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Comparative Assessment of Biological Activities of Mistletoes for Cosmetic Applications: *Viscum Album Var. Coloratum (Kom.) Ohwi* and *Loranthus Tanakae Franch. & Sav.*

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Synopsis

Mistletoes, hemiparasites, contain many components with various biological activities and have been used in cosmetics industry. Loranthacease (1,000 species) and Viscaceae (550 species) have the most dominant species in mistletoes (nearly 1,600 species). It can be expected that the biological activities vary from species to species; therefore, we have tested *Viscum album var. coloratum (Kom.) Ohwi* (belonging to Santalaceae) and *Loranthus tanakae Franch. & Sav.* (belonging to Loranthacease) for a comparative study of their cosmetic properties, including antioxidant, antimelanogenic, and antiwrinkle activities. As results, the ethanol extract of *L. tanakae* had higher phenolic content and showed effective antioxidant activity and elastase inhibition. Meanwhile, the ethanol extract of *V. album* more effectively inhibited tyrosinase. Comparing with ethanol extracts, the water extracts of both mistletoes showed lower biological efficacy than the ethanol extracts or no significant effect. Thus, these results show that different extracts of mistletoe have different levels of biological activities, presumably because of the differences in their phytochemical profiles and because of the different extraction methods used.

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INTRODUCTION

Mistletoes are semiparasitic plants that grow on deciduous trees, such as oak, pine, and elm. They have been widely used in traditional medicine in Asia, Africa, and Europe (1). Mistletoe extracts containing polyphenols, lectins (2), alkaloids (3), viscotoxins (4), and polysaccharides (5) have various biological properties, such as antioxidant (6), antitumor (7), antimicrobial (8), antiviral (9), and immunomodulatory activities (10,11). In addition to herbal medicines, mistletoes have been used in dietary supplements (12) and can be used as a cosmetic ingredient (13). Mistletoe extracts contain various phenolic derivatives such as phenolic acids and flavonoids (14), which have been attractive ingredients for cosmetics (15). For example, *Viscum album* (CAS No. 84929-55-5 in EU) contains secondary metabolites with antioxidant properties (11). In practice, *V. album* (CAS No. 84929-55-5 in EU) has already been registered as a cosmetic ingredient in the Cosmetic Ingredient Database. In Korea, mistletoe is considered a potent biological ingredient. *V. album* has been studied and is listed in the Korean Cosmetic Ingredient Dictionary, which implies that there is a great degree of interest for cosmetic and cosmeceutical applications.

Four species and four genera of the two families of mistletoe (Santalaceae and Loranthaceae) are distributed across the Korean Peninsula (16). The representative species of Santalaceae and Loranthaceae are *V. album var. coloratum (Kom.) Ohwi* (*V. album*) and *Loranthus tanakae Franch. & Sav.* (*L. tanakae*), respectively. The former is relatively well-studied than the latter regarding various aspects, as it is more widely distributed globally. Most studies using Korean mistletoe *V. album* have evaluated its medicinal properties (17,18), although a few studies have focused on the biological, nutritional, and cosmeceutical aspects (19,20). The latter has rarely been studied, in spite of its effective biological activity (21). To date, except for therapeutic approaches, mistletoes have been rarely studied despite their great potential in health and cosmetic industries. More importantly, thus far, there has been no comparative study among the different species of Korean mistletoes although their compositions are dependent on species.

We aimed to investigate the potential effects of two different types of mistletoe extracts as a cosmetic/cosmeceutical ingredient through a comparative study of *V. album* belonging to Santalaceae and *L. tanakae* belonging to Loranthaceae because different species can have a vast range of biological effects. Our study can provide a rational basis, depending on the species and extraction methods, for biological as well as cosmetic applications.

MATERIALS AND METHODS

PREPARATION OF MISTLETOE EXTRACTS

Both *V. album* and *L. tanakae* were provided by Prof. Kooyeon Lee from the Institute of Bioscience and Biotechnology, Kangwon National University. These mistletoes were authenticated by Prof. Yi Sung Shim and Dr. Bo Duk Lee, University of Seoul. In brief, *V. album* was collected from Jeongseon, Kangwon province, whereas *L. tanakae* was collected from Mt. Seorak, Kangwon province, South Korea. Both samples were dried naturally and extracted using double-distilled water (ddH_2O) or ethanol (100% EtOH). 2-Diphenyl-1-picrylhydrazyl (DPPH), mushroom tyrosinase, $_L$-tyrosine, *N*-succinyl-Ala-Ala-Ala-*p*-nitroanilide, porcine pancreatic elastase (PPE), potassium ferricyanide, trichloroacetic

acid, and iron chloride were purchased from Sigma-Aldrich (St. Louis, MO). All other chemicals used were of analytical grade.

TOTAL PHENOLIC CONTENT ASSAY

The total content of phenolic compounds in the mistletoe extracts were quantitatively determined by using the Folin–Denis method (22). In brief, 200 µL of the mistletoe extract was mixed with 200 µL of Folin–Denis reagent. After incubation for 3 min at room temperature, 400 µL of 2M Na_2CO_3 and 200 µL of ddH_2O were added to each sample. Subsequently, the mixture was allowed to stand for 30 min in the dark. The total content of phenolic compounds in the mixture was measured at 725 nm by using a microplate spectrophotometer (Synergy HT; BIOTEK Instruments, Winooski, VT).

DPPH FREE RADICAL SCAVENGING ACTIVITY ASSAY

Free radical scavenging activity of the mistletoe mixture is based on DPPH radical scavenging, which is popular for evaluation of antioxidant activity of natural product. In a given experiment, DPPH is used as a stable free radical, the color of which is changed from purple to yellow when scavenged. Antioxidants in mistletoe extracts react with DPPH and reduce it to DPPH-H, which can be evaluated by the degree of discoloration depending on the scavenging potential of antioxidants in terms of hydrogen donating ability. Based on the assay, the experiment was carried out as follows. Briefly, 100 µL of 0.2 mM DPPH was first added to 100 µL of mistletoe extract. Subsequently, the mixture was incubated for 10 min in the dark, and the absorbance was measured at 517 nm using microplate spectrophotometer (Synergy HT; BIOTEK). The antioxidant activity can be easily tested and relatively compared because this reaction is basically stoichiometric with respect to the number of hydrogen atoms absorbed. The results were calculated by using the following equation: free radical scavenging activity (%) = [1 – (experimental value – blank)/control] × 100 (%).

REDUCING POWER ASSAY

For evaluating the antioxidant activity of mistletoes, a reducing power assay was performed by using the Oyaizu method (23). In brief, 100 µL of 0.2 M sodium phosphate buffer (pH 6.6) was mixed with 100 µL of the mistletoe extract. Subsequently, 100 µL of 10% (w/v) potassium ferricyanide solution was added to the mixture. The mixture was incubated for 20 min at 50°C. Next, 100 µL of 10% (w/v) trichloroacetic acid was added and the mixture was centrifuged at 13,400 g. The solution in the upper layer was collected and allowed to react with 100 µL of 0.1% iron chloride solution and the absorbance was measured at 700 nm by using microplate spectrophotometer (Synergy HT; BIOTEK).

TYROSINASE INHIBITION ASSAY

For evaluating antimelanogenesis, a tyrosinase inhibition assay was performed, as tyrosinase plays an important role in melanogenesis. According to previous literatures, we chose

mushroom tyrosinase, which is frequently used because of its commercial availability (24,25). In brief, the test substance was dissolved in 0.1 M sodium phosphate buffer (pH 6.8). The reaction mixture was prepared with different concentrations of each mistletoe extract and phosphate buffer (200 μL) was mixed with 20 μL of the extract. Next, 20 μL of mushroom tyrosinase (2,000 U/mL; Sigma-Aldrich) and 20 μL of 1.5 mM $_L$-tyrosinase were added. The reaction mixture was incubated for 10 min at 37°C. The absorbance was measured at 490 nm by using a microplate spectrophotometer (Synergy HT; BIOTEK). Tyrosinase inhibition activity was expressed as the percentage inhibitory of tyrosinase, calculated as {[1 – (experimental value – blank)/control × 100(%)]}, where experimental value is the absorbance of the sample wells, blank is the absorbance of the sample wells without tyrosinase, and control is the absorbance of the control wells with tyrosinase but without sample.

ELASTASE INHIBITION ASSAY

PPE was assayed via a spectrophotometric method with the substrate *N*-succinyl-$(Ala)_3$-*p*-nitroanilide, which was prepared using 50 mM Tris–Cl buffer (pH 8.6). The reaction mixture was incubated for 10 min at 25°C, which contained 100 μL of the mistletoe extract at different concentrations, 100 μL of *N*-succinyl-$(Ala)_3$-*p*-nitroanilide, and 50 μL of elastase (0.6 U/mL). The absorbance was measured at 410 nm by using a microplate spectrophotometer (Synergy HT, BIOTEK). Elastase inhibition activity was expressed as the percentage inhibitory of elastase, calculated as {[1 – (experimental value – blank)/control × 100(%)]}, where experimental value is the absorbance of the sample wells, blank is the absorbance of the sample wells without elastase, and control is the absorbance of the control wells with elastase but without sample.

STATISTICS

Experimental data were expressed as mean ± standard deviation and were analyzed by GraphPad Prism (GraphPad Software, San Diego, CA). Statistical significance was determined based on *p* values. Statistically significant differences between the groups were determined by the Student's *t*-test; p values ≤ 0.05 were considered statistically significant.

RESULTS AND DISCUSSION

TOTAL CONTENT OF PHENOLIC COMPOUNDS

Previous studies have shown that mistletoes have high levels of phenolic compounds among various bioactive components, which have antioxidant activities (26). Similar to other mistletoes, Korean mistletoes also contain considerable amounts of phenolic compounds (27). To determine the amount of each phenolic compound in *V. album* and *L. tanakae*, the Folin–Denis method was used (Table I). Because the amount of polyphenols may vary depending on the extraction solution, both mistletoes were extracted using different solutions: ddH_2O and 100% ethanol, as described in the section of preparation of mistletoe extracts, Materials and Methods. The water extracts of *V. album* and *L. tanakae* contained 93.58 ± 2.85 mg/g and 139.83 ± 3.20 mg/g, of phenolic compounds, respec-

Table I
Total Amounts of Phenolic Compounds in *V. album* and *L. tanakae*

Types of mistletoe extract		Total amounts of phenolic compounds (mg/g)
V. album (Viscumalbum var. coloratum (*Kom.*) *Ohwi*	Water extract	93.58 ± 2.85
	Ethanol extract	160.81 ± 6.28
L. tanaka (*Loranthus tanakae Franch. & Sav.*)	Water extract	139.83 ± 3.20
	Ethanol extract	233.19 ± 4.30

tively, whereas each ethanol extract of *V. album* and *L. tanakae* contained 160.81 ± 6.28 mg/g and 233.19 ± 4.30 mg/g, respectively (Table I). These data show that *L. tanakae* has a higher amount of phenolic compounds (about 1.45–1.49 times) than *V. album.* In particular, ethanol is more effective in extracting phenolic compounds from mistletoes than water. The *V. album* ethanol extract had 1.72 times more phenolic compounds than the water extract. Alternatively, the *L. tanakae* ethanol extract had 1.67 times more phenolic compounds than the water extract. Thus, the total amount of phenolic compounds in mistletoes was different depending on their species and extracting solutions. Based on these results, we presumed that mistletoe extracts have antioxidant activity because phenolic compounds in natural extracts have important antioxidant properties, leading to prevention and treatment of skin diseases (28). To further clarify this, DPPH scavenging activity assay and reducing power analysis were additionally performed.

DPPH FREE RADICAL SCAVENGING ACTIVITY

To assess the antioxidant activity of the mistletoe extracts, DPPH free radical scavenging assay was used, as described in the Materials and Methods section. Using the DPPH free radical scavenging assay, it was determined that stable DPPH radicals encounter a proton-donating substrate in the sample, which lead to radical scavenging. Four mistletoe extracts (water and ethanol extracts of *V. album* or *L. tanakae*, respectively) were evaluated with concentrations ranging from 100 to 1,000 μg/mL. $_L$-Ascorbic acid was used as the standard, which is a well-known antioxidant agent. As shown in Figure 1, the ethanol extracts showed a relatively high scavenging effect compared with the water extracts of both mistletoes, except for the ethanol extract of *V. album* (100 μg/mL). Its scavenging effect (%) was above 87%, which was effective, compared with that of $_L$-ascorbic acid. Interestingly, the ethanol extract of *L. tanakae* also showed a high scavenging efficacy (85.52%) even at low concentrations (100 μg/mL) compared with the ethanol extract of *V. album* (48.48%), which indicates that the extract of *L. tanakae* may contain more natural components with antioxidant properties. As concentration of mistletoes increases, scavenging effects were slightly increased and saturated. Above 300 μg/mL, both mistletoe extracts with EtOH showed statistically similar effects. To complement this, reducing power analysis was additionally performed.

REDUCING POWER ANALYSIS

The antioxidant activities of both mistletoes were also evaluated using the widely used reducing power assay (Figure 2). Using this assay, it was determined that reducing antioxidant

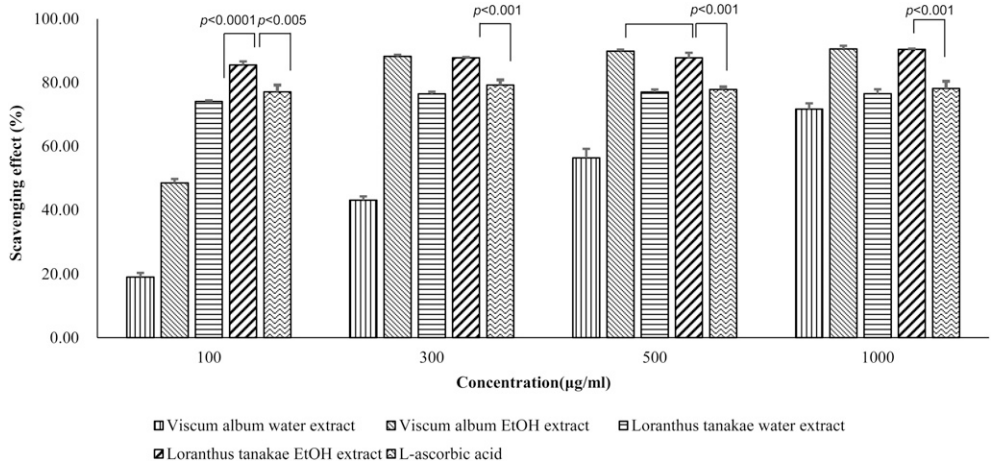

Figure 1. DPPH scavenging activity using the DPPH scavenging assay, *V. album* and *L. tanakae* were compared in the range of 100–1,000 μg/mL. *L*-ascorbic acid was used as a standard.

power measures the reducing ability against ferric ion, which indicates the ability of hydrolysates to donate an electron to the free radical in the extracts. Experimentally, the reduction ability is determined by measuring the colored complex at 700 nm as described in the Materials and Methods section. The yellow color of the sample changes to a color between green and blue, depending on the reducing power of each sample in the presence of reducers (antioxidants). The antioxidants reduce the Fe^{3+}/ferricyanide complex to the ferrous form (Fe^{2+}), which was monitored at 700 nm. Figure 2 shows the reducing power of the *V. album* and *L. tanakae* extracts: *V. album* water extract, *V. album* ethanol extract, *L. tanakae* water extract, and *L. tanakae* ethanol extract. Ascorbic acid was used as the standard. The absorbance at 700 nm increased in a dose-dependent manner, which did not correlate well with the DPPH free radical scavenging assay (Figure 1). In the experiment,

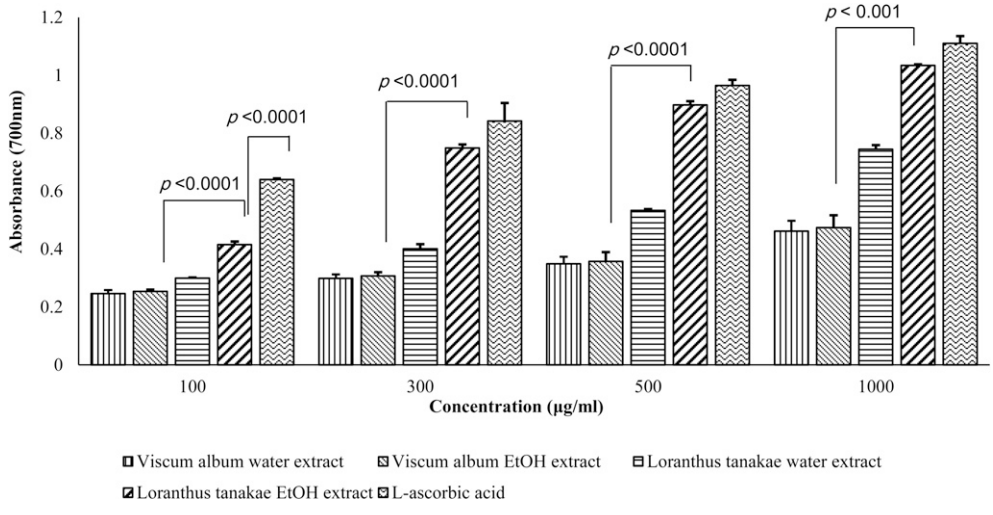

Figure 2. Reducing power analysis using the reducing power assay, *V. album* and *L. tanakae* were compared in the range of 100–1,000 μg/mL. *L*-ascorbic acid was used as a standard.

the ethanol extract of *L. tanakae* showed a higher absorbance than that from *V. album.* Furthermore, the water extract of *L. tanakae* showed a higher absorbance than that from *V. album.* Based on the absorbance, the ethanol extract of *L. tanakae* showed a similar antioxidant activity to that of ascorbic acid in the range of 300 to 1,000 µg/mL. Ascorbic acid had a marginally higher reducing power but was statistically not significant. Taken together, our results demonstrate that the antioxidant activity depends on the species and extraction conditions. In addition, antioxidant components as well as the phenolic compounds might be present in these extracts, considering the slight differences in the result values.

INHIBITION OF TYROSINASE

Figure 3 shows the inhibition of tyrosinase activity by the mistletoe extracts of *V. album* and *L. tanakae* in the range of 100 to 1,000 µg/mL. Each measurement was compared with that of arbutin, a glycosylated hydroquinone-inhibiting tyrosinase, as the standard. The ethanol extracts of both mistletoes inhibited tyrosinase, whereas their water extracts showed no significant inhibition. The ethanol extracts of both mistletoes had a lower inhibitory effect on tyrosinase than arbutin; the ethanol extract of *V. album* showed a higher inhibitory effect. When 1,000 µg/mL of the extract was used, the inhibitory effect was 35.96%, which was similar to the value obtained when arbutin was used at 500 µg/mL. These results show that the ethanol extracts contain more natural compounds with anti-tyrosinase activity (e.g., tyrosinase inhibitor) and the extract of *V. album* is more effective than that of *L. tanakae*. In comparison, the water extracts of *V. album* and *L. tanakae* did not show any significant effects, whereas their ethanol extracts inhibited tyrosinase. Physiologically, tyrosinase, a glycoprotein in melanosomes, plays an important role in melanogenesis; tyrosinase is involved in the hydroxylation of $_L$-tyrosine to $_L$-dihydroxyphenylalanine ($_L$-DOPA) and the subsequent conversion to $_L$-DOPA-quinone (29). The maintenance of melanogenesis is critical because a high level of tyrosinase activity causes hyperpigmentation disorders, such as melasma, lentigo, and drug/UV-induced hyperpigmentation (30). Even if not diseases, abnormal hyperpigmentation is rarely preferred aesthetically. Skin lightening (in Asia)/brightening (in West), through removal of dark spots or uneven skin

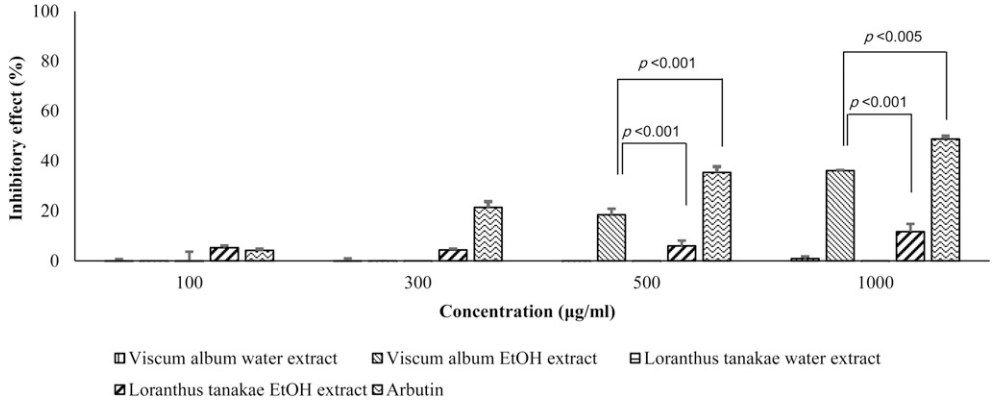

Figure 3. Inhibition of tyrosinase activity using the tyrosinase inhibitory assay, *V. album* and *L. tanakae* were compared in the range of 100–1,000 µg/mL. Arbutin was used as a standard.

tone due to the overproduction of melanin, has been the recent area of interest of in the cosmetic industry (31). In light of this, the suppression of tyrosinase activity is a potential strategy for inhibiting hyperpigmentation, and mistletoe extract could be useful in inhibiting tyrosinase activity, although bioactives with hypopigmentation effect are different depending on types as well as extracting methods.

INHIBITION OF ELASTASE

Elastase inhibitory effect was analyzed using the elastase inhibition assay, as described in Experimental. Ursolic acid was used as the standard. Both extracts of *V. album* and *L. tanakae* showed considerably low efficacies with respect to inhibition of elastase at 100 μg/mL; however, there were no significant differences among the test extracts. At concentrations above 300 μg/mL, the ethanol extract of *L. tanakae* effectively inhibited elastase, which was even higher than the efficacy of ursolic acid at 300 and 500 μg/mL ($p < 0.05$). Both extracts of *L. tanakae* were comparable with those of *V. album* at 100–1,000 μg/mL. The ethanol extract of *L. tanakae* showed a higher inhibitory effect than the water extract of *L. tanakae*. The effects of their ethanol extracts were 3.2, 2.4, and 1.9 times higher than those of their water extracts at 300, 500, and 1,000 μg/mL, respectively. Our findings revealed that *L. tanakae* demonstrated a higher inhibitory effect on elastase activity than *V. album*. In a biological system, elastase, a protease secreted by fibroblast, reduces the elasticity and tortuosity of dorsal skin by breaking down elastic fibers. An increase in elastase activity can cause various diseases, such as cystic fibrosis and psoriasis, and delay wound healing and trigger wrinkle formation through the cleavage of collagen and elastic fibers (32). Therefore, the inhibition of elastase can prevent these diseases as well as the damage of elastic fibers in the skin, leading to reduction in wrinkle formation.

As such, the inhibition of key enzymes, such as tyrosinase and elastase, is important in biomedical and esthetic aspects. As described, it is meaningful that inhibition efficacy of mistletoe extracts on tyrosinase and elastase (Figures 3 and 4, respectively). Based on their inhibitory effects, both *V. album* and *L. tanakae* are attractive natural sources with numerous biological activities, which could be applied to various fields such as cosmetics and cosmeceuticals.

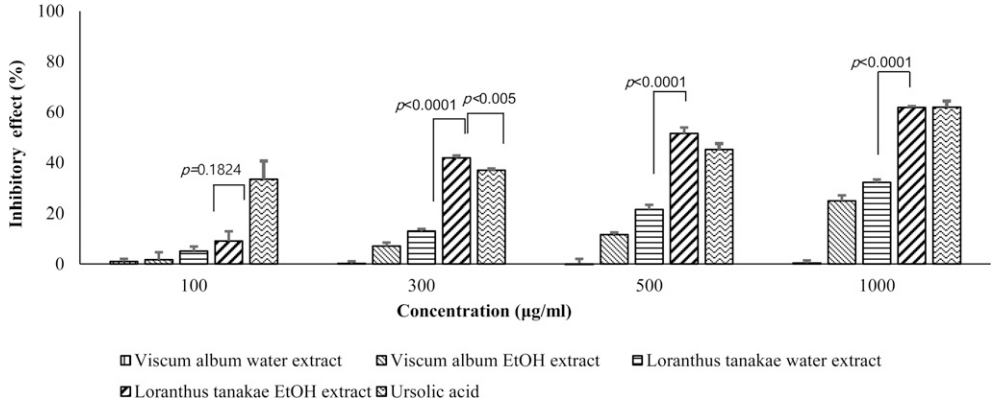

Figure 4. Inhibition of elastase activity using the elastase inhibitory assay, *V. album* and *L. tanakae* were compared in the range of 100–1,000 μg/mL. Ursolic acid was used as a standard.

Recently, the cosmetic market has been emerged and driven toward natural, organic ingredients because of consumers' concerns about synthetic ingredients. A number of these phytochemicals are today being developed, used, or considered for antiaging effects in spite of synthetic ingredient developed. For example, although synthetic antioxidants have been reported to be effective for inhibiting oxidation, they have been restricted because of possible health risks and toxicity (33). Also, cosmetic market and consumers still continue to demand natural cosmetic ingredient (34). Thus, the use of natural ingredients from botanicals accomplishes for preventing degradation of natural ingredients in cosmetic product and for protecting the skin cells from being damaged as well as aged (35). Like other phytochemicals, a previous report demonstrated that mistletoe extract could be a safe natural antioxidant and antimicrobial agent in food products (36), which are also useful biological activities as cosmetic ingredients. In light of this, in our study, we believe mistletoe extracts can provide potential biological function in cosmetic products to beautify and maintain the physiological balance of our skin.

CONCLUSIONS

In this study, we evaluated biological activities of mistletoes in aspect of cosmetics. Both *V. album* and *L. tanakae* showed antioxidant activities and inhibitory effects on tyrosinase and elastase, which are important for preventing skin aging. Depending on mistletoe family and extracting solvent, they showed different levels of these activities because of different phytochemical profiles, suggesting the importance of choosing cosmetic ingredients. Our findings suggest that appropriate mistletoes and extraction conditions should be carefully chosen to broaden cosmetic and cosmeceutical applications.

DISCLOSURE

The authors declare no conflict of interest in this work.

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