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Dermatological Consequences of Photosensitization with an Approach to treat them Naturally

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Abstract: Photosensitization is a process in which the skin reacts to exposure to ultraviolet radiations. There are various associated dermatological consequences like photoxicity and photoallergic reactions which make the disease more complicated. There are various drugs which together with solar radiations worsen the situation of photosensitivity and hence termed as photosensitizers. The developments on the use of phytoconstituents from the herbal extract is the ardent need for fighting against the deleterious photosensitization reactions. This review attempts to highlight the problems of photosensitivity its pathological manifestation with the approach to treat them naturally with the help of skin rejuvenating herbs.

Key words: Photosensitivity, photosensitizer, photoallergic reaction , phototoxicity, ultraviolet radiations

INTRODUCTION

Photosensitization is the term used to describe the manifestations encountered during exposure to the ultraviolet radiations. These are the chain of disorders in which human skin produces an abnormal response towards solar radiation. Normally, change in skin color due to melanin synthesis and an increase in skin thickness are the protective measure adopted by the skin but by photosensitized individuals the normal adaptive response is impaired disabling the skin photo protective mechanism (Gruber *et al*., 2007; Ouhtit and Ananthaswamy, 2001) This condition is termed as Photosensitization. The aim of the present review lies in highlighting the pathological consequences of photosensitivity which directly is related to photoaging and photocarcinoma. Ultraviolet radiation inhibitory herbal bioactives contains specific actions to cure photosensitivity.

The sunlight is composed of electromagnetic radiation having ultraviolet, visible and infrared region of great interest. From all the three regions, the ultraviolet radiations of the range 320-400 nm is known to exert remarkable biological effects The UV radiations consist of UVA, UVB and UVC type of radiation. Out of these, UVC is blocked and reflected back by the ozone layer surrounding our earth. But the UVA and UVB both reaches earth in sufficient quantity. The UVB radiation is maximally absorbed by the DNA as well as the associated proteins and ultimately leading to the alteration in their normal functioning, photosensitivity, mutation, DNA damage, apoptosis or carcinogenicity (Ouhtit and Ananthaswamy, 2001; Burgeson and Christiano, 1997) The UVA radiation in comparison to the UVB radiation are less photocarcinogenic and leads to photoaging when acting alone but along with UVB radiation causes fatal photochemical damage to the DNA and to the immune system.

UVA is the radiations known to generate reactive species in the dermis and act as a promoter to UV induced skin cancer (Burgeson and Christiano, 1997; Young, 2009; Wondrak *et al*., 2005). These highly reactive chemical species damages DNA, in the form of base pair damage, strand breaks and DNA-protein crosslinks or impairing. UV radiation mediated skin cancer progress into two different ways:

- Absorption of Ultraviolet radiation through chromospheres present on the cell
- Causing Photosensitization which causes the release of Reactive Oxygen Species (ROS)

Thus, It is a state in which photoecited chromophores on absorbing the UV photons does not come to their normal state but leads to the initiation of reactive species cascade causing generation of reactive oxygen or nitrogen species. The chemical nature of chromophores and UV photon decides the degree of damage caused by them to the sensitive skin.

The epidermis consist of various molecular sites which when irradiated with ultraviolet radiations causes certain biochemical changes inside the cell. These

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molecular sites are termed as chromophores which are important for us as they exhibit various necessary synthesis process required by our body for metabolism (Wondrak *et al*., 2005; Ichihashi *et al*., 2003). An example is 7-dehydrocholesterol which, upon activation by UVB, forms provitamin D3 necessary for Vitamin D synthesis. The hypersensitivity of skin towards ultraviolet radiation is a result of series of biochemical changes arised due to the excitation of these molecular sites which are termed as "Chromophores" leading to skin damage. This occurs because of the direct molecular modification i.e. either isomerization, breaking of double bonds, or oxidation or production of free radicals, which completely or partially modify unsaturated lipids of cell membranes, proteins, or DNA or RNA bases of nucleic acids. In the absence of repair mechanism the skin cell undergoes apoptosis causing the generation of inflammatory mediators like prostaglandins, IL-1, 6, 8, other cytokines and chemokines with leads to the formation of skin lesions. Sometimes, the energy absorbed by the chromophore leads to its complete transformation into a new entity also called as photoproduct which on conjugation with an endogenous peptide forms a hapten or an allergen. These allergens are identified as a foreign substance by the body's immune system the results of these responses are similar to that of allergic photodermatitis.

Photosensitaization further constitute of two different dermatological consequences which on concurrent exposure to ultraviolet radiations are observed specifically i.e, Phototoxicity and Photoallergy (Fig. 1). (Wondrak *et al*., 2005; Ichihashi *et al*., 2003; Hawk, 2004) These are abnormal reaction of the sensitized skin when exposed to solar radiations.

Photosensitization also occurs from the formulations which are being applied to the skin topically or

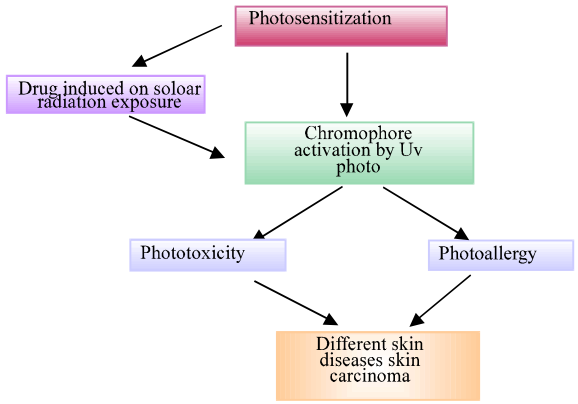

Fig. 1: Process of photosensitization

administered in a specific regimen. There is a group of agents which causes skin sensitization either in the presence of solar radiations causing rare chemical reactions with the extracellular matrix components or mediating other reactive species generation cascade (Lim and Hawk, 2008; Oliveira *et al*., 2000; Friedmann *et al*., 2003). Some of the Photosensitizing agents have found to play crucial role in various skin diseases (Table 1).

Phototoxic reactions: Phototoxicity can be designated as a fundamental reaction of ultraviolet radiation over the

Table 1: Illustrating the category of drugs causing photosensitization of skin

Category of drugs	Drugs for photosensitization
Antibiotics	Tetracyclines (doxycycline, tetracycline)
	Fluoroquinolones (ciprofloxacin, ofloxacin, levofloxacin)
	Sulfonamides
Nonsteroidal anti-inflammatory drugs	Ibuprofen
	Ketoprofen
	Naproxen
	Celecoxib
Diuretics	Furosemide
	Bumetanide
	Hydro-chlorothiazide
Retinoid	Isotretinoin
	Acitretin
Hypoglycemic	Sulfonylureas (glipizide, glyburide)
HMG-CoA* reductase inhibitors	Statins (atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin)
Epidermal growth factor receptor inhibitors	Cetuximab, panitumumab erlotinib, gefitinib, lapatinib, vandetanib
Photodynamic therapy prophoto -sensitizers	5-Aminolevulinic acid
	Methyl-5-aminolevulinic acid
	Verteporfin
	Photofrin
Neuroleptic drugs	Phenothiazines (chlorpromazine, fluphenazine, perazine, perphenazine, thioridazine)
	Thioxanthenes (chlorprothixene, thiothixene)
Antifungals	Terbinafine
	Itraconazole
	Voriconazole
	Griseofulvin
Other drugs	Para-aminobenzoic acid
	5-Fluorouracil
	Paclitaxel
	Amiodarone
	Diltiazem
	Quinidine
	Hydroxychloroquine
	Coal tar
	Enalapril
	Dapsone
	Oral contraceptives
Sunscreens	Para-aminobenzoic acid
	Ciunamates
	Benzophenones
	Salicylates
Fragrances	Musk ambrette
	6-Methylcoumarin

Table 2: Illustrates the details of some herbal drugs having promising skin scavenging activity against solar radiations

Name of the Botanicals	Family	Chemical constituents	Activity spectrum
Aloe vera	Liliaceace	Alone,	Moisturizer, Sun Screen, Emollient
Centella asiatica	Apiacae	Asiatic acid, madecassic acid and asiaticoside	Wound Healing, Reduce Stretch Marks
Cichorium intybus	Compositae/Asteraceae	Inulin, lactucin, lactucopiciin, citric, tartaric acids, Coumarinschicoriin, Esculetin, Esculin,Scopoletin.	Clears Skin Of Blemishes
Curcuma longa	Zingiberaceae	Curcumin, Desmethoxycurcumin, curcuminoids dihydrocurcumin,Etc	free radicals scavenging activity
Glycyrrhiza glabra		Glycyrrhizin, liquirtin, isoliquertin liquiritigenin and rhamnoliquirilin	Antioxidant, anticancer, antifungal, Etc
Marticaria chamomilla	Compositae/Asteraceae	A-Bisabolol, Azulenes,-Chamazulene, Guiazuline and Matricine, Flavonoids, Patuletin, Qu Ercetin, Spiroethers and Coumarins	Used In Skin Problems
Moringa oleifera	Anacardiaceae	Citric And Ascorbic Acids ,Carotenoids ,Phenolic Compounds, Flavonoids,β-Amyrins, Gallotannin, Glucogallin,I Ndicol,taraxerol,friedelin,lupeol	Skin Rejuvenation, used in skin Diseases and as anti ageing agent
Cydonia oblonga	Rosaceae	Glycoside amygdalin, tannin,mucilage, fattyoil, Pectin, ionone glycosides, octadienoic acid, Thiamine, riboflavin, nicotinic acid,Vit B6, inositol, pantothenicand folic acids, biotin	Skin protection, smoothing agent
Jasminum grandifolrum	Oleaceae	Benzyl Acetate, Benzyl Benzoate,Phytol, Jasmone, MethylJasmonate	Used as sunscreen agent, potent antioxidant
Pistia stratiotes	Araceae	2-Di-C-Glycosylflavones of vicenin and lucenin, Anthocyanincynidin 3-Glucoside, Liteolin 7-Glycoside	Used in chronic skin disorders
Prunus amygdalaus	Rosaceae	3,4-Dihydroxy Benzoic,Chlorogenic And Vanillic Acids,Quecertin,Quercitrin,Rutin,Hypero Side and Kaempferol, cyanidin,caffeicacid and P-Coumaric acid	Revitalizingactivity,anti-keratinocytes skin activity
Sesamum indicum	Pedaliaceae	Sterols,Lignans,Sesamin,NitrolactOne,Sesamolin, Thiamine,Niacin,Ri Boflavin,Nicotinic Acid,Vit A,Pyridoxine and Ascorbic Acid	Skin rejuvenation action, nourshing agent
Aegle marmelos (L.) Correa	Rutaceae	Marmelosin, marmesin, imperatorin, marmin, alloimperatorin, methyl ether, xanthotoxol, scopoletin, scoparone, umbelliferone, psoralen and marmelide, Aeglin, aegelenine, dictamine, fragrine	Freeradicalscavenger,anti-inflammatory, woundhealing,astringent,antibacterial etc
Cammelia sinesis	Theaceae	Polyphenols,Flavonoids,Tannins,Methyl Xanthines	Anti-Oxidant, Antiinflammatory, Photo Aging,Anti-Acne.
Ciunamomum zeylanicum	Lauraceace		
Scorpia dulcis	Scrophulariaceae	Scopadulcic acid A, scopadulciol scopadiol Scopadulin scoparic acid a dulcidiol acacetin	Antioxidant, Antidiabetic, Antiinflammatory
Camellia japonica	Theaceae	camellianoside	Antioxidant, Antiallergeic
Termenilia chebula	Combretaceae	Chebulic acid, tannin and ellagicacid	Antioxidant
Cleome viscosa	Capparaceae	Cleosandrin,cleomiscosins	Antimicrobial,analgesic,woundhealing
Minusops elengi	Sapotaceae	quercitol hentriacontane, carotene and glucose. D-mannitol,D-glucoside and quercetin	antibacterial, antifungal, anticariogenic, free radical scavenging analgesic, astringent, cooling effect, diuretic,
Trigonella foenum-graecum	Leguminosae	fibers, flavonoids, polysaccharides, saponins, flavonoids and polysaccharides fixed oils and some identified alkaloids viz., trigonelline and choline	Used In Abscess, Pigmentation and Discoloration Of The Face
Pterocarpus marsupium Roxb.	Lguminosae	Pterostilbene, Isoliquiritigenin, liquiritigenin, 7,4'-Dihydroxyflavone, marsupsin, pterosupin	Used in leprosy, leucoderma and other skin diseases.
Pongamia pinnata	Fabaceae	Bioflavonoids, Furanoflavonoids, E.G., Karanjin, Pongapin, Kanjone	Leprosy, leucoderma, lumbago and rheumatism.
Calendula officinalis	Asteraceae	Flavonoids, coumarines, quinones, volatile oil, Carotenoids, and amino acids.	Cell rejuvenation, wound healing, Reducing inflammation, soothing, And softening the skin

skin. The term toxicity here defines the extent of damage caused to the skin on one time exposure which are often associated with the nature of the compounds capable of causing such reactions (Lim and Hawk, 2008; Friedmann *et al*., 2003; Breathnach and Hintner, 1992). These compounds get activated by different wavelengths within the Ultraviolet range.

It is a type of photosensitivity in which the photoactivated mediators causes significant damage to the skin cells. The characteristic feature of phototoxicity is that it is independent of immunologic response. It can arise from an iinitial exposure to solar radiations also. The process of phototoxicity is divided into two stages. The first steps involves the generation of free radicals and the second involves generation of reactive oxygen species which degrades the extracellular matrix components of the epidermis and dermis region. These two steps act synergistically to damage the cellular components (Crowson *et al*., 2003). Generation of Reactive oxygen species such as an oxygen anion, superoxide anion and hydrogen peroxide etc. interact with the cell membrane and the genetic materials like DNA. It

further leads to the production of proinflammatory cytokines and arachidonic acid metabolites which give rise to inflammation which is a clinical manifestation of sunburn.

Clinical features of phototoxic reactions in skin: The ultimate detination of damage of ultraviolet radiation is the DNA where these agents causes mutation. The primary clinical manifestation are erythema, inflammation, redness etc. of the exposed part. And last two weeks to months leading to hyperpigmentation (Crowson *et al*., 2003; Ferguson, 1999; Wolkenstein and Revuz, 1995). Depending upon the severity of reactions it can be further classified as chronic and acute phototoxicity. The symptoms of these reactions are very similar to sunburn but can become sever if left untreated. There is another aspect of phototoxicity which is mediated by a group of drugs which induces phototoxicity reactions when exposed to ultraviolet radiations. The example of psoralen is significant to discuss which forms an additional product when gets bind to DNA on exposure (Wolkenstein and Revuz, 1995; Bigby, 2001; McKenna and Leiferman, 2004).

Photoallergic reactions: Photoallergic reactions are less to predict about their onset. They are being noticed in only a minority of individuals exposed to solar radiations and are uncommon than phototoxic skin reactions (P drugs. They ichler, 2004). Photoallergic response of the skin is immunologically mediated having delayed onset of action irrespective of the photoxicity reactions. The photoallergic reactions gets induced in minute quantity also. In Photoallergic reactions the antigen i.e IgE, participating in the reaction is a light-activated drug. IgE which is an antigen gets activated leading to the generation of immune response mediated by T-cells. These T-cells are responsible for the accumulation of photoallergic components (Pichler, 2004; Darvay *et al*., 2001; Khoury and Warrington, 1996; Schauder and Ippen, 2006). The photoallergic reactions depend on the pre-exposure of the photosensitizer (Scheuer and Warshaw, 2006; Nigen *et al*., 2003; Vervloet and Durham, 1998).

Photoallergic reactions in skin: The duration of photosensitization is from 24-48 h in which the individual develops a type of allergic reactions in the part of the skin which comes under the contact of ultraviolet radiations (Vervloet and Durham, 1998; Jensen *et al*., 2008; McCarthy *et al*., 2007). The hypersensitivity comprises of inflammation, erythema, acute dryness, hardning of the skin etc. (Kerr *et al*., 2007; Collins and Ferguson, 1994). Although the pigmentory changes are not evoked during the onset of photoallergic reaction (Hawk, 2004).

Herbs for photosensitization reaction: Photosensitization and its effects had driven the therapies towards natural medication system to cure the disease (Wagner *et al*., 2002; Waters *et al*., 2009). Drugs and solar radiation induced photosensitivity can be well treated through herbal formulations (Chanchal and Swarnlata, 2008). The combined effects of herbal constituents can treat the associated features of phototoxicity and photoallergic responses simultaneously (Wen *et al*., 2011; Duncan *et al*., 2009; Kaur and Saraf, 2011a). The category of antioxidant drugs are widely used as photoprotective herbs (Kaur and Saraf, 2012; Saraf and Kaur, 2010). Some of the herbs having promising effects to cure such complications are enlisted in Table 2.

Phytoconstituents are unstable in nature, being especially susceptible to photodegradation and the presence of oxygen. Instability makes them difficult to be formulated in an acceptable, stable composition for therapeutic use (Chanchal and Swarnlata, 2009). The research is moving towards development of novel herbal photoprotective formulations (Kaur and Saraf, 2011b, 2011c; Saraf *et al*., 2011).

CONCLUSION

Photosensitization is a common problem faced by the people when exposed to solar radiations but still it is being ignored. Photosensitization is an alarming sign for the various associated skin disease. It is an absolute reason for photocarcinoma also, if left untreated. There is also a strong need to understand drug induced photosensitivity. The risk of the associated with photosensitizing agent before its exposure to the patient is required. Sunscreen preparations containing photosensitizers have been removed from the market but still there is a chance that any novel agent may cause phototoxicity or photoallergy on exposure. Thus a complete assessment of all such formulations is needed to minimize such incidence. Various phototesting parameters are there which can be utilized for prior evaluation of any drug or formulation. The use of photopatch test can be a good option to study the photoallergic response of individuals without having any previous history of hypersensitivity towards any drug, ultraviolet radiations or any sunscreen formulation (Kurumaji and Shono, 1992). This test helps in diagnosing various types of skin sensitivity like dermatitis, solar dermatitis, chronic Actinic dermatitis, photosensitive eruption etc.

Moreover, the use of alternatives i.e., herbs which offer a natural defense against free radical generation and protect the cellular components of skin should be emphasized to reduce the drug induced phototoxicity. There are various herbs which act synergistically to combat multiple degradation done to the extracellular matrix components by the solar radiations. The present needs lies in the development of such sunscreen formulation which not only minimize the effects of ultraviolet radiations on the skin but also rejuvenate them and should be free from all such drug induced photosensitivity reactions. A better clinical understanding of photosensitization and its management can help the disease to restrict its prevalence as endemic.

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