Parapheromones Suppress Chemotherapy Side Effects

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Received June 12, 2018; accepted August 17, 2018

ABSTRACT

The cytotoxic drugs used in chemotherapy are often accompanied by nausea and vomiting. Despite the use of antiemetic drugs, chemotherapy-induced nausea and vomiting (CINV) remain significant side effects for cancer patients and are associated with serotonin type 3 receptor (5-HT₃R) activation in the brainstem. Farnesol and nerolidol are sesquiterpene alcohols found in essential oils of plants such as roses, citronella, and lemon grass and are used as antiemetic parapheromones. Medicinal plants often are effective in treating gastrointestinal disorders, including CINV, although the mechanism of action remains unclear. In the current work, the antiemetic efficacy of the naturally occurring racemic mixture of farnesol (*m*-farnesol) and nerolidol (*m*-nerolidol) against cisplatin CINV was tested using the pica behavior (consumption of nonnutritive substances) of rats. Animals treated with *m*-farnesol or *m*-nerolidol consumed a smaller

amount of kaolin than of saline-treated control animals. This result is consistent with the antiemetic efficacy of farnesol and nerolidol. Compared with controls, *m*-farnesol- but not *m*-nerolidol-treated animals consumed more food and lost less body weight. Thus, farnesol effectively reduced appetite suppression and weight loss induced by cisplatin. In separate experiments, isomers of farnesol and nerolidol were tested on 5-HT-induced responses of acutely isolated nodose neurons using patch-clamp methods. All the tested constituents inhibited 5-HT₃R-mediated current in a noncompetitive manner. Thus, both farnesol and nerolidol may exert antiemetic efficacy by inhibiting 5-HT signaling in cranial visceral afferents, resulting in interruption of emetogenic signaling; however, nerolidol failed to suppress cisplatin-induced anorexia and weight loss, suggesting that additional mechanisms may contribute.

Introduction

The cytotoxic drugs used in chemotherapy cause diverse adverse effects that include nausea and vomiting (NV), diarrhea, anorexia, and weight loss (Hofman et al., 2004; Devlin et al., 2017). These chemotherapy-induced side effects often interrupt drug treatment and negatively impact outcome of the therapy (Andreyev et al., 1998; Hess et al., 2007). NV, the most common and debilitating of side effects, is commonly treated with antiemetic drugs, including serotonin type 3 receptor (5-HT₃R) antagonists, corticosteroids, and substance P antagonists. Activation 5-HT₃R in the brainstem is associated with triggering nausea pathways, and vagal afferents appear critical in these responses (Babic and Browning, 2014). Nevertheless, many cancer patients still suffer chemotherapy-induced nausea and vomiting (CINV) (Haiderali et al., 2011; Hernandez Torres et al., 2015). To suppress CINV further, medicinal plants (i. e., ginger and bitter orange) are often recommended (Pillai et al., 2011; Suryawanshi, 2011; Ryan et al., 2012). Sesquiterpene alcohols farnesol and nerolidol

(Fig. 1) are common constituents of those medicinal plants and widely exist in fruits and herbs.

These compounds are used widely in perfumes as well as in food additives to enhance flavors (Suryawanshi, 2011; Nampoothiri et al., 2012; Chan et al., 2016). These constituents have antimicrobial and antineoplastic activity; however, their actions in CINV are not understood (Jabra-Rizk et al., 2006; Joo and Jetten, 2010). Plant-derived monoterpenoids with 5-HT₃R-inhibiting potency have potential antiemetic efficacy to inhibit diverse gastrointestinal symptoms, including NV (Tyers and Freeman, 1992; Ashoor et al., 2013; Jarvis et al., 2016). Such evidence suggests that farnesol and nerolidol may have potential antiemetic efficacy against CINV.

To evaluate this assumption, we tested the functional efficacy of farnesol and nerolidol on CINV in a rat-pica model. We also assessed their potential mechanism of action by assaying effects on 5-HT₃R-mediated currents in acutely isolated visceral afferent nodose neurons.

Materials and Methods

Ethics Statement. All animal procedures were conducted with the approval of the institutional Animal Care and Use Committee of

This work was supported by the National Research Foundation of Korea [NRF-2017R1D1A1B03033436].
<https://doi.org/10.1124/jpet.118.251363>.

ABBREVIATIONS: 5-HT₃R, serotonin type 3 receptor; ACSF, artificial cerebrospinal fluid; CINV, chemotherapy-induced nausea and vomiting; MA, meggestrol acetate; *m*-farnesol, *racemic mixture* of farnesol; *m*-nerolidol, *racemic mixture* of nerolidol; NV, nausea and vomiting; RM ANOVA, repeat measures analysis of variance.

Fig. 1. Chemical structures of nerolidol, farnesol, and linalool.

Kyung Hee University (KHUASP(SE)-17-123). These procedures were in accordance with the National Veterinary Research & Quarantine Service guidelines of the Republic of Korea.

Kaolin Preparation. Kaolin (hydrated aluminum silicate; Sigma-Aldrich, St. Louis, MO) was mixed with 1% gum Arabic (Sigma-Aldrich), molded to rods the same size as that of the food pellets, and then dried at room temperature. Kaolin and food were provided in separate compartments in a divided food hopper.

Experimental Protocol and Drug Administration for Pica Test. Seven-week-old male Wistar rats (Orient Bio Inc., Seongnam, Korea) were housed in plastic cages (26 × 42 × 18 cm) and allowed free access to food, kaolin, and water. The cages were in a temperature-controlled room with 12 hours of light from 09:00 and 12 hours of darkness from 21:00. All animals were sacrificed at the end of the study by exposure to a rising concentration of CO₂. The rats were adapted for 3 days before the start of the experiment. The animals received cisplatin (6 mg/kg) or saline intraperitoneally for 4 consecutive days. The dose of cisplatin was chosen based on previous studies of kaolin intake in the rat (Takeda et al., 1993; De Jonghe et al., 2009). The volume of cisplatin solution administered was adjusted with saline to 100 ml/kg body weight. Farnesol (100 or 500 mg/kg), nerolidol (100 or 500 mg/kg), and ondansetron (3 mg/kg) were administered orally 60 minutes before the administration of cisplatin. All experimental parameters (body weight, food and water intake, kaolin consumption) were measured daily between hours 10:00 and 11:00 throughout the study.

Acute Dissociation of Nodose Neuron. Visceral afferent neuron cell bodies, including those innervating the gastrointestinal system, are contained in the nodose ganglion. Nodose neurons were dissociated using procedures previously described elsewhere (Kim et al., 2015). Briefly, in deeply anesthetized (Zoletil, Virbac, France) 3- to 4-week-old male Wistar rats, the vagus nerve and the attached ganglion were separated from surrounding tissue and immediately placed into a Petri dish containing 4°C artificial cerebrospinal fluid (ACSF), which was composed of the following (in mM): 125 NaCl, 3 KCl, 1.2 KH₂PO₄, 1.2 MgSO₄, 25 NaHCO₃, 10 glucose, and 2 CaCl₂, and bubbled with 95% O₂-5% CO₂. After removing excess connective tissues. Then the nodose

ganglion was incubated for 30–45 minutes at 31°C in an ACSF solution containing protease (type 2S trypsin, 5 to 6 mg/ml at 1310 U/mg; Sigma-Aldrich). After protease treatment, the ganglion was placed in enzyme-free ACSF for 2–4 hours at room temperature. The ganglia were mechanically dispersed using fire-polished Pasteur pipettes in a glass-bottom perfusion chamber filled with artificial external recording solution containing (in mM): 150 NaCl, 5 KCl, 1 MgCl₂, 2 CaCl₂, 10 HEPES; 10 glucose (pH was adjusted to 7.4 with Tris base).

Electrical Measurements and Data Analysis. For voltage-clamp recording, isolated neurons were visualized using a phase-contrast microscope (Eclipse Ti; Nikon, Tokyo, Japan). Recordings used a Multiclamp 700B (Molecular Devices, Sunnyvale, CA) and pClamp 9 software (Molecular Devices). To minimize changes in intracellular constituents, we used a perforated-patch method (Akaike and Harata, 1994). Recording electrodes were back-filled with a nystatin-containing pipette solution composed of the following (in mM): 50 KCl, 100 K gluconate, and 10 HEPES; the pH of this solution was adjusted to 7.2 with Tris-OH. Final concentration of nystatin was 450 μg/ml. The nystatin-internal solution-filled patch pipettes had 5 to 6 MΩ resistance. Under our recording conditions, acutely dispersed nodose neurons have a resting membrane potential -52 ± 4 mV ($n = 6$). Currents were sampled at 10 kHz with 3-kHz filtering. All experiments were conducted at room temperature (21–22°C). Data were analyzed off-line using pClamp 9 software. Concentration-response relations were fit according to a modified Michaelis-Menten equation (eq. 2) using a least-square fitting routine 1:

$$I = I_{\max} [C^n / (C^n + EC_{50}^n)], \quad (1)$$

where I is the drug-induced current amplitude, $I_{\max}$ is the maximum current amplitude, and C is the corresponding drug concentration. EC_{50} and n denote the half-maximum effective concentration and the Hill coefficient, respectively. The data for the concentration-inhibition curve were analyzed using the following equation (eq. 2) by a least-square method:

$$I = I - [C^n / (C^n + IC_{50}^n)], \quad (2)$$

where I is the current amplitude without antagonists, C is the concentration of the antagonist, and IC_{50} is the concentration at the half-maximum inhibition.

Drugs. Serotonin (5-HT), trans, trans-farnesol, racemic mixture of farnesol (*m*-farnesol), *trans*-nerolidol, *cis*-nerolidol, racemic mixture of *cis* and *trans* nerolidol (*m*-nerolidol), and linalool were purchased from Sigma-Aldrich. The 5-HT₃R selective antagonist ondansetron was purchased from Tocris Cookson (Ballwin, MO). Farnesol and nerolidol were first dissolved in ethanol, and then the stock solution was diluted with the external solution just before use. The final concentrations of ethanol were always <0.01%. At these concentrations, ethanol alone had no effect on membrane potential or on electrical activity. All drugs were applied via a rapid application Y-tube microperfusion system that provided complete changes in the solution surrounding the recorded neurons within 0.1 second (Murase et al., 1989).

Statistical Analysis. Values were expressed as the mean ± S.E.M. Statistical comparisons between two groups were analyzed by the Student's *t* test. For multiple comparisons, one-way or two-way analysis of variance (ANOVA) was followed by post hoc testing for multiple comparisons (Bonferroni/Dunn's correction, StatView; SAS Institute Inc., Cary, NC). Differences were considered statistically significant for P values < 0.05.

Results

Nerolidol and Farnesol Reduce Cisplatin-Induced Kaolin Consumption. Antiemetic effects of farnesol and nerolidol were tested on cisplatin-induced emesis in a rat-pica model with their naturally occurring racemic mixtures *m*-farnesol and *m*-nerolidol. Animals were conditioned for 3 days before the

Fig. 2. Effects of ondansetron (Ondan) on cisplatin-induced increase in kaolin intake. Cisplatin or vehicle (saline) was administered on day 1. Ondansetron was administered 60 minutes before cisplatin. Data are expressed as mean $\pm$ S.E.M. $n = 6$. * $P < 0.05$; ** $P < 0.01$ vs. saline-treated group.

experiments by intraperitoneal cisplatin injections (6 mg/kg per day). In a control experiment, cisplatin administration significantly increased kaolin consumption [$P < 0.01$, repeat measures analysis of variance (RM ANOVA) compared with days before injection (Fig. 2). On days 1 and 2 of cisplatin administration, kaolin intake was significantly greater than the in saline-treated group ($n = 6$, $P < 0.01$, RM ANOVA). Treatment with the 5-HT₃R antagonist, ondansetron (3 mg/kg, p.o.) prevented cisplatin-mediated increases in kaolin intake. Kaolin intake was not significantly different in the saline-saline and cisplatin-ondansetron group animals. In the same conditions, *m*-nerolidol and *m*-farnesol (100 mg/kg) significantly inhibited the cisplatin-induced increase in kaolin intake at days 2 compared with the cisplatin-saline group (*m*-nerolidol $P < 0.05$, *m*-farnesol $P < 0.01$; Fig. 3). When their concentrations were increased to 500 mg/kg, both compounds reduced the cisplatin-induced kaolin intake at days 1 and 2 ($P < 0.01$). Neither *m*-farnesol nor *m*-nerolidol alone had a significant effect on the kaolin intake (Fig. 3B).

Farnesol and Nerolidol Effects on Cisplatin-Induced Changes in Body Weight, Food and Water Intake.

In addition to NV, cytotoxic chemotherapy also suppress appetite for food and reduces body weight (for review, see Suzuki et al., 2013). In our experiments, cisplatin reduced body weight and food and water intake (Fig. 4). Unexpectedly, animals treated with *m*-farnesol were less affected by cisplatin-induced side effects. Cisplatin caused weight loss in all tested groups but was significantly reduced by 100 mg/kg ($P < 0.05$, RM AVOVA) and 500 mg/kg ($P < 0.01$, RM AVOVA) *m*-farnesol treatment (Fig. 4A). After 4 days of cisplatin administration, rats treated with *m*-farnesol, 100 and 500 mg/kg, retained $86\% \pm 2.4\%$ and $92\% \pm 4.8\%$ of their original body weight, respectively, and that was significantly higher than the control group weight ($83\% \pm 2.2\%$, $P < 0.05$). In contrast, neither *m*-nerolidol nor ondansetron affected cisplatin-induced weight loss. Cisplatin-treated animals consumed progressively smaller amounts of food, whereas animals treated with *m*-farnesol (500 mg/kg) consumed significantly more food than did the control groups on days 1 and 4 ($P < 0.05$, RM AVOVA) (Fig. 4B). Moreover, *m*-farnesol (100 and 500 mg/kg) and ondansetron significantly inhibited the cisplatin-induced decreases in water intake at day 4 ($P < 0.05$ or 0.01). Meanwhile, *m*-nerolidol had no effect on cisplatin-induced decrease in food and water intake (Fig. 4C). *M*-farnesol (500 mg) alone did not affect body weight or food and water intake compared with saline-treated controls ($P > 0.05$).

Farnesol and Nerolidol Inhibit 5-HT Currents in Sensory Neurons. Our work has revealed a novel antiemetic efficacy of farnesol and nerolidol against CINV. The mechanisms or sites of action for these antiemetic compounds are not known. Recent studies of the natural monoterpenoids (i.e., menthol, citral, and linalool) indicate efficacy in 5-HT₃R inhibition (Ashoor et al., 2013; Jarvis et al., 2016). These results, coupled with the finding that 5-HT₃R selective antagonists suppress CINV (Tyers and Freeman, 1992), suggest that this receptor may be targeted. As 5-HT₃R are prominently

Fig. 3. Effects of *m*-nerolidol (Nel) and *m*-farnesol (Far) on cisplatin-induced kaolin intake. (A) Nerolidol (100 and 500 mg/kg, p.o.) and farnesol (100 and 500 mg/kg, p.o.) were administered 60 minutes before cisplatin. * $P < 0.05$; ** $P < 0.01$ vs. cisplatin-saline-treated group. (B) Nerolidol and farnesol were administered 60 minutes before saline. All data are expressed as mean $\pm$ S.E.M.

Fig. 4. Effects of farnesol (Far), nerolidol (Nel), and ondansetron (Onda) on cisplatin (Cis)-induced body weight (A), food intake (B), and water intake (C) in rats. Farnesol (100 and 500 mg/kg, p.o.), nerolidol (100 and 500 mg/kg, p.o.), and ondansetron (3 mg/kg, p.o.) were administered 60 minutes before cisplatin (6 mg/kg, i.p.) injection. Data are expressed as mean $\pm$ S.E.M. $n = 6$ to 7. * $P < 0.05$; ** $P < 0.01$ compared with cisplatin-saline.

expressed in vagal afferents, which participate in emetic pathways (Babic and Browning, 2014), we decided to test farnesol and nerolidol on visceral afferent nodose neurons.

5-HT induced inward currents in 38% ($n = 70/184$ neurons) of the tested neurons, as previously reported (Kim et al., 2015). This response was completely inhibited by the 5-HT₃R-selective antagonist ondansetron ($n = 8$). The 5-HT-evoked inward currents increased in a concentration-dependent manner (Fig. 5). The 5-HT current amplitude was well fit by the Michaelis-Menten equation, in which the EC_{50} and the Hill coefficient were 9.1 and 1, respectively. Thus, fast application of $\geq 1 \mu\text{M}$ 5-HT evoked inward current responses in nodose neurons by activating 5-HT₃Rs.

We tested the effect of farnesol and nerolidol on the 5-HT₃R currents, including their stereoisomers and racemic mixtures independently. In addition, we compared linalool, a monoterpene alcohol, to compare with farnesol and three forms of nerolidol (*cis*- and *trans*-isomers and their racemic mixture) (Fig. 6A). The order of inhibitory potency was

cis-nerolidol > *m*-nerolidol > *trans*-nerolidol. The IC_{50} of *m*-nerolidol was 2-fold lower than *trans*-nerolidol and 1.3 times higher than *cis*-nerolidol (Table 1). Farnesol has four different isomers; among them, *trans, trans* from isomer is the most common in nature. *Trans, trans*-farnesol, and a racemic mixture of farnesol (*m*-farnesol) inhibited the 5-HT response in a concentration-dependent manner (Fig. 6B) with an estimated IC_{50} s of 2.7 and 3.9 μM for *trans, trans*-farnesol, and *m*-farnesol, respectively (Table 1); however, linalool failed to inhibit 5-HT response, even at 100 μM . In summary, *cis*-nerolidol and *trans, trans*-farnesol have the highest inhibitory efficacies against 5-HT currents in nodose neurons, respectively.

Farnesol and Nerolidol Act as Noncompetitive Antagonists. To characterize the inhibitory mechanism of farnesol and nerolidol on the 5-HT₃Rs, 5-HT concentration-response curves were examined in the presence of *cis*-nerolidol or *trans, trans*-farnesol. The maximum responses to 1 mM 5-HT were significantly decreased by *cis*-nerolidol ($P < 0.05$, $n = 5$) to $82\% \pm 5.9\%$, $45\% \pm 3.5\%$, and $19\% \pm 2.0\%$ of control values for

Fig. 5. 5-HT-induced inward current in acutely dispersed afferent vagus neurons. The traces show that 5-HT evoked currents at selected concentrations. In the same neurons, 100 nM ondansetron (Ondan) blocked 1 mM 5-HT-induced currents. The graphs show concentration-response relationships for 5-HT. Points and vertical lines represent the mean and S.E.M. from eight different neurons. All current recordings were made at a holding potential of -50 mV.

2, 5, and 10 μM , respectively (Fig. 7); however, the EC_{50} value for 5-HT was not affected by *cis*-nerolidol ($P > 0.05$). Analysis with Lineweaver-Burk double reciprocal plot indicates that *cis*-nerolidol inhibits the 5-HT response noncompetitively. Similarly, *trans, trans*-farnesol significantly decreased 1 mM 5-HT responses ($P < 0.05$, $n = 5$) to $98\% \pm 0.1\%$, $67\% \pm 11.2\%$, and $48\% \pm 12.4\%$ of control values, for 1, 3, and 5 μM , respectively, without altering the 5-HT EC_{50} ($P > 0.05$).

Fig. 6. Effects of isomers and racemic mixtures of the nerolidol and farnesol on 5-HT-induced responses. The neurons were pretreated for 1 minute with an external solution containing each compound before the simultaneous application with 5-HT. (A) The traces shown are inhibition of 3 μM 5-HT-evoked current by *cis*- and *trans*-nerolidol. Upper and lower traces were taken from different sets of neurons. The graph represents the concentration-inhibition relationship of *cis*-, *trans*-, and racemic mixture-nerolidol. (B) The traces shown are inhibition of 5-HT-evoked current by racemic mixture- and *trans, trans*-farnesol. Upper and lower traces were taken from different set of neurons. The graph represents the concentration-inhibition relationship of racemic mixture- and *trans, trans*-farnesol and linalool. All responses were normalized to the peak current induced by 3 μM 5-HT alone. Each point and the vertical lines represent the mean and S.E.M. from five to seven neurons.

Lineweaver-Burk analysis shows that *trans, trans*-farnesol also inhibits the 5-HT response noncompetitively.

Discussion

Our experiments indicate that naturally occurring racemic mixtures of *m*-farnesol and *m*-nerolidol acting at 5-HT₃Rs exert antiemetic efficacy in a cisplatin-induced pica behavior assay. *M*-farnesol also reduced the cisplatin-induced decreased weight and food and water intake. A selective 5-HT₃R antagonist, ondansetron, and *m*-nerolidol had no effect on the cisplatin-induced decrease in weight and food and water intake. Our electrophysiologic recordings indicate that sesquiterpene alcohol isomers of farnesol and nerolidol inhibited 5-HT-evoked responses in a concentration-dependent manner at vagal afferent neurons, a potential site of action in the behavioral assays. The order of inhibitory potency was *trans, trans*-farnesol > racemic mixture-farnesol (*m*-farnesol) > *cis*-nerolidol > racemic mixture-nerolidol (*m*-nerolidol) > *trans*-nerolidol. The highest potency inhibitors, *trans, trans*-farnesol, and *cis*-nerolidol, noncompetitively inhibited 5-HT nodose responses.

Antiemetic Action of Farnesol and Nerolidol against Cytotoxic CINV. Pica behavior in rats closely parallels the pharmacologic mechanisms of vomiting in humans (Takeda et al., 1993). Here, we found that naturally occurring racemic mixtures of farnesol suppressed cisplatin-induced kaolin consumption. Thus, both farnesol and nerolidol exerted antiemetic efficacy against cytotoxic CINV.

Isomers of the farnesol and nerolidol inhibited 5-HT₃R-mediated 5-HT responses on visceral afferent neurons. Emetogenic chemotherapy increases 5-HT concentrations in the plasma and intestine (Schwörer et al., 1991; Castejon et al., 1999), and this elevated the activity of the gastrointestinal visceral afferents through 5-HT₃R activation (Horn et al., 2004). Hence, selective 5-HT₃R competitive antagonists are prescribed to alleviate CINV. Despite the appropriate use of diverse kinds of antiemetic drugs, many cancer patients still suffer from CINV (Pillai et al., 2011; Hernandez Torres et al., 2015) suggesting the need for new, alternative classes of antiemetic agents. Recent clinical trials found that add-on use of ginger augmented conventional

Fig. 7. Characterization of the inhibition by *cis*-nerolidol and *trans, trans*-farnesol (*t,t*-farnesol). (A) Lineweaver-Burk plot showing the mode of inhibition of *cis*-nerolidol. The concentration-response curves for 5-HT-induced responses were obtained in the presence of 2 ($\square$), 5 ($\circ$), and 10 μ M ($\triangle$) of *cis*-nerolidol. (B) Lineweaver-Burk plot showing the mode of inhibition of *t,t*-farnesol. The concentration-response curves for 5-HT-induced responses were obtained in the presence of 1 ($\square$), 3 ($\circ$), and 5 μ M ($\triangle$) of *t,t*-farnesol. All responses were normalized for the peak current induced by 1 mM 5-HT alone. The IC₅₀ value was calculated by fitting the data using nonlinear regression (Origin 7). Each point is the average of five experiments. Vertical bars show +S.E.M.

antiemetic medications for resistant NV (Ryan et al., 2009; Pillai et al., 2011). These ginger-mediated antiemetic actions have been attributed to the noncompetitive inhibition of 5-HT₃Rs by its major constituents, gingerol and shogaol (Jin et al., 2014). Until now, several 5-HT₃R noncompetitive antagonists have been derived from plant constituents (i.e., citral, linalool, eucalyptol, and menthol) (Ashoor et al., 2013; Jarvis et al., 2016); however, none of these has greater inhibitory efficacy at 5-HT₃Rs than ginger constituents. Besides their antiemetic efficacy against CINV, their characterizations are quite incomplete. In contrast, isomers of the farnesol and nerolidol have lower IC₅₀ values than any currently known compounds. Taken together, our current results indicate that

isomers of the farnesol and nerolidol have promising potency in therapy-resistant CINV.

Farnesol Effects on Cisplatin-Induced Reduced Food Intake and Weight Loss. In addition to NV, cytotoxic chemotherapy causes appetite loss (anorexia) and weight loss (Kokal, 1985; Holmes, 1993; Andreyev et al., 1998; De Jonghe et al., 2009). Patient weight loss is associated with poor outcomes (Andreyev et al., 1998; Hess et al., 2007). The progesterone derivative megestrol acetate (MA) and cannabis-based medicines stimulate appetite and reduce weight loss in cancer patients (Jatoi et al., 2002; Walsh et al., 2005; Brisbois et al., 2011; Cuvelier et al., 2014). Despite their positive efficacy, significant side effects can curtail their use. For example, MA treatment can cause adrenal insufficiency in cancer patients with weight loss (Meacham et al., 2003; Orme et al., 2003). Meanwhile, the cannabis-based medicine induces psychotropic side effects through activating cannabinoid type 1 receptor in the central nervous system (Parmar et al., 2016). In contrast, farnesol is a common plant constituent long used in food, medicine, and perfume (Suryawanshi, 2011; Scheman et al., 2014). In many countries, farnesol flavors food so that there are no specific health concerns related to its ingestion (Lewis, 1989). Farnesol has antimicrobial and antineoplastic use (Jabra-Rizk et al., 2006; Joo et al., 2010). Our report now shows promising use in chemotherapy-associated appetite and

TABLE 1

Half-maximum inhibition concentration (IC₅₀) for nerolidol and farnesol isomers on serotonin (5-HT)-evoked currents in nodose neurons

The IC₅₀ was determined by fitting the data obtained from five to six cells to concentration-inhibition equation in the method using a least-square fitting routine.

Compound	IC ₅₀ (M)
<i>Cis</i> -nerolidol	4.89×10^{-6}
<i>Trans</i> -nerolidol	1.32×10^{-5}
<i>Racemic mixture</i> -nerolidol	6.58×10^{-6}
<i>Trans, trans</i> -farnesol	2.66×10^{-6}
<i>Tacemic mixture</i> -farnesol	3.96×10^{-6}

weight loss. Farnesol alone did not affect food intake in our saline-treated control animals (Fig. 3). Hence, its appetite-stimulating efficacy is specific for anorexia of chemotherapy. The mechanism of action of farnesol represents a quite different approach compared with MA or cannabis-based therapies. Further studies are needed to elucidate these mechanisms.

In conclusion, we have found a novel antiemetic efficacy of the farnesol and nerolidol. These edible sesquiterpene alcohol constituents noncompetitively inhibited 5-HT₃-induced responses. This antiemetic mechanism of action may help inhibit conventional antiemetics (5-HT₃R competitive antagonists) by overlapping the inhibition of serotonergic emetogenic signaling. Therefore, farnesol has promising efficacy for suppress antiemetic drug-resistant CINV and improving appetite and weight loss without serious side effects.

Acknowledgments

We thank Dr. M. C. Andresen for the critical reading of this article.

Authorship Contributions

Participated in research design: Lee, Jin.

Conducted experiments: Lee, Yang, Kim.

Performed data analysis: Lee, Kim, Jin.

Wrote or contributed to the writing of the manuscript: C. -S. Park, Y. S. Park, Jin.

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