

GROUP  
**FLORENCE NIGHTINGALE**  
HOSPITALS

# ANTIOXIDANTS



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# SUBJECT CONTENT



- Vitiligo and oxidative stress
- Antioxidants
- Role of antioxidants in the management of vitiligo

# Vitiligo and oxidative stress



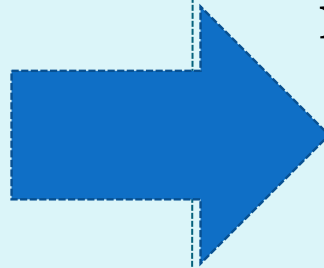
- According to autocytotoxic hypothesis:
  - Oxidative stress has been suggested to be the initial pathogenic event in melanocyte degeneration and loss
  - With  $H_2O_2$  accumulation in the epidermis of patients with active disease.
- Significantly higher levels of **superoxide dismutase (SOD)** has been observed in the skin, erythrocytes, peripheral blood mononuclear cells and serum of vitiligo patients.
- Reduction in **catalase (CAT)** activity has been demonstrated in the epidermis, peripheral blood mononuclear cells and in melanocytes.

# OXIDATIVE STRESS AND VITILIGO

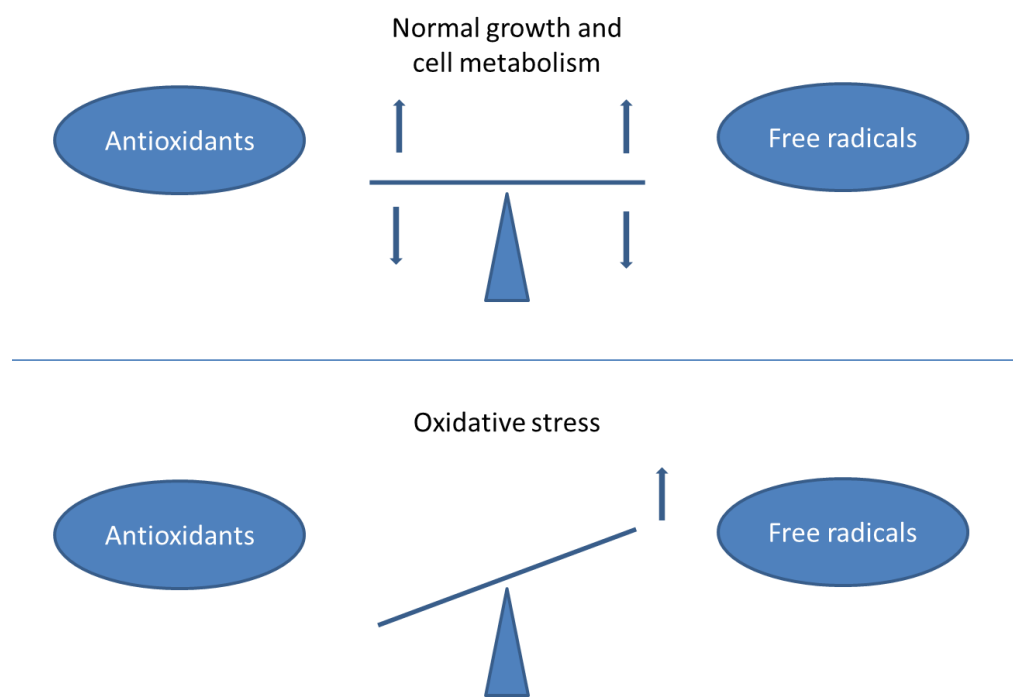
- Lower levels of;
  - Total antioxidant activity
  - Superoxide dismutase
  - Glutathione peroxidase
  - Catalase
  - Vitamin E
  - Vitamin C
- Higher levels of;
  - Oxidative stress indicators

Koca R, Armutcu F, Altinyazar HC, Gürel A. Oxidant-antioxidant enzymes and lipid peroxidation in generalized vitiligo. Clin Exp Dermatol. 2004 Jul;29(4):406-9.

- Imbalance of reactive oxygen species(ROS) system in vitiligo melanocytes



- ROS cause lipid peroxidation of cellular membrane of melanocytes



Hilde Grindvik Nielsen. Exercise and Immunity. INTECH, Chapter 4

- Consequently increased levels of ROS are capable of bleaching constitutional melanin and causing membrane lysis through lipid peroxidation reactions.

**Increased  
oxidative stress+  
Depletion of  
antioxidants  
reserves**



**SKIN OXIDATIVE  
DAMAGE**

# Antioxidants



- **Antioxidants** are chemicals that can prevent or slow cell damage
- Antioxidant is not a substance; it's a behavior
- Antioxidant properties can **donate electrons** and **counteract free radicals**
- Natural antioxidants are mainly found in **fruits and vegetables, marine plants, and some seafood that eat marine plants.**
- There are thousands of antioxidant compounds, the most common dietary ones are vitamins A, C, and E and beta-carotene
- Antioxidants can also be produced artificially and consumed in supplement form.

# ANTIOXIDANTS



- VITAMIN C
- VITAMIN E
- GINKGO BILOBA
- VITAMIN A
- POLYPODIUM LEUCOTOMAS EXTRACT
- POLYUNSATURATED FATTY ACIDS
- QUERCETIN FLAVONOIDS
- TEA POLYPHENOLS
- SOY ISOFLAVONES
- RESVERATROL
- CURCUMIN
- CAPSAICIN
- GLUTATHIONE
- ALPHA LIPOIC ACID
- PHENYLALANINE
- CUCUMIS MELO
- MINERALS
- .....

# VITAMIN C (L-ascorbic acid)



- Essential co-factor for collagen synthesis.
- Topical L-ascorbate benefits ;
  - ✓ improves epidermal barrier function
  - ✓ anti-aging effects
  - ✓ photoprotection from UV A & B
  - ✓ causes neocollagenesis
  - ✓ inhibition of melanogenesis
  - ✓ improvement of a variety of inflammatory skin disorders.

Stamford NP. J Cosmet Dermatol. Stability, transdermal penetration, and cutaneous effects of ascorbic acid and its derivatives. 2012 Dec;11(4):310-7.

Darr D et al. Effectiveness of antioxidants (vitamin C and E) with and without sunscreens as topical photoprotectants. Acta Derm Venereol 1996;76(4):264-8.





- Studies demonstrate; Oral combination of vitamins C and E in high doses provide protection against UV induced erythema\*
- Oral vitamins C, E, A, B12, folic acid and broadband UVB, has been followed by definite repigmentation in vitiligo patients\*\*

\*Eberlein-Konig B et al. Protective effect against sunburn of combined systemic ascorbic acid (vitamin C) and d-alpha tocopherol(vitamin E). J Am Acad Dermatol 1998;38:45-8.

\*\* Don P et al.Treatment of vitiligo with broadband ultraviolet B and vitamins. Int J Dermatol. 2006;45(1):63-5.

# VITAMIN C



- Orange
- Lemon
- Melon
- Kale
- Passion fruit
- Spinach
- Lime
- Cranberry
- Tomato
- Blueberry
- Pineapple

- Papaya
- Strawberry
- Cauliflower
- Garlic
- Grapefruit
- Raspberry
- Kiwi
- Mandarin
- Mango
- Blackberry
- Potato
- Broccoli

# VITAMIN E



- Exists in 8 forms: 4 tocopherols and 4 tocotrienols,
- $\alpha$ -tocopherol is the most represented in humans.
- Topical  $\alpha$ -tocopherol
  - ✓ reduces photo-aging and photo-carcinogenesis,
  - ✓ prevents UV-induced erythema,
  - ✓ prevents lipid peroxidation
  - ✓ prevents immunosuppression.
- Lin JY et al. demonstrate an increase in protection against UV-induced damage after oral administration of vitamin E combined with vitamin C



Studies demonstrate;

- Oral vit E has shown to increase narrow band-UVB effectiveness in vitiligo patients.

Elgoweini M et al. Response of vitiligo to narrowband ultraviolet B and oral antioxidants. *J Clin Pharmacol* 2009;49(7):852-5.

# VITAMIN E :



- Wheat germ oil
- Sunflower oil
- Safflower oil
- Green leafy vegetables
- Tomato products
- Pumpkin
- Asparagus
- Papayas

- Nuts
- Nut oils
- Sweet potato
- Rockfish
- Mangoes
- Broccoli
- Avocados



# GINKGO BILOBA



- Ginkgo Biloba is one of the oldest tree species and the leaves of this herb has antioxidant effects
- Ginkgo biloba contains bioactive constituents mainly flavonoids and some diterpene trilactones
- A recent study has reported an association between daily ingestion of Ginkgo biloba with a significant improvement in total VASI (Vitiligo Area Scoring Index) and VETF (Vitiligo European Task Force) staging in vitiligo patients.\*
- While the mechanism of *Ginkgo biloba* in the treatment of vitiligo is unknown, ginkgo's immunomodulatory, antioxidant, and anxiolytic properties may be of benefit to vitiligo sufferers.

\*Szczurko O, Shear N, Taddio A, Boon H. Ginkgo biloba for the treatment of vitiligo vulgaris: an open label pilot clinical trial. BMC Complement Altern Med. 2011 Mar 15;11:21. doi: 10.1186/1472-6882-11-21.

A systematic review of natural health product treatment for vitiligo Szczurko O, Boon HS. BMC Dermatol. 2008 May 22;8:2. doi: 10.1186/1471-5945-8-2.

Effectiveness of oral Ginkgo biloba in treating limited, slowly spreading vitiligo.Parsad D, Pandhi R, Juneja A. Clin Exp Dermatol. 2003 May;28(3):285-7.

# VITAMIN A



- Includes retinol and carotenoids ( $\alpha/\beta/\gamma$ -carotene, lycopene and the xanthophylls lutein and zeaxanthin)
- Vit A is fat-soluble and can be stored in keratinocytes as retinyl esters.
- Carotenoids are useful to protect against UV-induced damage

Camera E et al. Astaxanthin, canthaxanthin and beta-carotene differently affect UVA-induced oxidative damage and expression of oxidative stress-responsive enzymes. *Exp Dermatol* 2009; 18:222–231.



## Studies demonstrate;

- Daily oral  $\beta$ -carotene (30mg) can prevent and repair photoaging and increases synthesis of procollagen type I\*
- Topical  $\beta$ -carotene (2mg/cm<sup>2</sup>) provides protection against reactive oxygen species in the human skin exposed to infra-red radiation\*\*
- Oral supplementation with vit A plus vit C and vit E, and minerals promoted vitiligo lesion repigmentation in the mice settings\*\*\*

\*Cho S et al. Differential effects of low-dose and high-dose beta-carotene supplementation on the signs photoaging and type I procollagen gene expression in human skin in vivo. *Dermatology*. 2010;221:160-71.

\*\* Darvin ME et al. Topical beta-carotene protects against infra-red-light-induced free radicals. *Exp Dermatol* 2011;20:125-9

\*\*\*Jaleel A et al. Vitiligo treatment with vitamins, minerals and polyphenol supplementation. *Indian J Dermatol* 2009;54(4):357-60.



# VITAMIN A:

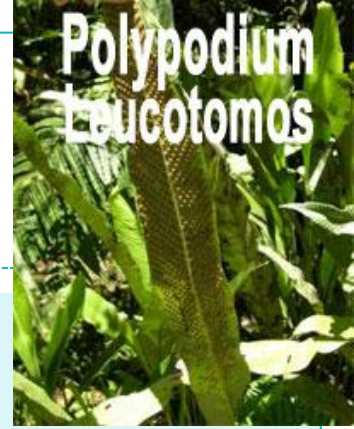


- Liver (beef, pork, chicken, turkey, fish)
- Sweet potato
- Cheese
- Cantaloupe
- Apricot
- Papaya
- Mango
- Pea
- Broccoli
- Carrot
- Broccoli leaf

- Butter
- Kale
- Spinach
- Pumpkin
- Collard greens
- Cheddar
- Melon
- Egg
- Milk



# Polypodium leucotomos (PL)



- Polypodium leucotomos extract comes from a tropical fern plant grown in Central and South America.
- Recently, clinical research has shown that it has antioxidant and photoprotective properties
- ✓ PL acts as a scavenger to mop up free radicals and reactive oxygen species (ROS),
- ✓ PL inhibits the depletion of Langerhans cells
- ✓ PL reduces the number of sunburn cells
- ✓ PL protects DNA by inhibiting the formation of cyclobutane pyrimidine dimers induced by UVB radiation
- ✓ PL preserves skin tissue structure by inhibiting the infiltration of mast cells into skin

Edlich RF, Winters KL, Lim HW et al. Photoprotection by sunscreens with topical antioxidants and systemic antioxidants to reduce sun exposure. *Journal of Long-Term effects of Medical Implants* 2004;14(4):317-340

Middelkamp-Hup MA, Pathak MA, Parrado C et al. Oral Polydium leucotomos extract decreases ultraviolet-induced damage of human skin. *J AM Acad Dermatol* 2004;51:910-8

# Omega-3(three) polyunsaturated fatty acids:



- They are antioxidants and inhibitors of pro-inflammatory cytokines and free radicals
- They protect auto-immunity by enhancing antioxidant enzymes
- The enrichment of cell membranes with Omega-3 has been reported to increase the glutathione (GSH) peroxidase activity\*
- High doses of Omega-3 have been shown to decrease UVB-induced erythema\*\*
- Omega-3 seem to influence depressive disorders, that affect many patients with vitiligo\*\*\*

\*Joulain C . Increased glutathione peroxidase activity in human blood mononuclear cells upon in vitro incubation with omega-3 fatty acids. *Biochem Pharmacol* 1994;47:1315-23.

\*\*Rhodes LE et al. Dietary fishoil supplementation in humans reduces UVB-erythral sensitivity but increases epidermal lipid peroxidation. *J Invest Dermatol* 1994; 103(2): 151-4.

\*\*\*Namazi MR et al. Vitiligo and diet: A theoretical molecular approach with practical implications. *Indian J Dermatol Venereol Leprol*2009;75:116-8

# Omega -3 polyunsaturated fatty acids



- Cold water
- Oily fish (salmon, herring, mackerel, anchovies, sardines)
- Fish oil
- Flaxseeds
- Nuts
- Eggs
- Brussel sprouts
- Blackberry
- Raspberry



# Flavonoids and green tea extracts



- Flavonoids are the antioxidants most commonly found in the diet.
- Common sources of flavonoids in the diet are: wine, beer, tea, vegetables, fruit, and soy products.
- Both quercetin and green tea extract were found to have strong cytoprotective effects on H<sub>2</sub>O<sub>2</sub> induced cell death.



Jeong YM, Choi YG, Kim DS, Park SH, Yoon JA, Kwon SB, Park ES, Park KC. Cytoprotective effect of green tea extract and quercetin against hydrogen peroxide-induced oxidative stress. Arch Pharm Res. 2005 Nov;28(11):1251-6.

# QUERCETIN



- Quercetin is a member of the flavonoids
- In vitro studies demonstrate that quercetin can efficiently prevent keratinocyte oxidative damage induced by H<sub>2</sub>O<sub>2</sub> exposure.\*
- Topical application of the quercetin has been shown to prevent UVC-induced liposome peroxidation, UVB-induced myeloperoxidase activity and glutathione depletion\*\*

\*Vicentini FT et al. Quercetin in w/o microemulsion: in vitro and in vivo skin penetration and efficacy against UVB-induced skin capersdamages evaluated in vivo. *Eur J Pharm Biopharm* 2008; 69(3): 948-57.

\*\* Fahlman BM et al. UVA and UVB radiation-induced oxidation products of quercetin. *J Photochem Photobiol B.* 2009; 97:123-31.

# QUERCETIN



- Apples
- Onions (++red onion)
- Red grapes
- Citrus fruit
- Tomato
- Broccoli
- Leafy green
- Vegetables
- Lovage
- Legumes
- Caparis spinosa plant

- Raspberry
- Whortleberry
- Lingonberry
- Cranberry
- Chokeberry
- Rowanberry



# SOYBEANS



- Soybeans and associated food products are a rich source of flavonoids
- Genistein is an oestrogen that occurs naturally in soya beans
- Oral genistein is shown to decrease UVB-induced skin photoaging, carcinogenesis, inflammation and immunosuppression in a rodent model\*
- Topical genistein reduces erythema and histologic inflammation induced by PUVA in mice\*
- Genistein has collagen-stimulating effects, by increasing collagen (COL1A2) gene expression\*\*

\*Wei H et al. Isoflavone genistein: photoprotection and clinical implications in dermatology. J Nutr 2003; 133(11s1): 3811S-3819S.

\*\*Greenwel P et al. Tyrosine dephosphorylation of nuclear proteins mimics transforming growthfactor beta-1 stimulation of alpha-2(I) collagen geneexpression. Mol Cell Biol 1995;15:6813-9.



# Green tea polyphenols



- The term green tea polyphenols is used to refer to several potent antioxidants that appear in green tea leaves.
- The most (60-80%) polyphenols contained in green tea leaves are **catechins**: epicatechin, epicatechin-3-gallate ,epigallocatechin,
- **Epigallocatechin-3-gallate (EGCG)** is the most important molecule
- As antioxidants, catechins are more potent than vitamins C and E
- Catechins are able to regenerate oxidized vitamin E



# Epigallocatechin-3-gallate (EGCG)



- Has photo-protective, anti-inflammatory, anti-carcinogenic effects and it can inhibit collagenase activity.
- Several studies demonstrate that, oral administration of EGCG significantly increases the minimal erythema dose to UV and improves microcirculation\*
- Topical application of EGCG inhibits carcinogenesis and selectively increases apoptosis in UVB-induced skin tumors\*\*

\*Jeon HY et al. Effects of oral epigallocatechin gallate supplementation on the minimal erythema dose and UV-induced skin damage. *Skin PharmacolPhysiol* 22; 2009:137–141.

\*\*Lu YP et al. Topical applications of caffeine or (-)-epigallocatechin gallate (EGCG) inhibit carcinogenesis and selectively increase apoptosis in UVB-induced skin tumors in mice. *Proc Natl Acad Sci U S A* 2002; 99: 12455–60.

# RESVERATROL



- Resveratrol is a type of natural phenol
- Its beneficial effects: anti-oxidant, anti-inflammatory, anti-cancer, blood sugar-lowering
- Studies demonstrate that oral resveratrol can prevent UV-induced tumorigenesis and cutaneous inflammatory disorders and increases cell survival\*
- Topical use of resveratrol on hairless mice before UVB; decreased erythema, reactive oxygen species production and inflammation\*\*

\*Ndiaye M et al. The grape antioxidant resveratrol for skin disorders: promise, prospects, and challenges. Arch Biochem Biophys 2011;508(2):164-70.

\*\* Aziz MH et al. Longley BJ, Ahmad N. Chemoprevention of skin cancer by grape constituent resveratrol: relevance to human disease? Faseb J 2005;19(9): 1193-5.

# RESVERATROL



- Grapes
- Wines
- Pinot noir
- Peanuts
- Mulberries
- Blueberries
- Apples
- Cocoa
- Powder baking
- Chocolate



# CURCUMIN



- Curcumin; a polyphenol derived from *Curcuma longa*, is an active ingredient in the spice turmeric
- In the recent studies; Curcumin has anti-oxidant , anti-proliferative, anti-inflammatory, antiviral, antibacterial and antifungal properties
- It reduces wound-healing time, improves collagen deposition and increases fibroblast and vascular density in wounds
- Curcumin could be effective in treatment of different skin diseases (Phototoxic dermatitis, vitiligo, psoriasis, chronic inflammatory diseases...)

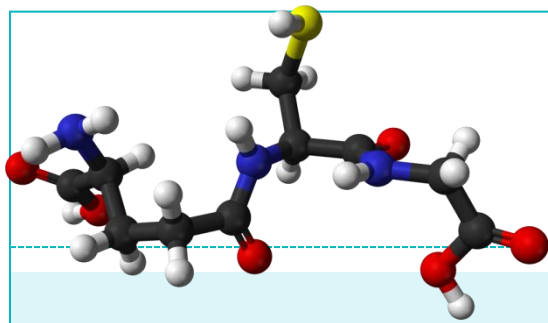
Rowe DL, et al. Modulation of the BRCA1 protein and induction of apoptosis in triple negative breast cancer cell lines by the polyphenolic compound curcumin. *Breast Cancer: Basic and Clinical Research* 2009; 3: 61–75.

Cho JW et al. Curcumin attenuates the expression of IL-1beta, IL-6, and TNF-alpha as well as cyclin E in TNF alpha-treated HaCaT cells; NF-kappaB and MAPKs as potential upstream targets. *Int J Mol Med* 2007; 19: 469-474.

# CAPSAICIN



- Is an active component of chili peppers, which are plants belonging to the genus *Capsicum*.
- Capsaicin is a potent anti-inflammatory agent which has been used for : pain and itch relief, because of its desensitization property
- It's benefits; cancer prevention, cardiovascular diseases, weight reduction.
- High antioxidant and anti-apoptotic potential of capsaicin have been recently described.
- Becatti M et al. demonstrate; Pre-treatment with capsaicin inhibits keratinocytes apoptosis in peri-lesional vitiligo skin, increases cellular total antioxidant capacity and improves mitochondrial activity and cell metabolism.



# GLUTATHIONE

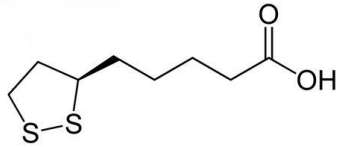


- Glutathione (GSH) is a tripeptide
- Contributes to the functional vitality and morphological integrity of cells
- GSH provides efficient protection against UVB-rays damages\*
- A severe GSH depletion has been documented inside keratinocytes after UV irradiation\*\*
- A few studies demonstrate; GSH supplementation is providing intrinsic wide-spectrum photo protection, cancer prevention and anti-aging effect\*\*\*

\*Schäfer M et al. Nrf2 establishes a glutathione-mediated gradient of UVB cytoprotection in the epidermis. *Genes Dev* 2010;24:1045-58.

\*\*Zhu M et al. Molecular mechanisms for UV-B irradiation-induced glutathione depletion in cultured human keratinocytes. *Photochem Photobiol* 2004; 80:191-6.

\*\*\*Sekhar RV et al. Deficient synthesis of glutathione underlies oxidative stress in aging and can be corrected by dietary cysteine and glycine supplementation. *Am J Clin Nutr* 2011



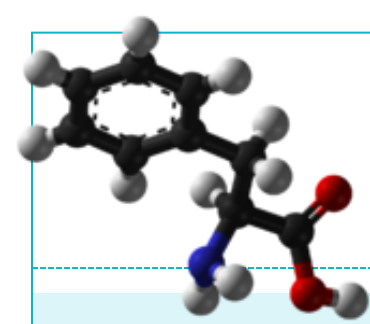
# alpha lipoic acid



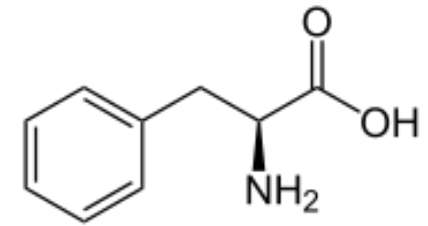
- Alpha-lipoic acid or ALA is a naturally occurring compound that's made in the body. It serves vital functions at the cellular level, such as energy production.
- ALA is an antioxidant!
- There are food sources of ALA such as yeast, organ meats like liver and heart, spinach, broccoli, and potatoes.
- The study of Dell'Anna et al. demonstrate; Oral supplementation of alpha-lipoic acid before and during NB-UVB significantly improves the clinical effectiveness of NB-UVB and reducing vitiligo associated oxidative stress.







# Phenylalanine



- Phenylalanine is an  $\alpha$ -amino acid and a precursor for tyrosine
- Phenylalanine is found naturally in the breast milk of mammals.
- Some studies demonstrate phenylalanine antioxidant effects on vitiligo with or without UVA\*

\* Siddiqui AH1, Stolk LM, Bhaggoe R, Hu R, Schutgens RB, Westerhof W. L-phenylalanine and UVA irradiation in the treatment of vitiligo. *Dermatology*. 1994;188(3):215-8.

Schallreuter KU, Zschiesche M, Moore J, Panske A, Hibberts NA, Herrmann FH, Metelmann HR, Sawatzki J. In vivo evidence for compromised phenylalanine metabolism in vitiligo. *Biochem Biophys Res Commun*. 1998 Feb 13;24,3(2):395-9.



# CUCUMIS MELO



- Cucumis is a plants genus in the Cucurbitaceae family, which includes the **cucumber, muskmelons, the horned melon, and the West Indian gherkin**
- Cucumis melo extract is a rich antioxidant that naturally contain a high superoxide dismutase activity

Ioannis Vouldokis et al. Antioxidant and anti-inflammatory properties of a Cucumis melo extract rich in superoxide dismutase activity

# MINERALS



- The best minerals with antioxidant effects are **Manganese, Selenium, and Iodine**
- These minerals either act as antioxidants on their own or act in conjunction with other cells in the body to stimulate the production of antioxidants
- A few studies demonstrated minerals antioxidants efficacy in vitiligo

Jalel A, Soumaya GS, Hamdaoui MH. Indian J Dermatol. Vitiligo treatment with vitamins, minerals and polyphenol supplementation. 2009;54(4):357-60.

Ines D, Sonia B, Riadh BM, Amel el G, Slaheddine M, Hamida T, Hamadi A, Basma H. A comparative study of oxidant antioxidant status in stable and active vitiligo patients. Arch Dermatol Res. 2006 Sep;298(4):147-52.



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- Up to date there are no definite dosing regiments for antioxidants
- More studies are needed to determine their side effect profile



Thank you for your attention!!