


## HERBAL MELANIN VE NIGELLA SATIVA

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### ÖZET

Melanin bitkilerde, mantarlarda ve bakterilerde yaygın olarak bulunmaktadır. Melaninin Eumelanin, Pheomelanin, Neuromelanin ve Allomelanin gibi farklı türevleri bulunmaktadır. Melanin, yüksek moleküler ağırlığa sahip amorf bir polimer olarak kabul edilir. Melaninin mikroorganizmalardan bitkilere ve insanlara kadar doğadaki varlığının pigmentasyon, anti-oksidatif aktivite ve güneş ışığından korunma gibi birçok işlevi vardır. Yapılan çalışmalarda melaninin fenolik ve indolik bileşiklerin polimerizasyonu sonucu oluştuğu görülmüştür. Bununla birlikte melaninin kesin kimyasal bileşimi hala belirsizliğini koruyor; birçok işlevi ve özelliği de yeni yeni anlaşılmaya başlıyor. Gıda endüstrisinde ve hastalıkların tedavisinde kullanılan sentetik taklitler, doğal melaninlerin yapı ve işlev ilişkilerinin çözümünde aktif rol oynamaya başlamıştır. Son on yılda bitkisel melanin, Nigella sativa L. gibi bazı gıda maddelerinden doğal olarak elde edilmiştir. Nigella sativa'dan elde edilen melaninin güçlü anti-inflamatuar, anti-ülser ve anti-diyabetik aktivitelere sahip olduğu görülmüştür. Melaninin, hastalıkların önlenmesi ve tedavisindeki potansiyel rolüne ilişkin mevcut incelemeler, popüler bir bitki olan Nigella sativa L.daha fazla klinik araştırmaya konu olabileceğini düşündürülebilir.

**Anahtar Kelimeler:** Melanin, Nigella Sativa, Kanser, Diyabet, Bitkisel Melanin.

## HERBAL MELANIN AND NIGELLA SATIVA

### ABSTRACT

Melanin is widely found in plants, fungi and bacteria. There are different melanin derivatives such as Eumelanin, Pheomelanin, Neuromelanin and Allomelanin. Melanin is considered an amorphous polymer with high molecular weight. The presence of melanin in nature, from microorganisms to plants and humans, has many functions such as pigmentation, anti-oxidative activity and protection from sunlight. Studies have shown that melanin is formed as a result of the polymerization of phenolic and indolic compounds. The exact chemical composition of melanin remains unclear, many of its functions and properties are also just beginning to be understood. Synthetic imitations used in the food industry and in the treatment of diseases have begun to play an

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active role in unraveling the structure and function relationships of natural melanins. In the last decade, vegetal melanin has been obtained naturally from some food stuffs such as *Nigella sativa* L. Melanin obtained from *Nigella sativa* has strong anti-inflammatory, anti-ulcer and anti-diabetic activities. Current reviews on the potential role of melanin in disease prevention and treatment may suggest that *Nigella sativa* L. a popular herb, may be the subject of further clinical trials

**Keywords:** Melanin, *Nigella Sativa*, Cancer, Diabetes Mellitus, Herbal Melanin.

## 1. INTRODUCTION

Melanin is a polymer found in many living organisms, as well as plants and animals. The primary function of melanin is to provide photoprotection for the continuation of the against the ultraviolet (UV) radiation of the Sun, which is the source of life. Because Melanin can largely absorb the energy from UV light, reducing damage to DNA (1).

Melanin can act as an antioxidant, scavenging reactive oxygen species (ROS). In humans, melanin can be produced not only in melanocytes in the skin, but also in retinal pigment epithelial cells, some special cells of the inner ear and the central nervous system (2). Between the layers of the skin, Eumelanin and Pheomelanin are found in the epidermis. In contrast, Neuromelanin is found in the brain. Additionally, Allomelanin is a class of melanin commonly found in fungi; Pyomelanin, a melanin intermediate, is a brown-black phenolic polymer and results from the oxidation of homogentisic acid (HGA) in the L-tyrosine pathway. The most common melanins that provide color diversity in living things are eumelanin and pheomelanin, which are responsible for the brown/black and yellow/red color phenotypes, respectively(3,4).

## 2. MELANIN SYNTHESIS

Inside the melanocyt cell, melanin is produced in a special organelle, the melanosome. After synthesized, it is transmitted to the nearest keratinocytes by exocytosis-like mechanisms. The primary signaling pathway that initiates melanin synthesis begins with the binding of the extracellular ligand alpha-melanocyte-stimulating hormone (alpha-MSH), derived from the pro-opiomelanocortin (POMC) gene, to one of several cognate receptors on the cell surface(2,5). In the cell, melanocortin receptor (MCRs) are G-protein coupled. Activation of these receptors results in increased intracellular cyclic adenosine monophosphate (cAMP) levels through stimulation of adenylate cyclase. As a result, after a few steps of cAMP-dependent protein kinase activation in the nucleus, the expression of melanogenic enzymes

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such as proteins covering the melanosome membrane and tyrosinase (TYR) increases. Tyrosine is the non-essential amino acid precursor of melanin. Tyrosine is converted to dihydroxyphenylalanine (DOPA) via the enzyme tyrosinase. Then DOPA is polymerized into melanin(6).

In the melanosome, tyrosine forms dopaquinone, the precursor of melanin. Dopaquinone is then processed to eumelanin in the absence of thiols or to pheomelanin in the presence of thiols. The copper ion-based enzyme-catalyzed oxidative transformation of the catecholamine derivative Dopa produces light-absorbing dopaquinone, which is then completed with the formation of DHICA (5, 6-dihydroxyindole-2-carboxylic acid) and dihydroxyindole (DHI). After melanin polymerization, indole-5, 6-quinone becomes clearly visible, the color of the pigment varies from red to dark brown(7,8). The resulting synthesis is lighter red/yellow, alkali-soluble sulfur-containing pheomelanin and dark brown/black insoluble eumelanin (Figure 1). Skin color is therefore determined by the mixture of different types of melanin and the type of storage and/or deposition in melanosomes. In addition to the presence of melanin, differences in skin color are also determined by the presence of carotenoids, oxy-/deoxy-hemoglobin and some other molecules(6-8). Especially in people living in Africa and the desert, black skin, which provides protection against the UV rays of the Sun, contains more eumelanin than light skin, and these people also have more and larger melanosomes. Melanocytes produce melanin in the innermost layer of the epidermis, called the basal layer. Keratinocytes then transport melanin to the skin surface. Because while Eumelanin is synthesized in elliptical melanosomes, pheomelanin is synthesized in smaller round melanosomes (5-8). Differences in skin pigmentation between people are due to the eumelanin/pheomelanin ratio as well as the number of melanocytes. Pheomelanin is responsible for the pinkish color of the lips, nipples and skin. Different hair colors result from different proportions of melanin forms (7,8).

The type and amount of melanin are decisive in determining hair color. For example, black hair color contains a large amount of eumelanin, brown hair color contains a medium amount of eumelanin, blonde hair contains a very small amount of eumelanin, and on the contrary, red hair color contains mainly pheomelanin and only a small amount of eumelanin(1,9).

Another melanine type Neuromelanin (NM) is a dark pigment found in the brain and structurally related to melanin. It is a polymer consisting of 5, 6-dihydroxyindole monomers. Neuromelanin is found in large amounts in the catecholaminergic cells of the substantia nigra

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pars compacta and locus coeruleus and gives the structures a dark color. So NM has been considered an inert waste product of dopamine auto-oxidation. NM has been found to accumulate during aging, especially after the first 2-3 years of life. It is believed to protect neurons in the substantia nigra from iron-induced oxidative stress(10,11). In vivo and in vitro tests have proven that melanin has various health-promoting effects, such as antioxidant and immunomodulatory activity, hypoglycemic and hypolipidemic effect, liver and gastrointestinal tract protection effect.

Some animal studies have also shown other potential benefits of melanin. It has also been shown that melanin can prevent liver damage by contributing to the reduction of inflammation in the body. Melanin may also play a role in regulating the immune system (12-14). While experimental studies with melanin show the potential role, clinical studies have not yet proven that the compound is safe and effective in humans.

### **3. MELANIN and FOODS**

Melanin can be added to a variety of foods as a natural colorant and preservative with high safety and virtually no toxicity. Melanin can be extracted from animal and plant byproducts or produced through microbial fermentation, which involves a variety of extraction and purification methods with their own pros and cons. Some forms of plant melanin, such as the commonly consumed grape melanin, have been shown to exhibit anti-inflammatory and immunomodulatory activities. Today, natural or synthetically produced melanin derivatives found in foods can be used for a healthy life (15,16). For example, melanin isolated from grapes has been shown to have possible anti-inflammatory and/or immunosuppressive properties. Grape melanin also has anti-edema properties in animals. It has also been suggested that grape melanin interacts with prostaglandin as well as inflammation mediated by the leukotriene and/or complement system(15,17). Grape melanin can potently inhibit lipid peroxidation in vitro, which is the primary inflammatory response of arthritis. Researchers produced a natural extract displaying the properties of melanin from the seed coat of NS, which may be as valuable as grape melanin. This research shows that melanin extracted from black cumin seed increases both primary and secondary antibody responses in rats(18).

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#### 4. FUNCTIONAL FOOD; NIGELLA SATIVA

Foods can be taken for both nutritional and therapeutic purposes, having the same effect as drugs. Functional (FF) is defined as food products that have the appearance of traditional food and are included in daily nutrition. According to European Union (EU) documents, a food product is considered FF if it can be proven to positively affect one or more targeted functions in the body. Unfortunately, as with all FFs, studies on NS are generally in vitro studies and there are relatively few experimental clinical studies (1,8,16).

Nigella Sativa has been widely used as a food additive throughout history. Therefore, there is no doubt about its safety of use. The oldest known evidence of the use of Nigella sativa dates back 3,500 years. For example, black cumin seeds and a bottle of oil were found in pharaoh tombs. Similarly, black cumin seeds have been found in ancient tombs in Anatolia. Additionally, Black Cumin has been highly recommended as a source of healing in all heavenly religions throughout history. Thymoquinone, the active ingredient of Nigella sativa, has been reported to have many potential medicinal properties, exhibiting activities such as antioxidant, anti-inflammatory, anti-cancer, tissue growth and division, hormone regulation, immune response and development, and cell signaling (19-21).

It has been used throughout history because NS also contains branched-chain amino acids and especially essential amino acids. It contains significant amounts of the amino acids arginine, glutamic acid, leucine and lysine. In addition, many of the fatty acids necessary for human health are found in NS. For example, NS oil has been shown to be dominant in terms of linoleic acid, oleic acid, myristic acid and palmitic acid. In addition, thymoquinone, the main active ingredient of NS, is a volatile oil derivative, and p-cymene, dithymoquinone, thymohydroquinone, carvacrol and thymol are other valuable volatile oils of NS (20-22).

Phenolic compounds are characterized as small molecules with at least one phenol unit. Some phenolic compounds such as kaempferol, quercetin, rutin, salicylic acid, p-hydroxybenzoic acid methyl-4-hydroxybenzoate and pyrogallol have been reported in Nigella sativa seeds. It is known that there are triterpenes such as saponins in the seeds of Black Cumin (NS) species. These naturally occurring compounds are considered the active compounds of NS. Of course, depending on the environment in which the plant grows, the phytochemicals of NS may differ even within the same species (22,23).

Herbal Melanin (HM) is a dark black pigment obtained from the seed coat of Black cumin. Its importance has begun to be better understood today, as synthetic or natural melanin, such

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as grape melanin, can be used in the treatment of various diseases (24,25). In nature, melanin serves a variety of functions, from camouflage and protection to energy harvesting. In terms of protection, it is well known that melanins protect against ionizing ultraviolet radiation, but this is just one example. Melanization has also been associated with various biotic factors, for example, host defense against pathogens as well as protection against abiotic factors (21). Such as heat, cold and osmotic stresses. The immune systems of some insects and nematodes are dependent on melanin, and some microbial pathogens use melanin to evade the host's immune defenses. Finally, many melanotic organisms use melanin to obtain energy from radiation. Melanin is considered an amorphous polymer with high molecular weight. Although it is known that melanin is formed by the polymerization of phenolic and indolic compounds, the detailed structure of melanin has not yet been defined (22-25). Nowadays, melanin extraction and characterization from NS can be performed successfully. Melanin obtained from NS with these methods has strong anti-inflammatory, anti-ulcer and anti-diabetic activities. Additionally, vegetative melanin extracted from NS has immunogenic properties through modulation of cytokine production via Toll-like receptor (TLR) 4. For example, HM has been shown to up-regulate interleukin-1 beta (IL-1 $\beta$ ) mRNA in cells administered HM compared to untreated cells and stimulate IL-1 $\beta$  secretion in a dose-dependent manner (26,27).

Because HM can increase the protein expression of IL-1 $\beta$ , TLR2, the main receptor for IL-1 $\beta$  production, and activate p38 mitogen-activated protein kinase, a key mediator of stress-induced IL-1 $\beta$  gene expression. In conclusion, these studies have revealed promising immunosuppressive potentials of HM against inflammatory-related diseases (28-30). Melanins are natural dark biological pigments produced by animals, plants and microorganisms and mediate apoptosis. NS is anti-proliferative, pro-apoptotic, against breast, colon, pancreas, liver, lung, skin, kidney, prostate and cervical cancers, as well as neoplasms. It exhibits anticancer properties, including anti-mutagenic and anti-metastatic effects. HM, which has immunomodulatory, collagenase activities and anti-diabetic properties, is abundant in the structure of NS. Perhaps HM may be responsible for some of the possible effects of NS on healthy life (31,32), (Figure 2).

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## 5. CONCLUSION

Approximately 2500 years ago, Hippocrates, with the saying "Let food be your medicine, let your medicine be your food", he emphasized the importance of consumed foods in maintaining health. Melanin; It is abundant in foods such as grape and Black cumin these foods are rich in melanin and/or support melanin production in the body. Finally HM and Black cumin can be a good example for the concept of "food is medicine", which is becoming more popular today. Of course, more clinical research is needed.

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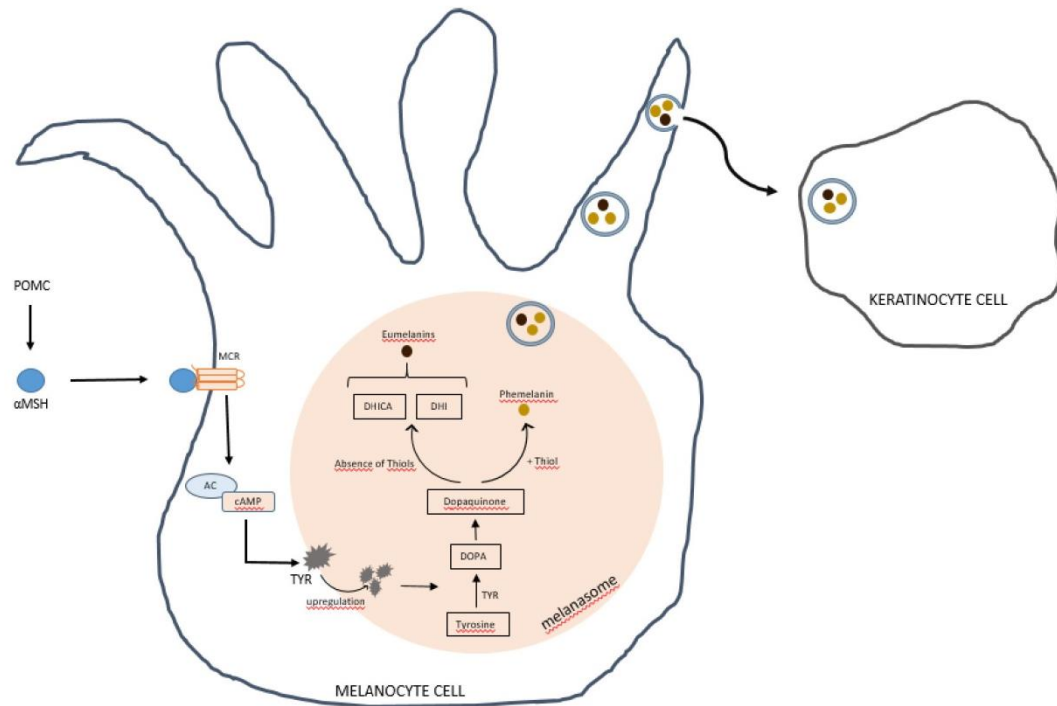
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Figure 1: Melanin synthesis in melanocyte cell.

POMC: pro-opiomelanocortin,  $\alpha$ MSH: alpha-melanocyte-stimulating hormone, MCR: melanocortin receptor, AC: adenylate cyclase, cAMP: cyclic adenosine monophosphate, TYR: tyrosinase, DOPA: dihydroxyphenylalanine, DHICA: 5, 6-dihydroxyindole-2-carboxylic acid, DHI: dihydroxyindole



## Figure 2: The functions of melanine

PG: Prostaglandin, TLR: Toll-like receptor, p38 MAPKs: p38 mitogen-activated protein kinase, IL-1 $\beta$ : Interleukin-1 beta,

