Green Tea and Its Photoprotective and Anticarcinogenic Effects on the Skin

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Of the many environmental and genetic factors that contribute to skin carcinogenesis, chronic UV radiation (UVR) exposure is by far the most important. UV radiation can cause many detrimental effects on our skin including sunburn, basal cell and squamous cell carcinoma, melanoma, cataracts, photoaging of the skin, and immune suppression. Primary prevention has reduced the incidence of skin cancers in populations at highest risk but further protection is necessary. Chemoprevention is defined as prevention of disease through dietary changes or pharmacologic intervention. Commonly used agents include nonsteroidal anti-inflammatory agents, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers, and green tea. The catechin derivatives from green tea have been shown to reduce UV-induced skin cancer, the most potent derivative being (-)-epigallocatechin-3-gallate (EGCG). The review is intended to highlight the anticarcinogenic, anti-inflammatory, and antioxidant properties of green tea that show its potential as a chemopreventive and photoprotective agent against skin cancers and photoaging.

GREEN TEA HISTORY

Tea is one of the most commonly consumed beverages in the world, second only to water. Of the total amount of tea consumed, 78% is black tea, 20% is green tea, and less than 2% is oolong tea.[1] *Camellia sinensis* is the species of plant from which green tea, white tea, oolong, pu-erh, and black tea are made. The way in which this species of plant is processed produces different types of tea. Although the basic process of manufacturing the different types of tea is similar, production of green tea is unique in that it does not involve fermentation.[2] By drying and steaming the tea leaves at elevated temperatures, the oxidizing enzyme, polyphenol oxidase, becomes inactivated and the antioxidant activities of the catechin derivatives (polyphenols) are preserved. The polyphenols in tea comprise approximately 20% to 40% of the extractable solids of dried tea leaves, depending on the subspecies of the plant and geographic location. Water and organic solvents

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such as methanol or ethanol can be used to extract the polyphenols from tea leaves. Green tea contains 4 major polyphenols: (-)-epicatechin-3-gallate (ECG), (-)-epigallocatechin (EGC), (-)-epicatechin (EC) and (-)-epigallocatechin-3-gallate (EGCG), the last of which is most abundant.[3] Of the 4 major polyphenols, EGCG has been shown to have the most anticarcinogenic effects against UV radiation (UVR).[4] Green tea polyphenols (GTPs) have been shown to have anticarcinogenic, anti-inflammatory, and antioxidant effects in numerous human, animal, and in vitro studies.

UV RADIATION

UV radiation is divided into 3 regions: UVC, 200 to 290 nm; UVB, 290 to 320 nm; and UVA, 320 to 400 nm. However, only UVA and UVB cause solar-induced damage to the skin because UVC is almost completely absorbed by the Earth's atmosphere.[5] Overexposure to UVA and UVB can have adverse effects on the skin including sunburn, basal cell and squamous cell carcinoma, melanoma, cataracts, photoaging of the skin, and immune suppression. The skin has endogenous mechanisms against UVR-induced damage including the light-scattering ability of the stratum corneum, the absorption of light by melanin, and the repair of UV-damaged DNA by repair enzymes. However, overexposure to UVR may overcome these barriers to cause photodamage and carcinogenesis.[6]

EFFECTS OF GREEN TEA

Anticarcinogenic Effects

Although there are multiple genetic and environmental factors that contribute to the development of skin cancer, chronic overexposure to solar UVR is the most important.[6] UVB can both directly and indirectly cause mutagenesis. UVB exposure damages critical cellular macromolecules such as DNA via the formation of cyclobutane pyrimidine dimers and pyrimidine pyridone photoproducts within DNA.[7] Accumulation of these products induces erythema and edema induction, keratinocyte damage, and mutation of critical genes resulting in carcinogenesis and immune suppression.[8] In a study done by Katiyar et al,[9] it was shown that both UVB-induced cyclobutane pyrimidine dimer formation and erythema response in human skin were inhibited by topical GTP treatment. By using immunohistochemistry to detect UV-induced DNA damage, the protection provided by GTP was found to be dependent on the dose and even prevented damage to the DNA of the deeper dermal cells.[9] Moreover, Elmets et al[6] excluded the possibility that topical application of GTPs acted as a sunscreen by performing spectrophotometric analysis on GTPs. It showed that GTPs did not absorb wavelengths within the UVB range and as a result did not filter out the wavelengths causing solar-simulated radiation-induced erythema.[6] Additional proof as to why it is doubtful that GTPs are acting solely as a sunscreen can be seen in a study done by Morley et al,[10] which demonstrated that oral consumption of green tea protected human cellular DNA from UV-induced radiation damage.

In addition, UVB can cause mutations in the DNA of both proto-oncogenes and tumor-suppressor genes resulting in the development of nonmelanoma skin cancers. Under normal circumstances, the tumor protein p53 is responsible for the repair of UVB-induced DNA damage and also prevents induction of skin tumors. However, if UVR causes mutation of the p53 gene and consequent loss of function, the activity of mutated proto-oncogenes may go unchecked resulting in carcinogenesis and tumorigenesis.[11] A study conducted by Lu et al[12] showed that application of GTPs and caffeine prior to UVR stimulated the presence of p53-positive cells. This was the first ever in vivo demonstration of up-regulation of a tumor-suppressor gene by a chemotherapeutic agent.

Anti-inflammatory Effects

With exposure to UVB radiation, there is a profound inflammatory response that contributes to the pathogenesis of photoaging, UVR-induced immune suppression, the development of nonmelanoma skin cancers, and the sunburn reaction.[13] Following UVR, CD11b+ macrophages migrate to the epidermis and are a major source of reactive oxygen species (ROS). Hydrogen peroxide and nitric oxide are produced and cause a state of oxidative stress which is involved in photoaging and photocarcinogenesis.[14] As the counterpart to CD11b+ macrophages, Langerhans cells (LCs) are bone marrow–derived antigen-presenting cells located within the epidermis. Their role is to initiate a T cell–mediated immune response to antigenic substances found within the epidermis. It has been shown that UV-induced DNA damage results in depletion of epidermal LCs by inducing migration of these cells to local lymph nodes. UV radiation also causes direct damage because LCs are extremely susceptible to UV injury.[13,15] Depletion of LCs contributes to the pathogenesis of photocarcinogenesis and to the decreased cell-mediated immune response to epidermal antigens.[13] A study done by Li et al[15] showed that green tea extracts (GTEs) 3% provide a partial, but statistically significant ($P<.05$) protection against UVR-induced LC depletion. On histologic examination,

Elmets et al[6] found that pretreatment with GTPs prior to UV exposure protected epidermal LCs from UV damage and resulted in a 58% reconstitution of the LC epidermal population.

Moreover, immune suppression by UVR is caused in part by the effects of UVR on the cytokines IL-10 and IL-12. IL-10 is an immunosuppressive cytokine that inhibits antigen presentation and down-regulates cell-mediated immune responses. It is secreted by UVB-irradiated activated macrophages including the aforementioned CD11b+ macrophages. On the other hand, IL-12 regulates the growth and functions of T cells and stimulates the development of helper T cells by increasing the production of IFN-γ. Therefore, in vivo, IL-12 reverses the immunosuppressive effects of IL-10. Exposure to UVR results in an imbalance in these cytokines in the skin: IL-10 increases while IL-12 decreases.[16] Katiyar et al[17] demonstrated that EGCG protects against UVB-immunosuppression by blocking UVB-induced infiltration of CD11b+ cells into the skin, which reduces IL-10 production in skin as well as in draining lymph nodes, and markedly increases IL-12 production in draining lymph nodes.

Antioxidant Effects

Reactive oxygen species are free radicals that contain the oxygen atom. Reactive oxygen species include singlet oxygen, peroxy radicals, nitric oxide, superoxide anion, and hydroxyl radicals.[7] They are naturally formed at low levels during the course of normal aerobic metabolism. The main purpose of release of ROS during the inflammatory process is to destroy invading microorganisms and/or to degrade damaged tissue structures.[18] The body has innate defenses against these ROS and free radicals which include nonenzymatic and enzymatic molecules that function as potent antioxidants. Nonenzymatic antioxidants include glutathione (GSH), alpha-tocopherol (vitamin E), and L-ascorbic acid (vitamin C), while examples of enzymatic antioxidants are glutathione peroxidase, superoxide dismutase, and catalase. However, excessive exposure to environmental stressors, including UVR, results in the dramatic increase in ROS and free radical levels and in the depletion of endogenous antioxidant enzymes, which overwhelms the body's natural defenses against oxidative stress.[19] The generation of ROS plays a major role in the promotion stage of carcinogenesis, photoaging, and immunosuppression while clinically, oxidative damage results in skin wrinkling, laxity, fragility, dull appearance, mottled brown pigmentation, and/or malignancy.[18,19] Free radicals and ROS have multiple deleterious effects including: damage to DNA resulting in point mutations, deletions, or rearrangements; lipid peroxidation; oxidation of amino acids in proteins; apoptosis in keratinocytes by altering mitochondrial membrane permeability; induction of proteolytic enzymes; and influencing the release of inflammatory cytokines.[18] Katiyar et al[20] showed that a single UV exposure of 4 times the minimal erythema dose to human skin increased catalase activity and decreased both glutathione peroxidase activity and total GSH levels. However, application of GTPs prior to UV exposure had multiple beneficial antioxidant effects including: inhibition of UV-induced hydrogen peroxide and nitric oxide production in both the epidermis and dermis; inhibition of UV-induced infiltration of CD11b+ cells; inhibition of UV-induced epidermal lipid peroxidase; decreased catalase activity; and increased both GSH levels and glutathione peroxidase activity.[20]

INHIBITION OF ANGIOGENESIS

Tumor angiogenesis is defined as the generation of blood vessels that permeate through cancerous growths to supply nutrients and oxygen and remove waste products.[16] Angiogenesis is required for nourishing tumor growth, including UV-induced tumors.[13] Angiogenic factors such as extracellular matrix metalloproteinases (MMPs) and vascular endothelial growth factors (VEGFs) are necessary for tumor growth.[21] Matrix metalloproteinase-2 and MMP-9 are the 2 MMPs most commonly overexpressed in activated endothelial cells which cause degradation of the extracellular matrix resulting in tumor generation and photoaging.[22] Green tea inhibits angiogenesis and tumor invasion by inhibiting metalloproteinases and VEGF receptor expression and signaling in tumor and endothelial cells, respectively.[23] Li et al[15] demonstrated that GTE 2% and 3% strongly inhibit the expression of MMP-9 and moderately suppress the expression of MMP-2 by UVR. In addition, Mantena et al[24] reported that both the protein expression and activity of MMP-2 and MMP-9 were inhibited by both oral and topical administration of GTP in mice. Furthermore, application of GTP resulted in an elevated expression of their natural inhibitor, TIMP metallopeptidase inhibitor 1, while the expression of vascular endothelial growth factor was down-regulated.

DOSAGE

The understanding of the in vivo effects of green tea consumption is far from complete and therefore experts have not come to a consensus on the optimal

dosage of oral supplementation with green tea. One epidemiologic study done by Imai et al[25] reported a negative association between green tea and cancer in females who consumed more than 10 cups a day. One cup (240 mL) of green tea contains approximately 200 mg EGCG.[2] Pharmacokinetic studies conducted in human participants show that serum concentrations of EGCG must be in the high nanomolar range to be considered physiologically relevant.[26] Therefore, because of the low oral bioavailability of tea catechins to obtain the anticarcinogenic effects of GTEs, an individual must drink multiple cups of green tea or ingest large quantities of EGCG. Chow et al[27] concluded that intake at the dose of 800 mg established peak serum concentrations of both free and total EGCG at the high nanomolar range and increased EGCG bioavailability. However, even at that oral dosage, there was no protection against UV-induced erythema. In a study done by Sung et al,[28] the total antioxidant capacity of plasma was significantly ($P<.0001$) increased after taking green tea in amounts of 300 mL and 450 mL. A small pilot study of 10 participants was conducted by Morley et al[10] that suggests that drinking 3 cups of green tea (totaling 540 mL) provide a sufficient exogenous source of extra antioxidants to provide additional cellular DNA protection from UVR. Regarding the side effect profile of oral supplementation, single oral dosages up to 1600 mg were found to be well-tolerated, and no clinical adverse effects occurred.[29] Similarly, daily EGCG administration of 800 mg produced only minor gastrointestinal side effects.[27]

In regards to topical application of GTPs, there is less of a discrepancy between recommended dosages but a dichotomy is still present. A study conducted by Li et al[6] noted that the use of GTE solution 3% provided the most efficient UV-protection. In another study done by Elmets et al,[6] it was reported that any concentration of GTE between 0.25% and 10% provided dose-dependent reduction in erythema with a GTE solution 10% producing almost complete protection at 48 and 72 hours. However, in a final study, Chiu et al[30] noted that a green tea cream 10% may cause too much irritation and sun sensitivity to be used in a commercial setting.

CONCLUSION

Comprehensive in vivo and in vitro laboratory studies have shown the anticarcinogenic, anti-inflammatory, and antioxidant properties of green tea. Although the suggested dose varies, both oral consumption and topical application of green tea can provide both chemoprotection and photoprotection. Furthermore, when used in combination with sunscreens, it may be possible for GTPs to further protect against radiation-induced skin cancers, photoaging, and other UV-induced disorders. However, more extensive human studies must be conducted to substantiate the effectiveness of GTPs against skin cancers in high-risk populations, ascertain the bioavailability of GTPs after oral ingestion, and determine the best vehicle for proper stability and penetration of topically applied GTP formulations.

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