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TOPICAL APPLICATION OF SILYBUM MARIANUM EXTRACT

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ABSTRACT
Most of the cosmeceuticals with herbal origin have strong antioxidant activity. Because oxidative stress is one of the major mechanisms for skin aging and dermatologic conditions, phytochemicals with proven antioxidant activity, such as silibinin, could be useful for treating many dermatologic conditions as well as skin aging. Silibinin is a flavonolignan compound from Silybum marianum that possesses strong antioxidant activity and also modulates many molecular changes caused by xenobiotics and ultraviolet radiation to protect the skin (Singh et al, 2009). Our aim was to give a brief description of the topical use of the active components of Silybum marianum.
Keywards: cosmeceuticals, topical application, Silybum marianum, silymarin, skin disorders

INTRODUCTION

Biocosmetics, cosmeceuticals of natural origin are becoming more popular than conventional cosmetics as they are mostly non toxic and possess strong antioxidant activity. The entire range of **biocosmetics** can be divided into two groups – plants and animals origin. Herbal Cosmetics or phytocosmetics includes extracts, essential oils, resins and other components, extracted from flowers, roots, leaves and fruit (Singh et al, 2009). Silybum Marianum (Milk thistle) is a well known medicinal plant that has been used for centuries as a herbal medicine for the treatment of liver-related diseases (Rasul A. et al, 2011). It is widely prescribed by herbalists and has almost no known side effects. The plant is native to the Mediterranean and grows throughout Europe and North America. It also grows in India, China, South America, Africa and Australia (Dixit N. et al, 2007). Silymarin , a flavonolignan complex that contains silibinin, was isolated from this plant in the 17th century and has been clinically used to treat various liver aliments for more than 3 decades (Singh et al, 2009). With the help of high performance liquid chromatography/tandem mass spectrometry (HPLC–MS/MS) method already eleven components were separated from the extract of Silybum marianum. The major bioactive flavonoligans in silymarin includes silychristins A and B, silydianin, silybin A and B, isosilybin A and B and an unknown compound. Furthermore, three additional components were also detected and partly separated; presumably two silybin stereoisomers and one isosilybin stereoisomer (Kuki et al, 2012). During the extraction process of Silybum marianum two phases, a solid powder and an oil extractum can be reached. Most of the articles deal with the internal and external effect of the powder phase but not with the therapeutic effect of the native Silymarin oil.

Protective effect of silymarin and silybin against chemically-induced skin damages

Some environmental toxins, including those that are skin tumor promoters, are generally nonmutagenic, and their exposure to skin can lead to epigenetic alterations that are manifested in to various dermatologic conditions. Chronic exposure may facilitate the process of skin carcinogenesis, provided that the skin epidermis has initiated cells that are characterized by the genetic alteration in tumor suppressor or protooncogenes. Specifically, it facilitates the clonal expansion of initiated cells, leading to the formation of benign tumors or papillomas that later become malignant. Oxidative stress is one of the mechanisms these toxicants use to cause skin injury and facilitate skin tumor promotion (Singh et al, 2009). Various studies have shown the protective effects of silymarin and silybin against chemically and UVB-induced skin damages both in cell cultures and animal experiments. Topical application or dietary feeding of silymarin resulted in highly significant protection of chemically induced skin carcinogenesis in several mouse models using 7,12-dimethylbenz[a] anthracene (DMBA) as initiating agent and benzoyl peroxide (BPO), 12-*O*-tetradecanoyl-phorbol-13-acetate (TPA), mezerein or okadaic acid as the tumor promoters. The effect of silymarin was manifested as reduction of tumor incidence, multiplicity and volume, inhibition of papiloma tumor growth and regression of established tumors. Silymarin also showed significant protection against tumor promoter-induced lipid peroxidation and depletion of antioxidant enzymes such as superoxide dismutase,catalase, glutathione peroxidase, inhibition of edema, myeloperoxidase activity and IL-1α protein level, as well as reduction of TPA-induced lipoxygenase and COX-2 activities in mouse epidermis (Gazák et al, 2007).

Protective effect of silymarin and silybin against UVB-induced skin damages

Skin exposure to solar UV radiation induces a number of skin disorders, including erythema, edema, immune suppression, photoaging, melanogenesis and skin cancers. UV irradiation, both its UVB (290-320 nm) and UVA (320-400 nm) component, induces the generation of reactive oxygen species (ROS), which create oxidative stress in skin cells and play an essential

role in the initiation, promotion and progression of skin aging and carcinogenesis.

Both silymarin and silybin have been shown to exhibit preventive effects against photocarcinogenesis in various animal models (Gazák et al, 2007). The most frequently used and reliable preclinical animal model to study the effect of UV radiation is the SKH-1 hairless mouse strain. UVB exposure is known to cause skin inflammation, edema, and epidermal hyperplasia in this mouse strain, whereas chronic UVB exposure leads to the formation of benign papillomas and subsequently squamous cell carcinomas (SCC), similar to the development of nonmelanoma skin cancer in humans (Gazák et al, 2007).

Solar UV radiation-induced skin cancer or photocarcinogenesis is a complex process that involves a series of individual steps. UV-induced tumor development has been generally considered to consist of three distinct stages: (i) tumor initiation which consists of genotoxic effects in normal cells, (ii) tumor promotion, consists

of clonal expansion of initiated cells and this stage is considered to be reversible, and (iii) tumor progression which consists of malignant transformation of papillomas to carcinomas and requires further genotoxic stimulus (Baligaa et al, 2006).

A schematic representation of these stages is shown in Fig. 1. (Vaid et al., 2010)

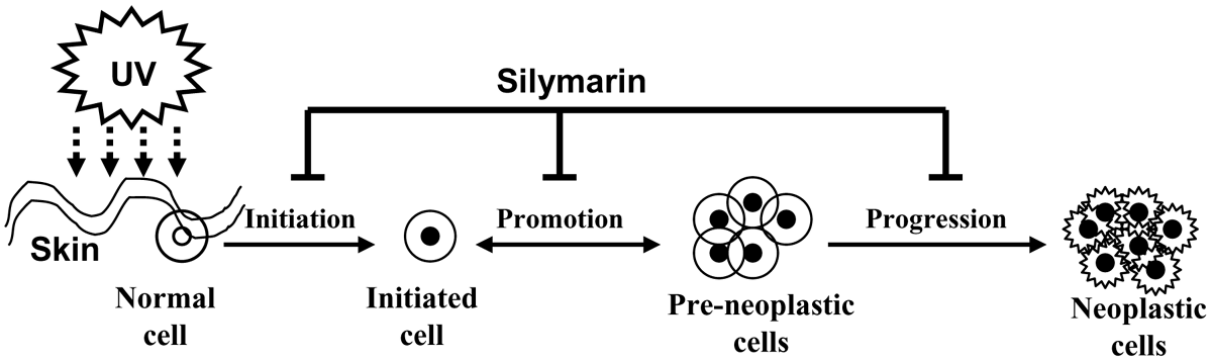

Figure 1. *Schematic representation of UV radiation-induced multi-stage skin carcinogenesis, showing initiation, promotion and progression stages. In the initiation stage genetic changes occurs in the cells. At the promotion stage, additional UV irradiation leads to the clonal expansion of initiated cells. Tumor progression stage involves the transformation of the benign tumor into an invasive and potentially metastatic malignant tumor. Silymarin can reverse, inhibit or retard the process of skin carcinogenesis at one or at all the stages of carcinogenesis. (Vaid et al., 2010)*

Topical or dietary administration of silymarin or silibinin is found to strongly inhibit UVB-induced tumor initiation, promotion, and complete carcinogenesis in the skin of SKH-1 hairless mice (Singh et al, 2009, Katiyar et al, 1997, Mallikarjuna et al, 2004).

Topical application of silymarin to SKH-1 nude mice reduced UVB-induced tumor incidence, tumor multiplicity and tumor size compared to those of non-treated animals (Katiyar et al, 1997). Silybin inhibited photocarcinogenesis in mice when applied topically or administered in the diet (Mallikarjuna et al, 2004).

Cutaneous photoprotection mechanisms triggered by silymarin and silybin are numerous and demonstrate mainly their ability to reduce and suppress harmful effects of solar UV radiation, such as UV-induced oxidative stress, inflammation, immune responses, DNA damage and cell proliferation. In addition, modulation of mitogenic, apoptotic and survival signaling, activation of p53, induction of cell cycle arrest and enhancement of DNA repair have been identified as essential molecular events involved in silybin/silymarin efficacy against skin carcinogenesis (Katiyar, 2005, Singh et al, 2005).

Topical application of silymarin reduces chemical-induced irritant contact dermatitis

Irritant contact dermatitis (ICD) is a non-allergic local inflammatory reaction of a skin and one of the most frequent occupational health problem. Topical application of 2,4-dinitrochlorobenzene (DNCB) induced an ear swelling in BALB/c mice and silymarin suppressed DNCB-induced increase in ear thickness. Prophylactic and therapeutic application of silymarin showed similar effect on DNCB-induced increase in ear thickness and skin water content. In addition, phobor ester- or croton oil-induced increase in ear thickness was also inhibited by silymarin treatment. Silymarin also blocked neutrophil accumulation into the ear induced by these irritants. Further study demonstrated that DNCB-induced tumor necrosis factor-α (TNF-α) expression in mouse ear was suppressed by silymarin. DNCB-induced expression of KC, one of the main attractors of neutrophil in mice, and adhesion molecules, including intercellular adhesion molecule-1 (ICAM-1) and E-selectin in mouse ear were also inhibited by silymarin. Moreover, TNF-α-induced expression of cytokines, such as TNF-α and IL-1β, and a chemokine, IL-8, were suppressed by

silymarin treatment in human keratinocyte cell line, HaCaT. Silymarin also blocked TNF-α- and DNCB-induced NF-κB activation in HaCaT. Collectively, these results demonstrate that topically applied silymarin inhibits chemical-induced ICD in mice and this might be mediated, at least in part, by blocking NF-κB activation and consequently inhibiting the expression of cytokines and adhesion molecules (Han et al, 2007).

Silymarin-based preparation in the prevention of radiodermatitis.

More than 80% of patients with breast cancer undergoing postsurgical radiotherapy (RT) will develop radiodermatitis and approximately 10% of these patients show grade 3 lesions. Side effects may reduce the patient's compliance and can be limiting factors to follow RT protocols. Therefore, there is a high need for more effective prophylactic treatments.

Leviaderm®, a silymarin-based cream (Silybum marianum, content 0.25%), represents a new concept by combining prevention and therapy of radiodermatitis (Becker-Schiebel et al, 2011).

Wound healing activity of silymarin

The major increase in morbidity and mortality of diabetes is due to the development of both macro and micro-vascular complications including failure of the wound healing process. Diabetic wound is one of the main complications in diabetes mellitus. Diabetic wounds are slow, non-healing wounds that can last for weeks despite adequate and appropriate care.

The topical administration of silymarin ointments in the concentration of 5,10 and 20% were effective in the treatment of diabetic wounds (Aliabadi et al, 2011).

TREATMENT OF ROSACEAE

Managing facial redness (erythema) is an important cosmetic goal in rosacea treatment. A cream combining silymarin, tacopheryl acetate, acetyl glucosamine, and hyaluronic acid in a hydrating oleosome base was formulated to provide control of cutaneous erythema and to improve homeostasis of cutaneous microcirculation. Silymarin cream was safe and effective in reducing facial redness associated with rosacea (Nield et al, 2002).

Anti-aging potential of Silybum Marianum extract

Skin aging is a complex process involving several environmental factors, most important of which is UV light from sun. Along with other factors about 80% of the facial wrinkling is considered due to the UV light. UV generates reactive oxygen species, and consequently triggers several mechanisms leading to collagen deficiency and eventually skin wrinkling (Fischer et al., 1997). w/o emulsion cream containing extract of Milk thistle was formulated. The formulation was observed to have skin moisturizing effects as it causes an increase in skin moisture content. The decrease in surface evaluation of living skin (SELS) parameters and also the transepidermal water loss (TEWL) showed that the formulation exerts anti-aging affects (Rasul et al, 2012).

Skin whitening effect of Silybum Marianum extract

Human skin exists in a wide range of different colors and gradations, ranging from white to brown to black. This is due to the presence of a chemically inert and stable pigment known as melanin, which is produced deep inside the skin (Costin and Hearing, 2007). Melanin determines the phenotypic appearance of humans and plays an important role in protecting human skin from the detrimental effects of ultra violet (UV) sun radiation and in scavenging toxic drugs and chemicals (Choi et al., 2002). The accumulation of an irregular melanin quantity in the skin might become an esthetic problem.

A topical w/o emulsion from milk thistle (S. marianum) extract was prepared by adding aqueous phase to the oily phase with continuous stirring. Oil phase comprised of paraffin oil and surfactant (Abil®-EM 90), and aqueous phase comprising of water was heated to 75 ± 1°C and then extract was added in it. The formulation could possess skin whitening properties as it significantly decreased skin melanin level. In addition, decrease in skin erythma/redness showed that the formulation has anti-inflammatory effects (Rasul et al, 2011).

CONCLUSIONS

Because of its potent antioxidant activity and recognized potential as an antiphotodamage and anticarcinogenic agent, the extract of Silybum Marianum appears to be compelling evidence for increased inclusion in topical skin care products and sunscreen (Hirsc et al, 2008).

The use of silymarin in combination with sunscreens or skin care lotions may provide an effective strategy for mitigating the adverse biological effects of solar UV radiation that will lead to the protection of the skin from various skin diseases caused by excessive sun exposure (Vaid et al, 2010).

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