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Melanin and Its Role in Hyper-Pigmentation – Current Knowledge and Future Trends in Research

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1. Introduction

The use of plants as medicines is dated back to early man (Phillipson, 2001). Humans relied on nature for their basic needs such as food, shelter, clothing, fertilizers, flavours, fragrances and last but not least medicines. Plants have formed the sophisticated traditional medicine systems that have been in existence for thousands of years (Anon, 1998, Yelisida, 2005; Cunningham, 1993).

Traditional medicine refers to the health practices, approaches, knowledge and beliefs incorporating plants, animals and mineral based medicines, spiritual therapies, manual techniques and exercises, applied singularly or in-combination to treat, diagnose and prevent illnesses or maintain well-being of individuals. Medicine, in several developing countries, using local traditions and beliefs, is still the mainstay health care till to date. The practice of traditional medicine is widespread in China, India, Japan, Pakistan, Sri Lanka and South Africa etc (Hoareau and Dasilva, 1999; Coetzee et al, 1999; Diederichs, 2002, Nair, 2005). In China 40% of the total medicinal consumption is attributed to traditional tribal medicines. In Japan, herbal medicine preparations are more in demand than mainstream pharmaceutical products (Hoareau and Dasilva, 1999).

Africa is a rich source of medicinal plants (Hoareau and Dasilva, 1999). They are an integral part of African culture, which is the oldest and most diverse in the world. Plants have been used in African medicine to treat fever, asthma, constipation, hypertension, skin diseases etc (Medical news press). About 80% of the black population uses traditional medicine as the primary healthcare system (Bussman and Sharon, 2006, Van wyk et al 1997).

1.1 Uses of plants

Plants are a source of fuel, building material, craft material, dyes, food supplements and medicine all over the world. Approximately 80% of black population make use/ rely on plants for these services (Light, 2005). Traditional medicine can be viewed as a parallel system to western health care. Approximately 3000 species are used by an estimated 200,000 indigenous traditional healers (Van wyk et al. 1997). Plants can be used for different purposes, some of them are mentioned below:

1.2 Plants as a source of food

Food is any substance composed primarily of carbohydrates, fats, water, and /or proteins that can be drunk or eaten by human beings or animals for nutrition or pleasure (figure 1.1). Food sources include plants, animals or other categories such as fungus or fermented products like alcohols (Davidson, 2006).

Many plant or plant parts are eaten as food. There are around 2000 plants species which can be cultivated for food, and many have several distinct cultivars (Davidson, 2006; Mander, 1999). Fruits are ripened extensions of plants including seeds within. Many plants have evolved fruits that are attractive as a food source to animals as well. Fruits, therefore, make up a significant part of the diets of most cultures. Some botanical fruits such as tomatoes, pumpkin etc are eaten by humans as vegetables.

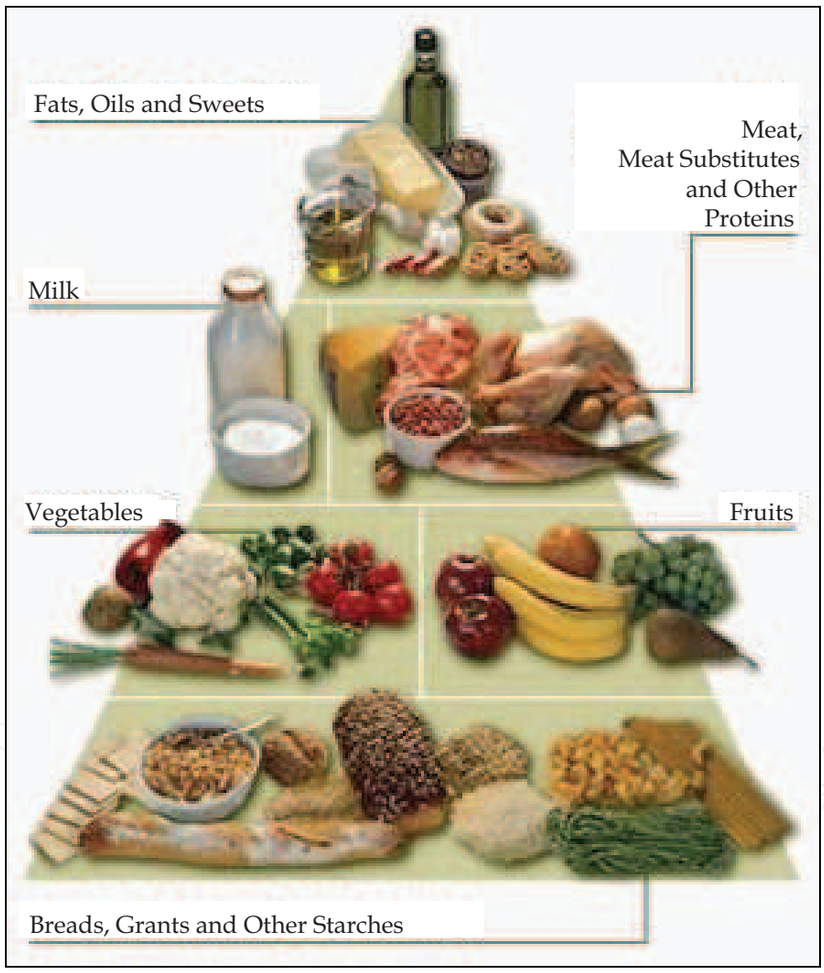

Fig. 1. Food pyramid (http://dietmotion.com/images/food-pyramid.jpg)

1.3 Drug discovery

Although natural products, particularly secondary metabolites, have formed the basis of medicines, the presence of these compounds in the biochemistry of the plant is very often difficult to justify. It has been suggested that these compounds may have been synthesized

by the plant as part of the defence system of the plant, e.g. plants are known to produce phytoalexins as a response to attack by bacteria and fungi (Louw et al, 2002). The presence of highly toxic natural products has also been highlighted in some animals namely the Amazonian frogs so as to deter predation by other animals. Whatever the reasons for the presence of these compounds in nature could be, it is needless to state that they provide invaluable resources that have been used to find new drug molecules. Table 1.1 gives an indication of the development of new drugs from natural products. Spectroscopic methods coupled with good extraction techniques like chromatography, have contributed to the phenomenal success of natural product chemistry over the past 50 years. A sound isolation strategy has helped in the isolation and characterisation of many bioactive molecules. Nowadays, bioassay-guided fractionation of medicinal plants is a feature of routine in the attempt to isolate components from natural sources. These techniques are not only being restricted to plant sources but they are also being applied to microbial and even fungal sources of metabolites. In practice as soon as the material is collected, in the case of plants, it needs to be identified by a taxonomist so as to ascertain the correct identity of the material. Voucher specimens for herbarium specimens are kept. Various parts of the plant are collected separately (leaves, flowers, stem, wood, bark, root, root bark etc.) and are dried quickly in drying cabinets preparing them for isolation of active compounds (Gurib-Fakim, 2006).

Drugs/ chemical	**Action**	**Plant source**
Acetyldigoxin	Cardiotonic	*Digitalis lanata* (Grecian foxglove, woolly foxglove)
Adoniside	Cardiotonic	*Adonis vernalis* (pheasant's eye, red chamomile)
Caffeine	CNS stimulant	*Camellia sinensis* (tea, also coffee, cocoa and other plants)
Camptothecin	Anticancerous	*Camptotheca acuminate*
Colchicine	Antitumor, antigout	*Colchicum autumnale* (autumn crocus)
Galanthamine	Cholinesterase inhibitor	*Lycoris squamigera* (magic lily, resurrection lily, naked lady)
Glycyrrhizin	Sweetener, treatment for Addison's disease	*Glycyrrhiza glabra* (licorice)
Irinotecan	Anticancer, antitumor agent	*Camptotheca acuminate*
Lapachol	Anticancer, antitumor	Tabebuia species (trumpet tree)
Monocrotaline	Topical antitumor agent	*Crotalaria sessiliflora*

Table 1.1 Plant based drugs and medicines (Taylor, 2000)

1.4 Plants as a source of cosmetics

Cosmetic product refers to any substance or preparation intended for application to any external surface of the human body (i.e. the epidermis, hair system nails, lips and external genitals organs) or teeth or buccal mucosa wholly or mainly for the purpose of cleaning, perfuming or protecting them or keeping them in good conditions or changing their appearance or combating body odour or perspiration except where such cleaning, perfuming, protecting, keeping and changing is wholly for the purpose of treating or preventing diseases (Aburjai and Natsheh, 2003; Dweck, 1996). Novel bioactive ingredients for cosmetics are derived from sea, earth and plant kingdom. Popular ingredients include Chinese herbs, Vitamins, minerals, antioxidants, enzymes, hormones and naturals.

Plants have been used for cosmetic purposes since time immemorial. They have once been the main source and foundation of all cosmetics before various methods were discovered of synthesizing substances with similar properties (Aburjai and Natsheh, 2003). The first cosmetic derived from plant is dated about 3100-2907 BC which was used in Egypt (Dold and Cocks, 2002; Cocks et al, 2003).

There are many plants which are being used for cosmetics. Ginseng is a traditional drug used for more than 2000 years. It activates the skin metabolism (Tanaka and Okada, 1991), reduces keratinisation (Kim et al, 1989), provides moisture and softens, alleviate wrinkling and enhance skin whiteness (Dweck, 1997). Other plants that have been used in cosmetics preparations are *Artemisia vulguris* and *Artemisia absinthum* which are used for skin diseases. The entire plant is made into decoction and is used as a wash for many kinds of wounds and skin ulcers (Dweck, 1997). *Salvia officinalis* (L) also called common sage, true sage or garden sage is used as a lotion to improve the condition of hair and skin. The major *S. officinalis* constituents responsible for the effect of hair are tannins, saponins as well as borneol and camphor (Aburjah and Natsheh, 2003; Boiceanu et al, 1986). Majority of South African plants such as *Calodendrum capensis*, are being used traditionally as cosmetics but they have not been scientifically validated.

2. Hyper-pigmentation

Hyper-pigmentation of skin is a common problem that is prevalent in middle aged and elderly people. Hyper-pigmentation can be caused by excessive exposure to UV light, drug reaction and can also occur during ageing. Dermatological disorders associated with hyper-pigmentation include age spots, melasma and site of actinic damage to mention the few (Pandya and Guevera, 2000).

Melanin is the pigment responsible for the colour of skin in humans. It also occurs in bacteria, fungi and plants. Tyrosinase is known to be the key enzyme in melanin biosynthesis (Nerya et al, 2003). Over-activity of this enzyme leads to overproduction of melanin leading to hyper-pigmentation of the skin and under-activity leads to disorders such as vitiligo (depigmentation spots that occurs on the skin) and whitening of hair. Overproduction of melanin can be prevented by avoiding excessive UV light exposure and can be treated with skin-lightening agents such as bleaching hydroquinone, kojic acid and retinoids (Halder et al, 2004). Inhibition of tyrosinase can also lead to reduced melanin production. Some commercially available chemical and fungal derived skin-lightening agents have been proven to have chronic, cytotoxic, mutagenic effects in humans (Nerya et al, 2003; Wang et al, 2006; Wu et al, 2003). Therefore, there is a need for alternative herbal derived and pharmaceutical agents for the treatment of hyper-pigmentation of human skin.

2.1 Structure and function of the skin

The skin is one of the heaviest body organs. It covers between 1.5 and 2 m, comprising about one sixth of the body's total weight. The skin performs several important physiological functions; this includes regulation of body temperature and metabolism, excretion (via sweat glands), synthesis of vitamin D in the epidermal layer when exposed to UV rays, uses specialised cells to protect us from UV rays of the sun etc (Murphy, 1995). The skin consists of three layers (figure 2.1) namely:

i. **Epidermis**- It is the outer layer of the skin which also consists of several layers- the basal cell layer, the spinous cell layer, the granular cell layer and the stratum corneum. Cells in the epidermis include the keratinocytes which are the most abundant cells in this layer, melanocytes which constitutes about 5% of the living cells in this layer (Murphy, 1995).

ii. **Dermis**- This layer is just below the epidermis. It consists of fats, collagen and also elastin fibres that provide strength and flexibility to the skin. In older persons the elastin fibres fragments and much of the skin's elastic quality is lost. This, along with the loss of subcutaneous fat, results in wrinkles (Murphy, 1995).

iii. **Subcutaneous layer or hypodermis**- This is the inner most layer of the skin. It serves as storage for fats. The fats stored in this layer represent an energy source for the body and helps to insulate the body against changes in the outside temperature (Murphy, 1995).

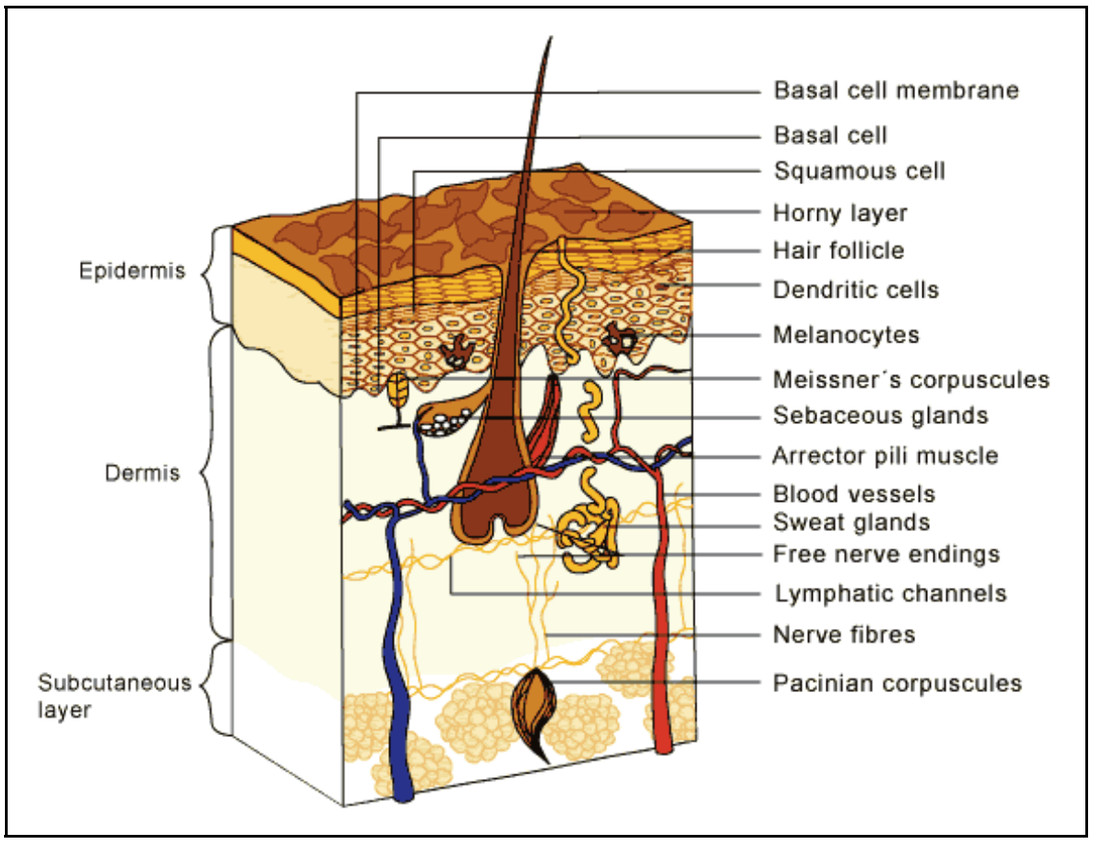

Fig. 2. Structure of the normal skin
(http://skincare.dermis.net/content/e01aufbau/e660/e661/e700/013_haut_aufbau_eng.gif)

2.2 Melanin biosynthesis and its importance

Melanin is a class of compounds found in the plant, animal and protista kingdoms, where it serves predominantly as a pigment (Kim and Uyama, 2005). In humans, melanin is the primary determinants of the color of the skin, hair and eyes. It is synthesized within melanosomes, membrane-bound granules, from melanocytes and is then transferred to keratinocytes through a physiological process called melanogenesis (figure 2.2) (Ancans et al, 2003; Kim and Uyama, 2005). Tyrosinase is known to be the key enzyme in melanin biosynthesis (figure 2.2). It catalyses two distinct reactions: hydroxylation of the amino acid tyrosine to 3,4 dihydroxyphenylalanine (DOPA) by monophenolase action and oxidation of DOPA in to o-dopaquinone by diphenolase action. This o-quinone is transformed into melanins in a series of non-enzymatic reactions (Baurin et al, 2002; Wang et al, 2006). There are two types of melanin pigments that can be produced by the melanocytes cells namely: 'eumelanin' (black or brown) and 'pheomelanin' (red or yellow) (figure 2.3) (Commo et al, 2004; Summers, 2006). The color of hair, skin etc in human is determined by the type, distribution and degree of melanin pigment synthesized. Each individual of different racial

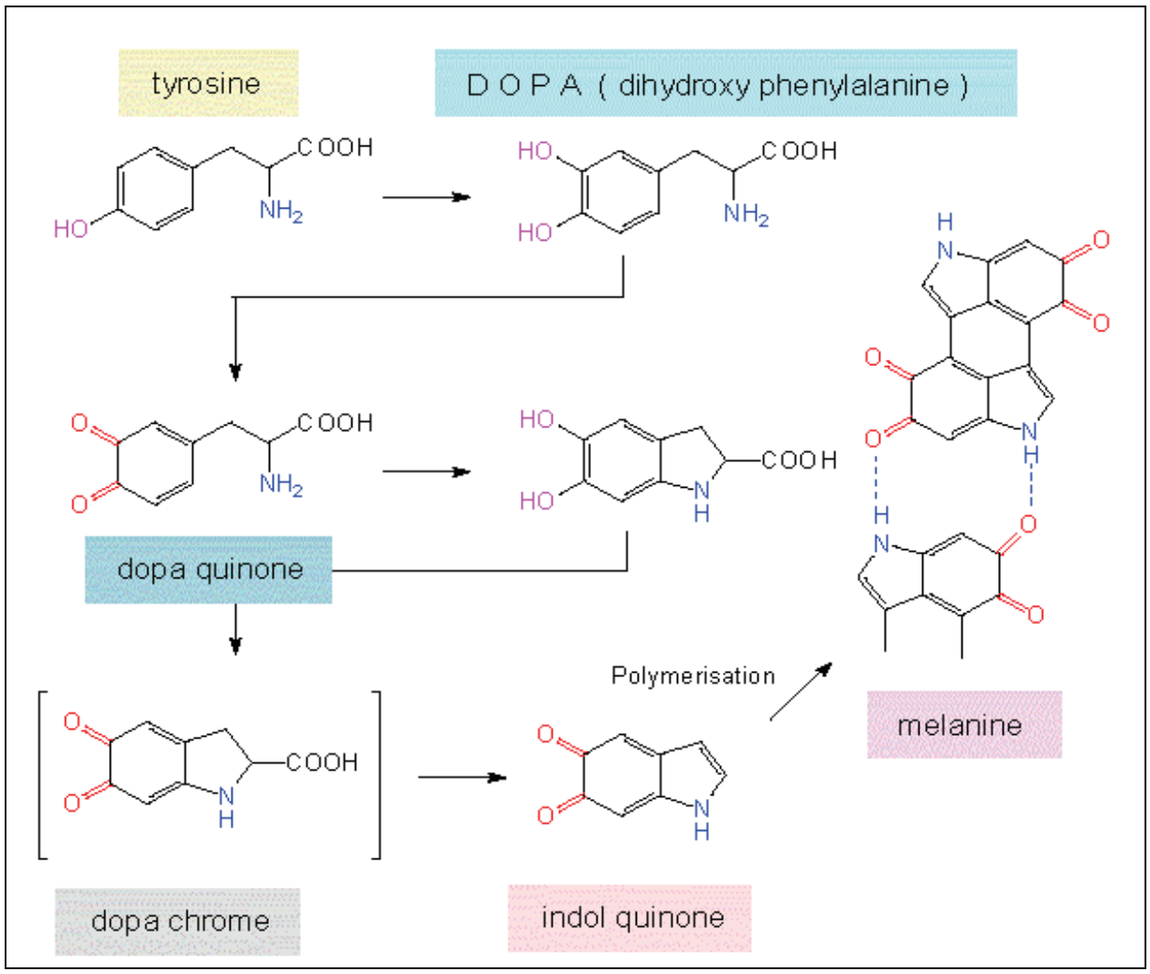

Fig. 3. Melanin biosynthesis pathway (Moss, 2005)
(http://www.chem.qmul.ac.uk/iubmb/enzyme/reacqwa tion/AminoAcid/melanin.html)

group have more or less the same number of melanocytes cells, thus the type of melanin produced depends on the functioning of the melanocytes e.g. people with darker skin are just genetically programmed to constantly produce higher levels of melanin even without exposure to UV light and the melanosomes remains singular (figure 2.4) (Commo et al, 2004; Baurin et al, 2002; Kim and Uyama, 2005; Summers, 2006; Sturm et al, 1998). In individuals with fair or lighter skin colour, melanosomes cluster in membrane bound organelles (figure 2.4) (Sturm et al, 1998). The role of melanin is to protect the skin against UV light damage by absorbing UV sunlight and by removing reactive oxygen species (Kim and Uyama, 2005; Summers, 2006).

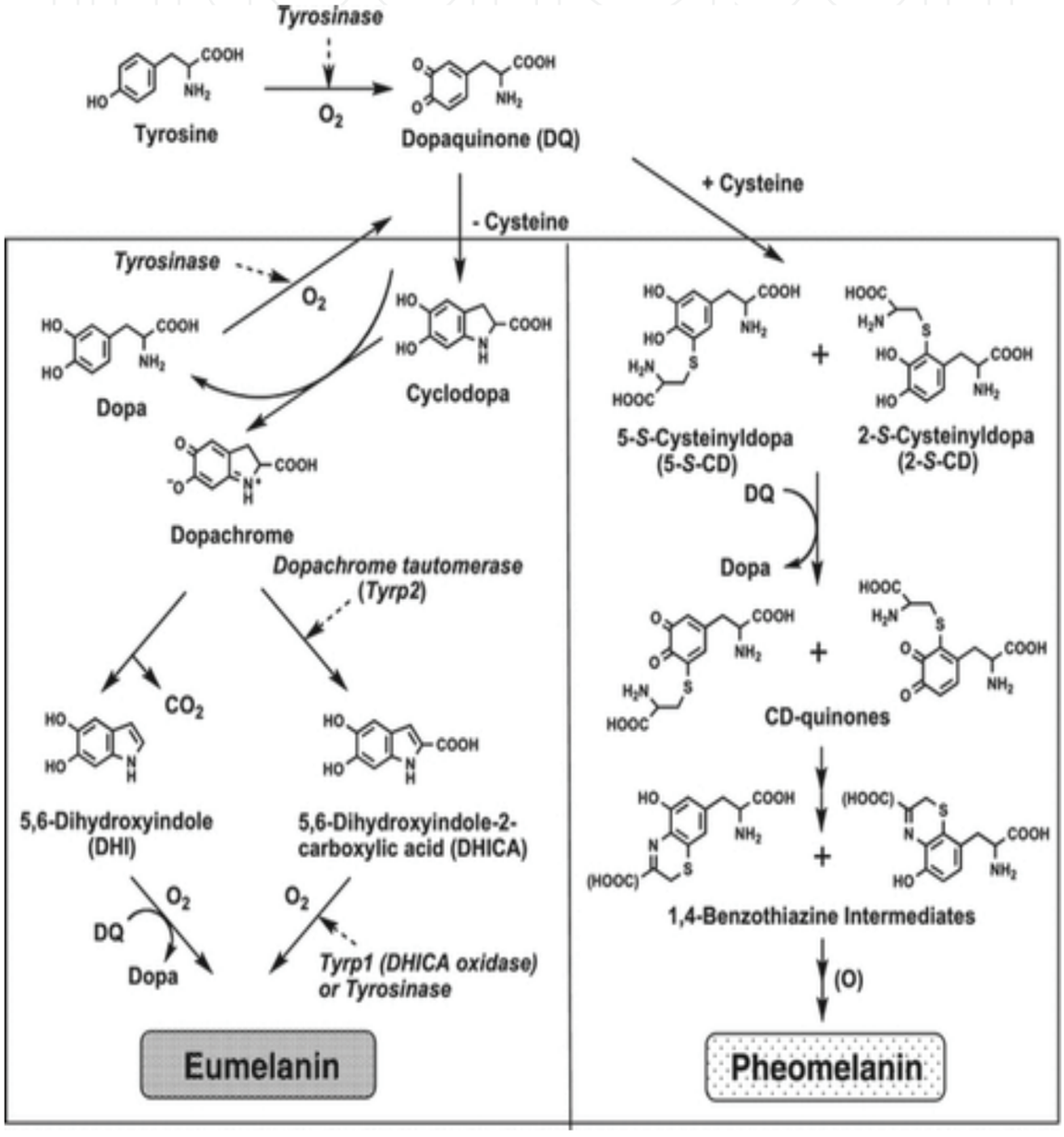

Fig. 4. Production of different pigments by melanosomes (Simon et al, 2008)

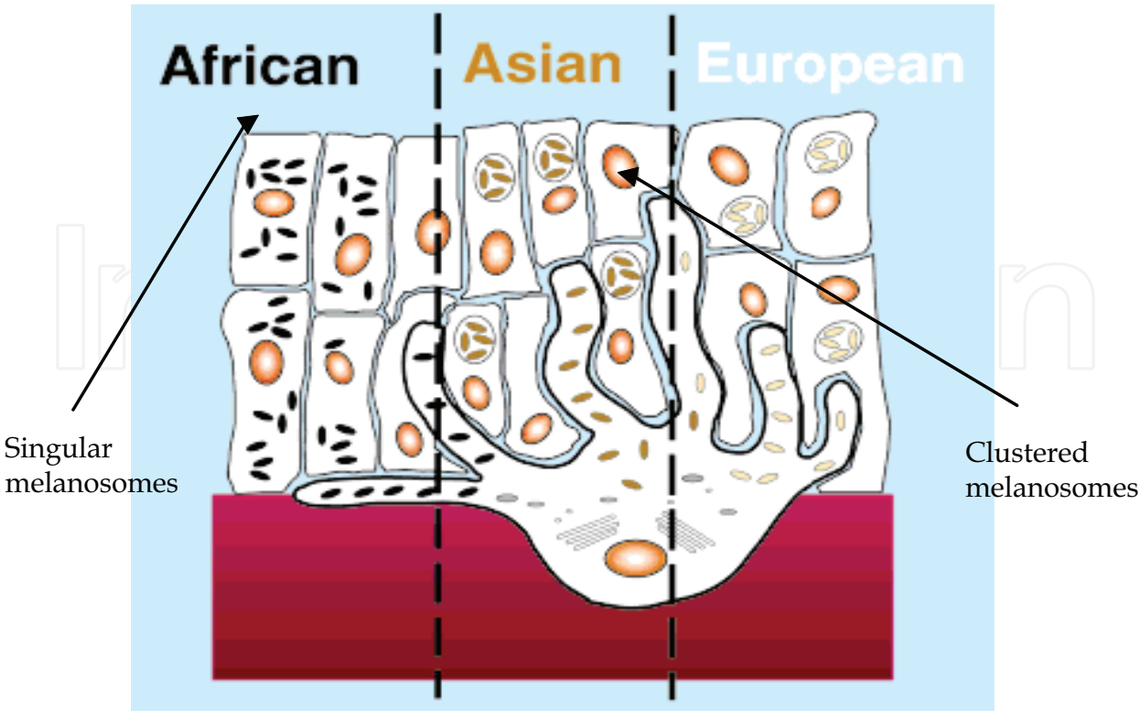

Fig. 5. Structure of melanosome distribution for different racial groups (Sturm et al, 1998)

2.3 Factors affecting skin pigmentation

The process of melanogenesis is affected by a variety of environmental, hormonal and genetic factors. Environmental factors include excessive exposure to UV light, which induces immediate pigment-darkening due to swelling and re-alignment of melanosomes (Rendon, 2003, Schulleuter et al, 1998; Simon et al, 2008). Example for hormonal factors is evident in pregnant women whereby during this period, dark brown patches occur on the forehead, face, cheeks and it can occur due to reactions caused by usage of drugs. Genetic factors are evident in cases like albinism whereby individuals loses the TPR1 gene which disrupts the correct formation of the melanosomal complex and thereby inhibits melanin synthesis, resulting in hypopigmented phenotype (Sturm et al, 1998)

2.4 Hyper-pigmentation disorders

Hyper-pigmentation is a common and distressing problem. Females report more often, although not rare in males. These disorders have a tremendous psychological impact especially in females. There are different kinds of hyper-pigmentation disorders that are encountered during life. Some of them are as follows:

2.4.1 Age spots

This is also known as brown spots, lentigines or liver spots. They usually appear on the hands, but can also appear on the face, arm and feet as brown patches. They are harmless and are caused by excessive exposure of the skin to the sun. It may also be caused by nutritional deficiency, impaired liver function dietary and ageing (Moss, 2005, Murphy, 1995).

2.4.2 Melasma

Melasma appears as blotchy, brownish pigmentation on the face of adults. Both sides of the face are usually affected. The most common sites of involvement are the cheeks, bridge of nose, forehead, and upper lip. The precise cause of melasma is unknown. People with a family history of melasma are more likely to develop melasma themselves. A change in hormonal status may trigger melasma. It is commonly associated with pregnancy and is also called chloasma, or the "mask of pregnancy." Birth control pills may also cause melasma, however, hormone replacement therapy used after menopause has not been shown to cause the condition. Sun exposure also contributes to melasma. While there is no cure for melasma, many treatments have been developed. Melasma may disappear after pregnancy; it may remain for many years, or a lifetime. Sunscreens are essential in the prevention of melasma (American Academy of Dermatologists press 2008; Montemarano, 2008; Daniel et al, 2003).

2.4.3 Freckles

Freckles are clusters of concentrated melanin which are most often visible on people with a fair complexion. A freckle is also called an “ephelis”. They can be found on anyone no matter the background; however, having freckles is genetic and is related to the presence of the dominant melanocortin-1 receptor (MC1R) gene variant. The formation of freckles is triggered by exposure to sunlight. The exposure to UV-B radiation activates melanocytes to increase the melanin production, which causes freckles to become darker. Freckles are predominantly found on the face, although they may appear on any skin exposed to the sun. Freckles are rare on infants and more common on children before puberty; they are less common on adults (Hanson et al, 2006; Daniel et al, 2003).

2.4.4 Melanoma

Excessive exposure to the sun is the most common cause of skin darkening. The darkening is due to the skin's increased production of melanin, which is a protective mechanism against the sun's harmful ultraviolet rays. In the last few decades, a suntan has been equated with a healthy, outdoor look, and large numbers of ordinarily fair-skinned people have deliberately exposed their skin to the sun to acquire suntans. This practice has led to an alarming rise in skin cancer, including **malignant melanoma,** which is often fatal. Fortunately, fashion is beginning to change, and deeply tanned skin is no longer considered chic.

Melanoma, also referred to as “malignant melanoma,” is the most serious form of skin cancer because - with the exception of some rare forms of skin cancer - it is the skin cancer most likely to spread to lymph nodes and internal organs. Today, melanoma accounts for 77% of all deaths from skin cancer.

Dermatologists believe that the number of deaths from melanoma could be significantly reduced if more people were able to recognize melanoma in its earliest stages. It is important to know that there are different types of melanoma. This article describes the four most common types of melanoma, which accounts for about 100% of diagnosed cases. Below you will find an explanation of what each of these four types of melanoma looks like and important points to remember. Here are a few of these key points:

- With early detection and treatment, the cure rate for melanoma is about 95%.

- Not all melanoma develops from a changing mole. Melanoma also can appear where there was not a previous lesion and look like a non-pigmented scar or cyst.
- Melanoma can appear as a nail streak or non-healing bruise.

Four types of melanoma

1. Superficial spreading melanoma (about 70% of diagnosed cases)
2. Nodular melanoma (about 15% of diagnosed cases)
3. Lentigo maligna melanoma (about 10% of diagnosed cases)
4. Acral lentiginous melanoma (about 5% of diagnosed cases)

2.4.4.1 Superficial spreading melanoma

Superficial spreading melanoma (SSM) is the most common type of melanoma in the United States, accounting for about 70% of all diagnosed melanoma cases. This type of melanoma can strike at any age and occurs slightly more often in females than males. SSM is the leading cause of death from cancer in young adults.

When SSM occurs in females, it most commonly appears on the legs. In males, it is more likely to develop between the neck and pelvis. However, this does not mean that females do not get SSM on their trunks or that males do not see SSM on their legs. This melanoma can occur anywhere on the skin's surface.

A typical SSM lesion has:

- Irregular borders
- Various shades of black, brown, gray, blue, pink, red, or white. Within the lesion there can be a remarkable variation in color involving white, pink, brown, and black.

In the early stages, SSM usually appears as a flat spot that looks like a freckle that is spreading sideways on the skin. Over time, the pigmentation in the lesion may darken, and the lesion may grow, develop increasingly irregular borders, and have areas of inflammation within the lesion. The area around the lesion may begin to itch. Occasionally, a SSM may become "less" pigmented as a person's immune responses try to destroy it. If a lesion becomes less pigmented, this does not mean that the lesion no longer requires treatment. It definitely needs to be examined by a dermatologist.

Superficial spreading melanoma can progress rapidly. If you see a lesion that you suspect could be melanoma, have it examined by a dermatologist.

2.4.4.2 Nodular melanoma

Nodular melanoma (NM) is the most aggressive type of melanoma and accounts for about 15% of all melanomas diagnosed in the United States. It can appear anywhere on the body and occurs more often in males than females. It can develop at any age; however, it is most often seen in people aged 60 and older.

NM differs from other types of melanoma in three ways:

- Tends to grow more rapidly in thickness (penetrate the skin) than in diameter
- May not have a readily visible phase of development
- Instead of arising from a pre-existing mole, it may appear in a spot where a lesion did not previously exist

Since NM tends to grow deeper more quickly than it does wide and can occur in a spot that did not have a previous lesion, the prognosis is often worse because it takes longer for a person to be aware of the changes.

NM is most often darkly pigmented; however, some NM lesions can be light brown or even colorless (non-pigmented). A light-colored or non-pigmented NM lesion may escape detection because the appearance is not alarming. An ulcerated and bleeding lesion is common.

The following photos show diagnosed cases of NM, which often appears as a dome-shaped, darkly pigmented lesion.

If a lesion appears where none existed before, have it examined as soon as possible by a dermatologist.

2.4.4.3 Lentigo maligna melanoma

Lentigo maligna melanoma (LMM) typically occurs on sun-damaged skin in the middle-aged and elderly, especially on the face. This melanoma may be mistaken in its early, and most treatable, stages for a benign "age spot" or "sun spot." LMM accounts for about 10% of the melanomas diagnosed in the United States. Since LMM is so easily mistaken, it can go undetected for years. This can be quite dangerous.

LMM begins as a spreading, flat, patch with irregular borders and variable colors of brown. This lesion is called "lentigo maligna." This spreading brownish patch may grow slowly for years and is often mistaken for lentigo simplex — a benign (non cancerous) brownish patch that can develop in the elderly after years of sun exposure.

As the lesion grows and evolves, both the pigmentation and borders tend to become more irregular. This often occurs slowly over a period of 10 to 15 years. It also can happen rapidly — in a matter of weeks or months. As the lesion grows deeper into the skin (thickness increases), it may become various shades of black and brown. Dark nodules may appear within the irregular borders. These nodules are the invasive tumor, and if large enough to be felt by touch, will feel lumpy.

If you have a large pigmented patch of skin, especially one with an irregular border, see a dermatologist as soon as possible.

2.4.4.4 Acral lentiginous melanoma

In the United States, acral lentiginous melanoma (ALM) accounts for about 5% of all diagnosed melanomas. It also is the most common form of melanoma in Asians and people with dark skin, accounting for 50% of melanomas that occur in people with these skin types.

ALM is sometimes referred to as a "hidden melanoma" because these lesions occur on parts of the body not easily examined or not thought necessary to examine. ALM develops on the palms, soles, mucous membranes (such as those that line the mouth, nose, and female genitals), and underneath or near fingernails and toenails.

ALM is often overlooked until it is well advanced because in the early stages, it often looks like a bruise or nail streak. Here is what it usually looks like on each area of the body:

- Palm or sole – Melanoma usually begins as an irregularly shaped tan, brown, or black spot. It is often mistakenly attributed to some recent injury — that is, the patient recalls a relatively recent bruise or blow in the general area of the pigmented spot.
- Mucous membranes – When melanoma develops on a mucus membrane, it is most likely to develop inside the nose or mouth. Early symptoms include nosebleeds and nasal stuffiness and a pigmented mass inside the mouth. Melanomas also can develop on the mucous membranes of the anus, urinary tract, and female genitalia.

- Under a nail - The first sign may be a "nail streak" — a narrow, dark stripe under the nail. ALM usually develops on the thumb or big toe; however, it can occur under any fingernail or toenail. Many individuals, especially dark-skinned people, have fixed nail streaks that are completely benign. A new nail streak not associated with recent trauma, an enlarging nail streak, a wide or very darkly pigmented streak, or a nail that is separating or lifting up from the nail bed should be examined by a dermatologist. A possible indication of advanced ALM is a nail streak with associated pigmentation in the nail fold skin or destruction of the nail plate.

ALM of the fingers or toes also can develop without an obvious nail streak — particularly the non-pigmented variety. ALM may, for example, look very much like a chronic infection of the nail bed. As an ALM tumor increases in size, it usually becomes more irregular in shape and color. However, some ALM lesions can be lightly colored or colorless. The surface of the ALM lesion may remain flat, even as the tumor invades deeply into the skin. Thickening ALM on the sole of the foot can make walking painful and be mistaken for a plantar wart.

The second photo shown above depicts an advanced tumor. This patient believed he had a long-standing bruise on his toe and refused to be examined by a physician. By the time ALM was finally diagnosed and surgically removed, it had invaded deeply into tissue and spread to other organs. The patient died of metastatic melanoma.

Be sure to see a dermatologist as soon as possible if you notice a:

- Bruise that does not fade or comes and goes
- Nail lifts up or separates from the nail bed
- New nail streak not associated with recent trauma
- Enlarging nail streak
- Wide or very darkly pigmented nail streak
- Pigmented mass in the mouth
- Nosebleeds and nasal stuffiness

2.4.4.5 Non-pigmented subtypes

While uncommon, melanoma occasionally does not have brown or black pigmentation. An uncommon subtype called **amelanotic melanoma** usually appears as a pink or red nodule (lump). Another uncommon subtype, **desmoplastic neutrotrophic melanoma** (DNM), usually looks like a non-pigmented scar. When a scar or keloid appears on the skin and the skin has not been injured, DNM is suspected. The lesion also can appear as a cyst that may or may not be pigmented. DNM tends to appear on sun-damaged skin in elderly patients, occurring mostly on the head and neck.

3. Treatment of hyper-pigmentation

Like other disorders hyper-pigmentation of the skin can be treated. Depending on the type and depth of pigmentation different treatment procedures are followed. The use of sun screens is important and this helps to reduce the development of pigmentation disorders. Skin lighteners are also used for the treatment of hyper-pigmentation this includes chemicals such as bleaching hydroquinone, retinoid etc which are available commercially (Cayce et al, 2004, Tiedtke et al, 2004).

3.1 Commercially available skin-lighteners

There are different types of skin-lightening agents that are available commercially to combat dark marks or skin hyper-pigmentation. Some of these chemically derived compounds have shown to have poor penetration of the skin and shows some cytotoxic and mutagenic effect on people. Among treatments the use of chemicals such as 'Kojic acid', 'Hydroquinone', 'Arbutin', 'Aloesin' etc are the most common ones. Descriptions of some of these chemicals are as follows:

3.1.1 Hydroquinone (HQ)

It is a hydroxyphenolic chemical that inhibits the conversion of L-DOPA to melanin by inhibiting the tyrosinase enzyme. Some of the possible mechanisms of action are the destruction of melanocytes, degradation of melanosomes and inhibition of the synthesis of DNA and RNA (Mashhood, 2006). Concentrations of HQ in commercially available formulations vary from 2% to 4%. Clinically and historically evaluation demonstrated clear improvements in most patients during the study done by Pandya and Guevara 2003. However, during this study 72% of the patients showed to develop irritant dermatitis over time, despite the low frequency of application.

3.1.2 Kojic acid (5-hydroxy-2-[hydroxyl methyl]-4-pyrone)

It is a naturally occurring hydrophilic, 'fungal derivative', evolved from certain species of *Acetobater*, *Aspergillus* and *Penicillin*. It acts by inhibiting the production of free tyrosinase with efficacy similar to hydroquinone. In Japan, kojic acid has been increasingly used in skin products. This is because until recently, topically applied kojic acid at 1% concentration had not exhibited any sensitizing activity. However, more recent long term Japanese studies have shown that kojic acid has a potential of causing 'contact dermatitis' and 'erythema' (Nakagawa et al, 1995; Mashhood, 2006).

3.1.3 Arbutin (b-D-glucopyranoside derivative of hydroquinone)

It is a naturally occurring plant derived compound that has been used for post-inflammatory hyper-pigmentation. The action of arbutin depends on its concentration (Maeda and Fukuda, 1996). Higher concentrations are more efficacious than lower concentrations. A dose-dependent reduction in tyrosinase activity, as well as melanin content in melanocytes, is demonstrated. It was reported that it may cause paradoxical hyper-pigmentation (Mashhood, 2006).

3.1.4 Aloesin

It is a natural derivative of *Aloe vera* that inhibits tyrosinase at noncytotoxic concentrations. Aloesin acts as an inhibitor of DOPA oxidation. It is an experimental product and thus it is not available clinically (Rendon & Gaviria, 2005).

4. Cosmeceutical formulations from plants

Due to instability, poor penetration of the skin, irritation and mutagenic effects of chemical and fungal derived compounds in cosmetical applications, humans opt for herbal products for the treatment of different types of skin problems. There are many South African plants

which are being used in herbal cosmetics. Rooibos (*Aspalathus linearis*) is famous for being naturally caffeine free (Morton, 1983) and its low tannin content minimizes the risk of reduced iron absorption, a phenomena frequently found in tea drinkers due to iron-tannin complexation. Rooibos is rich in flavonoids, polyphenols, phenolic acids, oligosaccharides and polysaccharides (Dos et al, 2005). The major flavonoids found in Rooibos tea are aspalathin, iso-orientin, orientin and rutin (Shimamura et al, 2006).

The skin is the largest organ of the body and is exposed to environmental oxidative stress. The incorporation of Rooibos extracts in topical cosmetic formulations has become very popular in recent years because it can target the site of action to reduce ultraviolet radiation damage and photo-aging (Mavon et al, 2005; Van Niekerk and Viljoen, 2008). Rooibos proved to exhibit anti-inflammatory and antimicrobial properties in cosmetic applications. According to earlier reports, hair growth was found to improve with the use of hair care products containing Rooibos. There are many herbal products derived from rooibos (fig 2.5).

Fig. 6. Rooibos (*Aspalathus linearis*) (http://www.inheritanceskincare.com/)

Artemisia afra is also popular for skin ailments. An infusion or decoction is used as a lotion by natives in South Africa to bathe hemorrhoids, herpes and venereal sores, while a hot bath in the decoction is used to bring out the rash in measles, mumps and chickenpox. The plant is also held in the mouth to ease the pain of boils and to hasten their bursting. It also has similar uses to *Artemisia herba-alba* and used externally on boils, carbuncles, and large acne pimples. A poultice of the leaf is applied locally to relieve neuralgia, to the swellings in mumps, and to any glandular or skin inflammation. A lotion is also made from the plant for washing the body and rejuvenating the skin (Dweck, 1996). Due to the above mentioned side effects and poor skin penetration ability of the existing agents which are used for the treatment of hyper-pigmentation, it is imperative to find alternative agents from plants.

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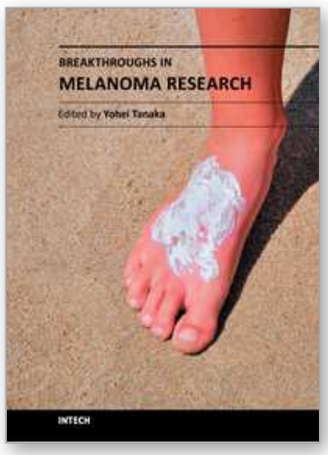

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Melanoma is considered to be one of the most aggressive forms of skin neoplasms. Despite aggressive researches towards finding treatments, no effective therapy exists to inhibit the metastatic spread of malignant melanoma. The 5-year survival rate of metastatic melanoma is still significantly low, and there has been an earnest need to develop more effective therapies with greater anti-melanoma activity. Through the accomplishment of over 100 distinguished and respected researchers from 19 different countries, this book covers a wide range of aspects from various standpoints and issues related to melanoma. These include the biology of melanoma, pigmentations, pathways, receptors and diagnosis, and the latest treatments and therapies to make potential new therapies. Not only will this be beneficial for readers, but it will also contribute to scientists making further breakthroughs in melanoma research.

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