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Tyrosinase Inhibitory Activity of Citrus Essential Oils

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Thirteen kinds of citrus essential oils and their volatile flavor constituents were investigated for tyrosinase inhibitory activity. Eureka lemon, Lisbon lemon, Keraji, and Kiyookadaidai significantly inhibited the oxidation of L-dihydroxy phenylalanine (L-DOPA) by mushroom tyrosinase. Citral and myrcene among volatile flavor constituents of citrus essential oils exhibited tyrosinase inhibitory activities with K_i values of 0.318 and 2.38 mM, respectively. The inhibition kinetics analyzed by a Lineweaver−Burk plot indicated that citral is a noncompetitive inhibitor and myrcene is a competitive inhibitor. These results indicated that citral and myrcene are responsible for the tyrosinase inhibitory activity of citrus essential oils.

KEYWORDS: Tyrosinase; citrus peel essential oil; volatile flavor constituents

INTRODUCTION

Tyrosinase (EC 1.14.18.1) is an enzyme, which is widely occurring in microorganisms, animals, and plants. The enzyme has three domains, and the central domain contains two copper binding sites (*1*). Copper binding sites are the active site in the tyrosinase catalytic reaction. Tyrosinase uses molecular oxygen to catalyze two different reactions, the hydroxylation of monophenols to *o*-diphenols (monophenolase or cresolase activity) and the oxidation of the *o*-diphenols to *o*-quinones (diphenolase or catecholase activity) (*2*, *3*). The *o*-quinones thus generated form melanin (*4*−*6*) through polymerization and a series of subsequent enzymatic and nonenzymatic reactions. Melanogenesis is a major defense mechanism in human skin against the ultraviolet light of the sun. However, abnormal melanin pigmentation such as melasma, freckles, ephelide, and senile lentigines is a serious aesthetic problem. Melanin pigments are also found in many disease states. In the human brain, tyrosinase plays an important role in neuromelanin formation, which could be central to dopamine neurotoxicity as well as contribute to the neurodegeneration associated with Parkinson's disease (*7*). In addition, undesired darkening caused by tyrosinase on the surface of seafood products has been of concern. It is responsible for not only melanization in animals but also browning in plants. There are many polyphenols in plants. So, using these compounds as substrates, enzymatic browning by tyrosinase is easily caused. This unfavorable browning from enzymatic oxidation generally results in a loss of nutritional and market value. Thus, in cosmetic (*8*), medicinal (*9*), and food products, tyrosinase inhibitors have become increasingly important to prevent hyperpigmentation and enzymatic browning.

A large number of tyrosinase inhibitors have already been reported. For example, kojic acid, known as one of the most popular tyrosinase inhibitors, has been widely used as a skin-whitening and antibrowning agent (*10*). Galangin, kaempferol, and quercetin have been identified as potent tyrosinase inhibitory polyphenols (*11*). A large number of aldehydes such as a series (2*E*)-alkenals were also isolated and characterized as tyrosinase inhibitors (*12*). Anisaldehyde characterized in the seed of *Pimpinella anisum* was reported as a noncompetitive inhibitor with an ID_{50} of 43 μg/mL (0.32 mM) (*13*). Cuminaldehyde, identified from cumin, a common food spice, is a noncompetitive inhibitor with an ID_{50} of 7.7 μg/mL (0.05 mM) (*14*). Recently, dimethyl sulfide (DMS) found in seawater was reported as an effective competitive and slow binding inhibitor. DMS is the first volatile tyrosinase inhibitor characterized (*15*).

Citrus fruits are widely cultivated and are the most popular fruits in the world. The peel of citrus fruit is used in traditional Chinese medicines. The essential oils extracted from citrus peel are a mixture of volatile compounds such as monoterpene hydrocarbons and give us fresh, light, and fine fruity aromas. Citrus essential oils have been used as flavoring agents in foods, beverages, liqueurs, and confectioneries and as aromatic agents in soaps, perfumery, and household products. Moreover, various products made from essential oils have been used in aromatherapy and may relax or stabilize some physical and psychological conditions (*16*). It is known that the essential oil has various functional properties such as an attractive aroma, a repellant against insects and animals, and inhibitory effects against microorganisms. Moreover, it was also found that citrus peel essential oils possess physiological activities such as antioxidative action against linoleic acid oxidation (*17*), 1,1-diphenyl- 2-picrylhydrazyl (DPPH) radical scavenging activity (*18*), and an inhibitory effect on carcinogen formation. As described above, aromatic or aliphatic aldehydes such as anisaldehyde, cuminaldehyde, and (2*E*)-alkenal were reported as tyrosinase inhibitors. Citrus essential oils contain a number of aliphatic aldehydes such as citral. For this reason, the authors

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Table 1. Citrus Samples

abbreviation	common name	scientific name
YUZ	Yuzu	*Citrus junos Sieb.* ex. *Tanaka*
ICH	Ichang lemon	*C. Wilsonii Tanaka*
PON	Ponkan	*C. reticulata Blanco*
MOC	Mochiyuzu	*C. inflata Hort.* ex. *Tanaka*
KAB	Kabosu	*C. sphaerocarpa Hort.* ex. *Tanaka*
TOS	Tosa-buntan	*C. grandis*
DAI	Daidai	*C. aurantium Linn.* var. *Cyathifera Y. Tanaka*
NAO	Naoshichi	*C. taguma-sudachi Hort.* ex. *Y. Tanaka*
KIM	Kimikan	*C. flaviculpus Hort.* ex. *Tanaka*
KER	Keraji	*C. keraji Hort.* ex. *Tanaka*
KIY	Kiyookadaidai	*Cistrus* sp
LIS	Lisbon lemon	*C. limon Burmann forma Lisbon*
EUR	Eureka lemon	*C. limon Burmann forma Eureka*

expect that citrus peel essential oils possess tyrosinase inhibitory activity. To elucidate the physiological activity of citrus peel essential oils in the present study, the tyrosinase inhibitory activity of 13 kinds of citrus essential oils was examined.

MATERIALS AND METHODS

Materials. Kojic acid and mushroom tyrosinase were from Sigma Chemical Co. (St. Louis, MO). Dimethyl sulfoxide (DMSO) and geranyl acetate were from Wako Pure Chemical Industries (Osaka, Japan). Citral and neryl acetate were from Tokyo Kasei Kogyo Co. (Tokyo, Japan). L-DOPA and myrcene were from Aldrich Chemical Co. (United States). The other chemicals were of the highest grade available and were used without further purification. Purified water from Auto Pure WQ 501 was used to prepare buffer and standard solutions.

Essential Oil of Citrus Fruit. The essential oils from 13 kinds of citrus fruits as shown in **Table 1** were used in this study. The citrus fruits were provided by Kochi Prefectural Fruit Tree Experimental Station, Ehime Prefectural Fruit Tree Experimental Station, Shizuoka Prefetural Fruits Experimental Station, Oita Prefectural Citrus Experimental Station Tsukumi Branch, Laboratory of Citrus Fruit of Hiroshima Prefectural Agriculture Research Center, and National Institute of Fruit Tree Science, Department of Citrus Research in Okitsu. The essential oils were prepared by a cold-pressing method (*19*). Briefly, the flavedo was prepared by cutting off the alvedo from the peel. The peel oils were extracted by hand-pressing the flavedo and were saturated with sodium chloride. The oil layer was centrifuged. The crude oils were dried overnight at 2 °C with anhydrous sodium sulfate. After the precipitate was filtered, the filtrates were used for analysis as a cold-pressed oil.

Gas Chromatography (GC) and GC-Mass Spectrometry (MS). Quantitative analysis of the volatile constituents of citrus peel essential oils was done according to our previous paper (*20*, *21*). Quantitative determination and identification of volatile constituents of the oils (Yuzu, Mochiyuzu, Kabosu, Daidai, Naoshichi, Kiyookadaidai, Lisbon lemon, and Eureka lemon) were carried out using a Shimadzu GC-14A gas chromatograph equipped with a flame ionization detector and a Hitachi model M-80B GC-MS or a Shimadzu GC-MS QP 5000. The data were shown as relative weight percents.

Enzymatic Assay of Tyrosinase. The enzymatic assay was performed according to the procedure of Kubo et al. (*11*−*14*). The mushroom tyrosinase was used for this assay. The enzyme was used for the experiment because of its availability. L-DOPA was used as the substrate in this experiment. For this reason, the tyrosinase inhibitory activity in this paper indicates diphenolase inhibitory activity. The activity of tyrosinase was determined spectrophotometrically (dopachrome formation at 475 nm, $\epsilon = 3700$). First, 1 mL of 2.5 mM L-DOPA solution was mixed with 1.8 mL of 0.1 M phosphate buffer (pH 6.8) and incubated at 25 °C for 10 min. Then, 0.1 mL of the sample solution and 0.1 mL of the tyrosinase solution (138 units) were added in this order to the mixture to immediately measure the initial rate as a linear increase in the absorbance at 475 nm. The value in the absence from sample was represented as the control. The inhibitory effect of sample was represented as relative activity as compared with the control. All samples were first dissolved in DMSO and used at 30 times dilution in the experiment. The data are the means ± standard deviations of three experiments.

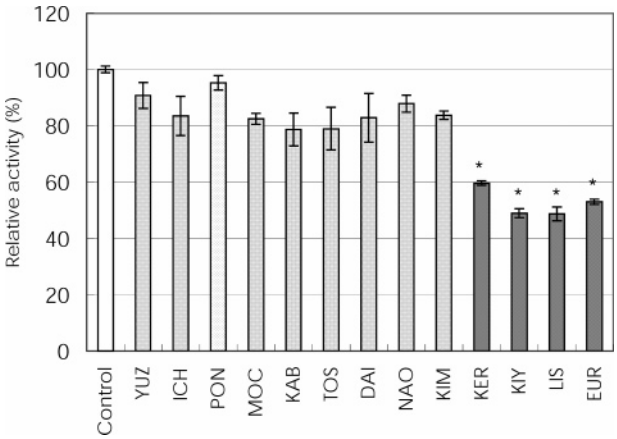

Figure 1. Tyrosinase inhibitory activity of citrus essential oils. All citrus oils were used at the concentration of 167 μg/mL. *Significantly different from control value; $p < 0.0001$.

Table 2. Volatile Flavor Constituents of Citrus Essential Oils[a]

volatile compound	YUZ	MOC	KAB	DAI	NAO	KIY	LIS	EUR
sabinene	0.24	0.09	0.09	0.19	0.13	0.70	2.32	2.20
neral	0.01		0.01	0.02		0.30	0.61	0.86
geranial			0.03		0.02	0.50	1.13	1.42
neryl acetate		0.02	0.08	0.04		0.60	0.31	0.48
geranyl acetate		0.02	0.04	0.09	0.02	0.20	0.23	0.48
myrcene	2.14	20.62	18.53	1.57	1.84	62.40	1.43	1.61

[a] Values are given in relative weight percent (in mg of flavor constituent per 100 mg of citrus CPO).

Determination of the Inhibition Type. Taking various concentrations of DOPA (1−4 mM) as the substrate, the tyrosinase inhibitory activity was measured according to the method descrived above. Inhibitory kinetics of the sample for tyrosinase was analyzed by Lineweaver−Burk plots.

RESULTS AND DISCUSSION

Tyrosinase Inhibitory Activity of Citrus Peel Essential Oils. Tyrosinase inhibitory effects were determined for 13 kinds of citrus essential oils (final concentration, 167 μg/mL each). Relative tyrosinase inhibitory activities of citrus essential oils are shown in **Figure 1**. Twelve citrus oils except Ponkan significantly showed tyrosinase inhibitory activity ($p < 0.05$). The extents of activity depended on citrus species, in which Eureka lemon, Lisbon lemon, Keraji, and Kiyookadaidai had strong tyrosinase inhibitory activities ($p < 0.0001$).

Tyrosinase Inhibitory Activity of Volatile Flavor Constituents in Citrus Essential Oils. The volatile flavor constituents of Yuzu, Mochiyuzu, Kabosu, Daidai, Naoshichi, Kiyookadaidai, Lisbon lemon, and Eureka lemon have been identified and quantified by GC and GC-MS analysis. Then, using the eight kinds of citrus oils, we searched the characteristic volatile constituents in citrus essential oils with tyrosinase inhibitory activity (Kiyookadaidai, Lisbon lemon, and Eureka lemon). Characteristic volatile constituents were shown in **Table 2**. Kiyookadaidai, Lisbon lemon, and Eureka lemon with tyrosinase inhibititory activities were relatively abundant in sabinene, citral (neral and geranial), neryl acetate, and geranyl acetate. Kiyooka-

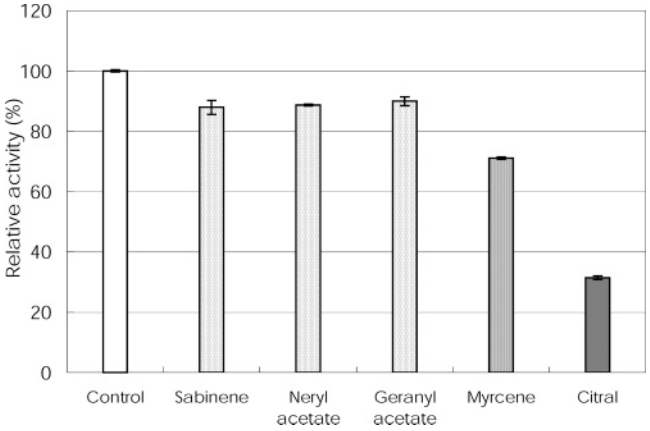

Figure 2. Tyrosinase inhibitory activity of constituents of citrus essential oils. All constituents were used at the concentration of 167 μg/mL.

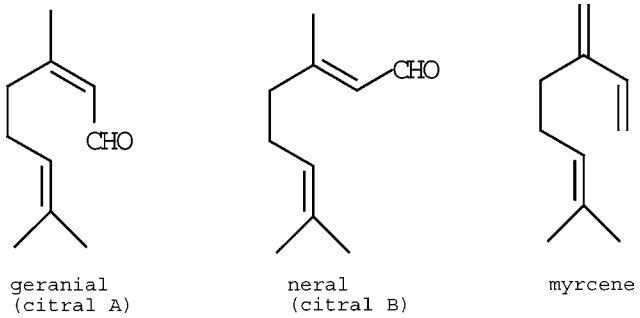

Figure 3. Structures of volatile flavor constituents of citrus essential oils with tyrosinase inhibitory activity.

daidai was also abundant in myrcene. The tyrosinase inhibitory activities of these volatile flavor constituents (final concentration, 167 μg/mL each) were examined. All constituents inhibited the oxidation of L-DOPA by tyrosinase, as shown in **Figure 2** ($p < 0.05$). However, even a high concentration (167 μg/mL) of sabinene, neryl acetate, and geranyl acetate only inhibited the tyrosinase activity by 15%. Citrus oils contain few amounts of these constituents. This suggests that sabinene, neryl acetate, and geranyl acetate contribute little to the tyrosinase inhibitory activity of citrus essential oils. So, we examined the tyrosinase inhibitory activities of citral and myrcene in detail.

The structure of citral is shown in **Figure 3**. Citral has a lemonlike aroma and contributes to the aromas of many citrus fruits. This acyclic monoterpene aldehyde was one of the main components in the aroma of citrus essential oil. It has been reported that citral had various activities such as tyrosinase inhibitory activity and antimicrobial activity (*22*). To investigate the contribution of citral to the tyrosinase inhibitory activity in citrus oils, we examined the relationship between citral amount and tyrosinase inhibitory activity in citrus essential oils. Citral is present at 1.34, 2.92, and 3.81 μg/mL levels in the oils of kiyookadaidai, Lisbon lemon, and Eureka lemon (167 μg/mL). As shown in **Figure 4**, citral at the level contained in the oil significantly inhibited tyrosinase activity ($p < 0.05$). However, the tyrosinase inhibitory activity of citral in citrus oil significantly differed from that of the oil of even Eureka lemon ($p < 0.05$), which contained the highest concentration of citral. Citral occurs as *cis* and *trans* isomers (neral and geranial) (*23*). In many plants, the *trans* isomer of citral occurs more than the *cis* isomer. Kubo et al. reported that the tyrosinase inhibitory activity of *trans* isomer was higher than that of the *cis* isomer (*12*). As shown in **Table 2**, *trans* isomers were more than *cis* isomers in citrus oils with tyrosinase inhibitory activity. On the other hand,

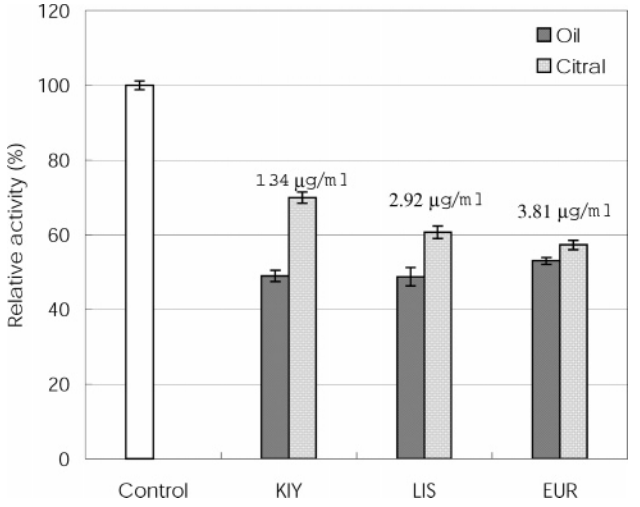

Figure 4. Tyrosinase inhibitory activity of citrus essential oil and citral. Citrus oils were used at the concentration of 167 μg/mL. The concentration of citral used in this experiment was described in the figure.

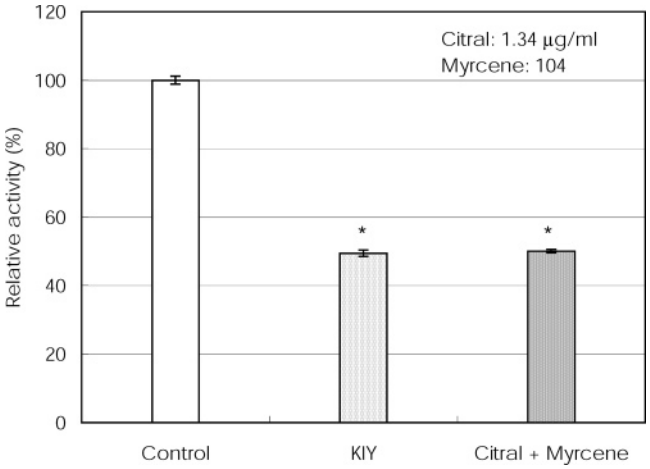

Figure 5. Tyrosinase inhibitory activity of Kiyookadaidai and the constituent. The concentration of citral and myrcene used in this experiment was described in the figure. *Values are not significantly different ($p < 0.05$).

the ratio of *trans* to *cis* isomers of synthesized citral used in this experiment was 1:2. For these reasons, it was suggested that the significant difference of the tyrosinase inhibitory activity between citral and citrus oil could be because of the difference of ratios of geometrical isomers in citral.

In Kiyookadaidai cold-pressed oil, myrcene was the most abundant compound among volatile constituents; the weight percentage of myrcene is 62.4% in oil. This monoterpene hydrocarbon with a structure shown in **Figure 3** gives a resinous odor and is the key aroma compound in Kiyookadaidai oil. Myrcene (167 μg/mL) presented a tyrosinase inhibitory activity of more than 25%. We expect that the tyrosinase inhibitory activity of Kiyookadaidai comes from myrcene and citral. Myrcene is present at a 104 μg/mL level in 167 μg/mL Kiyookadaidai essential oil. The tyrosinase inhibitory activity of a mixture of myrcene and citral (104 and 1.34 μg/mL, respectively) was examined and compared with that of Kiyookadaidai peel oil (167 μg/mL). **Figure 5** indicated that both tyrosinase inhibitory activities of the mixture and Kiyookadaidai cold-pressed oil did not differ significantly ($p < 0.05$). Therefore, it was suggested that citral and myrcene were responsible for the tyrosinase inhibitory activity of peel oil in Kiyookadaidai.

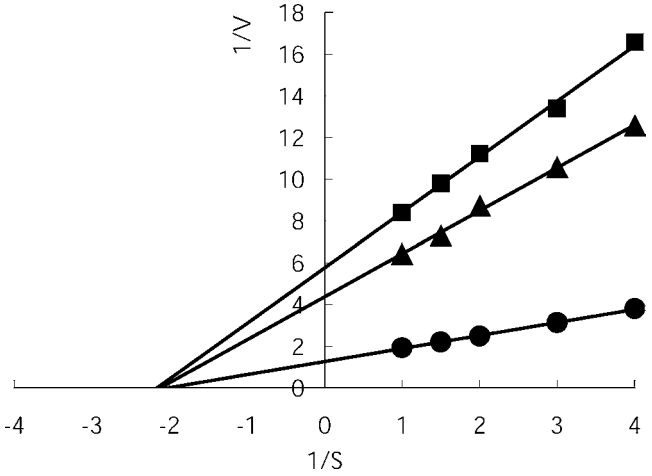

Figure 6. Lineweaver–Burk plots of tyrosinase and L-DOPA with 0 (●), 1.0 (▲), and 1.2 mM (■) citral.

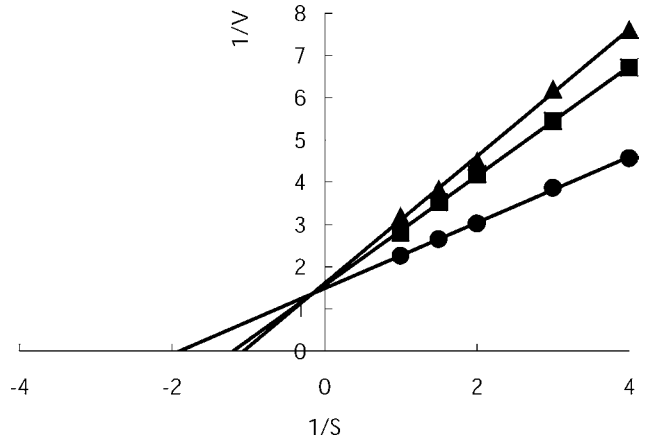

Figure 7. Lineweaver–Burk plots of tyrosinase and L-DOPA with 0 (●), 0.1 (■), and 2 mM (▲) myrcene.

We studied the inhibition mechanism of citral and myrcene against the oxidation of L-DOPA by tyrosinase. Inhibition kinetics were analyzed by Lineweaver−Burk plots (**Figure 6**). The three lines were obtained from three different concentrations (0, 1.0, and 1.2 mM) of citral. The lines were crossed on a 1/*S* axis. This result indicated that citral was a noncompetitive inhibitor. This finding agrees with that of Kubo et al. (*12*). The inhibitor citral is coupled with the free enzyme and the enzyme−substrate complex. The aldehyde compounds such as citral are protein reactive compounds and are known to react with biologically important nucleophilic groups such as sulfhydryl, amino, or hydroxyl groups. The aldehyde compound can react with the primary amino group in the enzyme tyrosinase to form a Shiff base. The comparison of tyrosinase inhibitory activity by various aldehydes showed that the stability of the Shiff base formed between tyrosinase and aldehyde was significantly related with the activity (*12*). For these reasons, it was considered that the tyrosinase inhibitory activity of citral could be based on Shiff base formation between citral and tyrosinase.

The kinetic behavior of myrcene for the inhibition of tyrosinase was also analyzed by Lineweaver−Burk plots. The three lines with different slopes were obtained from uninhibited tyrosinase and from two different concentrations of myrcene (0.1 and 2.0 mM) (**Figure 7**). These lines were crossed on a 1/*V* axis. This result indicated that myrcene is a competitive inhibitor of tyrosinase. It only binds free enzyme and not the enzyme−substrate complex.

Table 3. Inhibition Constants of Citral, Myrcene, and Kojic Acid for Tyrosinase

inhibitor	inhibition constant (mM)	inhibition type
citral	0.32	noncompetitive
myrcene	2.78	competitive
kojic acid	7.75	mix

Inhibition type and inhibition constants (K_i) of citral and myrcene, tyrosinase inhibitors in citrus oils, and kojic acid, a popular tyrosinase inhibitor, are summarized in **Table 3**. K_i values of citral and myrcene were 0.32 and 2.78 mM, respectively. On the other hand, the K_i value of kojic acid was 7.75 μM. It was shown that the tyrosinase inhibitory activities of citral and myrcene were weaker than that of kojic acid. However, citral and myrcene were hydrophobic compounds and expected a higher affinity to biological membranes such as human skin than kojic acid, a hydrophilic compound. Furthermore, in aromatherapy, the oils at a concentration of 0.001−0.01% level have been used, and some citrus oils indicated a tyrosinase inhibitory activity at these concentration levels. It is suggested that citrus oils can be practically used as tyrosinase inhibitors.

Ultraviolet light and environmental toxins cause reactive oxygen species such as various radicals. These radicals play important roles in the activation of tyrosinase in human skin. It has been reported that some citrus essential oils exhibited radical scavenging activity (*19*). For example, Eureka lemon essential oil with a strong tyrosinase inhibitory activity has DPPH radical scavenging activity. It was reported that the radical scavenging components in Eureka lemon oil were geraniol, terpinolene, and γ-terpinene. These components were different from the tyrosinase inhibitory components, citral and myrcene. Thus, it is suggested that citrus essential oil, consisting of hundreds of kinds of compounds, could inhibit melanogenesis by various actions and activities. Citral and myrcene have characteristic aromas in citrus oils. Thus, it is expected that citrus essential oils could be used as skin-whitening materials with citruslike aromas in confectioneries, soap, perfumery, and cosmetology.

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