A, *et al*. The expression of the c-kit receptor by epidermal melanocytes may be reduced in vitiligo. Brit J Dermatol. 1996; 134:299-306.
12. Boissy RE. Histology of vitiliginous skin. In: Hann S, Nordlund JJ, editors. Vitiligo. 1st ed. Oxford: Blackwell Science Ltd; 2008; pp. 23-3.
13. Tschopp J, Martinon F, Burns K. NALPs: A novel protein family involved in inflammation. Nature Reviews. Mol Cell Biol. 2003; 4:95-104.
14. Bondanza S, Maurelli R. Keratinocyte cultures from involved skin in vitiligo patients show an impaired in vitro behaviour. Pigment Cell Research. 2007; 20(4):288-300.
15. Speeckaert R, Dugardin J, Lambert J, *et al*. Critical appraisal of the oxidative stress pathway in vitiligo: A systematic review and meta-analysis. Journal of the Eur Acad Dermatol Venereol. 2018; 32(7):1089-98.
16. Sahera S, Reddy YV, Kumar DS. A rare case report of Vitiligo Vulgaris in pediatric patient in tertiary care hospital. IOSR J Dent Med Science. 2020; 20:42-47.
17. Richmond JM, Frisoli ML, Harris JE. Innate immune mechanisms in vitiligo: Danger from within. Cur Opin Immunol. 2013; 25(6):676-82.
18. Jimbow K, Chen H, Park JS, *et al* Increased sensitivity of melanocytes to oxidative stress and abnormal expression of tyrosinase related protein in vitiligo. Brit J Dermatol. 2001; 144(1):55-65.
19. Dell'Anna ML, Urbanelli S, Mastrofrancesco A, *et al* Alterations of mitochondria in peripheral blood mononuclear cells of vitiligo patients. Pigment Cell Research. 2003:553-59.
20. Schallreuter KU, Elwary SM, Gibbons NC, *et al* Activation/ deactivation of acetylcholinesterase by H2O2: More evidence for oxidative stress in vitiligo. Biochem Biophy Research Comm. 2004; 315(2):502-08.
21. Rodrigues M, Ezzedine K, Hamzavi I, Pandya AG, Harris JE: Current and emerging treatments for vitiligo. J Am Acad Dermatol. 2017; 77:17-29.
22. Brazzelli V, Antoninetti M, Palazzini S, Barbagallo T,

De Silvestri A, Borroni G: Critical evaluation of the variants influencing the clinical response of vitiligo: study of 60 cases treated with ultraviolet B narrowband phototherapy. J Eur Acad Dermatol Venereol. 2007; 21:1369-74.

23. Ezzedine K, Whitton M, Pinart M: Interventions for vitiligo. JAMA. 2016; 316:1708-09.
24. Mitra, S., De Sarkar, S., Pradhan, A., Pati, A. K., Pradhan, R., Mondal, D., Chatterjee, M. Levels of oxidative damage and proinflammatory cytokines are enhanced in patients with active vitiligo. Free Radical Research 2017; 51(11-12):986-94.
25. Takac, I., Schröder, K., Zhang, L., Lardy, B., Anilkumar, N., Lambeth, J. D., Brandes, R. P. The E-loop is involved in hydrogen peroxide formation by the NADPH oxidase Nox4. J Biol Chem 2011; 286(15): 13304-13.
26. Vaseghi, H., Houshmand, M., & Jadali, Z. Increased levels of mitochondrial DNA copy number in patients with vitiligo. Clin Exp Dermatol 2017;42(7): 749-54.
27. Caputo, V., Niceta, M., Fiorella, S., La Vecchia, M., Bastonini, E., Bongiorno, M. R., & Pistone, G. Vitiligo susceptibility and catalase gene (CAT) polymorphisms in sicilian population. Giornale Italiano di Dermatologia e Venereologia.
28. Xiao, B. H., Shi, M., Chen, H., Cui, S., Wu, Y., Gao, X. H., & Chen, H. D. Glutathione peroxidase level in patients with vitiligo: A meta-analysis. Biomedical Research International, 2016, 1 Article ID 3029810.
29. Mansuri, M. S., Jadeja, S. D., Singh, M., Laddha, N. C., Dwivedi, M., & Begum, R. The catalase gene promoter and 50 -untranslated region variants lead to altered gene expression and enzyme activity in vitiligo. Brit J Dermatol 2017; 177(6): 1590-1600.
30. Gibbons, N. C., Wood, J. M., Rokos, H., & Schallreuter, K. U. Computer simulation of native epidermal structures in the presence and absence of hydrogen peroxide (H_2O_2): Potential and pitfalls. J Inv Dermatol 2006;126(12): 2576-82.
31. Wang, P., Li, Y., Nie, H., Zhang, X., Shao, Q., Hou, X., Xu, A. The changes of gene expression profiling between segmental vitiligo, generalized vitiligo and healthy individual. J Dermatol Science 2016; 84(1):40-49.
32. Schallreuter, K. U., Gibbons, N. C. J., Zothner, C., Abou Elloof, M. M., & Wood, J. M. Hydrogen peroxide-mediated oxidative stress disrupts calcium binding on calmodulin: More evidence for oxidative stress in vitiligo. Biochem Biophy Research Comm 2007; 360(1):70-75.
33. Tang, L., Li, J., Lin, X., Wu, W., Kang, K., & Fu, W. Oxidation levels differentially impact melanocytes: Low versus high concentration of hydrogen peroxide promotes melanin synthesis and melanosome transfer. Dermatol 2012; 224(2):145-53.
34. Barygina, V., Becatti, M., Lotti, T., Moretti, S., Taddei, N., & Fiorillo, C. Treatment with low-dose cytokines reduces oxidative-mediated injury in perilesional keratinocytes from vitiligo skin. J Dermatol Science 2015;79(2):163-70.
35. Marie, J., Kovacs, D., Pain, C., Jouary, T., Cota, C., Vergier, B. Cario-André, M. Inflammasome activation and vitiligo/nonsegmental vitiligo progression. Brit J Dermatol 2014; 170(4): 816-23.
36. Sá, D. C., & Festa, C. N. Inflammasomes and dermatology. Anais Brasileiros de Dermatologia 2016; 91(5): 566-78.
37. Humpf, H. U., Schneider, C., & Stevens, J. F. Functional food—Where do we go? Molecular Nutrition & Food Research 2014; 58(1): 5-6.
38. Grimm, H., & Calder, P. C. Immunonutrition. British Journal of Nutrition 2002; 87(S1): S1.
39. Shipton MJ, Thachil J: Vitamin B12 deficiency - a 21st century perspective. Clin Med (Lond). 2015; 15:145-50.
40. Carmel R: How I treat cobalamin (vitamin B12) deficiency. Blood. 2008; 112:2214-21.
41. Montes LF, Diaz ML, Lajous J, Garcia NJ: Folic acid and vitamin B12 in vitiligo: a nutritional approach. Cutis. 1992; 50:39-42.
42. Chen SJ, Hseu YC, Gowrisankar YV, Chung YT, Zhang YZ, Way TD, Yang HL: The anti-melanogenic effects of 3-O-ethyl ascorbic acid via Nrf2-mediated α-MSH inhibition in UVA-irradiated keratinocytes and autophagy induction in melanocytes. Free Radic Biol Med. 2021; 173:151-69.
43. AlGhamdi K, Kumar A, Moussa N: The role of vitamin D in melanogenesis with an emphasis on vitiligo . Ind J Dermatol Venereol Leprol. 2013; 79:750-58.
44. Prietl B, Treiber G, Pieber TR, Amrein K: Vitamin D and immune function . Nutrients. 2013; 5:2502-21.
45. Finamor DC, Sinigaglia-Coimbra R, Neves LC, *et al.*: A pilot study assessing the effect of prolonged administration of high daily doses of vitamin D on the clinical course of vitiligo and psoriasis. Dermatoendocrinol. 2013; 5:222-34.
46. Shameer P, Prasad PV, Kaviarasan PK: Serum zinc level in vitiligo: a case control study. Ind J Dermatol Venereol Leprol. 2005; 71:206-07.

47. Bagherani N, Yaghoobi R, Omidian M: Hypothesis: zinc can be effective in treatment of vitiligo. Ind J Dermatol. 2011; 56:480-84.
48. Yaghoobi R, Omidian M, Bagherani N. Comparison of therapeutic efficacy of topical corticosteroid and oral zinc sulfate-topical corticosteroid combination in the treatment of vitiligo patients: a clinical trial. BMC Dermatol. 2011; 11:7.
49. Szczurko O, Shear N, Taddio A, Boon H. Ginkgo biloba for the treatment of vitilgo vulgaris: an open label pilot clinical trial. BMC Complement Altern Med. 2011; 11:21.
50. Trompezinski S, Bonneville M, Pernet I, Denis A, Schmitt D, Viac J: Gingko biloba extract reduces VEGF and CXCL-8/IL-8 levels in keratinocytes with cumulative effect with epigallocatechin-3-gallate. Arch Dermatol Res. 2010; 302:183-89.
51. Pacifico A, Vidolin AP, Leone G, Iacovelli P: Combined treatment of narrowband ultraviolet B light (NBUVB) phototherapy and oral Polypodium leucotomos extract versus NB UVB phototherapy alone in the treatment of patients with vitiligo. J Am Acad Dermatol. 2009; 60:154.
52. Mohammad A: Vitiligo repigmentation with Anapsos (Polypodium leucotomos). Int J Dermatol. 1989; 28:479.
53. Carlie G, Ntusi NB, Hulley PA, Kidson SH: KUVA (khellin plus ultraviolet A) stimulates proliferation and melanogenesis in normal human melanocytes and melanoma cells in vitro. Br J Dermatol. 2003; 149:707-17.
54. Rodríguez-García C, González-Hernández S, Pérez-Robayna N, Guimerá F, Fagundo E, Sánchez R: Repigmentation of vitiligo lesions in a child with celiac disease after a gluten-free diet. Ped Dermatol. 2011; 28:209-10.
55. Sushama S, Dixit N, Gautam RK, Arora P, Khurana A, Anubhuti A. Cytokine profile (IL-2, IL-6, IL-17, IL-22, and TNF-α) in vitiligo-New insight into pathogenesis of disease. J Cosmet Dermatol. 2019; 18:337-41.
56. Khandalavala BN, Nirmalraj MC. Rapid partial repigmentation of vitiligo in a young female adult with a gluten-free diet. Case Rep Dermatol. 2014; 6:283-87.
57. Amato L, Gallerani I, Fuligni A, Mei S, Fabbri P. Dermatitis herpetiformis and vitiligo: report of a case and review of the literature. J Dermatol. 2000; 27:462-66.
58. Karabudak O, Dogan B, Yildirim S, Harmanyeri Y, Anadolu-Brasie R. Dermatitis herpetiformis and vitiligo. J Chin Med Assoc. 2007; 70:504-06.
59. Cormane RH, Siddiqui AH, Westerhof W, Schutgens RB: Phenylalanine and UVA light for the treatment of vitiligo. Arch Dermatol Res. 1985; 277:126-30.
60. Colucci R, Dragoni F, Conti R, Pisaneschi L, Lazzeri L, Moretti S. Evaluation of an oral supplement containing Phyllanthus emblica fruit extracts, vitamin E, and carotenoids in vitiligo treatment. Dermatol Ther. 2015; 28:17-21.
61. Soumyanath A, Venkatasamy R, Joshi M, *et al.* UV irradiation affects melanocyte stimulatory activity and protein binding of piperine. Photochem Photobiol. 2006; 82:1541-48.
62. Lin Z, Hoult JR, Bennett DC, Raman A. Stimulation of mouse melanocyte proliferation by Piper nigrum fruit extract and its main alkaloid, piperine. Planta Med. 1999; 65:600-03.
63. Ahmad A, Husain A, Mujeeb M, *et al*. A review on therapeutic potential of Nigella sativa: a miracle herb. Asian Pac J Trop Biomed. 2013; 3:337-52.
64. Hamzavi I, Jain H, McLean D, Shapiro J, Zeng H, Lui H. Parametric modeling of narrowband UV-B phototherapy for vitiligo using a novel quantitative tool: the Vitiligo Area Scoring Index. Arch Dermatol. 2004; 140:677-83.
65. Gil MI, Tomás-Barberán FA, Hess-Pierce B, Holcroft DM, Kader AA. Antioxidant activity of pomegranate juice and its relationship with phenolic composition and processing. J Agric Food Chem. 2000; 48:4581-89.
66. Ning W, Wang S, Liu D, Fu L, Jin R, Xu A. Potent effects of peracetylated (-)-epigallocatechin-3-gallate against hydrogen peroxide-induced damage in human epidermal melanocytes via attenuation of oxidative stress and apoptosis. Clin Exp Dermatol. 2016; 41:616-24.
67. Zhu Y, Wang S, Lin F, Li Q, Xu A: The therapeutic effects of EGCG on vitiligo. Fitoterapia. 2014; 99:243-51.
68. Chow HH, Cai Y, Hakim IA, *et al.* Pharmacokinetics and safety of green tea polyphenols after multiple-dose administration of epigallocatechin gallate and polyphenon E in healthy individuals. Clin Cancer Res. 2003; 9:3312-19.
69. Asawanonda P, Klahan SO: Tetrahydrocurcuminoid cream plus targeted narrowband UVB phototherapy for vitiligo: a preliminary randomized controlled study. Photomed Laser Surg. 2010; 28:679-84.