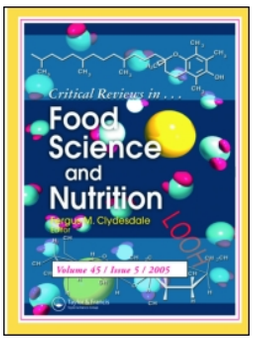

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Molecular mechanisms of green tea polyphenols with protective effects against skin photoaging

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ABSTRACT

Whereas green tea has historically been consumed in high quantities in Northeast Asia, its popularity is also increasing in many Western countries. Green tea is an abundant source of plant polyphenols exhibiting numerous effects that are potentially beneficial for human health. Accumulating evidence suggests that green tea polyphenols confer protective effects on the skin against ultraviolet (UV) irradiation-induced acceleration of skin aging, involving antimelanogenic, antiwrinkle, antioxidant, and anti-inflammatory effects as well as prevention of immunosuppression. Melanin pigmentation in the skin is a major defense mechanism against UV irradiation, but pigmentation abnormalities such as melasma, freckles, senile lentigines, and other forms of melanin hyperpigmentation can also cause serious health and aesthetic issues. Furthermore, UV irradiation initiates the degradation of fibrillar collagen and elastic fibers, promoting the process of skin aging through deep wrinkle formation and loss of tissue elasticity. UV irradiation-induced formation of free radicals also contributes to accelerated photoaging. Additionally, immunosuppression caused by UV irradiation plays an important role in photoaging and skin carcinogenesis. In this review, we summarize the current literature regarding the antimelanogenic, antiwrinkle, antioxidant, and immunosuppression preventive mechanisms of green tea polyphenols that have been demonstrated to protect against UV irradiation-stimulated skin photoaging, and gauge the quality of evidence supporting the need for clinical studies using green tea polyphenols as anti-photoaging agents in novel cosmeceuticals.

KEYWORDS

Green tea; polyphenols; skin; UV irradiation; photoaging

Introduction

As the elderly population in many countries continues to increase, dermatological concerns associated with skin aging are growing in medical importance. In social settings, the appearance of the skin is a major factor used to roughly estimate a person's age and health (Lorencini et al., 2014). The appearance of the skin is a central factor in the visual and social experience of interpersonal interactions, and while few people can visually identify the presence of cancer, diabetes, or cardiovascular diseases in another person, changes in the skin are widely recognizable and are therefore an area of considerable attention (Farage et al., 2013). The economic importance of skin aging lies in the enormous consumer demand for methods to prevent or mask skin aging (Gilchrest, 2013).

The skin is the largest organ of the human body (comprising a total surface area of approximately 1.5–2.0 m^2), forming an effective barrier against the detrimental effects of environmental and xenobiotic agents to protect the internal organs of the body. Skin aging is a complex, multifactorial process with a genetically determined baseline rate that can be accelerated by mechanical, environmental, or socioeconomic factors (Lorencini et al., 2014). It involves both the intrinsic process of senescence and extrinsic damage induced by external factors like chronic exposure to UV irradiation, a process known as photoaging. Although a number of environmental and genetic factors are responsible for the development of photoaging-related skin problems such as pigmentation, wrinkling, and skin dryness, the most important factor is the excessive damage inflicted by UV irradiation (de Gruijl and Van der Leun, 1994; Gilchrest, 1990; Ichihashi et al., 2003; Yaar et al., 2002). In particular, abnormal pigmentation and wrinkle formation after exposure to UV irradiation appear to be key factors in the process of photoaging (Berneburg et al., 2000; Wulf et al., 2004).

Green tea is the most commonly consumed beverage in a number of East Asian countries and has been consumed as a daily beverage in over 160 countries for decades. It is produced from the dried unfermented leaves of *Camellia sinensis*, and polyphenols constitute approximately 30% of its dry weight (Mukhtar and Ahmad, 2000). Various green tea polyphenols have been reported to exhibit potent biological properties, for example, inhibiting tooth decay and reducing blood pressure, in addition to antibacterial, antioxidant, and antitumor

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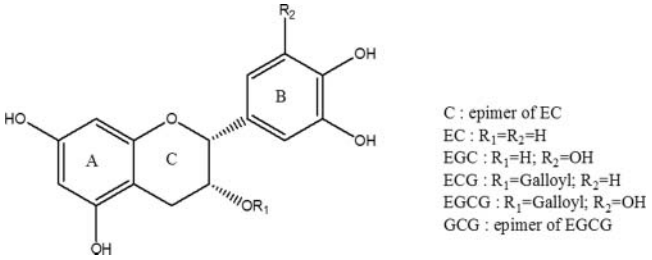

Figure 1. Chemical structure of green tea polyphenols.

properties (Cabrera et al., 2006; Coentrao Pde et al., 2011; Forester and Lambert, 2011; Lambert and Elias, 2010; Yu et al., 2013).

The majority of the green tea polyphenols are monomeric flavanols known as catechins. The major catechins found in green tea are: (−)-catechin (C), (−)-epicatechin (EC), (−)-epigallocatechin (EGC), (−)-epicatechin-3-gallate (ECG), (−)-epigallocatechin-3-gallate (EGCG), and (−)-gallocatechin-3-gallate (GCG). Green tea catechins are characterized by dihydroxy or trihydroxy groups on the B ring and the meta-5,7-dihydroxy groups on the A ring (Balentine et al., 1997), with the B ring appearing to be the principal site of antioxidant reactions (Valcic et al., 2000). Such antioxidant activity is further enhanced by the presence of a trihydroxy structure in the D ring (gallate) in ECG, EGCG, and GCG (Fig. 1). The most widely studied green tea component is (−)-epigallocatechin-3-gallate (EGCG), which is the major catechin, comprising over 50% of the total catechins in green tea (Dulloo et al., 1999; McKay and Blumberg, 2002). EGCG is also the most abundant and extensively studied catechin in terms of its therapeutic effects on human skin.

A summary of the known inhibitory mechanisms of green tea polyphenols against molecular processes involved in UV irradiation-induced skin photoaging, including hyperpigmentation and wrinkle formation, is presented in Table 1.

Green tea polyphenols and antiphotoaging mechanisms

Antimelanogenic (whitening) effect

Skin photoaging is primarily dependent on the presence of melanin. For example, visible pigmentation of the skin, hair, and eyes is directly correlated with the presence of melanin in those tissues. Although such pigmentation comprises the major defense mechanism against UV irradiation, an abnormal accumulation of melanin pigment is responsible for various pigmentation disorders such as melasma, freckles, and senile lentigo. These hyperpigmented phenomena can be substantially ameliorated by treatment with antimelanogenic compounds such as tyrosinase inhibitors.

Melanin is produced by specialized cells called melanocytes. Upon exposure of the skin to UV irradiation, melanogenesis is

Table 1. The antiphotoaging activity of green tea. A summary known inhibitory mechanisms of green tea polyphenols against molecular processes involved in UV irradiation-induced skin photoaging, including hyperpigmentation and wrinkle formation.

Category	Function	C	EC	EGC	ECG	EGCG	GCG
Antimelanogenic effect	Melanin production	↓(Sato et al., 2009)		↓(Sato et al., 2009)		↓(Sato et al., 2009; Kim et al., 2004a)	
	Tyrosinase expression	↓(Sato et al., 2009)		↓(Sato et al., 2009)		↓(Sato et al., 2009; Kim et al., 2004a)	
	Tyrosinase activity			↓(Liu et al., 2009)	↓(Liu et al., 2009; No et al., 2009)	↓ (Liu et al., 2009; No et al., 1999; Kim et al., 2004a)	↓(No et al., 1999)
Antiwrinkle effect	Collagenase expression					↓(Bae et al., 2008)	
	Collagenase activity	↓(Madhan et al., 2007)			↓ (Makimura et al., 1993; Jackson et al., 2010)	↓ (Makimura et al., 1993; Madhan et al., 2007; Jackson et al., 2010)	
	Collagenase degradation					↓(Bae et al., 2008)	
	MMPs expression					↓ (Bae et al., 2008; Song et al., 2004)	
	MMPs activity				↓(Demeule et al., 2000)	↓(Demeule et al., 2000)	
	Elastase activity	↓(Kim et al., 2004b)				↓(Thring et al., 2009)	
Antioxidative effect	Free/superoxide anion radical			↓(Beckman et al., 1990)	↓(Huang et al., 2005)	↓ (Vayalil et al., 2003; Scalia et al., 2013)	↓(Beckman et al., 1990)
	SOD-like activity				↑(Feng et al., 2013)		
Prevention of immuno suppression	CHS suppression					↓(Katiyar et al., 1995)	
	Cytokine expression					IL-10↓(Katiyar et al., 2001) IL-12↑(Meeran et al., 2006a)	
	Leukocytenumber/ infiltration					↓(Katiyar et al., 1999; Katiyar et al., 2001)	
	DNA damage					↓(Katiyar et al., 1999; Meeran et al., 2006b)	
	APCs					↑(Elmets et al., 2001)	

enhanced by the activation of tyrosinase, a key enzyme in melanocytes (Cichorek et al., 2013; Friedmann and Gilchrest, 1987). Mammalian melanocytes produce two chemically distinct forms of melanin pigment within melanosomes: black-brown eumelanin and yellow-red pheomelanin. Tyrosinase (monophenol monooxygenase, EC 1.14.18.1) is the rate-limiting enzyme in the melanin biosynthesis cascade, catalyzing the hydroxylation of tyrosine to L-DOPA and the subsequent oxidation of L-DOPA to dopaquinone (Hearing and Tsukamoto, 1991). In the presence of cysteine, dopaquinone reacts to form cysteinyldopa, which then oxidizes and polymerizes, giving rise to yellow-red soluble melanin (pheomelanin). In the absence of thiols (cysteine, glutathione, or thioredoxin), brown-black eumelanin is produced and dopaquinone undergoes cyclization to dopachrome. Dopachrome spontaneously forms DHI-2-carboxylic acid-melanin, appearing as a dark brown-black insoluble form of melanin (eumelanin) through the activity of tyrosinase-related proteins 1 and 2 (TYRP1, TYRP2/DCT) (Cichorek et al., 2013; Fitzpatrick and Breathnach, 1963).

Based on the current literature, the antimelanogenic effects of EGCG or green tea polyphenols appear to be mediated by: (i) inhibition of tyrosinase expression (single reference) or (ii) direct inhibition of tyrosinase activity (majority of references) thus leading to (iii) inhibition of melanin production. Several studies of green tea polyphenols have reported the central role of the inhibitory effects of tyrosinase activity.

According to No et al., ECG, GCG, and EGCG have IC_{50} values of 34.58, 17.34, and 34.10 μM, respectively, on mushroom tyrosinase activity. These three major components of green tea showed the most potent inhibitory effects of all compounds tested, indicating that a flavan-3-ol skeleton with a galloyl moiety at the 3-position is important for optimal inhibition of tyrosinase activity (No et al., 1999).

α-Melanocyte-stimulating hormone (α-MSH) stimulates melanin production in melanocytes (Abdel-Malek et al., 2000; Abdel-Malek et al., 1995). Sato et al. showed that EGCG inhibited α-MSH-induced melanin production in B16 melanoma cells. B16 melanoma cells were stimulated with α-MSH and the average melanin content of each cell was 113.5 picograms (pg). Treatment of α-MSH-stimulated cells with EGCG produced a dose-dependent inhibition of melanin production by approximately 87, 62, and 33 pg/cell at 5, 10, and 20 μM of EGCG, respectively (Sato and Toriyama, 2009). Furthermore, EGCG significantly inhibited protein expression levels of tyrosinase to an extent greater than catechin or EGC in these cells. The depigmentation effect of catechins was proposed to be due to the direct inhibition of tyrosinase activity and down-regulation of tyrosinase expression (Liu et al., 2009; Sato and Toriyama, 2009).

The inhibitory effect of green tea polyphenols on tyrosinase induction has also been shown to occur through decreased microphthalmia-associated transcription factor (MITF) production. MITF is inducible in response to cAMP (cyclic adenosine monophosphate) and acts as a major regulator of tyrosinase and its related enzymes (TYRPs or tyrosinase-related proteins 1 and 2), as well as a number of melanosome structural proteins such as pMel17 in the process of skin pigmentation (Bentley et al., 1994; Cheli et al., 2010). Kim et al. reported that EGCG not only acts as a tyrosinase inhibitor, but also suppresses MITF production during melanogenesis in Mel-Ab melanocytes (Kim et al., 2004). ERKs-activated p90RSK phosphorylates MITF at Ser409 downstream of c-Kit signaling, resulting in improved proteasome-mediated degradation of MITF (Wu et al., 2000). EGCG does not appear to activate the ERKs pathway and does not induce MITF phosphorylation or degradation. Studies are currently ongoing to elucidate the mechanisms responsible for the down-regulation of MITF production by EGCG (Kim et al., 2004). Green tea polyphenols can thus be considered as inhibitors of both tyrosinase activity and expression in melanocytes, thereby inhibiting melanin production induced by UV irradiation.

Antiwrinkle effects

Wrinkles on the face are a prominent characteristic of recognizable skin aging. Histological analysis of wrinkled skin typically reveals the degradation and degeneration of collagen and an accumulation of altered elastic fibers in the dermis (Leyden, 1990). Chronic UV irradiation promotes wrinkle formation and loss of tissue elasticity by inducing the degradation of type I collagen (Fisher et al., 1997; Scharffetter-Kochanek et al., 2000). Collagen is known to be relatively resistant to proteinases such as trypsin, but is decomposed rapidly by collagenase activity (Barrantes and Guinea, 2003). Collagen is the main structural material in the skin, accounting for 77% of its fat-free dry weight (Wilkes et al., 1973). More than 70% is type I collagen, with approximately 15% existing as type III collagen in the dermal extracellular matrix (ECM), constituting the majority of connective tissue in the skin (dermis) (Lovell et al., 1987). Collagen degradation in the ECM is mediated by matrix metalloproteinases (MMP), which are known to be a cause of skin wrinkling observed in both premature skin photoaging and normal skin aging processes (Dong et al., 2008; Kim et al., 2005). UV irradiation dramatically increases MMP production, which in turn initiates the cleavage of type I collagen fibrils (Fisher, 2005; Fisher et al., 2002). Human skin expresses a number of collagenolytic MMPs, including MMP-1 (interstitial collagenase-1), MMP-8 (neutrophil collagenase-2), and MMP-13 (collagenase-3), all of which attack native fibrillar collagen (Varani et al., 2002). UV-induced oxidative stress initiates important signaling cascades through the activation of several cell surface receptors. Receptor activation stimulates the mitogen-activated protein (MAP) kinases, p38 and ERKs, consequently inducing the transcription factor activator protein-1 (AP-1), which induces collagen degradation through the up-regulation of MMP-1, MMP-3, and MMP-9 (Fisher et al., 1999). The degradation of elastic fibers also contributes to skin aging, particularly wrinkle formation (Hussain et al., 2013). Therefore, the inhibition of collagenase activity may attenuate the formation of wrinkles in human skin, representing a potential therapeutic strategy for the prevention or treatment of UV irradiation-induced photoaging.

Green tea polyphenols exert antiwrinkle effects through collagenase by affecting both direct enzyme activity and physical volume. In 1993, Makimura (Makimura et al., 1993) first identified the steric structure of the 3-galloyl radical of catechin as important for the inhibition of collagenase activity. EGCG has an additional galloyl unit and hydroxyl groups compared to

catechin and, thus, can engage in better hydrogen bonding and hydrophobic interactions with collagenase, inducing significant changes in its conformation that result in potent inhibition (Madhan et al., 2007). EGCG and ECG bind to collagen through extensive hydrogen bonding augmented by hydrophobic interactions, preventing the free access of collagenase to active sites on the collagen chains (Jackson et al., 2010).

Other studies have also demonstrated that green tea polyphenols inhibit expression of collagenase. Bae et al. (Bae et al., 2008) reported that EGCG markedly suppresses collagen degradation induced in UVB-exposed human dermal fibroblasts. EGCG also inhibited UVB-induced production of collagenases and MMPs in a dose-dependent manner (Bae et al., 2008). Furthermore, EGCG and ECG inhibited activity of MMPs such as MMP-9 and MMP-2 (Demeule et al., 2000). Recent reports have shown that EGCG inhibits UVA-induced MMP-1 expression (Song et al., 2004), while oral administration of green tea polyphenols inhibits UVB-induced expression of MMP-2, MMP-3, MMP-7, and MMP-9 in hairless mouse skin (Vayalil et al., 2004). Moreover, catechin (Kim et al., 2004b) and EGCG (Thring et al., 2009) decreased elastase activity and polycondensates of catechine showed much amplified inhibition activities (Kim et al., 2004b). These studies support the notion that green tea polyphenol intake could be useful to attenuate UVB-induced premature skin photoaging.

Antioxidant effects

A major accelerator of photoaging is oxidative stress that arises from excess reactive oxygen species (ROS) in the skin tissue. UV irradiation-mediated production of ROS induces the transcription of AP-1, which causes the up-regulation of MMPs and degradation of dermal collagen and elastic fibers (Brenneisen et al., 2002). Furthermore, excessive UV irradiation causes peroxidation of lipids in cellular membranes, leading to further generation of ROS, which may stimulate melanocytes to produce excess melanin (Callaghan and Wilhelm, 2008; Farage et al., 2008). Joshi et al. reported that ROS formation induces the oxidation of tyrosine and L-DOPA to melanin (Joshi et al., 1987). In cells, ROS are formed during the energy-producing process of reducing molecular oxygen to water. The ROS formed include superoxide radicals ($O^{2\bullet-}$), hydrogen peroxide (H_2O_2), and the hydroxyl radical ($^{\bullet}OH$). An overproduction of ROS depletes physiological levels of ROS-scavenging enzymes (such as superoxide dismutase (SOD) and catalase), resulting in damage to proteins, lipids, and DNA (Ott et al., 2007), and premature photoaging, skin diseases, immunosuppression, and the development of skin cancer. These observations suggest that a potent free radical scavenger might prevent UV-induced skin damage by inhibiting the induction of MMPs.

According to Vayalil et al. (Vayalil et al., 2004), green tea polyphenols can inhibit chronic UV irradiation-induced protein oxidation in mouse skin tissue. EGCG is a potent scavenger of ROS with exceptionally strong antioxidant activity (Norwood et al., 2006). Feng et al. observed that EGCG was effective against H_2O_2-induced human dermal fibroblast injury acting by enhancing the activity of SOD and glutathione peroxidase (GSH-px), as well as by decreasing malondialdehyde levels (Feng et al., 2013). Their results indicated that EGCG may have potential for further development as a therapeutic to prevent photoaging-related skin disorders. Similarly, Beckman et al. (Beckman et al., 1990), suggested that the ortho-trihydroxyl group in the B ring and the galloyl moiety at the 3-position of the flavan-3-ol skeleton of ECG and GCG are the most important structural requirements for the free radical scavenging effects. Huang et al. (Huang et al., 2005) have reported that ECG also acts as a free radical scavenger when keratinocytes are photodamaged, while Vayalil et al. (Vayalil et al., 2003) found that EGCG or green tea polyphenols added to hydrophilic ointments inhibit UVB-induced oxidative stress through MAP kinase signaling pathways. Bianchi et al. (Bianchi et al., 2011) reported that EGCG undergoes rapid and marked degradation in model dermatological formulations (emulsions) exposed to UV irradiation. A number of additional studies focusing on a combination of EGCG and other compounds have also been conducted. EGCG photostabilization was reportedly achieved using the water-soluble UVB filter, benzophenone-4 (BP-4), suggesting that EGCG-containing formulations with photostabilizers represent a promising strategy for the development of efficacious topical products to treat skin photodamage (Bianchi et al., 2011). Furthermore, Scalia et al. (Scalia et al., 2013) suggested that cotreatment with vitamin C and lipoic acid significantly reduces the photodegradation of EGCG and preserves its antioxidant activity under UV irradiation. Therefore, the application of EGCG with co-antioxidant agents such as vitamin C and lipoic acid should be considered in topical treatments for UV irradiation-induced skin photoaging.

Prevention of UV-induced immunosuppression

The immune response is important in maintaining and restoring tissue homeostasis (Nestle et al., 2009). A normal skin immune system protects the skin from infection and removes damaged cells, but chronic UV irradiation induces immunosuppression, which can contribute to photoaging and skin cancer (Halliday, 2005; Muller et al., 1995). Immunosuppression induced by UV irradiation occurs through multiple mechanisms, including suppression of contact hypersensitivity (CHS), infiltration of leukocytes, DNA damage, and attenuation of antigen presenting capacity.

UVB-induced suppression of CHS is associated with an increase in the levels of the immunosuppressive cytokine, interleukin-10 (IL-10), and a decrease in the immunostimulatory cytokine, interleukin-12 (IL-12) (Howard and O'Garra, 1992; Katiyar, 2007). IL-10 inhibits antigen presentation and cytokine secretion by macrophages, thereby downregulating CHS response (de Waal Malefyt et al., 1991; Fiorentino et al., 1991a; Fiorentino et al., 1991b). Infiltration of leukocytes (monocytes/macrophages and neutrophils) into UV-irradiated skin plays a critical role in inducing immunosuppression and tolerance. UVB irradiation induces the number and infiltration of CD11b+ cells (cell surface markers of macrophages and neutrophils) into skin inflammatory lesions, which are considered to be responsible for creating the UV-induced immunosuppressive state. Infiltrating leukocytes could cause keratinocyte injury to the UV-damaged epidermis that results in

keratinocyte disassociation and further breakdown in the structure of the UV-exposed epidermis (Hammerberg et al., 1996). Katiyar et al. (Katiyar et al., 2001; Katiyar et al., 1999) demonstrated that treatment with EGCG significantly reduced the infiltration of CD11b+ cells and also decreased the amount of IL-10 production in skin, suggesting a possible mechanism by which EGCG prevents UVB-induced immunosuppression in mice. Also, UVA-induced ROS production can lead to initiation of AP-1 or nuclear factor kappaB (NF-κB) transcription, and eventually induces the production of IL-10, which are responsible for local and systemic immunosuppression (Ullrich, 2005). Topical application of green tea polyphenols, especially EGCG, was shown to protect against the local and systemic suppression of CHS by UVB irradiation (Katiyar et al., 1995). This group assessed immunosuppression by contact sensitization with 2,4-dinitrofluorobenzene applied to UVB-irradiated skin (local suppression) or to a distant site (systemic suppression). Meeran et al. (Meeran et al., 2006a) demonstrated that IL-12-deficient mice are at greater risk of photocarcinogenesis, and EGCG inhibited UVB-induced immunosuppression in mouse skin through the induction of IL-12, an immunostimulatory cytokine.

UV irradiation-induced DNA damage is an important molecular trigger for the suppression of immune responses because DNA damage impairs the capacity of antigen presenting cells (APCs) to present antigen (Applegate et al., 1989). Cyclobutane pyrimidine dimers (CPDs) are an indicator of UV-induced DNA damage (Kripke et al., 1992; Yarosh et al., 1992). Green tea polyphenols reduced UVB-induced DNA damage in the form of CPDs and this effect was mediated through the stimulation of IL-12 production (Meeran et al., 2006b). Furthermore, Katiyar et al. (Katiyar, 2003) showed that topical treatment with green tea polyphenols prevents UVB-induced CPD formation, which are considered to be mediators of UVB-induced immunosuppression.

Chronic low-dose UVA irradiation reduced epidermal Langerhans cell (LC) density (Bestak and Halliday, 1996). LCs are critical APCs that initiate T-cell-mediated immune responses to antigenic substances encountered by the epidermis in the induction phase of CHS and contributes to production of IL-12 (Toews et al., 1980). Solar UV irradiation decreases the number of LCs, which leads to the downregulation of the antigen presenting capability in human skin (Dumay et al., 2001; Elmets et al., 1992; Toews et al., 1980). Green tea polyphenols reconstituted the population of epidermal LCs against UV-induced reduction of LCs (Elmets et al., 2001).

Concluding remarks

UV irradiation significantly induces pigmentation, skin wrinkling, and immunosuppression, resulting in the acceleration of visible photoaging. In this article, we have provided a brief overview of the inhibitory mechanisms of green tea polyphenols on skin photoaging induced by UV irradiation. Green tea polyphenols exhibit anti-melanogenic effects by inhibiting the activity and expression of tyrosinase. Furthermore, these polyphenols inhibit collagenases, MMP activity, and ROS induction, resulting in potent antiwrinkle and antioxidant effects. Moreover, green tea polyphenols prevent UV-induced immunosuppression. Thus, skin photoaging can likely be significantly delayed with the addition of green tea polyphenols in future treatment strategies. Further investigations are needed focusing on the potential application of green tea polyphenols in cosmetic formulations for skin care, to determine how they can best contribute to improvements in photoaging-related skin problems such as hyperpigmentation and wrinkling.

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