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Review Article

Protective Mechanisms of Green Tea Polyphenols in Skin

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Skin is frequently exposed to a variety of environmental, chemical, and genotoxic agents that contribute to disease and carcinogenesis. Ultraviolet light (UVR) is the main external stress that leads to immunosuppresion, oxidative stress, premature aging, and tumor formation. Scientists and health professionals emphasize the importance of prevention strategies to circumvent such unfavorable outcomes. Plant polyphenols are a promising approach to disease prevention and treatment. Green tea is an abundant source of plant polyphenols that exhibit significant antioxidant, chemopreventive, and immunomodulatory effects in protecting the skin.

1. Introduction

Ultraviolet radiation (UVR) is a major environmental source of damage to the skin. Its effect on the skin's biology and immune system plays a major role in photoaging, inflammation and carcinogenesis [1]. Approximately 3.5 million skin cancers are diagnosed annually in the United States and the incidence of nonmelanoma (NMSC) increased dramatically from 1996 to 2006 [2]. The morbidity and economic burden of this malignancy is significant as the estimated total direct costs for treatment of NMSC and melanoma are $1.5 billion and $249 million, respectively [3, 4]. Sun avoidance, regular use of sunscreen, and protective clothing are the recommended methods of preventing UVR-induced damage but patient compliance is a major challenge. For example, a recent study by Buller and colleagues surveyed 4837 adult skiers and snowboarders about their sunscreen use and reapplication. Only 4.4% of adults were compliant with the recommended guidelines of applying sunscreen up to 30 minutes before sun exposure and reapplication every 2 hours [5]. Therefore there is a need to identify additional photoprotection strategies to engage the community at-large about the importance and benefits of sun protection.

In the last few decades there has been a dramatic increase in the use of plant and herbal supplements as people are seeking different methods of disease prevention [6]. Green tea consumption has become a popular trend in western cultures as its beneficial effects in human disease have shown promising results. Scientists searching for alternatives to preventing and treating disease have recognized its powerful beneficial effects in many organ systems. Green tea extracts were found to be effective at suppressing environmentally induced breast cancer [7], inhibiting T lymphocyte expansion in autoimmune diseases [8], and suppressing inflammatory responses in coronary vessels in rodent experiments [9]. Favorable results have also been demonstrated in skin disease and carcinogenesis. Recent *in vitro* and *in vivo* animal and human skin studies also showed its anti-inflammatory, antioxidant, photoprotective, and chemopreventative effects after topical application and oral consumption [10–14]. This review will discuss the chemical properties of green tea that make it effective in skin biology and immunology and how its mechanisms of action play a role in antioxidant, photoprotective and chemopreventative functions in the skin.

2. Background

Polyphenols are naturally occurring chemicals derived from plants, fruits, nuts, and vegetables. They have been proven to

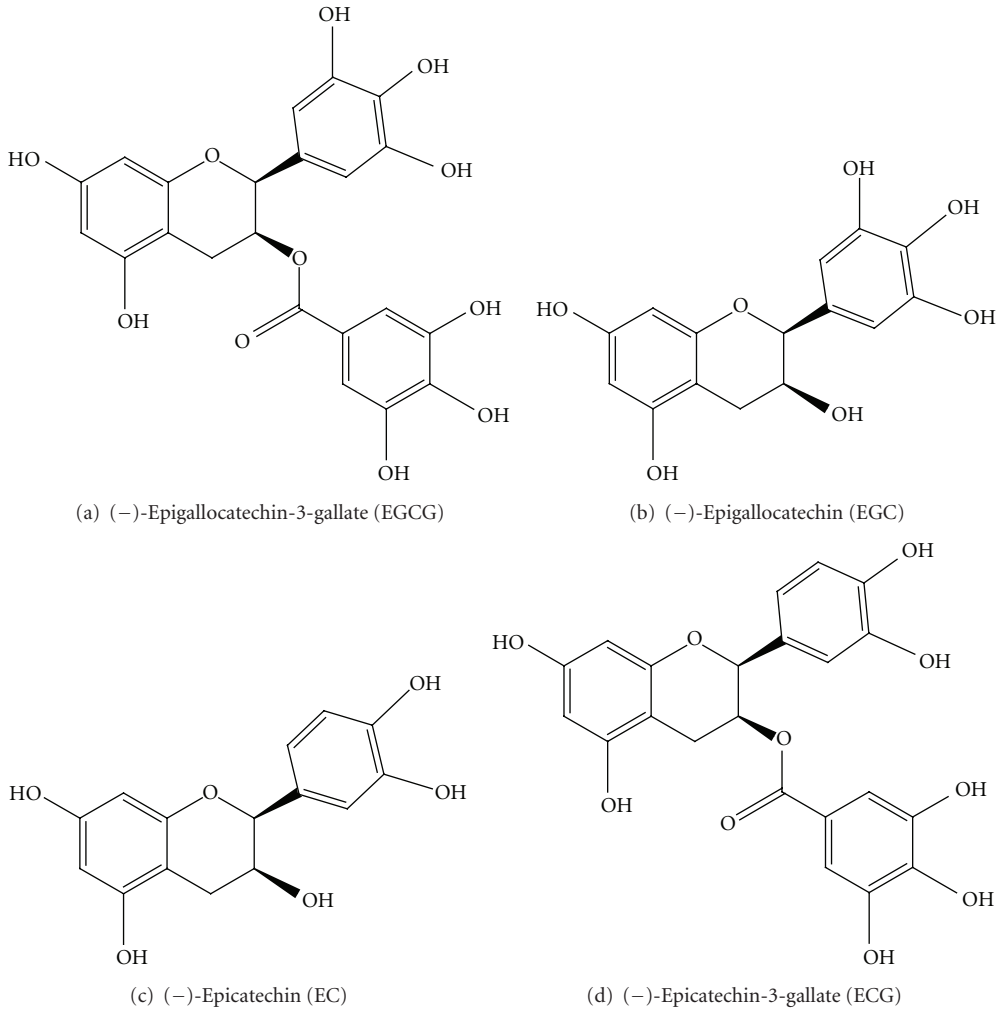

Figure 1: Structure of green tea polyphenols.

have many beneficial health benefits. Being widely abundant and relatively inexpensive, the use of polyphenols is highly attractive to researchers as a strategy for a cost-effective alternative to current pharmacologic therapeutics [15]. Tea is an important dietary source of plant polyphenols and next to water it is the second most commonly consumed beverage in the world. It is produced mainly from a single plant species *Camellia sinensis*. The tea plant originated in Southeast Asia over 4,000 years ago and is currently produced in over 35 countries with China, India, Sri Lanka, and Kenya generating three-quarters of the world's production. The six different types of tea (white, yellow, green, oolong, black, and post fermented teas) are categorized based on the wilting and enzymatic oxidization that takes place during processing [16].

There are three main types of polyphenols (flavonoids, stilbenes, and lignans) that are classified by the number of phenol rings they contain and the binding properties of the ring structures. The phenol rings are comprised of phenyl and hydroxyl group structures that possess anti-inflammatory, immunomodulatory and antioxidant properties [17]. Each class of polyphenols can be further subclassified by the interactions of their respective phenyl rings to carbon, oxygen, and organic acid molecules [18]. This creates the huge diversity of polyphenol compounds that can be found in many naturally occurring food products. Flavonoids are divided into 6 subclasses: flavonols, flavones, isoflavones, flavanones, anthocyanidins, and flavanols. Majority of the green tea polyphenols (GTPPs) are monomeric flavanols called catechins. The four main catechin compounds are (−)-epigallocatechin-3-gallate (EGCG), (−)-epigallocatechin (EGC), (−)-epicatechin-3-gallate (ECG), and (−)-epicatechin (EC) (Figure 1). EGCG is the most abundant and extensively studied catechin with potent therapeutic effects in skin.

3. Skin Damaging Effects of Ultraviolet Light

Sunlight is an important source of energy to sustain life. However, except for vitamin D synthesis, it has several harmful effects to the skin. Solar UVR can be divided into three categories based on wavelength: UVA (320–400 nm),

UVB (280–320 nm), and UVC (<280 nm). High energy short wavelength UVC (<280 nm) and a portion of UVB (280–295 nm) are absorbed by the ozone layer and atmosphere; therefore it does not reach the Earth's surface where it is capable of causing extreme damage to DNA and biomolecular molecules [19]. Longer wavelength UVB (295–320 nm) makes up only 5–10% of atmospheric UVR but it has been implicated in a variety of skin diseases, nonmelanoma and melanoma skin cancers. DNA is a chromophore for UVB and this direct interaction produces cyclobutane pyrimidine dimers (CPD) and pyrimidine-pyrimidone (6–4) mutagenic photoproducts that lead to tumor initiation and tumor promotion [20–22]. UVB also has indirect detrimental effects on the skin's immune system, oxidative stress responses, and photoaging [22, 23].

UVA radiation is far more abundant (90%) and penetrates much deeper into the epidermis and dermis of the skin. It is weakly absorbed by DNA but reacts with other nonDNA chromophores that lead to the formation of ROS which damage DNA, proteins, and lipids in the skin [24–26]. Singlet molecular oxygen produced by UVA targets DNA base guanine producing 8-oxo-7,8-dihydroguanine (8-odHG) which is an important marker of oxidative stress [27, 28]. With the increased use of high-intensity UVA tanning booths and UVB-absorbing sunscreens, human exposure to UVA has become a public health concern [29]. UVA-induced mutagenesis is still an area of debate; however, it is clear it plays a significant role in producing bipyrimidine photoproducts that have genotoxic effects [30]. *In vivo* human studies have also demonstrated the immunosuppressive effects of UVA and its increasing role in carcinogenesis [31]. In order to avoid potential mutations, UVR-induced DNA lesions are repaired by nucleotide excision repair (NER) and base excision repair (BER) mechanisms before DNA replication occurs. Additionally, stress signals created by UVR trigger protective signaling responses in the cell membrane, nucleus, and mitochondria that lead to cell cycle arrest or apoptosis [32–34]. Chronic and excessive UVR exposure overwhelms and depletes these cutaneous defense mechanisms. Therefore, compounds with antioxidant and cell repair potential are promising additions to our sun protection armamentarium.

4. Oral Consumption and Topical Application of GTPP

Human and animal studies using both topical and oral preparations of GTPP have shown significant protective effects against UV-induced skin damage and immunosuppression. As an external organ system, skin allows for direct pharmacological intervention with topical products. This mode of delivery also minimizes the potential for systemic toxicity. Topical application of EGCG in a hydrophilic ointment demonstrated better photoprotective properties versus oral consumption in mice [35]. In this *in vivo* study, topical application provided significantly greater benefit against UVB irradiation-induced depletion of antioxidant enzymes and signaling protein phosphorylation. These photoprotective functions of GTPP may be mediated through interactions with inflammatory signaling molecules. Upon UVR exposure Interleukin-12 (IL-12) is known to enhance NER enzyme activity in keratinocytes [36]. Meeran et al. proposed an IL-12-dependent mechanism of DNA repair by topically applied EGCG [37]. In this study, UV-induced suppression of CHS responses was maintained in IL-12 knockout mice in comparison to wild type mice. Subcutaneous injection with IL-12 three hours prior to UV exposure in the IL-12 knockout mice diminished the amount of CPD positive cells produced in contrast to the untreated group. Earlier studies using topical and orally consumed GTPP in mice decreased UVR-induced carcinogenesis, by inhibiting the activity of chemical tumor initiators and promoters [38–40].

Recent studies by Katiyar et al. demonstrated a dose-dependent decrease in UVR-induced immunosuppression via contact hypersensitivity response (CHS) to 2, 4-dinitrofluorobenzene in mice that were fed purified GTE [41]. This decrease in immunosuppression was persistent 4 weeks after resumption of a normal liquid diet in the animals. The authors further demonstrated that GTPs in drinking water of UV-irradiated mice reduced the migration of CPD positive cells to lymph nodes and improved the NER mechanisms. Similar results were seen in adult human subjects that ingested 7.5 mg of pure (commercially available) green tea brewed in 540 mL of boiling water. There was a significant decrease in UVR-induced DNA damage of peripheral white blood cells [42, 43]. Human studies using topically applied GTPP prior to exposure with 2-MED of SSR demonstrated a decrease in SSR-induced erythema, DNA damage, Langerhans cell damage, and production of 8-OHdG in healthy human subjects [44, 45].

5. Toxicity of GTPP

In general, GTPP has been shown to be well tolerated in animal and human trials. Topical preparations have the least harmful effects with minor irritation being the most significant finding [46]; however, adverse effects of oral consumption have been demonstrated. In a 9-month chronic study in fasting Beagle dogs, oral ingestion of green tea extract capsules caused unexpected morbidity and mortality (16 deaths out of 24 treated animals) in the treated versus control group resulting in early termination of the study group [47]. Clinical signs of toxicity, weight loss were observed as early by day 9 of this chronic study group with fasting animals. Follow-up studies by the authors demonstrated more favorable results when the green tea capsules were administered in a fed state. Although the exact mechanism of the toxicity was not determined, the authors suggested gastrointestinal irritation, organ, and hematologic evidence of immune-mediated hemolysis may have played a role in the toxicity of ingesting a capsular form of the green tea extracts. Studies by Isbrucker et al., where mice were fed liquid and powered purified green tea extracts, did not show any genotoxic effects [48].

In vitro culture experiments by Navarro-Peran et al. showed that EGCG inhibits the activity of dihydrofolate reductase (DHFR) which is an important enzyme

in nucleotide biosynthesis [49]. The authors suggested that this effective inhibition provides evidence for EGCG's chemotherapeutic mechanism of action. Their results provide an interesting insight into the reported association of maternal tea consumption and neural tube defects [50]. There are a limited number of published studies showing this teratogenic effect especially given the large amount of tea consumed globally. Experiments evaluating reproductive and developmental toxicity of EGCG in rats did not show teratogenic effects [51].

6. Antioxidant Activity of GTPP in Skin

The skin has a complex defense system to deal with harmful environmental and chemical substances but excessive or chronic exposure can overwhelm the system leading to oxidative stress and oxidative damage. In cells, reactive oxygen species (ROS) are formed during the energy-producing process of reducing molecular oxygen to water. These are superoxide radicals ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($^{\bullet}OH$). An overproduction of ROS depletes physiologic ROS-scavenging enzymes (superoxide dismutase, and catalase) which cause damage to proteins, lipids, and DNA [52] that contribute to skin diseases, immunosuppression, and development of skin cancer. GTPPs have been shown to be effective in curbing these harmful effects because their chemical structures can chelate metal ions and decrease free radical damage to cellular structures [53, 54].

Photoaging is caused by chronic UV exposure. *In vitro* studies using cultured human skin fibroblasts pretreated with GTPP showed a decrease in hydrogen peroxide (H_2O_2)-induced ROS. In this study, the authors demonstrated the ability of GTPP to improve fibroblast cell shape and absolute cell numbers when compared to control groups [10]. To assess the effect of GTE on lipid peroxidation (LPO), Jorge et al. conducted an *in vitro* assay using liposomal phophatidylcholine structure. They demonstrated a significant decrease in the concentration of hydroperoxides after a 3-hour reaction with an oxidative compound [55].

The inhibitory effect of GTPP on hydrogen peroxide formation and cell signaling is paramount to its antioxidant properties. There are few *in vivo* human studies demonstrating this protective event. In 2001, Katiyar and colleagues demonstrated this protective effect in adult human volunteers exposed to a single dose of (4xMED) UV irradiation prior to topical EGCG administration [56]. These authors confirmed what is already known about EGCG inhibition of UV-induced H_2O_2, NO and LPO production. They also demonstrated blockage of UV-induced infiltration of ROS-producing $CD11b^+$ cells and restoration of epidermal antioxidant enzymes reduced glutathione, catalase, and glutathione peroxidase.

7. Mechanism of Action of GTPP

Mitogen-activated protein kinases (MAPKs) are a group of serine/threonine proteins that are involved in cellular functions in the skin including cell growth, differentiation, proliferation, and apoptosis [57]. These proteins include extracellular signal-regulated kinases (ERK), c-Jun NH_2-terminal kinases (JNK), and p38. MAPK signaling cascades and downstream effectors are triggered in response to UVR-induced oxidative and genotoxic stress. The activity of GTPP is likely due to free radical scavenging activity that prevents MAPK activation. Topical application of GTPP in SKH-1 hairless mice showed inhibition of UVB-induced phosphorylation of ERK1/2, JNK, and p38 expression [58]. These results were also seen in human dermal fibroblasts where EGCG inhibited the UVB-induced activation of these downstream effector pathways [59]. Bae et al. also demonstrated the attenuation of nuclear transcription factors c-Jun, p53, and c-fos within 30 mins of UVB irradiation of the cultured cells. UVB-generated hydrogen peroxide stimulates membrane epidermal growth factor receptors (EGFRs) that activate ERK proteins which contribute to cell proliferation and differentiation that may be involved in tumor promotion [60]. Pretreatment of normal human epidermal keratinocytes (NHEKs) with EGCG prior to UVB exposure inhibited H_2O_2 production and phosphorylation of ERK1/2, JNK, and p38 proteins [61]. Green tea extracts have been implicated in immunoregulatory signaling functions. Rodent experiments by Kim et al. demonstrated a dose-dependent decrease in histamine production by peritoneal mast cells incubated with GTPP [62]. Further experiments by these authors proposed that the altered histamine release was due to a GTE-mediated decrease in cAMP and calcium levels which led to a NFκB and p38 MAPK-dependent inhibition of proinflammatory cytokines, TNF-α and IL-6. Table 1 lists the major cellular and molecular targets of GTPP on normal skin.

8. Role of GTPP in Chemoprevention and Carcinogenesis

Cancer remains the second leading cause of death in the United States [15]. Studies have shown that 30–40% of all cases of cancers can be prevented by combining a healthy diet, exercise, and maintaining a healthy body weight, and more than 20% of all cases of cancer can be prevented just by consuming an ample and varied amount of fruits and vegetables [15, 63]. EGCG has been shown to inhibit tumor invasion and angiogenesis thereby preventing tumor growth and metastasis [64]. Dermatologists are considerably interested in green tea polyphenols (GTPP) as preventative products for skin cancer, as their use have shown promising results.

Skin cancer is the most common of all cancers; however it is very preventable and curable if diagnosed early. Chronic exposure to UVR is the key factor in initiating skin cancer. UVB radiation induces both direct and indirect biologic effects, including multiple effects on the immune system, inducing oxidative stress, and damaging DNA, all in which play an important role in the generation and maintenance of neoplasms [65]. *In vitro* and *in vivo* systems have both shown the protective effects from polyphenols on the biochemical processes that are induced or mediated by UV radiation, suggesting that routine use of polyphenols both topically and

Table 1: Summary of effects of green tea polyphenols on skin.

GTPP protective effect	Cellular and/molecular response	References
UV protection	Inhibits UVB-induced MAPK activation and phosphorylation of ERK1/2, JNK and p38.	[51–54, 57]
	Attenuates nuclear transcription factors, c-Jun p53, and c-fos	
Antioxidant	Free radical scavenging activity	[35, 48, 53, 54, 56, 57]
	Inhibits NOS, H_2O_2 production	
	Prevents UVB-induced depletion of antioxidant enzymes: catalase, glutathione peroxidase, superoxide dismutase, and glutathione	
	Inhibits UVB-induced LPO and protein oxidation	
Anti-inflammation	Prevents UV-induced depletion of CD1a + LC and APC Inhibits UV-induced infiltration of monocytes, macrophages, neutrophils	[37, 45, 55, 57, 60]
	Protects UVB-induced immunosuppression via IL-12 production	
	↓ in histamine release by mast cells	
Anticarcinogenesis	Inhibits DNA damage.	[45, 48, 59, 60]
	Inhibits UV-induced CPD, 8-OHdG formation	
	DNA repair enzyme activation	
	Modulates transcriptions factors AP1, NFKB	
	Inhibits tumor growth, progression and angiogenesis	

LC: langerhans cells; LPO: lipid peroxidase; MAPK: mitogen-activated protein kinase; NOS: nitric oxide synthase.

orally may provide effective protection against UV radiation and ultimately skin cancer [65].

Polyphenols are shown to possess anti-inflammatory, immunomodulatory, and antioxidant properties [65]. EGCG and green tea extract are non-toxic for humans and have a wide range of target organs making it significantly different than the standard form of preventative cancer drugs. Not only is EGCG widely distributed throughout the body, but studies also show that multiple oral administrations causes a synergistic effect leading to higher concentrations of EGCG in the cells. This effect was first seen in a study involving mice, where 3H-EGCG was administered and measured in the excretions. 24 hours after the intubation, radioactivity was still found in multiple organs including the skin. After multiple administrations of 3H-EGCG, radioactivity increased 4–9 times in most organs, suggesting that routine consumption or topical treatment may provide efficient protection against UV radiation in humans. These results eventually led to a study in humans, where researchers looked at green tea consumption and the average age of cancer onset. Cancer onset of male patients consuming more than 10 cups of green tea was approximately 3.2 years later than male patients who consumed less than 10 cups of green tea per day, and cancer onset for women drinking more than 10 cups of green tea per day was 7.3 years later. These results allowed researchers to determine the effective cancer preventative amount to be approximately 10 Japanese-size cups (120 mL/cup) of green tea per day, which is equivalent to about 2.5 g of green tea extract [66]. Another study observed that regular intake of EGCG increased the minimal dose of radiation required to induce erythema, suggesting that the EGCG is able to strengthen the skin's tolerance by inhibiting the UV-induced skin damage from the radiation [65]. From these findings it can be seen that orally consumed EGCG has two different mechanisms of action and can act as both a chemopreventive and photochemopreventive drug; it can protect the body by suppressing, slowing down, and reversing the process of carcinogenesis, as well as protecting the skin from damaging radiation caused by harmful UVB rays.

As mentioned before, UVB radiation induces oxidative stress and DNA damage, and also affects the immune system. In separate experiments, it has been shown that topical treatments containing EGCG significantly inhibits acute or chronic UV irradiation-induced protein oxidation in the skin of mice, suggesting that GTTP's may be able to reduce photo damage in the skin and prevent premature aging [45, 65, 67]. Another study showed that the pretreatment of mouse skin with EGCG inhibited UVB-induced infiltration of leukocytes, specifically $CD11b^+$ cells in the skin which mediate UV-induced immunosuppression. These infiltrating leukocytes can be a potential source of H_2O_2 and NO which play important roles in initiating and promoting tumor cells. Less damage to the epidermal structure of the mouse skin was also observed with the topical application of EGCG before being exposed to UVB light. The data collected in this study demonstrated the potent preventative effects of topical EGCG in mice against UV radiation-induced infiltration of leukocytes, suggesting that GTTP's may have preventative effects against the development of skin cancer in humans [68]. Inflammatory responses are implicated in skin disease, tumorigenesis, and tumor metastasis. EGCG effectively inhibited human melanoma cell culture growth by decreasing IL-1β secretion and NFκB activity [69].

9. Concluding Remarks

As discussed in this paper, GTPPs have important antioxidant, immunomodulatory, and photoprotective functions.

Their ability to modulate critical biochemical functions through topical and oral formulations makes GTPPs a promising candidate for chemoprevention and treatment of disease. Future collaborative studies are needed to clarify optimum dosing amounts that will provide therapeutic benefits.

Conflict of Interests

The authors declare no conflict of interests.

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