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Original Article**In vivo evaluation of black and green tea dermal products against UV radiation**Murat Türkoğlu^{1,*}, Timuçin Uğurlu¹, Gülşah Gedik¹, Ayşe M. Yılmaz², A. Süha Yalçın²¹ Pharmaceutical Technology Department, Faculty of Pharmacy, Marmara University, Istanbul, Turkey;² Biochemistry Department, Faculty of Medicine, Marmara University, Istanbul, Turkey.

ABSTRACT: Aqueous extracts of black and green tea (*Camellia sinensis*) were obtained by freeze-drying for this study. The extracts were evaluated based on tea quality control tests, UV, IR scans, and *in vitro* antioxidant capacity tests. Dermal products from the tea extracts were designed and manufactured. Black and green tea gels were tested *in vivo* in the forearms of six subjects using an artificial UV (200-400 nm) source. The tested formulations were green tea gel, black tea gel, 0.3% caffeine gel, carbomer gel base, and a control. Depending on tea quality, the samples resulted in water soluble fractions of 24.5-39.5%. UV and IR scans specifically showed peaks for alkaloids like caffeine, catechins such as epigallocatechin gallate, and polyphenols with dimeric and polymeric structures such as theaflavins (TFs) and thearubigins (TRs). Antioxidant and free radical scavenging activities of black and green tea samples were found to be high and comparable; activity levels for black tea, green tea, high quality black tea, and L-ascorbic acid were 0.48, 0.50, 0.82, and 1.32 mM TR/mg, respectively. No UV-induced erythema was observed at the black and green tea gel sites in any of the subjects. UV-induced erythema was consistently present in various grades at caffeine gel, carbomer gel, and control sites. Results led to the conclusion that freeze-dried black and green tea extracts had strong UV absorbance. Formulating those extracts into dermal gels protected the skin against UV-induced erythema. Therefore, tea extracts were found to be promising candidates for their ability to protect against the harmful effects of UV radiation, such as erythema and premature aging of the skin.

Keywords: Black tea, green tea, UV, human subjects, CUPRAC, DPPH, erythema, antioxidants, freeze-drying

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1. Introduction

Tea, a valuable plant, has three distinct species: *Camellia sinensis* var. *sinensis*, which has small leaves and is a northern plant grown at higher elevations; *Camellia sinensis* var. *assamica*, which has larger leaves and is a southern plant; and *Camellia assamica* subsp. *lasiocalyx* (1). Tea can be studied as tea leaves directly from the plant or as fully fermented black tea. During the fermentation of black tea, polyphenol oxidase leads to the formation of orange-red colored dimeric theaflavins (TFs) and dark-brown polymeric pigment thearubigins (TRs) from smaller catechins (2,3). Partially fermented oolong tea or unfermented green tea contains epicatechin (EC), epigallocatechin (EGC), epicatechin gallate (ECG), and epigallocatechin gallate (EGCG) as the basic polyphenols of tea leaves. Tea leaves also contain caffeine, theanine, myricetin, quercetin, and kaempferol as examples of alkaloids, amino acids, and flavonols (3-6). This diverse chemical composition of tea with high antioxidant potential makes it a unique drink with great health benefits. The antioxidant activity of black tea was reported to be higher than that of most dietary agents, and among the twenty-one botanical infusions tested black tea had the highest antioxidant activity (4,7). Yoshino *et al.* (8) reported that TFs and TRs of black tea, like green tea catechins, inhibited lipid peroxidation and that black tea was as potent as green tea in terms of antioxidative activity. Green tea extracts are reported to result in the inhibition of UV-induced erythema on the skin and to reduce the DNA damage inside the skin; EGCG and ECG are reported to be the most efficient among the catechins (9). Turkoglu *et al.* (10) reported that a tea gel formulation produced from the aqueous extract of black tea prevented UV-induced erythema on the forearms of six human subjects. Black tea extract was found to be effective against UVB-induced erythema in human subjects and was found to inhibit UVB-induced tyrosine phosphorylation of epidermal growth factor receptor in mouse skin; TRs are also reported to inhibit mouse skin TPA-induced cell proliferation (11,12). Furthermore, oral administration of 600 mg green tea extract per day

for a year was used in the chemoprevention of human prostate cancer (13,14) and tea polyphenols and TFs are reported to be present in the prostate tissue of humans and mice after green and black tea consumption. Finally, Mulder *et al.* (15) showed that both green and black tea have the same metabolic fate in humans and that they are all converted into hippuric acid. Therefore, a limited human study was carried out here along with *in vitro* antioxidant and free radical scavenging activity tests to compare the skin protection provided by freeze-dried green and black tea extracts.

2. Materials and Methods

2.1. Materials

The teas used were cut black and green teas from the Black Sea region of Turkey (Çaykur, Green Tea, 53-18/09 02630, Exp. date: 2012; Çaykur, Black Tea 53-6/04, 29/08966 Exp. Date: 2012), Carbomer Carbopol Ultrez 21 (Lot. EC521ZR291, Noveon, Inc., Cleveland, OH, USA) was obtained as a free sample. Sodium hydroxide and benzyl alcohol were of reagent grade. The artificial UV source used was a Philips HPA 400, which is a high-pressure iron-cobalt metal halide lamp with a 400-W power source (Philips, Turnhout, Belgium). A UVX Radiometer (UVP, Inc., Upland, CA, USA, Serial Number: E27858) was used to monitor UVA ($\lambda_{\max} = 365$ nm), UVB ($\lambda_{\max} = 310$ nm), and UVC ($\lambda_{\max} = 254$ nm) radiation from the UV source with three probes. A UVmini 1240, UV/VIS spectrophotometer, and FTIR 8400S (Shimadzu, Kyoto, Japan) were used for photometrical analyses.

2.2. Tea infusions and freeze-drying

Water soluble fractions and the moisture content of tea samples were determined gravimetrically according to ISO 9768 and 1573. Ten-percent (w/w) infusions of tea leaves were prepared from green or black tea as previously described (10). The infusions were frozen at -18°C before further processing. Using a laboratory size freeze-dryer (Alpha 1-2 LD Plus, Martin Christ, Osterode, Germany), frozen tea samples were lyophilized at -52°C and 0.1 mBar. Freeze-dried samples were stored at -18°C for further quality control tests and used as tea actives.

2.3. Preparation of tea gels

Gels were obtained using a carbomer resin. One hundred mL of 1% (w/w) carbomer solution were prepared and 3 g freeze-dried black or green tea extract was added to the carbomer dispersion. A 20% sodium hydroxide solution was added drop by drop until a viscous gel was obtained by monitoring the pH with a pH meter to determine the end point. One percent benzyl alcohol was added as a

preservative. The gels were stored in glass jars at room temperature. A caffeine gel containing 0.3% caffeine and a gel-base that did not contain anything but carbomer were also prepared as described above.

2.4. Assay of antioxidant activity

Freeze-dried samples (100 mg) were powdered and suspended in 1 mL ultra-pure water. After vortex mixing, samples were kept at 37°C for 2 h and centrifuged at $9,000 \times g$ for 2 min. The supernatants were diluted 100 times and used for antioxidant activity measurements. The cupric ion-reducing antioxidant capacity (CUPRAC) of samples was determined using an assay described by Apak *et al.* (7). Briefly, 0.2 mL of 10 mM CuCl_2 , 0.2 mL of 7.5 mM neocuproine, and 0.2 mL of 1 M ammonium acetate (pH 7) were added to a test tube. After vortex mixing, a suitable amount of sample (20 or 50 μL) and ultra-pure water was added and the absorbance at 450 nm was read after 30 min. Trolox equivalent antioxidant capacity was calculated using a calibration curve obtained by the serial dilution of 1 mM trolox.

2.5. Assay of free radical scavenging activity

The free radical scavenging activity of samples was measured with 1,1-diphenyl-2-picrylhydrazil (DPPH) using an assay described by Peksel *et al.* (16). Briefly, DPPH was dissolved in ethanol (4 mg/100 mL) and 100 μL of this solution were added to an equal volume of a sample. The mixture was shaken vigorously and the decrease in absorbance was measured at 515 nm after 30 min. Water was used as a control. The percent inhibition activity was calculated using the following equation: Inhibition activity (%) = $[(A_0 - A_1)/A_0 \times 100]$, where A_0 and A_1 are the absorbance of the control and sample, respectively.

2.6. In vivo study

Six subjects, two males and four females (skin types I and II), aged 23-55 were selected after signing an informed consent form. A template made of dermal tape was applied to the forearms of the subjects (See Figure 4A for the template and the position of the formulations). First, three square-shaped openings 4 cm^2 in size were subjected to "black tea gel", "green tea gel", and "caffeine gel". The last opening was divided into two portions; the top was subjected to a "gel-base", which contained 1% carbomer, and the bottom served as the "control" and was left untreated. The forearms were exposed to the artificial UV source through a slit for 2.5 min.

2.7. Evaluation of erythema after UV exposure

UV-induced erythema was graded visually as

previously reported (17), with 0 indicating no erythema; \pm indicating slight patchy erythema; 1 indicating slight but confluent erythema; 2 indicating moderate erythema; and 3 indicating severe erythema with or without edema

3. Results

3.1. In vitro study

Table 1 summarizes the water soluble fractions and moisture content of the tea samples studied. The water soluble fraction of the samples ranged between 24.5-39.5% and the moisture content varied between 2.50-3.80% depending on the tea quality and type. Freeze-dried black and green tea samples were freely water soluble and hygroscopic. The free radical scavenging and antioxidant activities of freeze-dried tea samples were compared to those of L-ascorbic acid. As shown in Table 2, the values varied between 0.48-0.82 mM TR/mg based on the water soluble fractions of the tea samples. Green and black tea samples were found to be similar (0.48 vs. 0.50). One of the tea samples (black tea A) resulted in a value of 0.82 and L-ascorbic acid resulted in one of 1.32 mM TR/mg. Results based on the DPPH test, which indicates the free radical scavenging activity of the samples, showed that tested black tea samples were similar to each other unlike in the CUPRAC antioxidant activity test (26.3% vs. 26.5% inhibition for black teas A and B, respectively, and 18.4% and 41.8% for green tea and L-ascorbic acid, respectively) (Table 2). IR spectra of freeze-dried green and black teas are shown in Figures 1A and 1B, respectively. In those spectra, hydroxyl groups due to stretching were observed between 3,350-3,600 cm^{-1} . Green tea resulted in six bands in that region while black tea resulted in three. For both tea types, caffeine and theobromine bands were observed in the

Table 1. Tea samples studied and their water soluble fractions

Tea type	Water soluble fraction (%, w/v)	Moisture (%)
Black tea A	39.51	3.49
Black tea B	38.20	3.80
Black tea C	35.24	2.76
Black tea D	24.50	2.50
Green tea	34.95	2.57

Table 2. Free radical scavenging and antioxidant activity of freeze-dried tea samples in comparison to L-ascorbic acid

Samples	CUPRAC (mM TR/mg)	DPPH (% inhibition)
Freeze-dried black tea A	0.480 \pm 0.167	26.3
Freeze-dried green tea	0.506 \pm 0.161	18.4
Freeze-dried black tea B	0.818 \pm 0.232	26.5
L-Ascorbic acid	1.317 \pm 0.503	41.8

1,558-1,695 cm^{-1} region. Catechins resulted in peaks in the 800-1,600 cm^{-1} region. With EGCG, a band was observed at 1,238, 1,141, and 1,034 cm^{-1} ; with GC, one was observed at 1,373-1,280 cm^{-1} ; with ECG, one was observed at 1,238 cm^{-1} ; with EC, one was observed at 820 cm^{-1} .

3.2. In vivo study

For the human study, an artificial UV source was used. UV irradiation were measured and monitored at 0.5 m from the source with a UV radiometer. The values were UVA = 4,550 $\mu\text{W}/\text{cm}^2$; UVB = 2,800 $\mu\text{W}/\text{cm}^2$; and UVC = 500 $\mu\text{W}/\text{cm}^2$. At these energy levels, subjects with skin types I and II can be expected to develop moderate UV-induced erythema after 2.5 min. Figure 2 compares the UV irradiation from the Philips HPA 400, used as UV source in the present study, and that from the sun. Table 3 summarizes the formulations used in the human study. Green and black tea gels (formulations 1 and 2) contained 3 g of freeze-dried extract, which corresponded to a 10% tea infusion. Such an infusion contains 0.3% caffeine, so formulation 3 contained only 0.3% caffeine in a carbomer gel. Formulation 4 was the base, which contained only carbomer. All of the formulations contained 1% benzyl alcohol as a preservative against fungi.

Table 4 summarizes the erythema grades for the aforementioned sites in each subject and Figure 3 graphs erythema depending on the time. In this study, the six human subjects showed no signs of erythema at green tea gel and black tea gel sites on the forearm after being exposed to UV radiation for 2.5 min. In contrast, UV-induced erythema was consistently present to a varying degree at the carbomer-base site, 0.3% caffeine site, and control site. As is typical of UV-induced erythema, erythema reached a peak around 24 h and diminished afterwards (Figure 3). Figure 4 shows the application of the template and grading of UV-induced erythema at 24 h on one subject's forearm.

4. Discussion

Black and green teas contain tea actives such as EGCG, EGC, TF, TR, and caffeine in an aqueous infusion. These components are responsible for the UV protection provided by tea gel formulations. Therefore, determination of the "water soluble fraction" of teas is one of the most important parameters of tea quality control tests and this fraction must be at least 35% (w/v) or more for a high quality tea. Based on the CUPRAC method, the present study found that tea samples were strong antioxidants. Using the CUPRAC test, Apak *et al.* reported that among tea types Ceylon blended black tea resulted in 4.41 mMT/g and ordinary black tea resulted in 0.38 mMT/g (7). Yoshino *et al.* (8) reported that there was no marked difference between

black and green tea. The current findings agree with both of those reports. A free radical scavenging assay (DPPH) indicated almost the same % inhibition levels for black tea samples (26.3 vs. 26.5) as for a green tea sample (18.4%) (Table 2), and results led to the conclusion that the black tea samples were superior

in terms of their free radical scavenging effect. The water soluble fractions of those two black tea samples (samples A and B) were also very similar. However, the CUPRAC assay did not confirm these findings. Black tea samples A and B led to a difference of 50% in terms of antioxidant activity while the green tea sample had

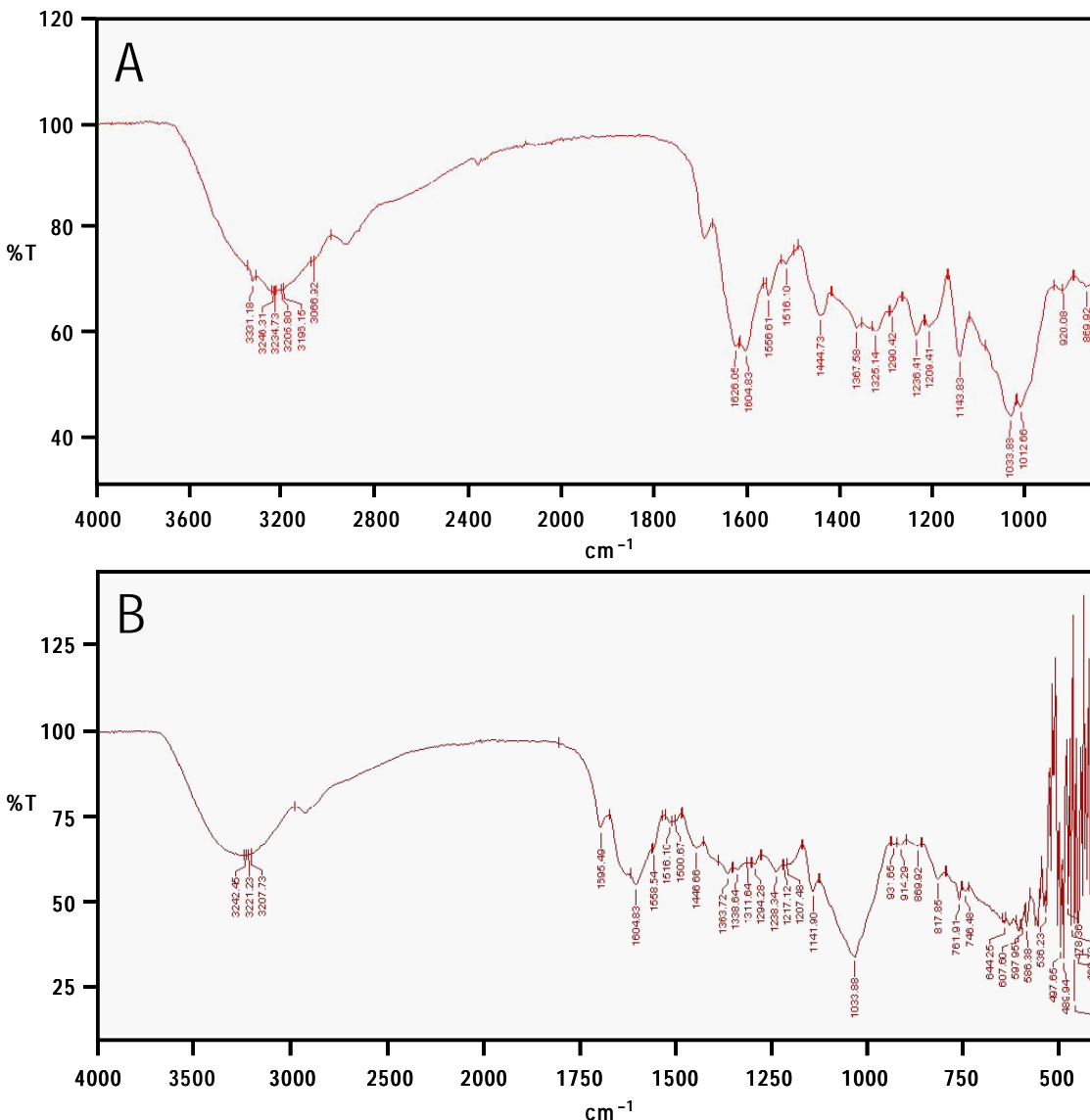


Figure 1. IR scan profiles of freeze-dried green tea (A) and black tea (B).

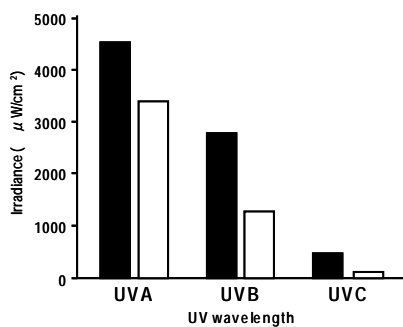


Figure 2. Comparison of UV irradiation from a Philips HPA 400 and the sun. Closed column, HPA 400; Open column, the sun.

Table 3. List of formulations tested on the forearms of subjects

Contents	Formulations (g/100g)			
	#1*	#2*	#3	#4
Freeze-dried black tea extract	3	—	—	—
Freeze-dried green tea extract	—	3	—	—
Caffeine	0.3	0.3	0.3	—
Carbomer, Carbopol Ultrez 21	1	1	1	1
Sodium hydroxide (20% solution)	1.47	1.47	1.47	1.47
Benzyl alcohol	1	1	1	1
Water	q.s.**	q.s.	q.s.	q.s.

* Formulations 1 and 2 naturally contain 0.3% caffeine as part of tea extracts. ** q.s.: quantum sufficit.

Table 4. Forearm erythema grades

Subjects	Erythema score at 6 h					Erythema score at 24 h					Erythema score at 48 h				
	BTG	GTG	CG	GB	C	BTG	GTG	CG	GB	C	BTG	GTG	CG	GB	C
1	0	0	1	1	±	0	0	1	1	±	0	0	±	±	±
2	0	0	0.5	0.5	1	0	0	±	±	±	0	0	0	±	±
3	0	0	1	1	±	0	0	2	2	2	0	0	1	1	1
4	0	0	1	1	±	0	0	1	1	±	0	0	0	±	0
5	0	0	±	1	±	0	0	±	1	±	0	0	±	±	0
6	0	0	±	±	±	0	0	1	±	1	0	0	±	±	±

UV was irradiated by a Philips HPA 400 UV for 2.5 min from a distance of 50 cm. BTG, black tea gel; GTG, green tea gel; CG, caffeine gel; GB, gel base; C, control.

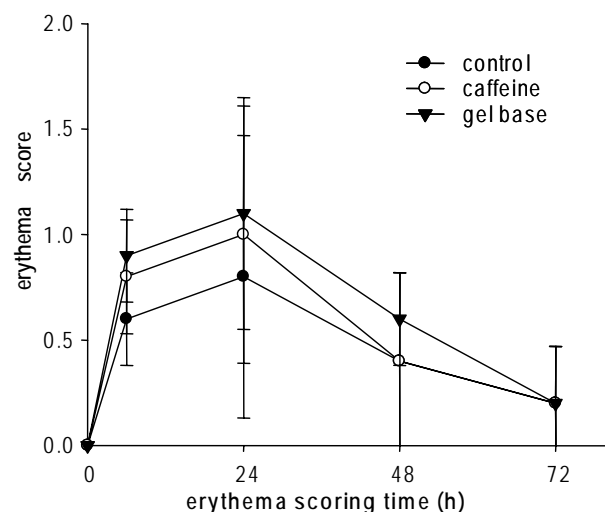


Figure 3. Grades of UV-induced erythema from a human study ($n = 6$) with a caffeine gel, carbomer base, and control site.

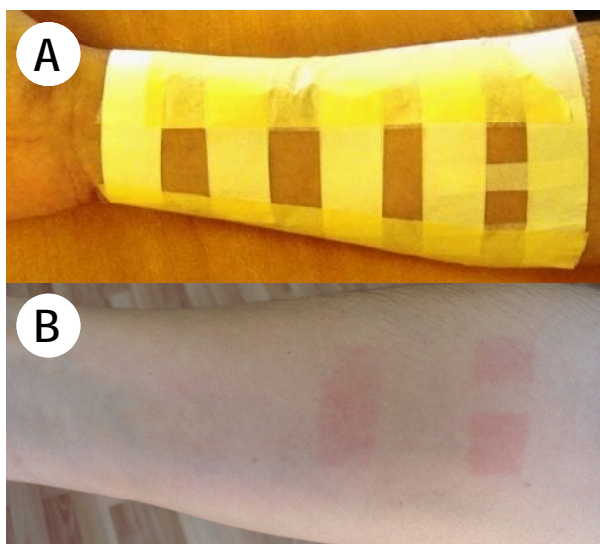


Figure 4. Application of the template and grading of UV-induced erythema on the subject's forearm at 24 h. (A) Application of a template to the forearm before UV irradiation. Starting from the left, the first three regions are "black tea gel", "green tea gel", and "caffeine gel". In the divided region on the right, the upper region is "carbomer gel" and the lower is the "control". **(B)** Typical UV-induced erythema after 24 h at "caffeine gel", "gel-base", and "control" sites. There was no erythema at "green tea gel" or "black tea gel" sites.

activity close to that of black tea sample A. Therefore, different methods must be used to gauge the antioxidant activity of tea samples in order to differentiate between the effects of different chemical groups, *e.g.* EGCG vs. TRs or TFs.

Figure 5 shows typical UV absorption for a tea infusion. In the current study, black or green aqueous tea infusions resulted in very similar UV spectra between 200-400 nm with a peak around 272 nm. When this spectrum was overlapped with the UV spectra for human erythema and skin DNA damage, the maximum absorbance region corresponded to that for tea infusions (Figure 5). Therefore, tea extracts are good candidates to provide UV protection against erythema or DNA damage. Aqueous tea samples absorb UV radiation with a maximum level where that radiation causes maximum damage to the skin.

In the present study, formulation 3 at the selected concentration (0.3% caffeine) did not protect the skin against UV-induced erythema. Caffeine greatly absorbs UV with a peak around 272 nm. However, the concentration in a 10% tea infusion may be insufficient for effective protection. Higher concentrations of caffeine in a dermal formula such as 2% would afford skin protection against UV-induced erythema. Caffeine is also capable of penetrating the skin and could affect the epidermis. Oral administration of green tea or a caffeine solution is reported to inhibit UVB-induced complete carcinogenesis in SKH mice (18).

Green tea contains smaller molecules such as EGCG, EC, and EGC, while black tea contains larger molecules (MW 700-1,400) such as TFs and TRs. TFs and TRs cannot penetrate human skin while EGCG, EGC, and caffeine can. However, a previous study by the current authors (10) and the current study both found that green tea and black tea gels successfully prevented UV-induced erythema. Based on these results, black tea cannot be considered superior to green tea or *vice versa*. Black tea TFs and TRs have been found to prevent human epidermal carcinoma and human malignant melanoma cell proliferation through apoptosis (19). Recent studies have further speculated on the molecular pathways by which tea constituents protect the skin (20,21). In conclusion, dermal gels of green or black tea have been found to prevent acute UV-

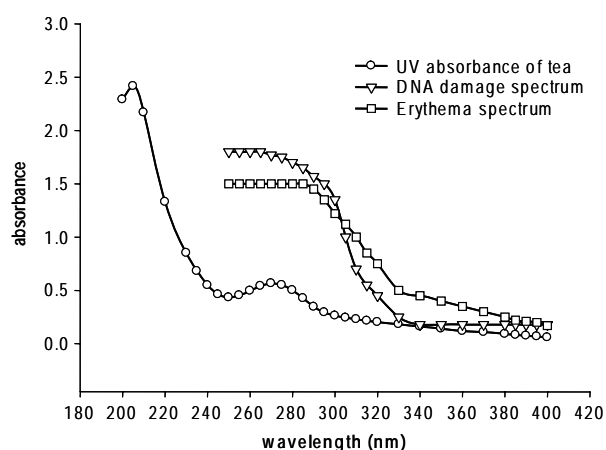


Figure 5. Overlapping spectra of DNA damage and human erythema and typical UV absorption of tea infusions.

induced erythema on human skin. Skin protection and the absence of any gradable erythema were observed in every subject.

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