INTRODUCTION

Plantar wart (Verruca plantaris) is a wart occurring on the sole or toes of the foot. Plantar warts can be painful due to their callused, endophytic papules that have deeply penetrating sloping sides and a central depression. Numerous coalesced warts on the plantar surface will form a tile-like pattern known as mosaic warts. Periungual warts are warts that cluster around the fingernail or toenail. They appear as thickened, fissured cauliflower-like skin around the nail plate. Periungual warts often cause loss of the cuticle and paronychia. Nail biting increases susceptibility to these warts.Warts affect 7–10% of the general population and are a common dermatological condition in general practice ***(James et al., 2006, Stulberg accessed, 2006).***

Human papilloma virus (HPV)(subtypes 1, 2, 4, 27 and 57) is the causative agent, which enters via breaches in the skin surface and infects keratinocytes, resulting in metaplasia and excessive skin growth ***(Handisurya et al., 2009).***

Transmission of warts occurs from direct person-to-person contact or indirectly by fomites. Swimming pools and bathrooms are common areas for the spread of warts if the skin is macerated and touches rough surfaces.Once HPV has infected the skin, autoinoculation can occur by scratching, shaving or traumatizing the skin ***(Stulberg, 2003).***

Plantar wart can be left to undergo spontaneous remission however treatment is generally recommended to lessen symptoms (which may include pain), decrease duration, and reduce transmission. However, they tend to relapse and the course of therapy is frustrating in many cases. No single therapy has been proven effective at achieving complete remission in every patient. As a result, many different approaches to wart therapy exist.

Destructive techniques include surgical destruction, cryosurgery, and superficial electrodessication, salicylic acid paint, liquid nitrogen, pulsed dye laser, carbon dioxide laser and photodynamic therapy ***(Morton et al., 2008).***

Immunotherapy include oral zinc sulphate, contact sensitizers as dipiphencyprone (DCP), squaric acid dibutyl ester (SADBE), intralesional injection of interferon, intralesional injection of candida or mumps antigen, 5 fluorouracil and imiquimod. Virucidal therapy includes glutaraldehyde and formic acid. Antimitotic therapy includes intralesional bleomycin, retinoids and podophyllin ***(Gibbs et al., 2006; Signore, 2002).***

Photodynamic therapy (PDT) is a modern, noninvasive treatment for skin disorders which involves local administration of a photosensitizing drug (as 5-aminolaevulinic acid (ALA), liposomal loaded methylene blue) act as prodrugs followed by illumination of the involved tissue with light within the visible

wavelength spectrum. When light of the appropriate visible wavelength is applied, the PS is energized to an excited state that can undergo molecular collisions with oxygen, resulting in the formation of reactive oxygen species particularly a toxic type of oxygen known as singlet oxygen which is responsible for a cascade of cellular and molecular events that end with immunomodulary or cytotoxic effects.

For a reason not entirely understood, hyperproliferating cells selectively uptake PS. This, together with the fact that cell death is spatially limited to regions where light of the appropriate wavelength is applied, makes PDT a highly selective and useful modality. Because microbial cells, much like neoplastic cells, grow at very fast rates, it was suggested that PDT could be used for microbial cell destruion. PDT has been successfully employed in the treatment of several dermatological problems, such as actinc keratoses, Bowen's disease, basal cell carcinoma, psoriasis, sarcoidosis, localized scleroderma, acne vulgaris and viral warts ***(Stender, 2000, Hunt, 2002, Gold, 2007, Fabbrocni et al., 2009).***

Photodynamic therapy has been shown to be successful for treatment of recalcitrant verrucae and is a useful modality for these lesions. Stender et al in 2000 published findings in hand and foot verrucous lesions in 45 patients treated with ALA-PDT which showed that relative reduction at 18 weeks was 100%. In 2001, Fabbrocini et al. reported their experience with recalcitrant planter warts in 67 patients which showed that

48 out of 64 warts was completely healed. Mizuki et al in 2003 reported the use of ALA-PDT in multiple plane wart on the face, five months after the final treatment the areas remained disease free. Gold and Pope reported a case of fractional laser resurfacing and use of ALA-PDT in treating recalcitrant verrucous lesion on the foot in 2008 ***(Stender et al., 2000, Fabbrocini et al., 2001, Mizuki et al., 2003, Gold et al., 2008).***

AIM OF THE WORK

To evaluate the efficacy and safety of liposomes loaded methylene blue based photodynamic therapy in treatment of plantar warts and periungual warts

Chapter One

WARTS

Prevelance and etiology:

Cutaneous viral warts are a very common skin condition caused by the human papilloma virus (HPV), and most people experience warts in one form or another at some point in their lives ***(Sterling, 2004)***.

Common warts (verrucae vulgaris) and plantar warts (verrucae plantaris) are the most common types. Up to one third of primary school children have cutaneous warts ***(van Haalen et al., 2009).***

Although cutaneous warts have a benign natural history, they cause significant physical and psychological inconvenience. Therefore, patients with warts frequently consult physicians, mostly in primary care ***(Bruggink et al., 2010)***.

The prevalence of cutaneous viral warts in children and adolescents is between 3% and 5%, occurring with similar frequency in adults aged 25 to 34 years ***(van Haalen et al., 2009).***

More than 120 HPV types, distributed over 5 genera and 16 species, have been described based on their DNA sequences ***(Bernard et al., 2010).*** HPV 2, 7, 27 and 57 from the alpha

genus, HPV 4 and 65 from the gammagenus, and HPV 1 from the mu genus have most frequently been detected in cutaneous warts ***(Tomson et al., 2011).***

Virology:

DNA genome is divided into 3 main regions: the long control region (LCR), the region of early proteins (E1-E8), and the region of late proteins which translate major L1 (late protein) and minor L2 capsid proteins. They cover 10%, 50% and 40% of the virus genome respectively ***(Stern et al., 2000).***

Human papilloma virus infection is limited to the basal cells of stratified epithelium, the only tissue in which they replicate. The virus cannot bind to live tissue; instead, it infects epithelial tissues through micro-abrasions or other epithelial trauma that exposes segments of the basement membrane. The infectious process is slow, taking 12–24 hours for initiation of transcription. It is believed that involved antibodies play a major neutralizing role while the virions still reside on the basement membrane and cell surfaces ***(Schiller et al., 2010).***

The two primary oncoproteins of high risk HPV types are E6 and E7. The “E” designation indicates that these two proteins are expressed early in the HPV life cycle, while the "L" (late gene) designation indicates late expression. The HPV genome is composed of six early (E1, E2, E4, E5, E6, and E7)

ORFs(open reading frames), two late (L1 and L2) ORFs, and a non-coding long control region (LCR**)** ***(Ganguly et al., 2009).***

After the host cell is infected viral early promoter is activated and a polycistronic primary RNA containing all six early ORFs is transcribed. This polycistronic RNA then undergoes active RNA splicing to generate multiple isoforms of mRNAs. One of the spliced isoform RNAs, E6*I, serves as an E7 mRNA to translate E7 protein ***(Tang et al., 2006).***

However, viral early transcription subjects to viral E2 regulation and high E2 levels repress the transcription. HPV genomes integrate into host genome by disruption of E2 ORF, preventing E2 repression on E6 and E7. Thus, viral genome integration into host DNA genome increases E6 and E7 expression to promote cellular proliferation and the chance of malignancy. The degree to which E6 and E7 are expressed is correlated with the type of cervical lesion that can ultimately develop ***(Scheurer et al., 2005).***

The E6/E7 proteins inactivate two tumor suppressor proteins, p53 (inactivated by E6) and pRb (inactivated by E7**)** ***(Chaturvedi et al., 2010).***

Human papillomaviruses are small non-enveloped, double-stranded DNA viruses approximately 55-nm in diameter ***(Horvath et al., 2010).*** Its capsid is icosahedral with a diameter ranging between 50nμ and 60nμ; the virus is not coated by a

lipid envelope; it has 72 capsomeres and species-specific antigenic determiners in its outer surface and internally ***(Castro, 2007)*** **(Figure 1).**

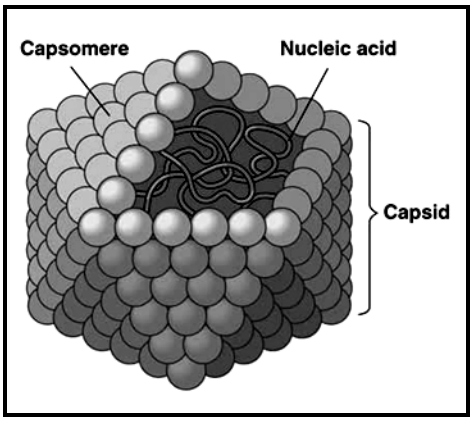

Figure (1): Structure of HPV ***(Stern et al., 2000).***

Human pappiloma virus were originally classified to cutaneous and mucosal types ***(Longworth et al., 2004).*** Group 1 includes cutaneous associated skin warts, and group 2 includes cutaneous associated epidermolysis verruciformis. Regarding group 3, it is an independent group for HPV-2, HPV-57 as they occupy an intermediate position between cutaneous and mucosal viruses. Group 4 includes mucosal lesions, mostly in the genital area and the most common HPVs are 6, 11, 16, 18 ***(Ranst et al., 1992).***

Group 4 are further classified to low risk and high risk groups according to the oncogenic potential. HPVs in the low risk group are the cause of benign genital warts and are never found in invasive carcinomas ***(Ranst et al., 1992).*** They may

form dysplasia or cervical intraepithelial neoplasia grade1 {CIN-1} ***(Longworth et al., 2004).*** About 15 HPVs are found in the high risk group, they are usually associated with invasive cancers. Numerically HPV 16 and 18 are the most important HPV viruses causing invasive cancers ***(Ranst et al., 1992)***

Human papillomavirus infects the basal cells of the epithelium and multiply in its upper more differentiated layers of the epithelium (Figure 2). Hyperplasia and hyperkeratosis are the hallmarks of skin infection by dermatotropic HPV. It is transmitted through direct skin-to-skin contact; however infection can spread through penetrative vaginal or anal intercourse ***(Braaten and Laufer, 2008).***

Infection with high-risk HPV combined with other risk factors such as immunosuppression, cigarette smoking and coinfection with human immunodeficiency virus can lead to the development of cervical cancer ***(Beglin et al., 2009).*** Also, high sexual activity has been reported to increase the risk of HPV infection in some women ***(De Sanjose' et al., 2007).***

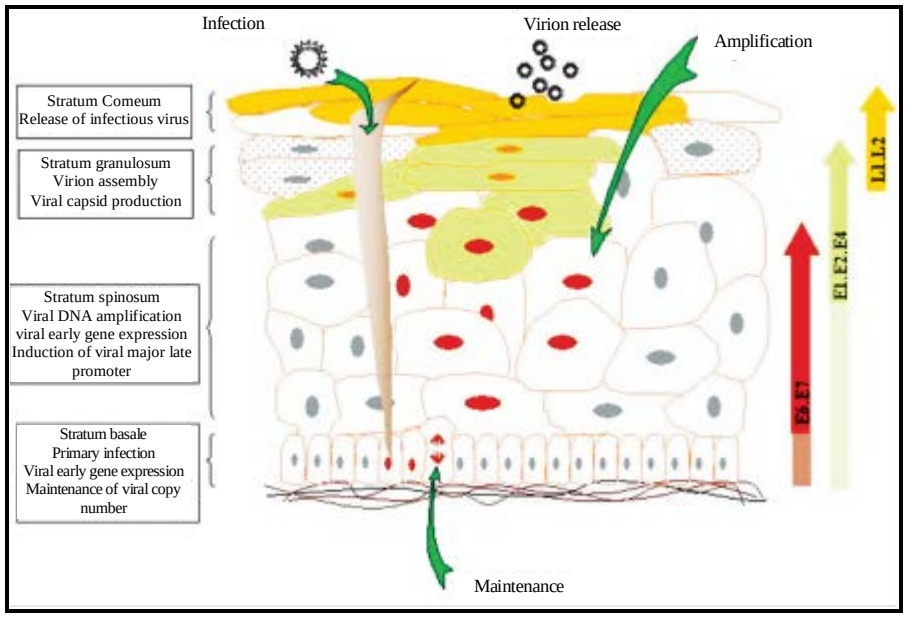

Figure (2): The HPV life cycle. Shown is the coordinate expression of the different viral proteins during the course of a productive infection ***(Coote and Arrand, 2000).***

Manifestations of HPV infection *(Gearhart, 2006)* (Table 1):

Table (1): Manifestations of HPV *(Gearhart, 2006)*

Cutaneous manifestations	Extracutaneous manifestations
▪ Common warts ▪ Filiform warts ▪ Periungual warts ▪ Plantar wart ▪ Plane wart ▪ Bowen's disease ▪ Epidermodysplasia verruciformis	▪ Condyloma acuminate ▪ Buschke- Lowenstein tumor(giant condyloma) ▪ Bowenoid papulosis ▪ Oral warts ▪ Focal epithelial hyperplasia(Heck:s disease) ▪ Oral florid papillomatosis ▪ Recurrent respiratory papillomatosis

Table (2): Diseases and Associated HPV Subtypes ***(Gearhart, 2006).***

Diseases and Associated HPV Subtypes	HPV Type
Nongenital Cutaneous Disease	
Common warts (verrucae vulgaris)	1, 2, 4, 26, 27, 29, 41, 57, 65
Plantar warts (myrmecias)	1, 2, 4, 63
Flat warts (verrucae plana)	3, 10, 27, 28, 38, 41, 49
Butcher's warts	1, 2, 3, 4, 7, 10, 28
Mosaic warts	2, 27, 57
Ungual squamous cell carcinoma	16
Epidermodysplasia verruciformis	5, 8, 9, 10, 14, 17, 20, 21, 22, 23, 24, 25, 37, 38
Nongenital Mucosal Disease	
Respiratory papillomatosis	6, 11
Squamous cell carcinoma of the lung	6, 11, 16, 18
Laryngeal papilloma	6, 11, 30
Laryngeal carcinoma	16, 18
Maxillary sinus papilloma	57
Squamous cell carcinoma of the sinuses	16, 18
Conjunctival carcinoma	16
Oral focal epithelial hyperplasia (Heck disease)	13, 32
Oral carcinoma, Oral leukoplakia	16, 18
Anogenital diseases	
Condylomata acuminate	6, 11, 30, 42, 43, 44, 45, 51, 52
Bowenoid papulosis	16, 18, 34, 39, 42, 45
Bowen disease	16, 18, 31, 34
Buschke-Löwenstein tumors	6, 11
Intraepithelial neoplasia	30, 34, 39, 40, 53, 57, 59, 61, 62, 64, 66, 67, 68, 69
Carcinoma of vulva	6, 11, 16, 18
Carcinoma of vagina &cervix	16, 18, 31
Carcinoma of penis	16, 18

Common Warts:

Common warts (verrucae vulgaris) are irregularly surfaced, domed lesions that can occur almost anywhere on the body. Multiple warts are common and are spread by skin-to-skin contact or contact with a contaminated surface. After initial infection, warts frequently are spread by autoinoculation from scratching, shaving or other skin trauma ***(Goodheart, 2000).***

Characteristic features are punctuate black dots representing thrombosed capillares and capillary bleeding that follows shaving of the hyperkeratotic surface ***(Kirnbauer et al., 2003)***

Individuals with atopic dermatitis have higher prevalence of infection, the exact cause is unknown but they might have mild T-cell defect. Atopy is suspected in children or adults with more than 10 warts and with no other cause of immunosuppression. HPV-1, HPV-2, HPV-4 are the most common types causing common warts. They usually don't cause genital lesions with the exception of HPV-2 which can cause common, oral and genital lesions ***(Naylor, 2000).***

Periungual warts:

Those occurring around the nail are referred to as periungual, whereas those occurring beneath the nail are referred to as subungual.Human Papilloma Viruses (HPV) 1, 2,

4, 27, and 57 are generally the cause of benign ungual warts, commonly affecting children and young adults ***(Kirnbauer et al., 2007).*** HPV 16 and 18 are rare causes and are associated with malignant transformation to squamous cell carcinoma (SCC) ***(Zaiac et al., 2001).*** There is a specific subset of periungual warts known as "butcher's warts, " which occur in people handling animal products and are caused by HPV 2 and 7 ***(Finkel et al., 1984).***

Ungual warts begin in skin that contains a granular layer, such as the proximal and lateral nail folds and the hyponychium. Appearing as skin-colored, rough papules, warts can progress to larger, verrucous papules coalescing into plaques. Black dots can often be seen on the surface clinically or with a dermatoscope, which correlate with blood vessels and help distinguish the wart from other growths. Diffuse or linear onycholysis and splinter hemorrhages can be seen with subungual warts. A hyperkeratotic nail bed is associated with warts of the hyponychium, whereas a hyperkeratotic cuticle is due to warts of the proximal nail fold. Ridges and grooves of the nail plate are due to pressure of the wart on the nail matrix ***(Herschthal et al., 2012).***

Plantar wart (Verruca plantaris)

Plantar wart is a wart occurring on the sole or toes of the foot. Plantar warts can be painful due to their callused, endophytic papules that have deeply penetrating sloping sides

and a central depression. Numerous coalesced warts on the plantar surface will form a tile-like pattern known as mosaic warts ***(James et al., 2006; Stulberg, 2006).***

Autoinoculation of the virus into opposed lesions is common. The HPV can survive for many months and at low temperatures without a host. Therefore an individual with plantar warts can spread the virus by walking barefoot. Clinically detectable verrucae develop from a few weeks to 18 months after inoculation. In most infected individuals, the virus is carried subclinically and never produces apparent lesions ***(Nebesio et al., 2001).***

They are remarkable for their thickness due to their presence in the acral skin of the hands and feet. The greater their depth, the more difficult is their treatment ***(Naylor, 2000).*** There are two forms of warts, endophytic and exophytic, also a mosaic form may be detected. Endophytic warts are deep and painful. They are characterized by keratinous plaques with a black pointed central area (thrombosed capillaries) and a thick white keratinous ring at the periphery. Exophytic warts are multiple, superficial warts that are slightly raised. They are found mostly on heels, and usually painless. HPV-1, HPV-2, HPV-4 are the most common etiology ***(Guerra-Tapia et al., 2009).***

Plantar warts must be differentiated from callosities which are ill defined areas of waxy, yellowish thickening,