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Angaben zur Veröffentlichung / Publication details:

Zink, Alexander, and Claudia Traidl-Hoffmann. 2015. "Green tea in dermatology - myths and facts." *JDDG: Journal der Deutschen Dermatologischen Gesellschaft* 13 (8): 768–75. https://doi.org/10.1111/ddg.12737.

Green tea in dermatology – myths and facts

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Summary

Green tea consumption has a long tradition in Asian countries – especially China. The epidemiologically and experimentally observed anticarcinogenic and antiinflammatory effects of green tea have led to the implementation of green tea extracts in multiple therapeutic applications – both in dermatological and cosmeceutical preparations. The most abundant evidence exists for the anticarcinogenic and chemopreventive effect of green tea or its major constituent epigallocatechin-3-gallate. Almost equally evident is the effect in infectious diseases such as cutaneous viral infections. For external genital warts, a topical ointment with green tea extracts was licensed in the USA in 2010, and recently also in Europe. Experimental evidence pinpointing the block of central signal transduction factors in inflammatory mechanisms has led to the evaluation of catechins in inflammatory disorders such as atopic dermatitis. The belief of green tea as a "wonder weapon" against diseases dates back thousands of years. According to a Chinese legend, ancient Emperor Shen Nung noted a delightful aroma after some leaves of a nearby tree had fallen into boiling water. He immediately proclaimed the new "drink" as "heaven-sent", starting the belief – persisting until today – of green tea as a medication from nature against many different diseases. This review summarizes biological effects and clinical implications of green tea.

Introduction

From early history until today, medicine has provided evidence that there is a clear association between diet and disease. While natural products, herbs, and spices have in the past been used in the prevention of diseases, they have been increasingly gaining consideration in phyto-therapeutic applications in recent years. One of the best examples in this context is green tea. It is consumed worldwide as a popular beverage, not only because of its characteristic taste but also because of its attributed health benefits. Cultivated in China and South East Asia for thousands of years, green tea today accounts for 20 % of the tea consumption in the world. To date, almost 6 000 publications have been cited in *pubmed* discussing epidemiological and experimental data on health effects of green tea and providing basic research evidence for the mode of action of green tea-derived catechins.

Various components of green tea have been discussed in the literature for their beneficial effects. Catechins, a group of very active flavonoids, are a major component of green tea representing 60–80 % of all polyphenols. Four major catechins have been identified in green tea: epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechingallate (ECG) and epicatechin (EC) (Figure 1). These epicatechin derivatives all possess antioxidant, anti-inflammatory, antimicrobial, and anticarcinogenic properties. However, the major and most highly bioactive constituent in green tea, responsible for its biochemical and pharmacological effects, is (-)-EGCG [1]. Other relevant compounds of green tea include caffeine, organic acids, protein, chlorophyll, and theanine. The chemical composition of green tea is influenced by climate, season, horticultural practices, and especially the age of the leaves. An average cup of green tea contains between 300 to 400 mg

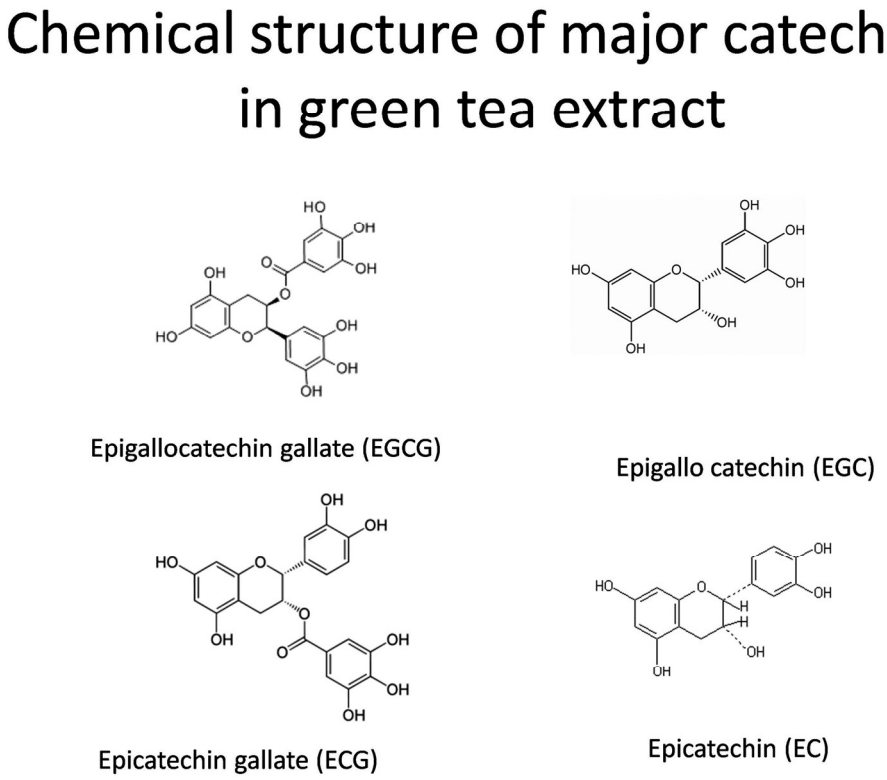

Figure 1 Chemical structure of major catechins in green tea extracts.

of polyphenols. On average, the concentration of total polyphenols in dried green tea leaves is about 10 %. In other words, only about 10 % of the entire cup are polyphenols, with the most beneficial polyphenol EGCG representing an even smaller percentage [2]. In this context, the central question in chemopreventive considerations of green tea is the local concentration of bioactive compounds after oral administration. Consequently, anticarcinogenic effects observed with much higher concentrations in vitro may not be relevant to in vivo effects. Studies investigating local concentrations of green tea after systemic administration are rare. However, some of them have shown that frequent consumption of green tea results in significant levels of green tea polyphenols in the body, and that the concentrations achieved are sufficient for biological effects such as chemoprevention [3]. On the other hand, there are several green tea supplements and green tea powder preparations, which have emerged in the past few years. Many of them claim that they yield higher green tea polyphenol (GTP) blood levels compared to the consumption of green tea. However, real evidence is lacking and respective clinical studies are missing. Eventually, clinical effects observed in topical application will give the final answer as to whether the concentration of the respective drug is sufficient in dermatologic diseases or not.

Biological effects of green tea and its components

Green tea and its constituents interfere with cellular mechanisms, target molecules, and specific signal transduction pathways. The major polyphenol derived from green tea, EGCG, has been shown to bind directly to several receptors and signaling molecules, and to inhibit the functions of key receptors, kinases, proteinases, and other enzymes [4]. Thus, GTPs interfere with cellular targets at the crossroad between inflammation and carcinogenesis, which does not merely open up a broad spectrum of indications, from inflammatory diseases to the prevention of cancer, but also an avenue to block the inflammatory path towards cancer development (Figure 2).

Green tea as antioxidant

Although oxidation reactions are essential for life, they can also be damaging. In the skin, oxidative stress has been linked to inflammation, photo damage, cancer, and skin aging. As a logical consequence, all living organisms maintain complex systems of multiple types of antioxidants to protect their cells from oxidative damage, which have been increasingly discovered as potential targets in the development of new

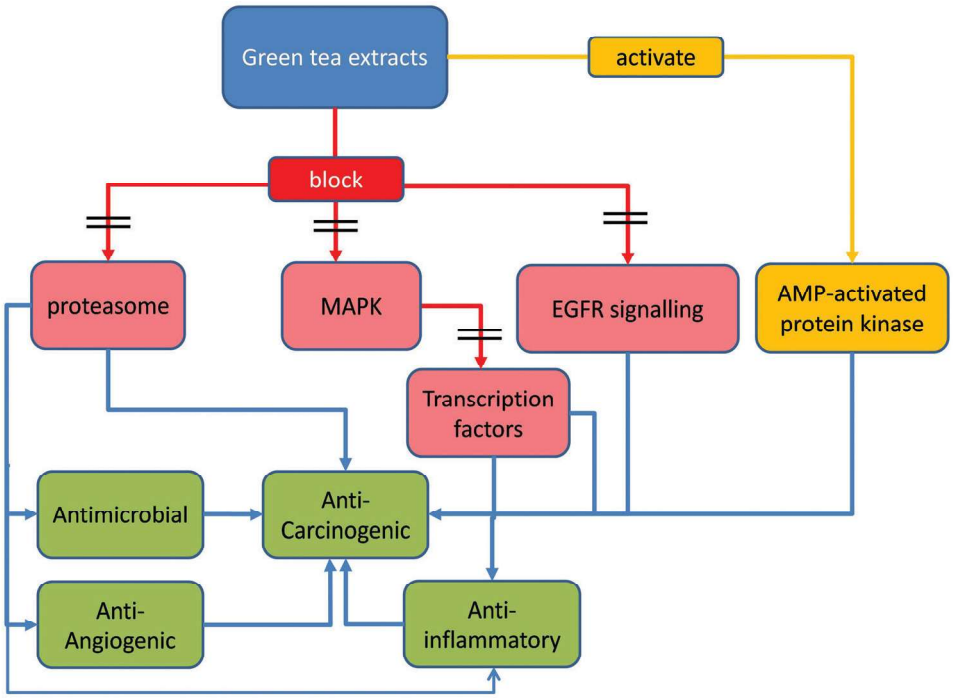

Figure 2 Biological effects of green tea extracts.

treatments. Antioxidant activity is among the first immunological evidence of cancer protection described for GTPs. The polyphenolic structure of GTPs allows electron delocalization and confers the ability to quench free radicals [5]. Furthermore, GTPs have been shown to improve differentiation in human osteoblasts during oxidative stress. Finally, the protective effect of GTPs against oxidative stress is due to an increased expression of the antioxidative enzyme HO-1 [6].

In vivo experiments have shown that administering EGCG to old rats reduces oxidative stress and leads to decreased levels of lipid peroxidation and protein carbonylation in EGCG-treated animals. Moreover, these animals also exhibited increased levels of antioxidants and antioxidant enzymes in the liver, skeletal muscle, and brain. Interestingly, such effects were not observed in young rats, suggesting that the antioxidative effects of EGCG only come to play in the presence of excessive oxidative stress [7]. Human studies have also provided evidence for the antioxidative activity of green tea polyphenols. In healthy human volunteers, dietary supplementation with tea catechins (500 mg daily) for four weeks resulted in a significant decrease in plasma oxidized low-density lipoprotein compared to the control population [8].

Blocking of mitogen-activated protein kinases and metalloproteinases

Mitogen-activated protein (MAP) kinases orchestrate a complex chain of proteins that communicate a signal from a membrane-bound receptor to the nucleus of the cell. Oxidative stress is involved in the activation of signal transduction pathways of MAP kinases. Various in vitro studies have revealed that green tea, and in particular EGCG, hamper distinct cellular pathways. Notably, most of these cellular pathways are interconnected with MAP kinase-induced molecules [9, 10]. Several publications describe an interference of green tea EGCG with MAP kinases, affecting metalloproteinase activity in different cells such as chrondrocytes, breast cancer cells, and fibroblasts [9, 11–14]. In all these publications, clear effects of GTPs on MAP kinase pathways and metalloproteinase activity inhibition are convincingly shown, although most of these mechanisms have not yet been confirmed in in vivo studies [4]. In turn, inhibition of protein phosphorylation can block further steps in the cascade. Since deregulation of MAP kinases paralleled by an upregulation of metalloproteinases is frequently observed in cancer, modulation of MAP kinases by EGCG and inhibition of metalloproteinases has been repeatedly suggested as a novel strategy for the prevention or treatment of cancer.

Effect of EGCG on the proteasome

The proteasome is responsible for the degradation of more than 90 % of intracellular proteins. By this mechanism, the proteasome regulates turnover of cyclins and cyclin-dependent kinase inhibitors (CIP/KIP family). Consequently, the inhibition of proteasome functions can result in cell cycle

arrest and proves crucial for cell survival and proliferation. In cancer cells, this homeostatic function is deregulated by cellular oncogenic factors leading to hyperactivation of the proteasome. Increased proteasome activity in turn promotes the degradation of tumor suppressor proteins, resulting in cancer cell survival and proliferation as well as the development of drug resistance. As a consequence, proteasome inhibitors have been repeatedly suggested for anticancer treatment, and are currently being tested in (pre-)clinical trials. EGCG has been shown to block the proteasome, potentially indicating an antitumor effect of green tea [15].

Effects on growth factor-associated signaling

Epidermal growth factor (EGF) is a general growth factor with action not only on epithelial cells but also on a large variety of other cells, accounting for disparate cellular activities such as proliferation, angiogenesis, survival, differentiation, migration, and apoptosis [16]. Today, it has been established that there is an epidermal growth factor receptor tyrosine kinase (RTK) family, which is currently extensively studied for its role in human development, physiology, and cancer [17]. EGCG and other GTPs have been shown to interact with epidermal growth factor-associated signaling by inhibiting EGFR autophosphorylation in carcinoma cells [18]. Moreover, EGCG can inhibit cell transformation by directly interacting with cellular target proteins such as the SH2 domain of Fyn tyrosine kinases [19]. Targeted disruption of the EGF receptor has been shown to block the development of papillomas and carcinomas from human papillomavirus-immortalized keratinocytes [20], which could in part account for the chemopreventive and antipapillomatous activity of topically applied EGCG.

EGCG has also been shown to block other growth factors such as platelet derived growth factor (PDGF) [21], fibroblast growth factor (FGF) [22], vascular endothelial growth factor (VEGF), and insulin-like growth factors (IGF-1 and IGF-2) [23]. Interactions of EGCG with growth factor-associated signaling have been shown to be in part due to the inhibition of intracellular signaling cascades but also due to "trapping of growth factors" by EGCG [22].

Antiinflammation and blocking of DNA synthesis

EGCG has an antiinflammatory effect by elevating the expression of the Tollip protein, a negative regulator of TLR signaling [24]. GTPs also prevent tumor progression of chemically induced benign skin papillomas to carcinomas, probably by stabilizing DNA and protecting against free radical-mediated enhancement of genetic instability [25].

In summary, green tea with its components has been shown to interact with multiple cellular mechanisms, giving rise to several potential clinical implications.

Clinical applications of green tea in dermatology

Green tea extracts in dermatological diseases

Today, various studies suggest a beneficial effect of green tea on several dermatological diseases. Not only do GTPs block the damaging effects of UV, thus resulting in a reduction in sunburn response, UV-induced immunosuppression, skin cancer risk, and photoaging. GTPs have also been shown to have antimicrobial and antiinflammatory effects by targeting cells or cellular interactions in the skin as well as the skin microbiome. With all its effects on skin, topical application of green tea is assumed to result in sufficient penetration of active substances through the skin. And in fact, pharmacokinetic studies have provided evidence that topical application of GTP in hydrophilic ointment leads to high concentrations in the skin but negligible systemic availability of GTPs [26]. Not surprisingly, green tea extracts are used in various dermatological diseases and indications (Figure 3).

UV protection and skin cancer

GTPs are highly UV protective, probably by suppressing the carcinogenic activity of UV radiation and many other damaging effects. Their photoprotective nature is caused by various cellular, molecular, and biochemical mechanisms. Green tea also provides protection against dangerous effects of UV when merely topically applied on human skin, suggesting a promising role of GTPs as future agents in sunscreen protection [27, 28]. Along with its UV protective effects, green tea also has definite effects on the viscoelastic properties of the skin [29]. Presumably, GTPs will therefore play a growing part in cosmetic and especially anti-aging products.

UV radiation causes nonmelanoma skin cancer, the most common cancer in Germany with an overall incidence of more than 195 000 [30]. Because of this high incidence, focusing on therapy alone is inadequate. Instead, simple but effective prevention techniques should preferentially be employed. This explains why chemoprevention by dietary modification is currently receiving widespread attention. For instance, diets rich in naturally occurring polyphenols – such as green tea – have been associated with a reduced incidence of many types of human cancer including skin cancer. Several studies also suggest that GTPs interfere with every step of carcinogenesis, thus preventing cancer development especially in the skin. However, respective large interventional studies have not always been as unequivocal as previous in vitro results. Moreover, it still remains unclear whether systemic administration of green tea or GTPs leads to local concentrations sufficient for skin cancer prevention.

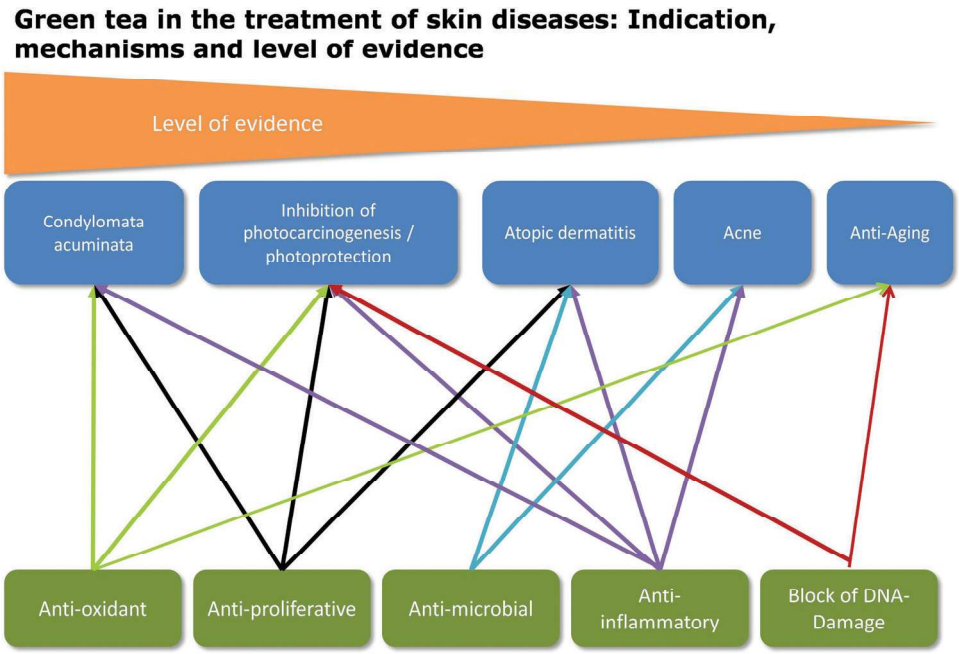

Figure 3 Green tea in the treatment of various skin diseases.

Green tea in infectious diseases

HPV and genital warts: Human papillomavirus (HPV) is a DNA virus capable of infecting human epithelial cells. HPVs establish productive infections only in keratinocytes of the skin or mucous membranes, and may cause benign papillomas as well as cancer of the cervix, genitals, anus, and oropharynx. By now, there is good data that GTPs are able to offer effective protection against malignant transformation of benign HPV-induced skin papillomas [31, 32]. Numerous studies have provided detailed evidence of the clinical benefits of green tea in different HPV infections and associated skin diseases, especially in genital warts and HPV-related cervical cancer. In several large studies, GTPs have been successfully used as treatment in condylomata acuminata, and today, GTPs are regarded as an effective and safe therapeutic option for external genital warts. In fact, an ointment containing a standardized green tea extract with a high content of EGCG (55–72 mg per 1 g ointment) has been shown to be highly effective in the treatment of condylomata acuminata, with a complete clearance rate of more than 50 %. Recently approved for prescription by the FDA in the United States and by the EMA in Europe, it is the first botanical drug to obtain such approval [33, 34].

Cervical cancer: Green tea is one of the most extensively studied antioxidant compounds. It has become apparent that green tea components hold great potential in the prevention and therapy of HPV-induced cervical cancer. Indeed, green tea extracts are already regarded as a potential option for a novel, pharmaceutical approach for cervical cancer patients in the future. Studies investigating the clinical efficacy of green tea components – delivered vaginally, orally or both – in patients with HPV-infected cervical lesions have shown overall response rates of 69 % in the treatment group compared to 10 % in the untreated control group [35]. This indicates that green tea extracts used orally and/or vaginally are effective in treating HPV-related cervical lesions, and suggests that they may potentially become a routine treatment for respective patients. However, not only do GTPs have a protective effect on cervical cancer, they also effectively inhibit tumor progression of chemically induced benign skin papillomas to carcinomas mediated by carcinogenic substances [31].

HIV: There is some evidence that the enhancement of human immunodeficiency virus 1 (HIV-1) infectivity by semen can be inhibited by green tea ingredients – especially EGCG – at nontoxic concentrations [36]. There have also been several reports that green tea extracts are able to inhibit HIV replication prior to its integration into host DNA. In addition, green tea extracts appear to be allosteric reverse transcriptase inhibitors with unique mechanisms compared to the currently approved nonnucleoside reverse transcriptase inhibitors (NNRTIs). Thus, future tools for the preventions of sexual HIV transmission as well as anti-HIV agents might be developed on the basis of green tea [37]. However, before therapeutic trials can be conducted, the respective efficacy first has to be exactly elucidated [38].

Besides its effects on HIV, GTPs have also been described as agents against *Leishmania major promastigotes* [39]. So far, however, there have not been any studies investigating the use of green tea-containing ointments in clinical

leishmaniasis lesions. Aqueous extracts of green tea used as mouthwash have also been shown to result in a major reduction of fungal cells of *Candida spp*. Thus, future use of green tea in the treatment of infections caused by *Candida albicans* can be expected [40]. Moreover, there are a few other studies showing a beneficial effect of green tea extracts against infectious agents, for example, such as bacteria on the skin or in wounds in vitro as well as in vivo.

Rosacea/acne

Not only does the main polyphenol component of green tea, EGCG, have antioxidant, immunomodulatory, and photoprotective properties, it is also marked by antiangiogenic and anti-inflammatory effects. In patients with significant facial erythema and telangiectasia, EGCG cream applied twice daily resulted in decreased expression of VEGF and HIF-1α, presumably explaining the efficacy of GTPs in the treatment of rosacea [41]. In addition, green tea extracts and especially EGCG have also been increasingly considered an effective candidate for the treatment of acne. Mechanisms of action include IGF-I-differentiated inhibition of lipogenesis as well as inflammation. Prospective studies on acne patients using a skin lotion with 2 % green tea extract daily have demonstrated efficacy [33, 42].

Atopic dermatitis

Regular bath therapy, for example, using green tea extracts has shown marked improvement of atopic dermatitis (AD) and has been proposed as an effective and safe treatment for patients with AD. Not only did subjects treated with green tea extracts show remarkable clinical improvement of their atopic dermatitis as assessed by the Scoring Atopic Dermatitis Index (SCORAD), they also reported a major decrease of daily pruritus as measured by a respective visual analogue scale [33, 43].

Keloids

Through their antioxidant effects, green tea polyphenols have also been shown to effectively inhibit type I collagen synthesis and to modulate collagen type I and fibronectin as well as dermal fibroblast function and activity. This suggests the use of green tea as adjuvant treatment option for keloids as well as in systemic sclerosis [44, 45].

Hair disorders

There is some evidence that green tea extracts may be beneficial in hair disorders. By selectively inhibiting 5-alpha reductase activity, they can prevent or treat androgenetic alopecia. In ex vivo studies, EGCG also promotes hair growth, rendering it a potential future treatment option. Another possible future indication for GTPs may be hirsutism, as there is some evidence of ornithin decarboxylase (ODC) and 5-alpha reductase inhibition [46, 47].

Green tea and wound healing

EGCG is also known to regulate the secretion of cytokines and the activation of skin cells during wound healing. In fact, several studies suggest that green tea extracts enhance wound healing in full thickness by accelerating cell infiltration, re-epithelialization, and angiogenesis [46, 48, 49]. But green tea also has anti-infective properties, which additionally enhances wound healing. Especially its antibacterial effects have been intensively analyzed and it has been shown that green tea is effective against numerous bacteria including multidrug-resistant strains such as methicillin-resistant *Staphylococcus aureus* (MRSA) [50].

Conclusion

There have been an increasing number of studies and trials investigating green tea and its extracts in the treatment of various dermatological diseases. Many studies are very promising and suggest the use of green tea as an effective therapeutic option in chronic, infectious, inflammatory, and hair disorders as well as a preventive tool not only against skin aging but also skin cancer. However, to date there are only a few studies on the use of green tea extracts with double-blind, randomized approaches and large patient numbers. More studies are required in order to be able to determine the true efficacy of green tea-derived treatment approaches in most dermatological diseases as well as their long-term safety and tolerability.

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