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Effect of Ingested Concentrate and Components of Sake on Epidermal Permeability Barrier Disruption by UVB Irradiation

MASATO HIROTSUNE,*,† AKINORI HARATAKE,‡ AYA KOMIYA,‡ JUN SUGITA,‡ TORU TACHIHARA,§ TSUYOSHI KOMAI,§ KAZUHISA HIZUME,† KENJI OZEKI,† AND TAKESHI IKEMOTO‡

General Research Laboratory, Ozeki Co., Nishinomiya, Hyogo 663-8227, Japan, Cosmetics Laboratory, Kanebo Cosmetics Inc., Odawara, Kanagawa 250-0002, Japan, and Technical Research Center, T. Hasegawa Co., Ltd., Kawasaki, Kanagawa 211-0022, Japan

Daily topical applications of the concentrate of sake (CS) have been shown to reduce epidermal barrier disruption in murine skin caused by ultraviolet B (UVB) radiation, while one of the components of sake, ethyl α-D-glucoside (α-EG), also reduces barrier disruption. We confirmed the effect of oral ingestion of various doses of CS on epidermal barrier disruption caused by UVB irradiation in hairless mice. Then, to identify the effective components, we quantitatively analyzed α-EG, organic acids, and glycerol, the main components of CS, and examined the effect of various concentration of each on barrier disruption. α-EG and organic acids showed comparable results to CS itself, and transepidermal water loss levels in murine skin were significantly decreased as compared with the control. Furthermore, an investigation of the dose dependency of these agents was performed and the results showed the significant effectiveness of α-EG. In addition, red wine concentrate (WC) and beer concentrate (BC) were examined in order to confirm the unique effects of CS. Similar effects were not found with WC and BC.

KEYWORDS: Rice wine; ethylα-D-glucoside; organic acids; transepidermal water loss; oral administration

INTRODUCTION

Alcohol intake is a risk factor for several types of cancer (*1*, *2*). In contrast, results of epidemiological studies have indicated that moderate alcohol consumption may reduce the risk of coronary heart disease (*3*, *4*) and some have found that red wine in particular is associated with a reduced risk of coronary heart disease (*4*, *5*), although other results have not been able to confirm that association (*3*). Duarte et al. (*6*) reported that quercetin, a component of red wine, has the ability to lower blood pressure in spontaneously hypertensive rats, while another human study concluded that alcohol-free red wine extract and quercetin were able to inhibit low density lipoprotein (LDL) oxidation in vivo (*7*). In addition, McCaul et al. (*8*) reported that alcoholics showed decreases in skin conductance, heart rate, and skin temperature when given placebo versions of drinks that typically contained alcohol.

Sake, also known as rice wine, has played a central role in the life and culture of Japanese people for at least 2000 years. It is a brewed alcoholic beverage; however, the process is more complex than that employed for beer or wine. Sake brewing begins with the introduction of koji, microbes that are similar to those used in blue cheese production, which break down rice starch into glucose in a process known as saccharification. Following that, sake yeast is added and fermentation begins. This process, in which saccharification and fermentation take place in the same vat at the same time, is called multiple parallel fermentation, which is a unique feature of sake brewing that distinguishes it from other brewing processes. The major components in sake have been reported to be D-glucose, ethyl α-D-glucoside (α-EG), glycerol, organic acids, and amino acids, in addition to water and ethanol (*9*), with α-EG thought to account for its distinct taste (*10*).

It has also been reported that sake has a vasodilator action, with some amino acids isolated from sake shown to be the active substances (*11*−*13*). Furthermore, sake has been used as a skin care lotion by Japanese people since ancient times. Previously, we demonstrated that a topical application of sake concentrate suppressed epidermal barrier disruption caused by ultraviolet B (UVB) radiation (*14*). Furthermore, α-EG was found to suppress barrier disruption by enhancing keratinocyte differentiation (*14*). Although scientific evidence is lacking, generations of Japanese have understood the positive effects of sake on various skin conditions, and there is a strong tendency among women living in the northern region of Japan, where high levels of sake consumption are common, to have a smooth complexion. Therefore, we speculated that oral ingestion of sake or its components would have a positive effect on skin.

* To whom correspondence should be addressed. Tel: +81-798-32-2168. Fax: +81-798-34-7475. E-mail: masato.hirotsune@ozeki.co.jp.
† Ozeki Co..
‡ Kanebo Cosmetics Inc.
§ T. Hasegawa Co., Ltd.

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In the present study, we examined the effects of sake, as well as those of several of its major components, on epidermal barrier disruption caused by UVB radiation in order to investigate its effect on skin.

MATERIALS AND METHODS

Animals. Six week old hairless mice (Hos:HR-1) were purchased from Japan SLC (Hamamatsu, Japan) and kept under controlled conditions (ambient temperature, 22 ± 1°C; relative humidity, 55 ± 10%; light condition, 12 h light/dark cycle). They were fed commercial pellets (CE-2, Clea Japan, Tokyo, Japan) and well water ad libitum. Animal husbandry procedures were conducted in accordance with the Guidelines for Animal Experimentation (Japanese Association for Laboratory Animal Science, 1987).

Samples and Materials. Two hundred grams of concentrate of sake (CS) was prepared from 4000 mL of commercial source Mechakara (produced by Ozeki Corporation, Nishinomiya, Japan), by concentration in a vacuum. Red wine and beer, purchased at a local market in Kanagawa prefecture, were concentrated to a 1/20 volume using the same method as for CS. α-EG was isolated from CS by silica gel column chromatography and eluted with chloroform/methanol. Glycerol, organic acids, and other reagents were purchased from Wako Pure Chemical Industries (Osaka, Japan).

Major Components in Sake, Red Wine, and Beer. To determine the amount of D-glucose, α-EG, glycerol, and organic acids (lactic acid, citric acid, succinic acid, and malic acid) in CS, high-performance liquid chromatography (HPLC) and capillary electrophoresis were employed. The HPLC system consisted of a pump (LV-10AD, Shimadzu, Kyoto, Japan), column oven (CTO-10AC, 50 °C, Shimadzu), and differential refractive index detector (RI model RID-10A, Shimadzu), with a ligand exchange column (Shodex sugar SZ5532 column, 6.11 mm × 150 mm, Showa Denko, Tokyo, Japan). The eluent was acetonitrile−distilled water (4:1, v/v), and the flow rate was 1.0 mL per minute. The content of organic acids was determined using capillary electrophoresis (CE3D system, Hewlett-Packard, Palo Alto, CA) and organic acid analysis kits (Agilent Technologies, CA). The separation capillary was an uncoated fused silica capillary (75 μm i.d., 72 cm in length, Agilent Technologies), and the separation buffer was Tris-phosphate (pH 5.6). All electrophoresis operations were carried out at ambient temperature.

UVB Irradiation. Four fluorescent sun lamp tubes (Toshiba FL-32SE, Toshiba Electric, Tokyo, Japan) were used as the source of UVB radiation. The dorsal skin of each mouse was irradiated with a single UVB dose equivalent to 7.5 times the minimal erythemal dose (MED), corresponding to 0.15 J per cm^2 (*15*).

Assessment of Barrier Function. Transepidermal water loss (TEWL) was measured on the dorsal surface using a HIDOGRAPH (AMU-100, K&S, Kariya, Japan), as described previously (*15*).

In Vivo Experiments. The experimental samples were given with water as the only source of drinking water from 1 week before until 4 days after UVB irradiation. CS was solubilized in water, while the major components of sake, α-EG, glycerol, and organic acids (lactic acid, citric acid, succinic acid, and malic acid), were solubilized in a vehicle solution composed of 12.6% glucose in water at the same concentration as found in CS. The control was the vehicle solution alone. TEWL was measured just before and then 3 and 4 days following UVB irradiation, and data are shown as the rate prior to treatment as compared to 3 and 4 days after UVB irradiation. At the first examination, we determined the effects of the samples diluted 20 times by water, which equaled their original concentration in sake. Then, samples were diluted 200-fold (10-fold dilution of original concentration) and 2000-fold (100-fold dilution of original concentration) and assessed. Finally, the effect of CS on TEWL was compared with that of the red wine concentrate (WC) and beer concentrate (BC) at their original concentrations, with several samples solubilized in water. The control was the vehicle (water) alone.

Statistical Analysis. Data are represented as the mean value ± SEM. Difference statistical analysis was performed using a Dunnett parametric type multiple comparison test with SAS (Version 6, SAS system).

Table 1. Contents of Components of Sake, Red Wine, and Beer Used in This Study[a]

components	sake content (%)	red wine content (%)	beer content (%)
glucose	12.5		
α-ethyl glucoside	18.4		
glycerol	11.1	11.8	0.7
organic acids	1.9	4.5	1.1
lactic acid	0.70	2.71	0.23
citric acid	0.10	0.95	0.72
succinic acid	0.71	0.57	0.07
malic acid	0.35	0.31	0.05

[a] Blank cells were less than limits of detection.

RESULTS

Analytical Results of Major Components in Concentrates. The major components of CS were as follows: α-EG (18.4%), D-glucose (12.5%), and glycerol (11.1%), while the organic acids comprised 1.86% (lactic acid, 0.71%; citric acid, 0.10%; succinic acid, 0.70%; and malic acid, 0.35%). WC contained glycerol (11.8%) and organic acids (4.5%; composed of lactic acid, 2.71%; citric acid, 0.95%; succinic acid, 0.57%; and malic acid, 0.31%), while those in BC were glycerol (0.74%) and organic acids (1.1%; composed of lactic acid, 0.23%; citric acid, 0.72%; succinic acid, 0.07%; and malic acid, 0.05%). α-EG and glucose were not detected in either WC or BC (**Table 1**).

Effects of CS and Major Components of Sake on Epidermal Barrier Disruption Caused by UVB Irradiation. A UVB dose of 7.5 MED (0.15 J/cm^2), previously shown to produce a maximal alteration in TEWL (*15*), was applied to mice along with oral administration of CS itself or each component of CS. All of the experiment groups consumed between 7 and 8 mL per day per mouse. First, we examined the effect on epidermal barrier disruption of the experimental samples at original concentrations, which were at the same levels occurring in sake brewed for regular consumption. Three days following UVB irradiation, mean TEWL with the control was significantly different as compared with just before the start of treatment. In contrast, TEWL with the α-EG or organic acid groups was significantly lower than in the control group (both, $p < 0.05$) (**Figure 1**). Furthermore, mean TEWL on day 4 was significantly decreased in the mice that received CS, α-EG, or organic acids as compared with the control ($p < 0.01$, $p < 0.001$, and $p < 0.05$, respectively) (**Figure 2**). In contrast, TEWL levels on days 3 and 4 after UVB irradiation were not affected by oral administration of glycerol.

We also examined the effects of oral administration of each sample diluted 10- and 100-fold on UVB-induced epidermal barrier disruption. With the 10-fold dilutions, TEWL levels in the CS, α-EG, or organic acid groups were significantly lower than in the control group ($p < 0.01$, $p < 0.001$, and $p < 0.01$, respectively) (**Figure 2**). Furthermore, mean TEWL on day 4 following UVB irradiation was also significantly decreased ($p < 0.01$, $p < 0.001$, and $p < 0.05$, respectively) (**Figure 2**). In contrast, TEWL levels in murine skin on days 3 and 4 after UVB irradiation were not affected by glycerol. On the basis of our results, we concluded that an oral administration of glycerol had no effect on barrier disruption caused by UVB irradiation. TEWL levels in murine skin 3 days after UVB irradiation were significantly decreased with the 100-fold diluted CS and α-EG samples as compared with the control ($p < 0.01$ and $p < 0.05$, respectively) (**Figure 3**). Furthermore, 4 days after UVB irradiation, mean TEWL with ingestion showed the same

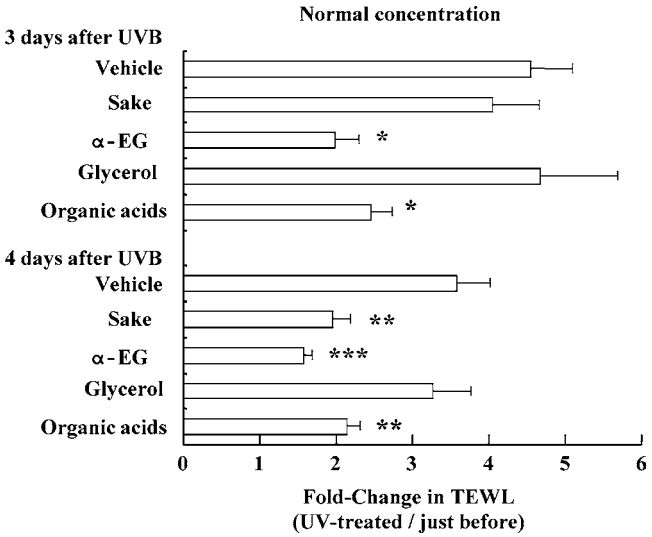

Figure 1. Effects on UVB-induced epidermal barrier disruption by oral administration of samples at original concentrations. Dorsal skin areas of the mice were irradiated with a single UVB dose equivalent to 7.5 times the MED, corresponding to 0.15 J per cm^2. The samples (vehicle, sake concentrate, α-EG, glycerol, and organic acids) were given with water as the only water source from 1 week before until 4 days after UVB irradiation. TEWL was measured just before and 3 and 4 days after UVB irradiation. Data are shown as means ± SEM (n = 10 mice per group). *p < 0.05, **p < 0.01, and ***p < 0.001 (vs vehicle).

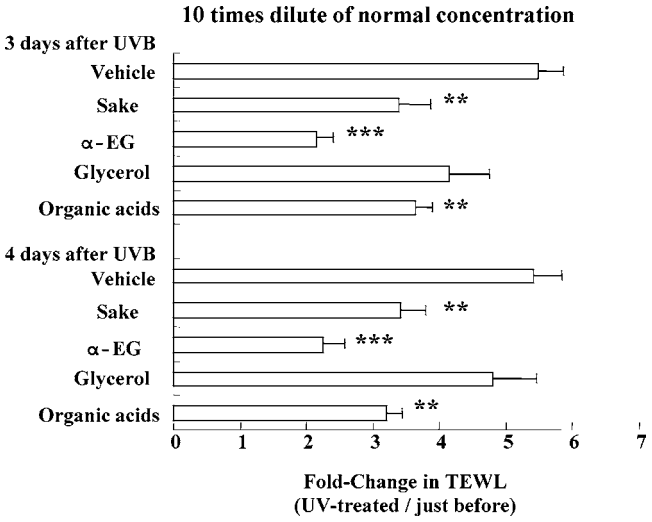

Figure 2. Effects on UVB-induced epidermal barrier disruption by oral administration of samples diluted 10-fold. Dorsal skin of areas of the mice were irradiated with a single UVB dose equivalent to 7.5 times the MED, corresponding to 0.15 J per cm^2. The samples were given in water as the only water source from 1 week before until 4 days after UVB irradiation. TEWL was measured just before and 3 and 4 days after UVB irradiation. Data are shown as means ± SEM (n = 10 mice per group). **p < 0.01 and ***p < 0.001 (vs vehicle).

tendency as the results on day 3; however, the effects were not significantly different when compared with the control (**Figure 3**).

Effects of CS, WC, and BC on Epidermal Barrier Disruption by UVB Irradiation. The effects of normal doses of CS, WC, and BC on barrier disruption were also examined. The "normal" dose was considered to be that taken when drinking sake, red wine, or beer. Mean TEWL levels on day 3 following UVB irradiation showed a tendency of decrease with oral administration of CS; however, it was not significant,

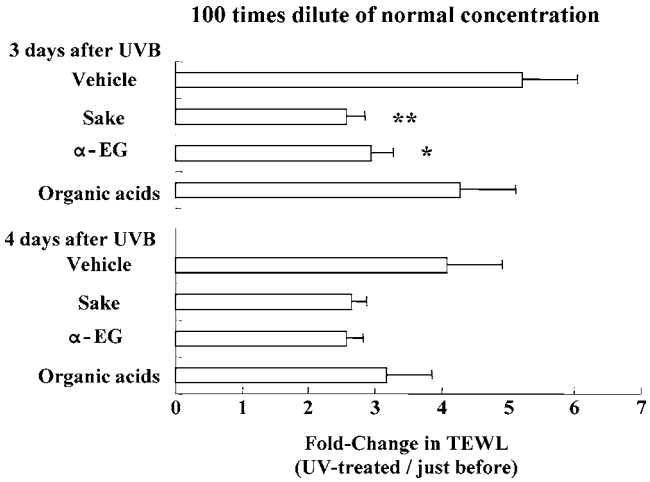

Figure 3. Effects on UVB-induced epidermal barrier disruption by oral administration of samples diluted 100-fold. Dorsal skin areas of the mice were irradiated with a single UVB dose equivalent to 7.5 times the MED, corresponding to 0.15 J per cm^2. The samples were given with water as the only water source from 1 week before until 4 days after UVB irradiation. TEWL was measured just before and 3 and 4 days after UVB irradiation. Data are shown as means ± SEM (n = 10 mice per group). *p < 0.05 and **p < 0.01 (vs vehicle).

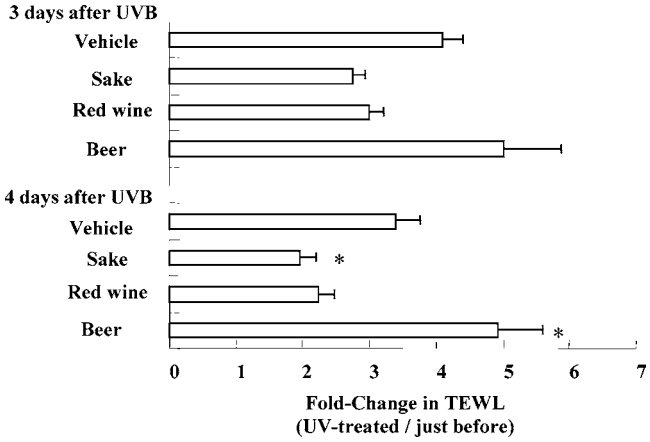

Figure 4. Effects on barrier disruption by oral ingestion of sake, red wine, and beer at original concentrations. Dorsal skin areas of the mice were irradiated with a single UVB dose equivalent to 7.5 times the MED, corresponding to 0.15 J per cm^2. The samples were given water as the only water source from 1 week before until 4 days after UVB irradiation. TEWL was measured just before and 3 and 4 days after UVB irradiation. Data are shown as means ± SEM (n = 10 mice per group). *p < 0.05 and **p < 0.01 (vs vehicle).

whereas on day 4 they were significantly lower than the control (p < 0.05) (**Figure 4**). TEWL levels on day 3 with WC showed the same tendency as those with CS; however, they were not significant when compared with the control (**Figure 4**). In contrast, mean TEWL levels on day 3 with BC showed an increasing tendency and were significantly higher on day 4 than the control (p < 0.05) (**Figure 4**).

DISCUSSION

In this present study, we analyzed the major components of CS (**Table 1**) and confirmed the single largest to be α-EG, which is known as the fourth major component, following water, ethanol, and glucose. Thus, the CS used in the present experiments had a higher α-EG content than sake used in a previous study (*14*). On the other hand, WC and BC did not

contain α-EG or glucose, showing that those experimental samples were not unusual.

In the present experiments, oral administration of CS had an improving effect on UVB-induced epidermal barrier disruption, which was maintained even when diluted with water. However, the effects seemed to have a strong correlation with the total amount of CS consumed by the mice. We speculate that the effect on UVB-induced barrier disruption by the 100-fold diluted sample may have represented the lower limit; however, the effects of each component require further investigation.

Previous studies have reported that UVB-induced barrier abrogation was delayed for at least 48 h after exposure and that the delayed disruption of the permeability barrier appears to be due to reduced levels of stratum corneum extracellular lipids resulting from the arrival of a band of lamellar body incompetent cells at the stratum granulosum and corneum interface (*16*). A previous study reported that the mechanism for UVB-induced barrier disruption appeared to involve both hyperplasia- and T-cell-mediated events (*15*), while administrations of drugs that inhibit epidermal hyperproliferation have been shown to attenuate UVB-induced barrier abnormalities (*15*). We also demonstrated that topical application of concentrated sake and α-EG suppressed epidermal barrier disruption caused by UVB radiation, with suppression by the latter brought about by an enhancement of keratinocyte differentiation (*14*). All of the ingested α-EG is not hydrolyzed in the small intestine, as most is absorbed into the blood stream in an intact form by the sodium-dependent transporter, SGLT 1, through the wall of the small intestine, after which it is hydrolyzed in the kidneys and finally excreted in urine (*17*). These data indicate that α-EG ingested along with an oral administration of CS may be carried by the blood flow to the epidermis.

As shown in **Figures 1**−**3**, our results demonstrated CS and α-EG, in concentrations from normal to diluted 100-fold, significantly reduced UVB-induced epidermal barrier disruption. We examined epidermis thickness by examining the samples 4 days after UVB irradiation and found that it slightly decreased with the sake concentrate and α-ethyl glucoside (data not shown). These data indicate that the administration of sake concentrate and α-ethyl glucoside accelerated keratinocyte differentiation. A previous study reported a delayed disruption of the permeability barrier that appeared to be due to reduced stratum corneum extracellular lipids, resulting from the arrival of a band of lamellar body incompetent cells at the stratum granulosum and corneum interface 3 days after UVB irradiation, while the upper stratum spinosum and lower stratum granulosum cells appeared normal, with increased numbers of lamellar bodies (*16*). Furthermore, epidermal synthesis of the major barrier lipid species was increased significantly 3 days after exposure to UVB (*16*). On the basis of those results, we considered that the reduction of barrier disruption by administration of sake concentrate or α-ethyl glucoside resulted from the replacement of normal cells by acceleration of keratinocyte differentiation. However, this mechanism has not been clarified and the issue requires further investigation.

Several studies of the activity of a buffered 12% ammonium lactate lotion have documented its moisturizing activity following topical application (*18*, *19*), while Smith (*20*) reported that topical application of 12% lactic acid resulted in increased epidermal and dermal firmness and thickness, as well as clinical improvement in skin smoothness and the appearance of lines and wrinkles. In addition, lactic acid salt has been proposed to be a part of the natural moisturizing system in human skin (*21*). However, there are no known results regarding the effects of topical or oral administrations of other organic acids on skin. In the present study, oral administration of the organic acids in CS showed a similar effect on UVB-induced epidermal barrier disruption as CS (**Figures 1**−**3**). Although there is little information to suggest that the present organic acids are directly linked to the results and further investigation is required, we speculate that organic acids, especially lactic acid, might also have an effect on epidermal barrier function.

We also investigated WC and BC administrations. TEWL levels in murine skin 3 and 4 days after UVB irradiation following WC ingestion showed a similar tendency as with CS; however, the effect was not as pronounced (**Figure 4**). A number of human studies have investigated the effects of red wine consumption on antioxidant status in plasma (*22*, *23*) and as a surrogate marker for the aortic intima and in vitro susceptibility of LDL to oxidation (*22*, *24*, *25*). Other studies that compared red wine with other alcohol-containing beverages showed reduced LDL oxidation only after red wine consumption (*24*, *26*). Furthermore, following a 7 day intervention with concentrated red grape juice, Day et al. (*27*) found an increased serum antioxidant capacity as well as reduced LDL oxidation, indicating that alcohol may not be the sole component responsible for this effect. In addition, a topical application of an antioxidant, for example, ascorbic acid, has been found to significantly decrease UVB-induced barrier disruption. In the present study, the organic acids in WC were found to be more abundant than those in CS and oral administration of CS organic acids improved the barrier disruption caused by UVB irradiation. Therefore, we consider that an oral administration of WC is effective for diminishing UVB-induced barrier disruption by the synergic effects of its antioxidant materials and organic acids; however, the effects are weaker than those of CS, which likely diminished barrier disruption by an acceleration of keratinocyte differentiation brought about α-EG. On the other hand, BC increased barrier disruption significantly (**Figure 4**), while epidermal thickness on day 4 following UVB irradiation was significantly increased as compared with the control (data not shown). The mechanism of epidermal barrier disruption by UVB irradiation is based on a disruption of the balance between proliferation and differentiation of keratinocytes. We found that the thickness of epidermis after the administration of BC was significantly higher than the control, which indicated that the administration of BC accelerated keratinocyte proliferation or inhibited keratinocyte differentiation (data not shown). Therefore, we considered that the negative effect on the barrier by the BC might have been the result of disruption of the balance between proliferation and differentiation.

In summary, CS was found to contain a high amount of α-EG and its oral administration notably improved barrier disruption induced by UVB radiation, which was considered to have occurred due to the combination of α-EG and organic acids. The improvement effect with CS was significantly greater than those with WC and BC. We concluded that topical or oral application of CS or its active components, α-EG and organic acids, may have a positive effect on skin.

ABBREVIATIONS USED

UV, ultraviolet; CS, concentrate of sake; WC, red wine concentrate; BC, beer concentrate; α-EG, ethyl α-D-glucoside; TEWL, transepidermal water loss; MED, minimal erythemal dose; LDL, low density lipoprotein.

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