INTRODUCTION

Melasma is a common acquired condition of symmetric hyperpigmentation, typically occurring on the face, with higher prevalence in females and darker skin types. Multiple etiologies, including light exposure, hormonal influences, and family history, have been implicated in the pathogenesis of this disorder. Various topical, oral, and procedural therapies have been successfully used to treat melasma. Traditional topical therapies including hydroquinone, tretinoin, corticosteroids, and triple combination creams; however, other synthetic and natural topical compounds have also shown varying efficacies. Promising oral therapies for melasma include tranexamic acid and glutathione. Procedures, including chemical peels, microneedling, radiofrequency, and LASERs, are also often used as primary or adjunctive treatments for melasma. Notably, combination therapies within or across treatment modalities generally result in better efficacies than monotherapies. Yet satisfactory results are not met in every patient with high percentage of recurrences and resistance to treatments appears especially in deep dermal type ***(Ogbechie-Godec and Elbuluk, 2017)***.

Vitamin C is one of the most powerful antioxidants in the skin which has been shown to protect against photoaging, ultraviolet-induced immunosuppression, and photocarcinogenesis. It also has an antiaging effect by increasing collagen synthesis,

stabilizing collagen fibers, and decreasing collagen degradation. It decreases melanin formation, thereby reducing pigmentation. Vitamin C is the primary replenisher of vitamin E and works synergistically with vitamin E in the protection against oxidative damage. Topical vitamin C has a wide range of clinical applications, from antiaging and antipigmentary to photoprotective. Currently, clinical studies on the efficacy of topical formulations of vitamin C remain limited, and the challenge lies in finding the most stable and permeable formulation in achieving the optimal results ***(Al-Niaimi and Chiang, 2017).***

The use of drugs synthezised with nanotechnology in treatment of many diseases is strongly emerging. This is achieved by the use of nanoscale particles (nanosomes) that is 100nm and smaller ***(Saraceno et al., 2012 and DeLouise, 2012)***.

Peelings are among the oldest and widespread procedures used in aesthetic dermatology worldwide. Chemical peels are classified as superficial, medium, and deep according to the depth of penetration of the peeling solution. The glycolic acid (GA) peel is the most used alpha hydroxy acid peel, producing a very superficial, superficial, or even a medium-depth peel, all of them usually well tolerated by patients and without systemic toxicity. The depth of glycolic acid peel depends on the concentration of the acid used, time of exposure, and skin condition. Acne (inflammatory and non-inflammatory), acne scars, melasma, photoaging and post-

inflammatory hyperpigmentation can be treated with GA peel. As other AHA peels, it needs to be neutralized to end its action, and it should be repeated several times to achieve the desirable cosmetic result ***(Steiner and Pascini, 2018).***

Aim of the Work

The aim of this work is to assess the efficacy of topical nanosome vitamin C cream and to compare its effect with topically applied Glycolic acid 70% chemical peeling in the treatment of facial hyperpigmentation.

Chapter One

MELASMA

Melasma is a common acquired disorder of hyperpigmentation characterized by irregular light brown to dark brown patches of hyperpigmentation commonly affecting the face. The trunk and arms are also occasionally involved. Multiple studies have documented the negative impact of melasma on quality of life ***(Yalamanchili et al., 2015).***

Skin pigmentation is determined by melanin synthesis in melanocytes, melanosome transfer to keratinocytes, and melanosome degradation. Melanosome degradation could be induced by autophagy through delivering targeted materials to lysosomes ***(Ho and Ganesan, 2011; Kim et al., 2013).*** An inverse relationship between autophagic activity in keratinocytes and skin color determination has been identified ***(Murase et al., 2013)***.

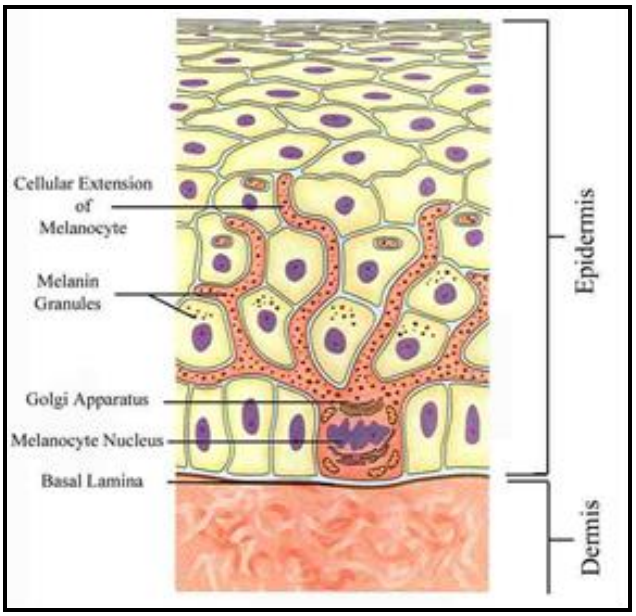

Fig. (1): Melanin production and distribution pathway on the epidermis, through melanosome ***(Health, medicine and anatomy reference pictures, 2014).***

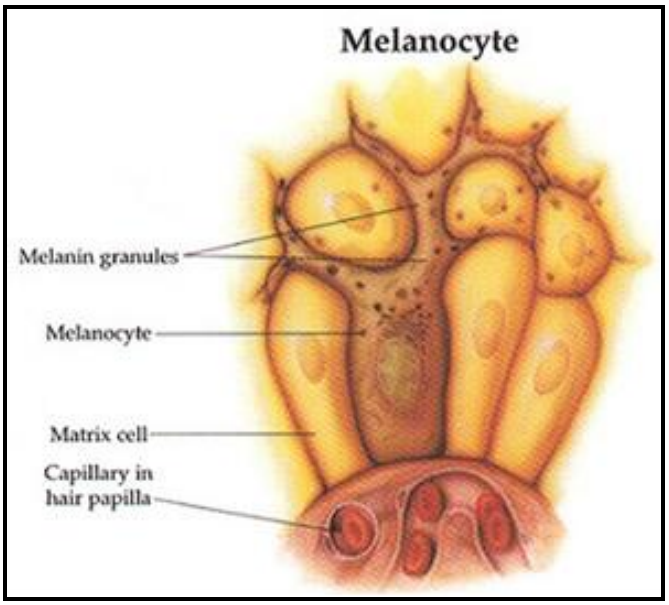

Fig. (2): Diagram of melanocyte within the epidermis ***(Dermweb. com, 2015).***

1.1 Clinical Presentation and Distribution

Morphologically, melasma presents as symmetric reticulated hyperpigmented patches with irregular borders on the centrofacial region, malar cheeks, mandible, and rarely upper chest and extremities. While melasma is known to more commonly affect darker skin types, it can occur in all skin types ***(Guinot et al., 2010; Tamega et al., 2013; Hexsel et al., 2014).*** On dermoscopic examination, it is possible to see pronounced hyperpigmentation in the pseudo-rete ridges of the skin ***(Mishra et al., 2013)***. Melasma usually develops slowly and can last for many years. It is of varying severity and tends to exhibit seasonal variation worsening in summer and improving in winter ***(Handog and Macarayo, 2012)***.

1.2 Incidence

Although melasma may affect any race, it is much more common in constitutionally darker skin types (Fitzpatrick's skin types IV to VI) than in lighter skin types. It may be more common in light brown skins, especially in people of East Asian, Southeast Asian, and Hispanic origin who live in areas of the world with intense solar ultraviolet exposure ***(Pasricha et al., 2007 and Shweta et al., 2011).***

Both sexes are affected, but the male population may represent up to only 10 % of cases ***(Nicolaidou and Katsambas, 2014).*** Extra-facial melasma is more frequent in postmenopausal women compared with those who were not experiencing menopause ***(Hexsel et al., 2014).***

1.3 Etiology

The pathogenesis of this condition is multifactorial and influenced by several factors including female sex hormones, genetic predisposition and ultraviolet light exposure. Estrogen and angiogenesis are significant factors in the etiology of melasma ***(Philip, 2017).***

1.3.1 Exposure Factor: Ultraviolet Radiation (UVA and UVB)

The higher level of solar elastosis in melasma skin implies that chronic sun exposure is a prerequisite for the development of melasma. Exacerbation is universally seen after prolonged sun exposure but the pigmentation fades after periods of avoidance and colder seasons. Repeated exposure to sunlight UV radiation increases the number of melanosome transfer to keratinocytes and increases the number of active melanocytes, as a result the density of melanocytes is twice greater in sun-exposed areas ***(Handog and Macarayo, 2012)***. Also Ultraviolet radiation can cause peroxidation of lipids in cellular membranes, leading to the generation of free radicals and consequently the stimulation of melanocytes to produce excess melanin. Ultraviolet B radiation (UVB) induces alpha-melanocyte stimulating hormone (α-MSH) production in keratinocytes. UVB is also known to increase adrenocorticotropin (ACTH) levels. The peptides (α-MSH) and ACTH are both derived from pro-opiomelanocortin (POMC) and bind to the melanocortin- 1 receptor, induce the formation of cyclic AMP.

Tyrosinase activity is then stimulated, leading to a proliferation of melanocytes and a subsequent increase in melanin production ***(Shweta et al., 2011).***

1.3.2 Genetic Factors and Predisposition

Family history is also known to be an important risk factor for developing melasma, strengthening the hypothesis of a genetic predisposition to the condition. Some studies have reported that 55–64% of patients with this condition have a positive family history ***(Handel et al., 2014)***. No genome-wide study has been performed to examine associated genes, but current findings would suggest that the genes responsible involve pigmentary, inflammatory, hormonal, and possibly vascular responses. Patients with Fitzpatrick skin type (FST) II and III are less likely to have a positive family history than patients with darker skin types (IV–VI) ***(Hexsel et al., 2014).***

1.3.3 Hormonal Factors

Hormonal influences play a significant role in the pathogenesis of melasma in females as seen by the increased prevalence with pregnancy, oral contraceptive use and other hormonal therapies ***(Handel et al., 2014)***. However, hormonal factors possibly have no role in male melasma ***(Handa et al., 2018).***

- **Pregnancy:** In 50-70% pregnant women melasma may be caused by an increase in placental, ovarian, and pituitary

hormones. It has been attributed to an elevation of melanocyte-stimulating hormone, estrogen and progesterone leading to increase in melanogenesis ***(Handog and Macarayo, 2012)***.

- **Hormonal replacement therapy:**

Melasma has been seen in postmenopausal women on treatment for osteoporosis which consists of combined estrogen and progesterone therapy. It has not been reported in women on estrogen-only regimens ***(Shweta et al., 2011).*** Estrogens stimulate melanogenesis in human melanocytes by inducing the synthesis of melanogenic enzymes, and melanocytes express estrogen receptors ***(Kim et al., 2012)***. An immunohistochemical analysis has shown that estrogen receptor and progesterone receptor expression levels are increased in affected skin ***(Tamega et al., 2015).***

- Oral contraceptive pills intake (OCT) ***(Handog and Macarayo, 2012).***

- Endocrinal disturbance as (thyroid dysfunction) ***(Achar and Rathi, 2011).***

1.3.4 Others factors

- Drugs as: phototoxic and anticonvulsant drugs ***(Iorizzo et al., 2006).***

- Emotional factors: Stress and depression are associated with higher cortisol levels and melanocortin production, which exert melanogenic activity ***(Handel et al., 2014).***
- Cosmetic chemicals ***(Pandya and Guevara, 2000).***

1.4 Pathophysiology

The cascade of events that leads to development of melasma in certain individuals is not fully understood. However it is known that the derangement in skin pigmentation seen in melasma is due to excessive amounts of melanin ***(Shweta et al., 2011).*** This can happen either by:

1. Increased production of melanin by melanocytes, termed "melanotic hyperpigmentation".
2. Increased number of melanocytes, termed "melanocytic hyperpigmentation" ***(Cayce et al., 2004).***

Melanin forms through a series of oxidative reactions involving the amino acid tyrosine in the presence of the enzyme tyrosinase The first reaction in melanin synthesis is the rate determining step, where tyrosinase enzyme converts tyrosine to dihydroxyphenylalanine (DOPA) ***(Shweta et al., 2011).***

1.5 Types

1.5.1 Clinical Types

Based on their clinical appearance and according to the surface anatomy of the face, patterns of melasma distribution are categorized into centrofacial, malar, and mandibular types.

1. The centrofacial pattern: is the most common pattern of melasma and involves the cheeks, forehead, upper lip, nose and chin.

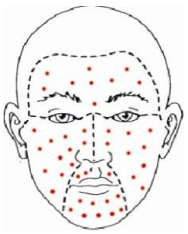

Fig. (3): Centrofacial pattern ***(Pandya et al., 2011).***

2. The malar pattern: has lesions limited to the cheeks and nose.

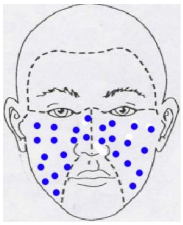

Fig. (4): Malar pattern ***(Pandya et al., 2011).***

3. The mandibular pattern: has lesions that occur over the ramus of the mandible ***(Sheth and Pandya, 2011).***

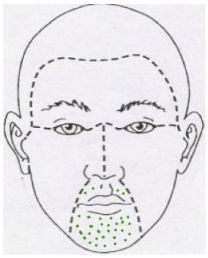

Fig. (5): Mandibular pattern ***(Pandya et al., 2011).***

1.5.2 Histological Types

A Wood lamp examination (emitting ultraviolet A radiation at 320 nm to 400 nm) may be used to demonstrate the difference in pigmentation between the effected and the non-effected areas ***(Handel et al., 2014).***

Generally, melasma is classified into one of 3 histologic types: epidermal, dermal, and mixed. However, some also include a fourth type known as Wood's light inapparent. Under Wood's light the epidermal type often shows a darkening of color when examined, as the light emitted by Wood's lamp is absorbed by the excess melanin. The dermal type, however, will not show this accentuation. The mixed type involves a deposition of melanin in both the epidermis and the dermis and color enhancement with Wood's light is seen is some places of the skin, but not others ***(Grime, 1995)***.

Melasma can be further characterized by the depth of involvement, which is often assessed by Wood's lamp illumination and divided into four categories: epidermal, dermal, mixed, and indeterminate ***(Grimes et al., 2005).*** Histologically, increased melanin in epidermal keratinocytes, dermal macrophages, or both are present ***(Kang et al., 2002).*** Wood's lamp can help distinguish between these entities because enhancement under the lamp suggests epidermal type and nonenhancement suggests dermal type. However, this assessment does not always correlate with histological findings

and melasma that is labeled epidermal is often mixed with areas of dermal involvement ***(Grimes et al., 2005).***

1.5.3 Classification according to Duration

Depending on the natural history of the lesions, melasma may also be classified into transient and persistent types:

- The transient type disappears within one year of cessation of hormonal stimuli like pregnancy or oral contraceptive pills ***(Handog and Macarayo, 2012).***

- The persistent type continues to be present more than one year after the hormonal stimulus is removed and is caused by the action of UV rays and other factors, that highlight the role of sun-avoidance in the management of melasma ***(Bandyopadhya, 2009).***

1.6 Treatment of Melasma

1.6.1 General management recommendations that assist in the clearing of melasma include

Discontinuation of birth control pills, scented cosmetic products, and phototoxic drugs, coupled with UV protection with use of broad-spectrum (UVA + UVB) sunscreens. Solar exposure exacerbates melasma, and its avoidance is fundamental for the successful management of the disease. Most patients using bleaching agents can expect a recurrence of the disease on exposure to sunlight and artificial UVA and

UVB light. This supports the importance of the use of broad-spectrum sunscreens (SPF>50) in melasma therapies. Broad-spectrum sunscreens must be applied every 2 hours daily throughout the year and continued indefinitely to minimize the reactivation of melanocytes by incidental exposure to the sun ***(Gupta et al., 2006 and Cestari et al., 2009).***

1.6.2 Protection from the Sun

Ultraviolet and visible light can induce melanin formation. The regular use of broad spectrum sunscreen (SPF of 50 + UVA filters) is effective in both preventing melasma and in enhancing the efficacy of other topical therapies once melasma has developed ***(Handog and Macarayo, 2012).***

The focus on UV photoprotection beyond the erythemogenic spectrum did not evolve until the late 20^{th} century. Like UVB (290–320 nm), UVA (320-400 nm) has biologic effects on immunosuppression, photoaging, and tumorigenesis. Because UVA is 1000-fold less erythemogenic than UVB, two biologic indices of UVA exposure were employed: immediate pigment darkening (IPD) and persistent pigment darkening (PPD). IPD appears within a few minutes of UVA exposure; it resolves in 2 hours. This is then followed by PPD, which lasts between 2 hours and 24 hours. Both IPD and PPD result from the oxidation of pre-existing melanin; no neo-melanogenesis occurs ***(Lim et al., 2001).***