View Point

Vitiligo and diet: A theoretical molecular approach with practical implications

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The psychologically devastating disorder vitiligo affects 1% of the world's population.[1] Over the years, the neurological, biochemical, immunological and genetic aspects of the pathobiology of this enigmatic disorder have been explored. Vitiligo has a multifactorial, multistep etiology, always characterized by an increase of external or internal phenol/catechol concentrations and reactive oxygen species.[2,3] It is recently suggested that reactive oxygen species can alter melanocyte-specific factors to produce neo-antigens and can also amplify antigen presentation and autoimmune destruction of melanocytes.[3] It is also proposed that phenol-containing chemicals can compete with tyrosine to produce reactive quinones. This conversion is reinforced by a disturbed redox balance seen in vitiligo (increased hydrogen peroxide). Such reactive quinones can be covalently bound to the catalytic center of tyrosinase to give a neo-antigen. Micromolar (non-cytotoxic) quantities of *O*-quinones may be sufficient in this haptenation to mount an immune response. *O*-quinones derived from estrogen can serve as surrogate substrates of tyrosinase and cause haptenation.[2] Furthermore, estrogen is implicated to play an important role in the development of autoimmunity.[4] Given the important contribution of reactive oxygen species, estrogen and phenol-containing agents to the pathophysiology of vitiligo, this article tries to draw attention to the potential link between nutrition and vitiligo.

Given the pivotal role of oxidative stress in the pathobiology of vitiligo, α-tochopherol was used in combination with psoralen with ultraviolet A (PUVA) in order to shorten the duration of the treatment.[5] Also, α-tochopherol cream combined with weak to moderate topical corticosteroids or PUVA was proposed and used with success.[6] Some patients with active or stable vitiligo were treated with an antioxidant pool (tochopherol acetate, ubiquinone, selenomethionine, methionine) in order to increase both the enzymatic and the non-enzymatic antioxidant pattern. After 3 months of therapy, the progression of the vitiligo was stopped and, in some cases, repigmentation of the most recent lesions was observed.[7]

Given the pivotal role of oxidative stress in the pathogenesis of vitiligo, food contaminants/additives/preservatives and cosmetic products could aggravate vitiligo because they produce oxidative stress in the skin.[8] Increased consumption of omega-6 or a vegetable source of oils and decreased omega-3 intake may increase, *in vivo*, the production of free radicals and pro-inflammatory cytokines. Vegetable oil could exacerbate autoimmune disease by increasing the free radical formation through decreasing the antioxidant enzyme mRNA levels. In contrast, omega-3 lipid intake in the presence of an antioxidant supplement appears to exert protection against autoimmunity by enhancing antioxidant enzymes and transforming growth factor-β mRNA levels.[9] Omega-3 fatty acids and eicosapentaenoic acid, in particular, are well-documented inhibitors of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α).[10] In most human nutritional studies, the enrichment of cell membranes with omega-3 polyunsaturated fatty acids has been reported to increase the glutathione (GSH) peroxidase activity.[11] Moreover, the organic compound indole-3-carbinol, found in omega-3 fatty acids, induces CYP1A1, which hydroxylates estrogens into 2-hydroxyestrone.[12] It is advisable, therefore, that vitiligo patients avoid omega-6 lipids and use omega-3 lipids. Moreover, omega-3 fatty acids play a critical role in the development and function of the central

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nervous system and evidence from epidemiological, laboratory and clinical studies suggest that omega-3 fatty acids may favorably influence the vulnerability and outcome in depressive disorders.[10] This fact points further to the beneficial effect of these lipids against vitiligo, as 20% of the vitiligo patients are reported to be depressed about their illness.[12]

Mango, cashew, pistaschio, oak, cassava, areca nut, red chillies, cherry, raspberry, cranberry, blackberry and tea contain naturally occurring plant phenol and polyphenolic compounds (tannins), which may aggravate vitiligo by the mechanism outlined above. Moreover, it is reported that phenol molecules induce the release of interleukin-1α (IL-1α) and TNF-α from keratinocytes. Increased TNF-α and IL1-α levels in the lesional skin of patients with non-segmental vitiligo has been recently reported and it is suggested that these cytokines play important roles in the pathophysiology of vitiligo.[13] Additionally, tannins induce apoptosis *in vitro*, inhibit cellular enzymes, bind to cell membrane and make it fragile and chelate metal ions.[14] All these effects can aggravate vitiligo. The high phenol and tannin content of the foods widely consumed in India could explain why the highest incidence of vitiligo is seen in this country.[1]

Are there any beneficial foodstuffs for vitiligo patients?

As mentioned above, omega-3 fatty acids could be helpful for vitiligo patients. The potent free radical scavenging properties of carotenoids could also be harnessed to treat vitiligo.

Quercetin has been found to have strong cytoprotective effects on H_2O_2-induced cell death.[15] Onion and apple, the richest sources of quercetin,[16] are thus beneficial for vitiligo patients. Moreover, thiols, which are abundant in onion, exert an antioxidant activity toward superoxide anion, hydrogen peroxide and singlet oxygen. Thiols also block electrophilic metabolites and modulate several xenobiotic-metabolizing pathways.[17]

Crimini mushrooms are coffee colored and richer in flavor and nutrients than the more common white button mushroom. The range of traditional nutrients found in crimini mushrooms is impressive. Crimini mushrooms are an excellent source of selenium, riboflavin (vitamin B2), pantothenic acid (vitamin B5), niacin (vitamin B3) and copper. Five ounces of raw crimini mushrooms provide 52.6% of the daily value (DV) for selenium, 35.5% of the DV for copper, 10.0% of the DV for manganese, 40.6% of the DV for riboflavin, 21.3% of the DV for pantothenic acid and 10.4% of the DV for zinc. Selenium is a necessary cofactor of GSH peroxidase. Copper, along with manganese, is an essential cofactor of superoxide dismutase. Vitamin B2 is a cofactor for the enzyme GSH reductase, which reduces the oxidized form of GSH back to its reduced version. Notably, L-ergothioneine, a sulfur-containing amino acid synthesized by soil bacteria in fungal substrates and functioning as a powerful antioxidant, has been discovered in mushrooms.[18] L-ergothioneine scavenges superoxide and singlet oxygen and suppresses TNF-α.[19] Of the most commonly consumed mushrooms, portabellas and crimini have the most L-ergothioneine, followed by white buttons. L-ergothioneine is not destroyed when mushrooms are cooked. In a research presented at the 2005 American Chemical Society meeting in Washington, DC, an American research team revealed that mushrooms contain higher concentrations of L-ergothioneine than either of the two dietary sources previously believed to contain the most,: chicken liver and wheat germ. Mushrooms prevent circulating levels of estrogen in the body from becoming excessive. This effect appears to be accomplished through inhibition of aromatase (estrogen synthase) that is necessary for the production of estrogen. Mushrooms thus afford protection against breast cancer.[18] Crimini mushrooms could benefit vitiligo patients.

Whey, a protein complex derived from milk, is being touted as a functional food with a number of health benefits. Whey has potent antioxidant activity, mainly by contributing cysteine-rich proteins that aid in the synthesis of GSH. Cysteine contains a thiol (sulfhydryl) group that serves as an active reducing agent in preventing oxidation and tissue damage. Lactoferrin, an iron-binding glycoprotein found in whey, is a non-enzymatic antioxidant and anti-inflammatory agent. A mouse study revealed the ability of lactoferrin to downregulate levels of TNF-α and IL-6,[20] which are supposed to be involved in the pathogenesis of vitiligo.[21] Lactoperoxidase, an important enzyme in the whey fraction of milk, has the ability to catalyze certain molecules, including the reduction of hydrogen peroxide. Alpha-lactalbumin, also found in whey, can chelate heavy metals and reduce oxidative stress because of its iron-chelating properties. Whey also has GSH peroxidase activity.[20] Given these facts, vitiligo patents can gain benefit by consuming

whey. Interestingly, human studies demonstrated that whey protein improved cognitive function and coping ability in highly stressed individuals. A rise in serotonin is thought to improve adaptation to stress and the authors proposed that tryptophan available in whey provides a substrate to increase brain serotonin levels.[22] This fact points further to the benefit of whey for vitiligo patients, given the important role of stress in the exacerbation of vitiligo and the stress produced by the disorder itself.

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