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COMPREHENSIVE REVIEW ON HERBAL PHOTOPROTECTIVE PLANTS USED IN SUNSCREEN

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ABSTRACT

Sunlight emits visible light, UV radiation,prolong exposure to UV radiation causes immune suppression, early skin ageing, melanoma, erythema, skin pigmentation, skin cancer, sun burn, damaged to the skin, precancerous skin growth, formation of fine and coarse wrinkles, and photosensitivity reaction. Sunscreen are used to protect the skin from harmful effect of sunlight, sunscreen agent act by any one mechanism as to absorb, scatter or reflect sunlight. synthetic sunscreen produces various sensitizing reactions like photoirritation,contact dermatitis,blockage of pores,acne, systemic and local toxicity and allergic reaction because of that they have limited use. Flavonoids are polyphenolic constituents of plants which are mostly antioxidant and have the ability to scavange free radicals and produces protective effect from harmful UV radiation.This review discus in detail photoprotective potential of flavonoids, about more than 150 papers are selected for comprehensive review of photoprotective flavonoids from reputed journals.

KEYWORDS: Precancerous skin growth, photoirritation, dermatitis and sunscreen.

INTRODUCTION

Sunlight emits visible light, UV radiation and heat which are essential for our daily life, it also stimulate production of vitamin D and helps to control some chronic diseases like Psoriasis. The skin is one of the largest organs in the body in surface area and weight, it shield the rest of body from sunlight. Prolong exposure to UV radiation causes immune suppression, early skin ageing, melanoma, erythema, skin pigmentation, skin cancer, sun burn, damaged to the skin, precancerous skin growth, formation of fine and coarse wrinkles, and photosensitivity reaction.[1]

Sunscreen are the agent used to protect the skin from harmful effect of sunlight, aids the body's natural defense mechanism to protect the skin from harmful radiation. Sunscreen agent act by any one mechanism as to absorb, scatter or reflect sunlight. Several sunscreen are available in the market which contain synthetic photoprotective agent which produces various sensitizing reactions like photoirritation,contact dermatitis,blockage of pores,acne,systemic and local toxicity and allergic reaction because of that they have limited use.[2,3] Worldwide Indian herbs and its significance are popular. Herbal cosmetics are valuable gift of nature and its demand is growing in the World market. Herbal formulations attracted consumers because of their beneficial effect and comparatively less or no side effect.from the last few years the field of Herbal cosmetology have started to gain interest of consumer because of harmful effect of chemicals which are constantly used in cosmetics and their toxic effect on health and skin, to avoid harmful consequences various herbs are used in cosmetic formulations. From the last few years growth of sunscreens market is increased significantly, use of herbal extract and phytochemicals has been growing interest of consumer to avoid unwanted effect of sunlight on skin the use of sunscreen product is absolutely essential. Main purpose of sunscreen to protect skin from harmful effect of UVA and UVB radiation and to preserve moisture content of skin.[4] The sunscreen should be chemically inert, nontoxic, photostable, non-irritating and protective,all this properties should be included in herbal sunscreen. Various herbs, fruits, teas, oils and vegetables are used as sunscreen agent mainly they contain polyphenols, flavonoids, anthocyanidine, proanthocyanidine, tannins and vitamins which are mostly antioxidant they have the ability to scavange free radicals and have protective effect from harmful UV radiation.[5] Phytochemicals such as resveratrol, quercetin, apigenin, chrystin, silymarin, rutin, glycerhizin, gallic acid, caffeic acid, ferulic acid,curcumine, vitamin C, vitaminE, caretenoids, potato starch etc because of their antioxidant activity they scavenging free radicals ,act by absorbing,reflecting UV radiation, DNA protecting effect.[6,7,8]

UV- Radiation

UV light are classified according to its wavelength broadly in to three types-

1. Ultraviolet A (UVA) : 320-400 nm this rays cause skin ageing, wrinkles, damage to cells DNA and play role in some skin cancer.
2. Ultraviolet B (UVB) :280-320 nm this rays has slightly more energy than UVA rays they can damage directly DNA in skin cells, sun burns and skin cancer
3. Ultraviolet C (UVC) :280-200 nm This rays have more energy and more dangerous than UVA and UVBrays but they blocked by ozone layer and don't reach to the ground and skin normally hence they are not at risk of skin cancer but they can also man made source like welding torch,mercury lamps and UV sanitizingbulbs which are used to kill bacteria and germs.[9,10]

Harmful effect of Sunlight

Harmful effect of Sunlight shown in Fig.1

1. Premature aging –Exposure to sun rays causes premature skin aging called as photo aging, associated with freckling, fine wrinkling, dilation of capillaries irregular pigmentation and loss of elasticity. sun exposure is the significant factor in development of wrinkles in early age, UV rays damage collagen and elastic tissues of skin, which becomes fragile and sagging which does not spring back in to shape.sun exposure also causes white cysts and blackheads on the cheekbones and dark white spot on skin.[11,12]
2. Suppression of Immune system-Overexposure to to UV radiation it alter the immune system functions which reduces the body"s ability to fight with certain diseases and interfere with effectiveness of immunization given through the skin.[13] Cataract and eye disorder-excessive exposure to UV radiation increase the risk of cataract and other eye problem. Cataract. Corneal sunburn grows on the outer surface of the eye and causes retinal tissue damage and development of cloudy bumps along the cornea, which can grow over the cornea and prevent clear vision.
3. Heat Exhaustion-People working in hot environment are at risk of heat exhaustion which is associated with excessive water and salt loss, it includes nausea, dizziness, headache, weakness, thirst, elevated body temperature, decreased urine output.
4. Heat stroke-If heat exhaustion not treated then it then it can lead to heat stroke which cause death or permanent disability, symptoms are confusion, slurred speech, loss of consciousness, seizure, hot and dry skin with profuse sweating.
5. Sunburn-Sunburn cause due continuous exposure to sunlight symptoms include redness of skin, swelling, tenderness, blisters, nausea, fever, chills and headache Heat rash-Heat rashes develop at elbow creases, skin folds, on the neck and upper chest occurs due to sweat ducts trap perspiration under the skin, looks like red clusters of pimples or small blisters.
6. Skin cancer-Worldwide more than1milions of people per year are diagnosed with non melanoma skin cancer. Development of Skin cancer is the worst consequence of excessive exposure to sun. Commonly three types of skin cancer occurs due to sun exposure 1) squamous cell carcinoma 2) basal cell carcinoma and 3) malignant melanoma.[14,15]

- Squamous cell carcinoma- occurs due to long term sun exposure, burn scars or form chronic ulcers of the skin. Which can be spread to lymph nodes and other organ
- Basal cell carcinoma-It always occurs in sun damaged skin which is usually pink and shiny, it becomes very soft and may get easily injured, specially common in beard area of men where they used a razor, it get bigger and deeper over the time.
- Malignant melanoma-It occurs in young women especially at the age of 18 and 29 years, it is very dangerous and affected any area of skin where there are pigment producing cells, may include the entire skin. Harmful effect of Sunlight shown in Figure 1.

Photo protection-Photo protection is the biochemical process in which various tools are used to reduce molecular damage caused by sunlight, photo protection is an emerging need to avoid harmful effect of sunlight photocarcinogenesis, photoaging, photosensitivity etc. Full covering garments and use of sunscreen is an effective tool for complete protection from harmful UV radiation.

Future trends in sunscreen-Due to number of side effects of chemical and synthetic sunscreen agent there is need of safe photo protective agent to be incorporate in sunscreen, Natural sunscreen agent such as antioxidants vit.A, E, C, polyphenols, flavonoids,plant oligosaccharides acts as free radical scavangers, prevents UV induced immunosuppression,[16,17,18]

Photoprotective Mechanism of Phytochemicals-Photoprotective mechanism of phytochemicals has been shown in Figure 2.

Photoprotective mechanism of Flavonoids

Polyphenols- are secondary plant metabolites are widely distributed in various plant they are found in cereals, tea, coffee, vegetables red wines, fruits such as pear,cherries ,berries,apples and grapes.[19,20,21] Polyphenols are synthesized by shikimate and acetate pathway,[22] Recent studies showed that polyphenols rich foods intake decreased the risk of chronic diseases.[23] Polyphenols are biologically active antioxidant compounds involved in protection of various diseases as antiinflamatory,[24] anticancer,[25,26] antimicrobial,[27] antioxidant.[28] cardiovascular diseases[29,30] and photoprotectives Polyphenols are classified in to five main class phenolic acids, flavonoids, stiblins, phenolic alcohols, and lignans.[31,32,33]

Phenolic acid are classified as hydroxybenzoic acid and hydroxycinnamic acid

Flavonoids- Flavonoids represent 60 % of the total polyphenols.Flavonoids found in seeds, nuts, grains, spices, and different medicinal plants as well in beverages, such as wine particularly red wine, tea, and in beer at lower levels.[34,35] Flavonoids are secondary plant polyphenols with antioxidant and chelating effect.Basically flavonoids structure consists of two benzene ring linked through heterocyclic ring pyran or pyrone ring with double bond as shown in fig 1(Beecher,2003).Flavonoids produce protective effect in biological systems by transfer electrons free radicals, chelate metal catalysts activate antioxidant enzymes , reduce alpha-tocopherol radicals and inhibit oxidases,also protect plants from solar UV radiation and scavenge UV generated ROS.flavonoids having 3 different photoprotection effects including UV absorption, direct and indirect antioxidant properties, and modulate several signaling pathways.[36,37,38,39,40]

Flavonoids are further divided in to six subclasses

1)Flavone 2)Flavonols 3)Flavanonols 4)Isoflavones 5)Flavanols 6)Anthocyanidins

Fig 3.Basic Structure of Flavonoids

Flavone- Flavone are the class of flavonoids structurally 2-phenyl,1-benzopyran-4-one found in spice,red purple fruits,vegetables most,[41,42] common flavones are apigenin,luteolin,chrysin,tangeritin and 6-hydroxy flavones.[43] Cereals and herbs are rich source of flavones. They are potential health benefits in various chronic diseases such as osteoporosis, atherosclerosis, diabetes mellitus and cancer.

Apigenin- Apigenin is yellow crystalline dietary flavonoids beonging to flavones class found in fruits (citrus fruit, apple, grapes, cherries, vegetables (broccoli, celery, leeks, onion, bareley, beans, tomatos,carot)herbs (rosemary,thyme, arnica), beverages (tea,coffee,wine) and marigold[43] Apigenin was found to be effective as antitumor it induces apoptosis and cell death in lung epithelium cancer[44] Apigenin prevent UVA/UVB induce photocarcinogenesis in SKH-1 mice,[45] Number of biological effect are produced by apigenin on biological system, it act as potent antiinflammtory agent by reducing expression of COX-2, TNF-α and IL-8.[46,47,48] and inducible nitric oxide synthatase(iNOS)in lipopolysaccharide.[49]

Photoprotective effect of Apigenin-Photoprotective effects of apogenin against UVA and UVB radiation was investigated in human keratinocytes, and antioxidant capacity was determined by different methods as trolox equivalent antioxidant capacity (TEAC), ferric reducing antioxidant power (FRAP) and oxygen radical absorbance capacity (ORAC) assays,apigenin showed a slightly higher antioxidant capacity in antioxidant activity assays when compared with apigenin-K.These results suggest that both apigenins may be interesting candidates for the development of oral (nutraceutical) and topical photoprotective ingredients against UVA and UVB-induced skin damage[50] Photoprotective effect and antigenotoxic effects of flavonois compound apigenin,pinocembrin and naingenin investigated against UVB radiation in by using In-vitro photoprotection indices and SOS chromotest and enzymatic comet assay UV treated E-coli and Human HEK-293 cells respectively.Apigenin showed UV absorption potential from UVC to UVB region,while nariagenin and pinocembrin showed maximum absorption UVB and UVC range.[51] These flavonoid compound act as UV filters reducing UV induced genotoxicity both in bacteria and in human cells.

Chrysin – Chrysin is the5,7- dihydroxyflavone found in honey and propolis,passion flower.[52] Chrysin showed protective effect against against DNA-damage and disturbances in redox status induced by the metal compound[53] potent inhibitor of aromatase[54] antiinflamatory effect[55] human Immunodeficiency virus activation, antioxidant effec and cancer chemopreventive activity protective effect of chrysin have been investigated in animal studies against UVA /UVB induced skin damage apoptosis, downregulation of aquaporin (AQP-3) and COX-2 induction,ROS over production.[57]

Flavonols- Flavonols are3-hydroxy flavones,colorless compound present in outer and aerial tissues i,e skin and leaves of fruits,the green leaf contain rich amount of flavonols(apple ,grape,berries,),tea,red wine,cocoa and vegetables (onion,broccoli, kale,lettuce and tomato) Kaemferol, myricetin, quercetin, rutin and morin.[43,58]

Myricetin-Myricetin is 3,5,7,3′,4′,5′-hexahydroxyflavone a naturally occurring flavonoid found in many herbs,fruits,grapes, red wine,berries, vegetables and other plants. Presence of hydroxyl gp.at 3,5 position and 3,4,5 can increase the antioxidant activity.

Clinical studies repoted that myricetin having potential health benefits in chronic diseases.[59] Dietary intake of myricetin reduced the risk of type 2 diabetes mellitus (T2DM) myricetin control hyperglycemia in In vitro and In vivo studies, myricetin produce antidiabetic action by promoting glucose uptake in soleus muscle and liver in hepatocytes , promot the glycogen synthase I activity in diabetic rat,facilitate the glucose transporter -2 ,in this way myricetin inhibit or delay the glucose absorption. Myricetin inhibit the production of inflammatory cytokines in LPS stimulated (Lipopolysacchatride) macrophages and RAW264.7 macrophages, inhibit the production of interleukin -12.[61]

Quercetin- Quercetin is a polyphenol flavonoid, a plant pigment, found in many plants and foods, such as red wine, onions, green tea, apples, berries, Ginkgo biloba, buckwheat. Since long time quercetin is use as medicine.Quercetinis 3, 3′, 4′, 5, 7-pentahydroxyflvanone insoluble in water,poorly soluble

inhot water,soluble in alcohol and lipid.[62,63,64] Quercetin reduced visceral adipose tissue TNF- α,downregulated nitric oxide synthatase in obese zucker rats and nitric acid production,quercetin reduced clinical sign of arthritis in chronic rat induced arthritis.[65]

Photoprotective activity of quercetin is due to its antioxidant properties,quercetin protect skin antioxidant system against UV Radiation damage in rats.[66,67] Quercetin prevent UV radiation induced damage to plants after expose to UVB radiation due to increase of quercetin biosynthesis.[68,69] Quercetin absorb UV radiation with absorbance maxima in the (UVA□max = 365 nm and UVC □max = 256 nm),photoprotective effect of quercetin is due to direct absorption of UVR,which prevent formation of ROS and direct DNA damage.[70] Topical application of the quercetin produced protective effect against UVC radiation induced liposome peroxidation.[71]

Antiinflamatory activity of quercetin- Quercetin inhibits inflammatory enzymes cyclooxygenase (COX) and lipooxygenase, which decrease the inflammatory mediators such as prostaglandins and leukotrienes responsible for inflammation. Quercetin showed reduction in levels of inflammatory mediator in Invitro studies such as NO synthatase, CRP in human hepatocyte derived cell line and COX2.[72]

Rutin – Rutin is a plant pigment bioflavonoid found in vegetables,fruits,black and green tea,figs, buckwheat, apple is the richest source of rutin.

Rutin rapidly scavenge free radical oxygen species(ROS)due to its structure in which presence of three rings(two aromatic rings and a hexagonal ring) which is connected by three carbon atom,during radical reduction rutin transfer one or two hydrogen atom from hydroxyl group,result in formation of quinonoid structure.[73,74] rutin produce prolong protective effects on fibroblast metabolism during UV radiation, rutin prevent ROS formation by chelating transition metal ions, mainly ferric and cupric, by participating in hydroxyl radical generation in the Fenton reaction.[75]

Morin-Morin is flavonol type of flavonoids present in fruits,leaves,stem and branches of numerous Moraceaefamily plant like (Osage orange) Maclura pomifera.(old fustic) Maclura tinctoria and leaves of (common guava) Psidium guajava.[76] Morin having produced antioxidant, anti-inflammatory, antidiabetic, anticancer, antihypertensive, antibacterial, neuroprotective, photoprotective effect and hypouricemic effects.[77] Morin showeded photoprotective effect on UV radiation exposed rats nanoparticles of morin (NPs)showed excellent in vitro UV radical scavenging activity, antioxidant activity and photoprotective effect on UV radiation exposed rats.[78] Morin produced protective effect in bleomycin induced pulmonary fibrosis in mice, pulmonary fibrosis was induced with intratracheal instillation of bleomycin(3mg/Kg) for 21 days,followed by morin treatment significantly attenuated the infiltration of inflammatory cells, hydroxyproline content, lung index, and oxidative stress that were elevated in fibrotic lungs.[79]

Naringenin-Naringenin is a colorless,flavouless flavonone present present in various fruits and herbs like grapefruit, omatos,sour orange,bergamot,tart cherries, mints,beans etc. exert various biological effect like antioxidant, antibacterial, antifungal, antiinflamatory, anticancer, cardioprotective, photoprotective and used in Alzheimer disease.[79] Naringenin isolated from Citrus junos showed neuroprotective effect on myloid β protein (Aβ)-induced free radicalmediated neurotoxicity whichwas investigated using PC12 cells due to ita antioxidant effect it inhibited the Aβ-induced neurotoxic effect80]. Formulation containing naringenin and hesperetin evaluated for photoprotective effect against UV-B-induced skin damage was assessed monitoring the extent of erythema in human volunteers by means of reflectance spectrophotometry Hesperetin and naringenin from formulations effectively reduced UV-B-induced erythema.[81]

Hesperetin-Hesperetin is a 4-methoxy derivative of flavonone present in citrus fruit like lemons and sweet oranges,tangerines which is effective in chronic venous insufficiency and hemorrhoids, lowering blood pressure, photoprotective effect and helping with diabetes and its complications. Photoprotective effect of hesperetin evaluated by AnyamaneeChaiprasongsuk et al (2017),study showed that the protective effect of hesperetin on UVA-induced matrix metalloproteinase-1 (MMP-1) in primary human dermal fibroblasts and mouse skin through modulation of nuclear factor erythroid 2- related factor 2 (NRF2)-regulated antioxidant defenses, hesperetin produced antiphotoaging and photoprotective effect on UVA induced matrix metalloproteinase-1 through activation of Nrf2-regulated antioxidant defenses in HDFs and mouse skin.[82] In another study hesperetin loaded microemulsion showed significant skin whitening and photoprotectiveeffect.[83]

Genistein -Genistein is the isoflavone flavonoids potent antioxidant and inhibitor of tyrosine kinase present in soyabeans,soya foods,red clover and lignin.Genistein produced protective effect in various chronic diseases like cancer, osteoporosis, and ischemic heart disease.[84] Genistein provide protective effect and anticarcinogenic effect on Ultraviolet B-induced Pyrimidine Dimer Formation and PCNA Expression in Human Reconstituted Skin.[85] another study showed that topical application of 0.5% solutions of three individual genistein, daidzein and biochanin protecting pig skin from solar-simulated ultraviolet (SSUV)-induced photodamage, as measured by sunburn cell formation and/or erythema. However, the protection was less than that provided by a topical combination antioxidant

standard containing 15% L-ascorbic acid, 1%α-tocopherol, and 0.5% ferulic acid.[86]

Daidzein-Daidzein is the plant phytoestrogen present in soyabean,soya foods,alfa-alfa,legumes and red clover,raisins,nuts,coffee and cereals. Daidzein produce anticancer, antiproliferative estrogenic, antioxidant, cardiovasculardideases, postmenopausal syndromeand antiinflamatory effect.[87,88] The soy isoflavones daidzein and genistein in both their aglycone and glucoside forms, have an anti-inflammatory and a photo-protective effect on UVB-irradiated skin cell lines.[89]

Resveratrol- Resveratrol are polyphenolic fat soluble stilbene, potent antioxidant reduce oxidative stress by increasing GSH(glutathion), SOD (Superoxide dismutase), GSH-PX Glutathione peroxidase and by decreasing lipid per oxidation. Inhibition of melanogenesis by decreasing pigment index, tyrosinase, tyrosinase related protein1 (TRP-1), tyrosinase related protein2(TRP-2),decrease microphthalmia associated transcription factor(MITF)protein expression and melanin level,decrease pigmentation,melanoma cell proliferation. Antiphotocarcinogenetic effect is due to decrease (ERK)extracellular regulated kinase,decrease cellular proliferation signal.[90,91,92]

Sylimarin-UVA photoprotective effect of silymarin and silybin investigated,in this the cells were pretreated with sylimarin and sylibin for 1 hrs then exposed to UVA light. Photoprotective effect of sylimarin –sylibin were evaluated on ROS(reactive oxygen species,(GSH) glutathione level,(MMP-1) Protein levelof matrix metalloproteinase-1,(SSB)caspase-3activity,single strand breaks,(HO-1) hemeoxygenase-1and (HSP70)heat shock protein. Result showed both sylimarin and sylibin produced UVA photoprotective effect by significant decrease in UVA stimulated ROS and SSB production, decrease in in the activation of caspase-3 and protein level of MMP-1, reduction in (HSP70)heat shock protein level, prevention of glutathione depletion and increase in HO-1 level.[93]

Anthocyanidine-are the phenolic water soluble colored compound present in grapes,berries,vegetables, currants and other fruits,flowers like rose,hibiscus, responsible for red, purple and blue color in fruits.[94] Anthocyanins posses potential therapeutic effect like Anthocyanins possess antidiabetic, anticancer, anti-inflammatory, antimicrobial,cardiovascular disease and anti-obesity effects.[95] Anthocyanins have potent antioxidant and free radical scavenging property due to presence of phenolic group. Anthocyanins actas reducing agents in the electron-transfer reaction pathway, are able to donate electrons to the free radicals with unpaired electrons ,anthocyanins also scavenge free radicals through two pathways by the attack of hydroxyl group(s) of the B-ring of theanthocyanin structure and the second is the attack of oxonium ion on the C-ring.[96] Anthocyanin has the abilityto absorb greater amount of UVrays due to double bonds and oxygen lone pairs,Pi and non bonding orbitals,anthocyanins effectively intercept and absorb the UV rays and prevent sunburn.[97,98]

Proanthocyanins- Proanthocyanins are polyphenolic compound present in many plants like apples,maritime pine bark, aronica fruit, cocoa beans, grape skin and seed, red wines, green tea, black tea, black currant.[99.100.101] they potentially possess antibacterial activity, inhibit urinary tract infection,reduced the riskof coronary heart disease, antioxidant, antiinflamatory, anticancer, antiviral, antiallergic.[102]

Conclusion- Flavonoids are polyphenolic constituent of plant present in various part of the plant ,they are mostly antioxidant having potential free radical scavenging effect they, DNA protecting effect and photoprotective effect by absorbing or reflecting UV radiation.There are many sunscreen available in the market which are mostly synthetic, synthetic sunscreen produces various sensitizing reactions like photoirritation,contact dermatitis,blockage of pores,acne,systemic and local toxicity and allergic reaction because of that they have limited use. Polyphenols and Flavonoids are mostly antioxidant, produces more effective photoprotective effect (UV-absorbing effect), antinflamatory, antibacterial, free radical scavenging effect,antiwrinkle and wound healing effect,thus they produce benificial effect against the UV-radiation, There is a great concern for cosmetic industry and researcher to invent new formulation by using natural source and Photo-stable, photoprotective phytochemicals which would be cost effective, broad spectrum all in one sunscreen.

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