REVIEW

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Great green tea ingredient? A narrative literature review on epigallocatechin gallate and its biophysical properties for topical use in dermatology

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The purpose of this review is to examine epigallocatechin-3-gallate (EGCG) regarding its stability in different conditions (pH-value, concentration, temperature), its interactions with common cosmetic ingredients, and its application in the dermatological field. The literature research considered published journal articles (clinical trials and scientific reviews). Studies were identified by searching electronic databases (MEDLINE and PubMed) and reference lists of respective articles. Higher concentrations of EGCG were reported to correlate with better stability and the same can be said for low temperatures and pH values. The interaction between EGCG and hyaluronic acid strengthens its antioxidant activities. Titanium dioxide coated with EGCG proved a suitable ingredient in sunscreens. The polyphenol possesses antioxidant properties, which proved effective in the prevention of UV-induced skin damage and to alleviate the symptoms of Imiquimod-induced psoriasis. The three endpoints of this review not only showed interesting results but also highlighted some limitations of EGCG. Studies show that the molecule is unstable, which may hinder its dermatological and cosmetic applications. The reported interactions with cosmetic ingredients were limited. As the health aspects of EGCG are well-reported, ECGC has become a focus of interest for health professionals trying to treat common dermatological diseases.

KEYWORDS
cosmetic, dermatology, EGCG, Epigallocatechin-3-gallate, interaction, stability

1 | INTRODUCTION

Epigallocatechin-3-gallate (EGCG) is the most abundant catechin in green tea. The molecule is known for its many properties, which vary from antiangiogenic and anticarcinogenic to antioxidant, antimicrobial, and anti-inflammatory (Chakrawarti, Agrawal, Dang, Gupta, & Gabrani, 2016). Despite its beneficial properties, EGCG has not yet found a wide dermatological and cosmetic applications. This is mostly due to its reported lack of stability, especially when retained at high temperatures and pH values.

Many common cosmetic ingredients can enhance EGCG stability and its properties. Therefore, we examined the existing literature evaluating the interaction between some of the most common cosmetic ingredients and EGCG.

When we looked at the dermatological aspects, we examined how the topical skin application of EGCG-containing preparations

leads to various health benefits in the treatment of many common skin conditions such as psoriasis, atopic dermatitis (AD), alopecia, and UV-induced skin damage. Various factors can have an impact on its degradation process such as pH, temperature, concentration, the medium in which EGCG finds itself, and the presence of other substances with similar properties. EGCG seems to be very unstable even in its most natural form, *Folia Camellia sinensis*. A 28% lower average EGCG concentration has been shown in commercial tea bags, left in their original container at 20°C for 6 months (Friedman, Levin, Lee, & Kozukue, 2009).

The degradation process itself can take place via different chemical reactions, leading to different chemical products. In an aqueous system, EGCG goes through a process of oxidation which is generally recognizable by a change in the color of the aqueous system from transparent to brown. At higher temperature and at lower pH values, the main degradation process is the epimerization, which EGCG is transformed into its trans-epimer state, gallocatechin gallate (GCG) (Krupkova, Ferguson, & Wuertz-Kozak, 2016; Wang, Zhou, & Jiang, 2008).

In this review, we examined the literature with the purpose of analyzing the molecule in the context of its stability, its interaction with common cosmetic ingredients, and its health benefits.

2 | METHODS

2.1 | Literature research and databases

The literature research considered published journal articles, which were either clinical trials or scientific reviews. Studies were identified by searching electronic databases (PubMed and MEDLINE) and reference lists of respective articles. For the purpose of this review, we examined all the existing literature disregarded its year of publication. Only articles available in English were considered for this review. The search was performed on the January 26, 2019.

2.2 | Eligibility criteria

For each of the three subsection of this review different eligibility criteria applied.

First, we examined the literature to establish how different external factors influence stability. We focused on studies that examined the EGCG in its unaltered form and therefore not coated with another substance.

Second, we analyzed existing literature, examining the interaction between EGCG and the most common cosmetic ingredients which can be found in most products all over the world. To establish which the most common cosmetic ingredients are, we wrote a list and had it reviewed by a dermatologist (Cosmeticsinfo, 2019).

Furthermore, we examined EGCG in respect to possible health benefits it may induce or provoke. Due to the copious amount research about EGCG and its health benefits in various skin conditions, we

focused on some common skin diseases and topical polyphenol application. Literature describing per Os or IV application was therefore excluded.

2.3 | Stability

For this review, we focused on analyzing the influences of EGCG concentration, as well as solutions temperature and pH value on the molecules stability as described in the existing literature.

2.3.1 | Concentration

The concentration of the molecule seems to be important for solutions stability. Solutions show dose-dependency resulting in higher concentrations of EGCG correlating with better stability (Krupkova et al., 2016).

In 2005, a study investigated the relation between the EGCG concentration in water at 37°C and its stability. The half-life of EGCG increased from 30 min in a 20 μM solution to 150 min in a 96 μM solution. Additionally, the stability of three EGCG solutions (this time in mM range) at room temperature was compared over a 7-day period. The result showed that EGCG in the 0.51 mM (0.025%) and the 2.06 mM (0.10%) solutions did not stay stable and the EGCG concentrations gradually decreased by 20%, whereas the 6.99 mM (0.34%) solution stayed stable through the 7-day testing period (Krupkova et al., 2016; Sang, Lee, Hou, Ho, & Yang, 2005).

EGCG solutions in the physiological buffer *4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid* (HEPES), in concentrations varying from 25 μg ml^{-1} to 900 μg ml^{-1} (0.00056–1.96506 mM), were reported to have a similar dose-dependent stability (Fangueiro et al., 2014; Krupkova et al., 2016).

A comparable effect can be observed for EGCG solutions at 80°C. After 6 hr, the 1,666.7 mg ml^{-1} solution was still at 85.3% of its previous concentration, whereas the 5 mg ml^{-1} one was at 56.9% (Li, Taylor, Ferruzzi, & Mauer, 2012) (Table 1).

The stability of the molecule was examined under sunlight and air exposure. The results were consistent with the existing literature. After 48 hr, the 2 mg ml^{-1} solution had maintained more than 80% of its EGCG concentration, whereas both the 0.1 and the 0.5 mg ml^{-1} solution fully degraded (Zeng et al., 2018).

2.3.2 | Temperature

The temperature also has a large influence on the EGCG stability.

Different concentrations of EGCG in HEPES medium at physiological pH 7.4 were stored at temperatures of 4 and 25°C. After 2 days, the degradation was measured and the solutions, stored at 25°C, had a smaller concentration of EGCG (~10% less at 4°C vs. ~80% less at 25°C for the 100 μg ml^{-1} solution). Lower temperatures had slowed the degradation process (Fangueiro et al., 2014). Another study examined the degradation of green tea concentrate at
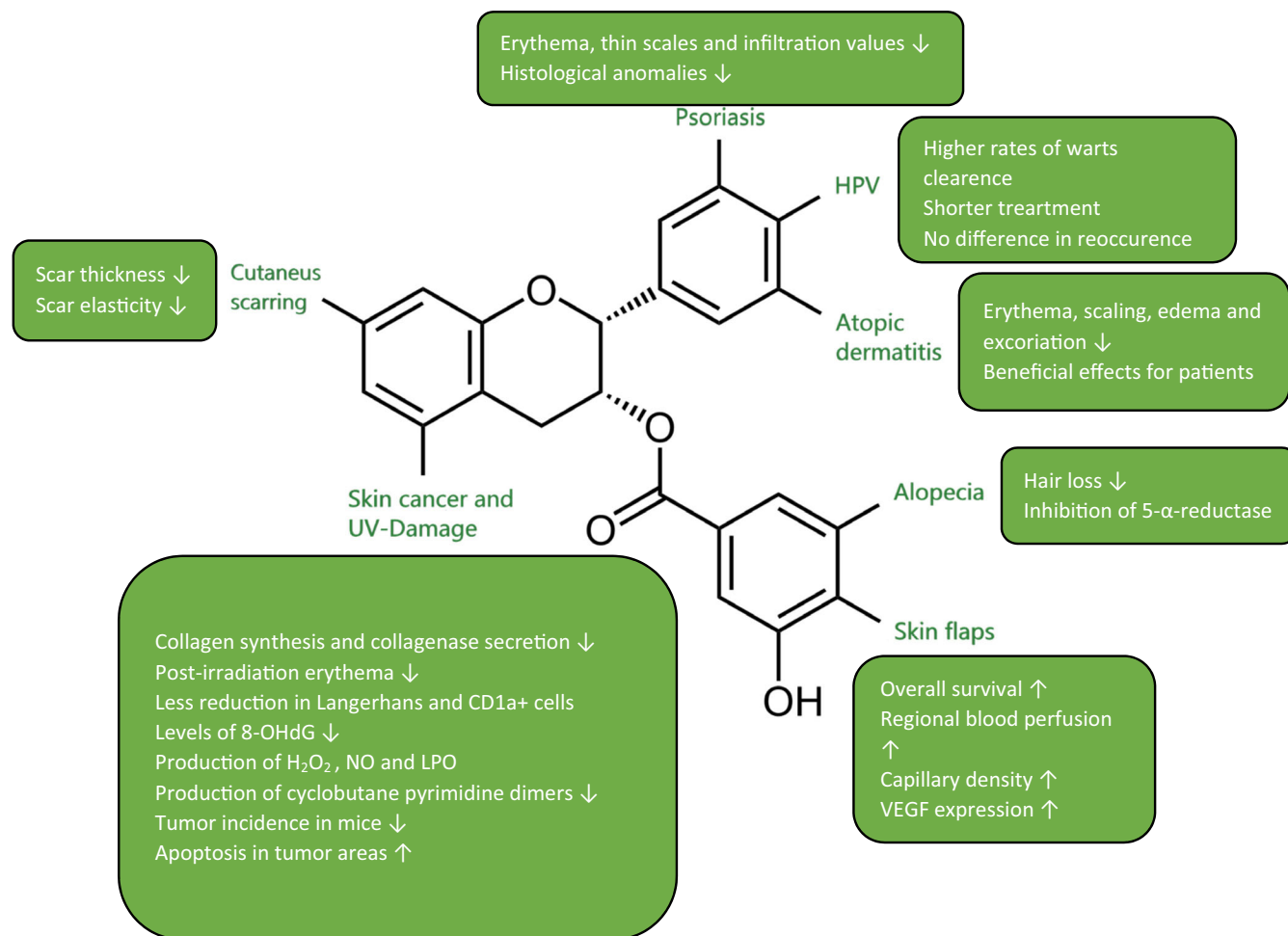
FIGURE 1 Dermatological application of EGCG on some common skin conditions. Seven out of the 8 hydroxy groups of the EGCG molecule have been replaced with the dermatological diseases we reviewed under the section "Health aspects."

25, 40, 60, 80, 100, and 120°C. At 120°C, the concentration fell, after only 105 min, to 30% of its initial concentration. Compared to that, the degradation process was slower at lower temperatures. The tc (time when 90% of the original concentration is left) was 27,797 min at 25°C, 544 min at 60°C and 3.273 min at 120°C (for both solutions the pH value was 7) (Li et al., 2012).

Furthermore, the temperature influences the relation between oxidation and epimerization, as shown in a 2008 study involving EGCG in aqueous systems (Wang et al., 2008).

At temperatures below 44°C, oxidation is the predominant reaction. With rising temperatures above 44°C, we start to see that the epimerization becomes the main reaction and with a further increase above 98°C the epimerization starts to be the predominant reaction (Wang et al., 2008).

A similar tendency can be seen in the interaction between pH and the temperature increase. At temperatures ranging between 4 and 25°C, a pH increase seems to have a more notable effect on the EGCG-degradation, but with raising temperatures the effect of the temperature on the degradation process seems to increase too (Proniuk et al., 2002).

This lack of stability at higher temperatures could obviously be problematic for the development of many dermatological products, which are not commonly stored cold (Table 1).

2.3.3 | pH value

Another parameter influencing the stability of EGCG is the pH value of the solution EGCG is solved in. Degradation of EGCG was measured in solutions with different pH values using UV/visible spectroscopy. To quantify degradation, changes in the absorption characteristics of the drug were compared to the changes in the medium. In a solution of pH 1.6, EGCG was stable for up to 96 h. Stability decreased with increasing pH of solution (pH 5, 48 h; pH 7, 24 h; pH 9, 4 h) (Radhakrishnan et al., 2016).

EGCG was reported to show the same stability in sodium phosphate buffer (pH 7.4) as it shows in boiling water. After only 6 hr both experiments led to remaining EGCG-concentrations close to zero (Su et al., 2003).

TABLE 1 Description of the effects of temperature and pH value on EGCG stability

Parameters	Study	Concentration	Setting/study design	Outcome
Concentration	(Sang et al., 2005)	0.51 mM	RT for 7 days	20% ↓ in C
		2.06 mM		20% ↓ in C
		6.99 mM		No change
		20 μM	HL in water at 37°c	30 min
		96 μM		150 min
	(Fangueiro et al., 2014)	900 μg ml^{-1}	2 days at 4°c	~0% ↓
		25 μg ml^{-1}		~40% ↓
		0.25 μg ml^{-1}		~100% ↓
	(Li et al., 2012)	1,666.7 mg ml^{-1}	At 80°c for 6 h	14.66% ↓
		5 mg ml^{-1}		43.13% ↓
	(Zeng et al., 2018)	2 mg ml^{-1}	At 25 to 28°c	~20% ↓ in C
		0.5 mg ml^{-1}		Fully degraded
		0.1 mg ml^{-1}		Fully degraded
Temperature	(Fangueiro et al., 2014)	900 μg ml^{-1}	C at 4°c – C at RT	~20% ↓
		25 μg ml^{-1}		~75% ↓
		0.25 μg ml^{-1}		Both fully degraded
	(Li et al., 2012)	1,666.7 mg ml^{-1}	In green tea concentrated solutions at neutral pH	t_{90}c at RT = 27,797 min
				t_{90}c at 120°c = 3. 273 min
	(Wang et al., 2008)		<44°c	R: Oxidation ↑↑↑
			>44; <98°c	R: Epimerization ↑↑; oxidation ↑
			>98°c	R: Epimerization ↑↑↑
pH-value	(Proniuk, Liederer, & Blanchard, 2002)		>4°c; <25°c	E: Temperature
			>25°c	E: Temperature and pH- value
	(Radhakrishnan et al., 2016)		pH 1.6	S: Up to 96 h
			pH 5	S: 48 h
			pH 7	S: 24 h
			pH 9	S: 4 h
	(Zhu, Zhang, Tsang, Huang, & Chen, 1997)		pH < 4	Great stability
			4 < pH < 8	Poor stability
	(Li et al., 2012)		Stability after pre-heating at 120°c for 30 min	3.8–5 pH → highest stability
	(Su, Leung, Huang, & Chen, 2003)		pH 7.4	After 6 h completely degraded
			100°c	

Note: C, concentration; E, parameter that mostly effects EGCG-degradation; EGCG, epigallocatechin-3-gallate; HL, half-life; R, reaction; RT, room temperature; S, stable for; ↓, decrease; ↑ = small increase; ↑↑ = medium increase; ↑↑↑ = large increase.

Stability in dilute aqueous systems was further investigated. After being heated at 120°C for half an hour, the molecule was the most stable within the pH range 3.8–5 (Li et al., 2012).

Overall EGCG was considered very stable at pH values smaller than 4, whereas at values between 4 and 8 the stability was rather poor. Increasing pH led to decreased stability (Li et al., 2012; Radhakrishnan et al., 2016; Su et al., 2003; Zhu et al., 1997).

Furthermore, the pH value can also cause oxidation. EGCG in neutral buffer (7.2 pH) reacts with molecular oxygen resulting in a radical molecule and a superoxide radical. This can start a radical chain reaction, which leads to further molecule degradation (Sang, Yang, Buckley, Ho, & Yang, 2007) (Table 1).

2.3.4 | Dermatological applications

Due to the low thermal stability (Fangueiro et al., 2014; Li et al., 2012; Proniuk et al., 2002; Wang et al., 2008), it is very difficult to use EGCG in sunscreens or lotions, where its antioxidant and anti-inflammatory effects might be very helpful.

TABLE 2 Description of the effects of some dermatological ingredients on EGCG stability and effects of topical EGCG-application on dermis and epidermis C, concentration; HL, half-life; ↓ = decrease by

Parameter	Study	Specific parameter	Setting	Outcome
Cosmetic ingredients	(S. Scalia et al., 2013)	EGCG only	Oil-in-water emulsions after 1 hr irradiation	76.9% ↓
		EGCG + vitamin E		79.1% ↓
		EGCG + BHT		84.5% ↓
		EGCG + vitamin C		20.4% ↓
		EGCG + alpha-lipoic acid		12.6% ↓
	(Bianchi et al., 2011)	Ethylhexyl methoxycinnamate (octinoxate)		61% ↓
		Butyl methoxydibenzoylmethane (avobenzone)		69% ↓
Topical application of 28.6 μg cm^{-2}	(Lambert et al., 2006)	Epidermis		C: 1365.7 ng ml^{-1}; HL:9.3 h
		Dermis		C: 411.2 ng ml^{-1}; HL:10.9 h

A 2013 study tried to compare different coantioxidants (vitamin E, butylated hydroxytoluene [BHT], vitamin C and alpha-lipoic acid) in an oil-in-water emulsions containing EGCG. Aim of this study was to asses which substance could stop the photochemical degradation. After 1 hr irradiation in a solar simulator at an irradiance corresponding to natural sunlight, EGCG concentration was measured. The cream containing only EGCG had lost 76.9% of initial EGCG. Both the creams with BHT and vitamin E had even higher photodecomposition percentages (84.5 and 79.1%). Creams with vitamin C and alpha-lipoic acid only had photodecomposition percentages of 20.4 and 12.6%, respectively.

Furthermore, the remaining antioxidant activity was tested, and vitamin C and alpha-lipoic acid had lower light-induced reduction of their properties (Santo Scalia, Marchetti, & Bianchi, 2013).

A similar study found that the UV-B filter ethylhexyl methoxycinnamate (octinoxate) caused a small decrease in the photodecomposition process (61 vs. 69%, $p < .001$). The UV-A filter butyl methoxydibenzoylmethane (avobenzone) led to no change in the photodecomposition process (Bianchi, Marchetti, & Scalia, 2011).

Topical application was reported to be a better delivery system for EGCG than oral delivery. About 15 min after application of 28.6 μg cm^{-2} EGCG to the dorsal face in SKH1 hairless mice, the maximal skin concentration in the epidermis and dermis was 1,365.7 ng ml^{-1} and 411.2 ng ml^{-1}, respectively. The half-lives were 9.3 hr for epidermis and 10.9 hr for dermis. Stability of the gel itself was tested at 4, 25 and 37°, showing, once again, that the lower temperature was by far the most stable (Lambert, Kim, Zheng, & Yang, 2006).

Emulsion and hydrogel preparations containing EGCG were prepared in order to test their percutaneous penetration. Totally, 36.1% of the EGCG contained in the emulsion and 35.5% of EGCG in the gel permeated into the stratum corneum. Furthermore, the study showed that the gel led to a significantly higher concentration in the superficial regions of the skin, while the emulsion led to a higher concentration in the deeper layers of the stratum corneum.

The emulsion was also less stable (S. Scalia, Trotta, & Bianchi, 2014) (Table 2).

3 | INTERACTIONS WITH COSMETIC INGREDIENTS

For the previously mentioned future development of EGCG-based dermatological products, it is necessary to establish the presence and the extent of the interactions between the most common cosmetic ingredients and EGCG.

3.1 | Vitamins

In addition to its therapeutic use in anti-acne treatment, vitamin A also has a cosmetic application due to its anti-photo-aging and anti-wrinkles properties. A derivate of vitamin A, all-trans-retinoic acid (ATRA), has been shown to assist EGCG in the inhibition of the growth of B16 melanoma cells in mice (a particular type of melanoma, known for its high metastasis rate) (Lee, Kishikawa, Kumazoe, Yamada, & Tachibana, 2010).

In addition to the properties that Vitamin C and A share (anti-wrinkle and anti-photo-aging), vitamin C has been shown to enhance skin lightening. Furthermore, vitamin C reduced light-induced photochemical degradation of EGCG and also improved the preservation of its antioxidant properties (S. Scalia et al., 2013). The results are consistent with a more recent study, which once more showed that Vitamin C was able to increase the stability of the EGCG molecule, particularly in an aqueous environment (Cano et al., 2019).

On the other hand, EGCG has been reported to enhance the lipid antioxidant effect of both vitamins C and E despite its concentration being significantly smaller than the vitamins one (Intra & Kuo, 2007).

Vitamin E is also an antioxidant and a very important cosmetic ingredient. As previously reported, it does not enhance the stability of EGCG. α-Tocopherol (a form of vitamin E) has been shown to positively interact with EGCG. EGCG protects endothelial cells from the damage caused by linoleic acid hydroperoxide (LoaOOH plays a role

in the process of atherosclerosis), and α-Tocopherol strengthens EGCG in its protection (Kaneko, Matsuo, & Baba, 1998; S. Scalia et al., 2013).

3.2 | UV filters

Titanium dioxide (TiO_2) is a very common ingredient of many cosmetic products. If used in sunscreens, it appears on a nanoscale concentration, as it absorbs UV light and leads to the formation of a clear film of sunscreen upon topical application. Furthermore, if used in its primary form (pigment-grade) to brighten food, toothpaste and some medication (cosmeticsinfo, 2019).

The interaction between EGCG and TiO_2 has been analyzed in a 2016 study. Nano-sized TiO_2 was coated with green tea extracts (GTE) of which EGCG was the most abundant. The coating with GTE decreased the decrement in photocatalytic activity of TiO_2. Therefore, the coated version of TiO_2 appeared to be more suitable for a cosmetic application in a sunscreen (Verma et al., 2016).

As previously mentioned in the subsection "Dermatological applications," butyl methoxydibenzoylmethane (avobenzone) did not reduce the photo-degradation process of EGCG. Benzophonene-4 was reported to decrease photo-degradation by 17% (Bianchi et al., 2011).

3.3 | Hyaluronic acid

Due to its very strong hydrating properties, hyaluronic acid (HA) is a very common cosmetic ingredient. A 2017 in vitro study inspected the interaction between HA and EGCG. The transferosomes with EGCG and HA on the excised skin of male Wistar rats showed better antioxidant effects and both higher skin permeation and deposition (Avadhani et al., 2017).

3.4 | Isopropyl myristate

Isopropyl myristate increases skin penetrations. Compared to four other polyphenols, EGCG had the second highest drug loading capacity and the second slowest release time. Both these properties are very important for the development of an emulsion for topical application (Chaiittianan & Sripanidkulchai, 2014).

3.5 | Butylated hydroxytoluene

As mentioned above, BHT does not improve the stability of EGCG after 1 hr irradiation with a sunlight simulator. However, another study analyzed stability at a defined temperature. For EGCG in a hydrophilic ointment with 0.10% BHT at the temperatures of 25 and 37°C it respectively took more than 180 and 130 days before the EGCG concentration went below 90%. For the ointment containing only EGCG, it took 7 days (Dvorakova, Dorr, Valcic, Timmermann, & Alberts, 1999).

4 | HEALTH ASPECTS

EGCG has been shown to feature several health benefits. Its properties vary from antioxidant to anti-inflammatory, anticarcinogenic, and many others (Zink & Traidl-Hoffmann, 2015).

4.1 | Psoriasis

Since the autoimmune pathogenesis of psoriasis is connected to inflammation, the anti-inflammatory properties of EGCG have been the subject of several studies to establish the extent of its potential healing effect.

These anti-inflammatory properties have been tested on BALB/C mice, which suffered from Imiquimod-induced Psoriasis-like dermatitis. Imiquomid normally finds its medical application in the treatment of *Condylomata acuminata*. However, it also leads to the development of Psoriasis-like lesions in mice (van der Fits et al., 2009; Zhang, Liu, Mei, Wang, & Fang, 2016).

In the early intervention group treated skin presented only a few erythemas, thin scales and no obvious infiltration at the end of the observation period of 6 days. In the medium-term intervention group, the mice presented erythema, scales, and infiltration after 2 days. They gradually diminished after the application of EGCG and reached, on the sixth days, values similar to the one of the early intervention group.

After the 6 days, the control group reached erythema, thin scales and infiltration values much higher than the one in the treated groups (Zhang et al., 2016).

In a similar study, flaky skin mice were treated either with only water or with water and GTE containing 40% EGCG. Water-treated mice had visible skin lesion after 10 weeks, which became severe at the 11th week. The GTE-treated group experienced the first lesions at week 11.5, which stayed moderate until death. Histological samples confirmed previously reported results. Samples of the GTE treated mice showed only moderate histological anomalies compared to the water treated mice (Hsu et al., 2007). A nanoparticle formulation of EGCG was reported to have a 20 times stronger therapeutic effect than the free EGCG-molecule (Chamcheu et al., 2018) (Figure 1).

4.1.1 | Human papillomavirus

The human papillomavirus (HPV) can cause several diseases spreading from anogenital warts to indirectly cervical cancer. Different HPVs lead to various conditions. For example, HPVs 6 and 11 are known to be the primary cause of external anogenital warts (*condylomata acuminata*).

A study examined the efficiency of an ointment containing a mixture of green tea catechins (65% EGCG) for the treatment of participants displaying 2–30 external anogenital warts.

Treatment groups had a two times higher rate of complete warts clearance compared to the control group. Time needed for the

clearance was shorter for the individuals treated with green tea catechins. There were no significant differences in reoccurrence (Tatti et al., 2010).

These results were consistent with two previous studies (Gross et al., 2007; Stockflth et al., 2008). However, gender-specific clearance rate and time needed for clearance differed between the studies (Gross et al., 2007; Meltzer, Monk, & Tewari, 2009; Stockflth et al., 2008).

In a 2018 case study, a cream with a 10% EGCG concentration was reported to lead to the disappearance of Bowenoid papulosis-like multiple condylomata in the groin area of a patient after a 3 months treatment. A previous 2 months treatment with Imiquimod had only led to a modest lesion reduction (Pizzini, De Luca, & Milani, 2019) (Figure 1).

4.1.2 | Skin cancer and UV damage

EGCG has been also reported to have UV-protecting properties, which could have a preventive effect in the development of skin cancer. Both UV-A and UV-B damage human skin.

J. Kim et al. (2001) measured UV-A-induced damage in hairless mice and on human dermal fibroblast cultures. Outcomes were collagen synthesis and collagenase secretion levels, as they are representative for UV-induced intracellular damage. The treatment with EGCG was reported to reduce collagen synthesis in mice and at collagenase secretion in the fibroblasts (24 hr post-treatment).

Furthermore, UV-B-induced damage was quantified by measuring UV-B-induced erythema in Guinea pigs. EGCG was reported to significantly reduce erythema up to 24 hr after irradiation (J. Kim et al., 2001).

These results are consistent with another study, which also analyzed the effects of EGCG on epidermal Langerhans cells (LCs) and describes a decrease in number when irradiated with UV light. The skin of the volunteers was acquired through biopsy. Histological tests showed that samples of participants treated with EGCG had a 58% reduction of epidermal LCs damage compared to the vehicle. Dose-dependent effects of green tea polyphenols was also tested using different concentrations (1–10%). Concentrations of 2.5% and higher exhibited appropriate protection (Elmets et al., 2001).

These results are consistent with a more recent study testing UV-induced oxidative DNA damage by measuring the depletion of CD1a +cells and UV-induced generation of anti-8-hydroxy-2′-deoxyguanosine (8-OHdG). 8-OHdG is linked with UV-induced nucleic acid base modifications.

Compared to unirradiated skin, UV-exposed skin previously treated with green tea, showed a 35% reduction in CD1a+cells. The skin treated with the vehicle showed after irradiation, a 57% reduction, a result similar to the one obtained on untreated skin.

There were no significant differences in the levels of 8-OHdG in the green tea-exposed skin when compared with the unirradiated skin. However, vehicle-treated skin showed higher levels of 8-OHdG (Camouse et al., 2009).

Further on, EGCG was reported to reduce UV-induced production of H_2O_2 and NO in both dermis and epidermis, to inhibit the infiltration of CD11b+cells (CD11b+is a marker which can be found on the surface of macrophages and neutrophils), which function as an indicator for oxidative stress. EGCG also inhibited the production of epidermal lipid peroxidation (LPO) and positively influenced the levels of other antioxidants (GSH) (S. K. Katiyar, Afaq, Perez, & Mukhtar, 2001).

EGCG might protect the skin by suppressing mitochondrial dysfunction and inhibiting the apoptosis of keratinocytes (Liu et al., 2016).

UV-induced damage can also be quantified by the detection of cyclobutane pyrimidine dimers (CPDs). They are linked to UV exposure, which may create interference during DNA replication and therefore lead to a DNA mutation. EGCG and green tea polyphenols seem to partially block the penetration of the UV rays in the deeper skin of human volunteers. This leads to less production of CPDs+ cells when compared to the control. This inhibition of CPDs production seems to be dose-dependent (S. K. Katiyar, Bergamo, Vyalil, & Elmets, 2001; S. K. Katiyar, Perez, & Mukhtar, 2000).

A possible effect of EGCG on tumor incidence, growth, and multiplicity was examined in SKH-1 hairless mice. Hydrophilic cream, containing EGCG, inhibited 60% of tumor incidence, 86% of tumor multiplicity, and 95% of overall tumor growth compared to control mice.

UVB-induced transformation of benign papillomas to carcinomas decreased by 79% (S. Katiyar, Elmets, & Katiyar, 2007; Mittal, Piyathilake, Hara, & Katiyar, 2003).

A similar study, involving the same type of mice, led to similar results and provided additional information regarding the extent of EGCG-induced apoptosis in tumor and non-tumor areas of the UVB-irradiated skin. After being irradiated with UV-B for 20 weeks, the mice were treated with EGCG once a day, 5 days a week, for 18 weeks. This treatment led to an increase in cell apoptosis of 72% in nonmalignant tumors, of 56% in squamous cell carcinomas and had no effect on hyperplastic or nontumor areas (Lu et al., 2002) (Figure 1).

4.1.3 | Atopic dermatitis

The effects of EGCG on individuals, suffering from AD, have already been examined in some studies involving mice. The application of the molecule was seen to help with many of the symptoms caused by AD such as erythema, scaling, edema, and excoriation, and the authors suggested that EGCG could play a role in the treatment of EGCG in the future (Noh, Cho, Kim, & Park, 2008). A 2015 randomized double-blind controlled clinical study investigated the effects of a cream containing EGCG in mild to moderate AD on the neck and head of humans. The application of the EGCG cream led to some significantly relevant results on the neck after 7 days (the results were also reached faster when compared to the vehicle), but it was not possible to reach significantly relevant results at the endpoint since both the vehicle and the product led to similar outcomes (Patrizi et al., 2016).

A GTC bath therapy was reported to be beneficial for the patients involved in the clinical experiment. This effect was examined on the basis of both the Scoring Atopic Dermatitis value (SCORAD) and the VAS score (visual analog Scala). Although the latter was deemed to be

not statistically significant (H. K. Kim et al., 2012; Zink & Traidl-Hoffmann, 2015).

Further research is nevertheless needed to establish if and to what extent EGCG plays a role in the treatment of AD (Figure 1).

4.1.4 | Alopecia

The application of EGCG in mice has been shown to reduce hair loss in follicular epithelial cells, by decreasing the testosterone-induced apoptosis and help with hair regrowth after epilation (Y. Y. Kim et al., 2011).

The basis for this therapeutic effect might be the EGCG-induced inhibition of 5-α-reductase, given the key role that 5-α-reductase plays in the pathophysiology of androgenetic alopecia (Hiipakka, Zhang, Dai, Dai, & Liao, 2002).

The effects of EGCG in human hair growth on individuals not affected by androgenetic alopecia were also documented in an in vivo trial involving human volunteers. After EGCG application, 10% ethanol solution on human scalps, beneficial effects on the human dermal papilla cells were noted. These effects were consistent with the previously reported in vitro results (Kwon et al., 2007) (Figure 1).

4.1.5 | Skin flaps

The application of surgical skin flaps plays a key role in both dermatology and plastic surgery. A problem that many surgeons are faced with is flap necrosis, which substantially complicates patients' recovery.

Skin flaps in mice were treated with both topical and locally injected EGCG. The topical application led to better overall survival, regional blood perfusion, capillary density and VEGF expression in the flaps when compared to the vehicle. When compared to the locally injected EGCG, the topical application had no significantly different results apart from better blood perfusion (Cheon, Tark, & Kim, 2012).

It should also be noted that the topical application is a significantly less invasive procedure (Figure 1).

4.1.6 | Cutaneous scarring

A 2019 double-blind randomized controlled trial compared a placebo with, respectively, the direct topical application of EGCG on a wound and on the area around the wound site (zonal priming). Both systems were shown to deliver better results than the placebo, the direct application in particular reduced scar thickness (after 1–3 weeks) and improved scar elasticity (after 4 weeks) (Ud-Din et al., 2019) (Figure 1).

5 | CONCLUSION

The purpose of this review was to establish the chemical–physical properties of EGCG. We focused on stability, interactions with cosmetic ingredients, and health aspects.

The different eligibility criteria for each subsection are listed under section "Eligibility Criteria."

As far as the stability is concerned, it could be determined that an increase in temperature and in pH value and a decrease in concentration negatively influence the stability of the molecule.

In particular concentration of 900 μg ml^{-1} were reported to remain stable for 2 days at the temperature of 4°C, whereas under the same conditions the 0.25 μg ml^{-1} concentration degraded fully (Fangueiro et al., 2014).

Regarding interactions with common cosmetic ingredients, it was found that the interactions may enhance EGCG stability and its properties. Titanium dioxide when coated with EGCG was seen to increase the polyphenol stability. Both vitamin E and C were reported to have their antioxidant effects strengthened by the interaction with EGCG and vitamin C, in particular, was also capable of improving the catechin stability (Intra & Kuo, 2007; S. Scalia et al., 2013).

The existing literature for this subsection of the review was lacking. Therefore, further research in pharmaceutical and cosmetic formulas is needed.

Furthermore, EGCG shows positive effects in the treatment of several dermatological conditions such as psoriasis, atopic eczema, or UV-induced skin damages.

EGCG was reported to filter a wide range of wavelengths, has anti-inflammatory and antioxidant effect on the UV-exposed skin, and specifically enhances the apoptosis in tumor areas (Lu et al., 2002).

The literature with regard to stability and health aspects was very copious and detailed. However, it was often difficult to compare the different studies as the endpoints and methods used were very different. This issue particularly concerns the stability-related literature. Many studies with similar endpoints used completely different EGCG concentration, temperatures, and pH values. So, even though they often came to similar results, it was not easy to compare their methods. A standard method (standard concentrations, temperatures and pH values) would make the research in this field easier to examine and to replicate.

Despite the copious existing literature, this review is one of the first to examine the properties of EGCG in relation to a possible future dermatological and cosmetic application. On the other hand, the standard for this kind of publication would be a systematic review and not a narrative one, reason for which and more indepth analyses of the existing literature and the application of systematic criteria are needed.

This review is the first to describe literature on stability, interactions, and health aspects of EGCG. All three subsections are linked to each other and the results of one strongly affects the others. In conclusion, EGCG has the chance of playing a key role in the future fields of dermatology and cosmetics. More research and comparable standards are needed to better understand the role and chances of EGCG in cosmetic and dermatological solutions.

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