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The Putative Glyoxalase 1 Inhibitor Piceatannol Exhibits Both Anxiolytic-like and Antitumor Effects in Mice

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Abstract. *Background/Aim: This study aimed to determine the anxiolytic effect of a putative glyoxalase 1 inhibitor, piceatannol, as well as its antitumor activities on the stress-induced tumor growth of Lewis lung carcinoma. Materials and Methods: The anxiolytic activities of piceatannol (1-30 mg/kg) were assessed using the elevated plus maze (EPM) test. We also evaluated the pharmacological modulation of stress-induced tumor growth; the mice were treated with piceatannol (3 and 30 mg/kg) from the 10th day till the 19th day after administration of the LLC cells. Results: At the low dose (3 mg/kg), piceatannol significantly increased the time spent in the open arms of the EPM test when compared with the vehicle. At higher doses (30 mg/kg), it significantly suppressed the stress-induced enhancement of tumor growth. Conclusion: A low dose of piceatannol exerts an anxiolytic effect, and high doses have an antitumor effect.*

In the glycolytic pathway, methylglyoxal, a highly reactive α-dicarbonyl compound, is produced through glyceraldehyde-3-phosphate, which is an intermediate product of glucose metabolism (1). Since methylglyoxal is known to be highly cytotoxic by itself, it is eliminated by the glyoxalase system (1). The major enzyme of the glyoxalase system is glyoxalase 1 (Glo1) (1). Behavioral analyses and genetic manipulation of Glo1 in the rodent brain suggest a link between Glo1 and anxiety disorder, making it a potential novel target for anxiolytic agents (2). For example, Glo1 overexpression in the mouse brain reportedly enhances anxiety-related behaviors (3). Conversely, in comparison to heathy individuals, a reduction in the Glo1 mRNA expression has been observed in major depressive and bipolar disorder patients (4). Presumably, these patients had high levels of Glo1 protein, which resulted in the down-regulation of mRNA expression. However, methylglyoxal has been reported to exert anxiolytic effects in mice (5). The concentration of methylglyoxal was altered in the brain tissues of a trait anxiety mouse model; higher levels of methylglyoxal were observed in animals with anxiolytic-like behavior compared to those with anxiety-related behavior (5), indicating that the brain methylglyoxal levels are negatively associated with anxiety.

Piceatannol (a natural analog of resveratrol) is a natural compound that is present in high concentrations in passion fruit seed (6). It has been reported that piceatannol has a more potent inhibitory activity against human Glo1 than resveratrol (7). The antiproliferative effects of piceatannol on several cancer cells have already been demonstrated (6), and several mechanisms leading to piceatannol-induced apoptosis have also been elucidated (8). Moreover, Takasawa *et al.* (7) have found for the first time that the antiproliferative effects of piceatannol are Glo1-dependent. Therefore, Glo1 is a novel target for piceatannol-based cancer treatment.

This study aimed to determine the effect anxiolytic of the putative Glo1 inhibitor piceatannol using the elevated plus maze (EPM) test. Moreover, we examined the antitumor activities of piceatannol on stress-induced tumor growth in Lewis lung carcinoma (LLC)-bearing mice.

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Key Words: Glyoxalase 1, piceatannol, anxiolytic effect, antitumor effect.

Materials and Methods

Animals. Male, 7-week-old C57BL/6N mice were purchased from Japan SLC (Shizuoka, Japan), housed in cages in groups of six, and given free access to food and water. The room temperature was controlled (23˚C±1˚C), and a 12-h light, 12-h dark schedule was maintained. All experimental protocols were approved by the Institutional Animal Care and Use Committee at the Tokyo University of Science.

Tumor cells. LLC cells (Riken Cell Bank, Tsukuba, Japan) were cultured in Dulbecco's modified Eagle's medium containing low glucose, L-glutamine, phenol red (FUJIFILM Wako Pure Chemical Industries, Osaka, Japan), 10% fetal bovine serum (Capricorn Scientific GmbH, Ebsdorfergrund, Germany), and penicillin–streptomycin solution (×100; FUJIFILM Wako Pure Chemical Industries). The cell culture was maintained in a water-humidified incubator at 37˚C and 5% CO_2.

Drugs. Piceatannol (Tokyo Chemical Industry, Tokyo, Japan) was dissolved in a vehicle solution containing 5% dimethyl sulfoxide (FUJIFILM Wako Pure Chemical Industries), 5% Tween 80 (Tokyo Chemical Industry, Tokyo, Japan), and 90% saline. Subsequently, sodium lactate solution (50%, FUJIFILM Wako Pure Chemical Industries) was diluted in saline (concentration: 10 mg/ml).

WST-8 assay. The WST-8 assay was performed as described previously (6). LLC cells were seeded on 96-well plates at a density of 1000 cells per well. The treated cells were cultured for 24 h in culture media that included piceatannol (10 or 100 μM) or the vehicle. Then, WST-8 reagent (Dojindo Laboratories, Kumamoto, Japan) was added to each well and the cells were incubated for 2 h at 37˚C. The absorbance was measured with a microplate reader at 450 nm.

EPM test. The EPM test was performed as described previously (9). The test consisted of four arms: two open arms (6×29.5 cm) and two closed arms (6×29.5 cm) enclosed by 55 cm-high walls. Each arm had a delimited central area (6×6 cm). The entire maze was elevated to a height of 55 cm above the floor and illuminated by a dim light (12 or 35 lux) at the end of each open arm. The mice were brought to the corner of the experimental room at least 60 min before the start of the experiment. At the beginning of a test session, the mice were placed in the center of the maze facing one of the open arms. Entry into an arm was defined as the animal placing the two front paws over the line marking that area. The number of open- and closed-arm entries and the time spent in the open arms were recorded during the 5 min test period. The proportion of time spent in the open arm of the maze [(open arm time/total test time) ×100] and the total entries (open arm entries + closed-arm entries) were calculated for each animal.

The pretreatment times and doses of drugs used were 30 min for piceatannol [1, 3, 10, and 30 mg/kg, subcutaneously (*s.c.*)] and 10 min for sodium lactate (100 mg/kg, *s.c.*). The effects of the drugs were examined while referring to their pharmacological potency as described previously (10, 11).

Stress model. Immobilization stress was performed as described previously (12). The mice were exposed to an immobilization stressor, wherein the animals were enclosed in a plastic tube (3 cm in diameter and 10 cm in length). A hole at the tip of the tube allowed for breathing, and the mice were immobilized for five consecutive nights during their active period each day (between 17.00 and 09.00).

Transplantation model (intraplantar tumor model). After immobilization stress, a tumor-bearing model was produced by the injection of LLC cells [50 μl; 1×10^6 cells suspended in D-PBS(–)] into the plantar surface of the right hind paw of mice under anesthesia with 3% isoflurane (Pfizer, Co., Ltd., Tokyo, Japan). The control group comprised naive mice (non-stress group) that were injected with 50 μl of LLC cells in the plantar surfaces of the right hind paws. Paw thickness (tumor volume) was measured at 10, 14, and 20 days using a Vernier caliper. All tumor-bearing mice were euthanized by day 20. The animals were individually housed after the implantation of the LLC cells.

To evaluate the pharmacological modulation of the stress-induced tumor growth, the mice were treated with piceatannol (3 and 30 mg/kg, *s.c.*) on the 10th day to 19th day after the administration of the LLC cells.

Transplantation model (subcutaneous tumor model). LLC cells were suspended in 0.1 ml of D-PBS (–) at a concentration of 1×10^6 cells as a mixture of 0.1 ml of Corning® Matrigel® Growth Factor Reduced Basement Membrane Matrix (Catalog #354230; Corning, NY, USA). This suspension mixture (0.2 ml) was then transplanted (*s.c.*) into the right flank of the anesthetized (3% isoflurane) mice. The tumor volume was measured at 10, 12, 14, 16, 18, and 20 days using a caliper and calculated as (length × width × width)/2. The animals were individually housed after the implantation of the LLC cells.

The mice were treated with piceatannol (30 mg/kg, *s.c.*) on the 10th day to 19th day after the administration of the LLC cells to evaluate the antitumor effect.

Data analysis. Data are expressed as mean±standard error of the mean (SEM) and were evaluated using the one-way analysis of variance (ANOVA) or two-way ANOVA tests followed by Bonferroni's *post-hoc* test. The statistical analysis for two-group comparisons was performed using unpaired *t*-test with Welch's correction. All statistical analyses were performed using Prism version 5.0 (GraphPad Software, Inc., San Diego, CA, USA).

Results

The EPM test. At low doses, piceatannol (1 and 3 mg/kg, *s.c.*) dose dependently and significantly increased the time spent in the open arms of the EPM test when compared with the vehicle [one-way ANOVA, $F(4, 25)=4.12$, $p=0.0107$; Bonferroni's test, 3 mg/kg, $^*p<0.05$ *vs.* vehicle; Figure 1a]. At doses greater than 3 mg/kg, a dose-dependent decrease in the time spent in the open arms of the EPM test was noted (Figure 1a). In contrast, sodium lactate (100 mg/kg, *s.c.*) decreased the time spent in the open arms of the EPM test compared with saline (T-tests, $p=0.0002$, $^{***}p<0.005$ *vs.* saline; Figure 1b).

The WST-8 assay. Piceatannol (100 μM) suppressed the viability (% of the vehicle) of LLC cells (Table I).

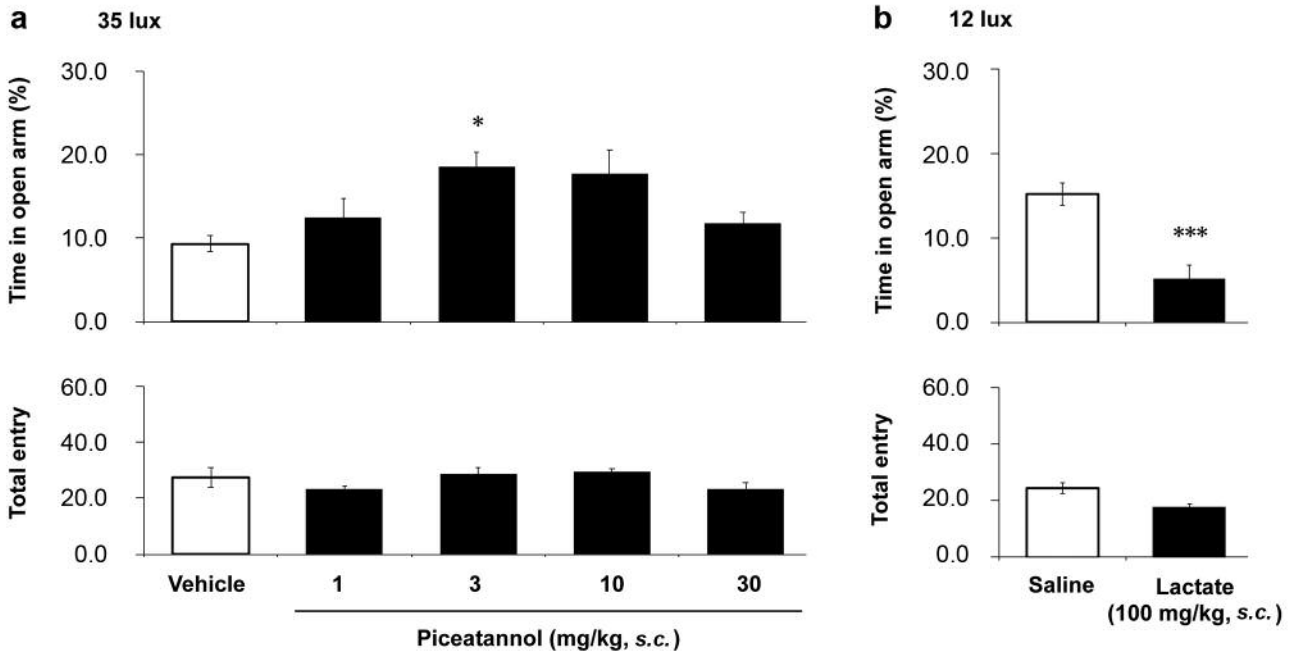

Figure 1. *Effects of piceatannol (a; n=6 mice per group) or sodium lactate (b; n=6 mice per group) using the EPM test in mice. Each column represents the mean±standard error of the mean (SEM) of the proportion of time spent in the open arms (upper panel) or the number of total entries (bottom panel) for 5 min. *p<0.05, ***p<0.005 versus the saline- or vehicle-treated groups.*

The effect of piceatannol on stress-induced tumor growth. Figure 2a shows the experimental timeline. As shown in Figure 2b, after 20 days, the mice exposed to immobilization stress presented with increased tumor volumes compared with those in the non-stress group (two-way ANOVA column factor, $p<0.0001$; row factor, $p<0.0001$; interaction, $p=0.0001$; Bonferroni's test, $^{***}p<0.005$ *vs.* non-stress). The antitumor activities of piceatannol were tested using LLC tumor-bearing mice after the immobilization stress. Piceatannol (3 and 30 mg/kg, *s.c.*) dose dependently and significantly decreased the paw thickness (tumor volume) when compared with the stress + vehicle group (two-way ANOVA column factor, $p<0.0001$; row factor, $p<0.0001$; interaction, $p=0.0001$; Bonferroni's test, $^{\#}p<0.05$, $^{\#\#\#}p<0.005$ *vs.* stress + vehicle; Figure 2b).

The effect of piceatannol on tumor growth in the LLC-bearing mouse model. Figure 3a shows the experimental timeline. As shown in Figure 3b, repeated administration of piceatannol (30 mg/kg) significantly suppressed tumor growth in the LLC-bearing mice when compared with the control mice (vehicle groups). No significant differences in body weight were observed between the two groups (Figure 3c).

Discussion

Epidemiological studies and animal experiments have shown that stress might alter tumor growth (13). For example, Thaker *et al.* (14) have reported that chronic behavioral stress results in higher levels of catecholamines in the tissues, greater tumor burden, and more invasive tumor growth in the mouse model. Conversely, it has been reported that the first weeks after cancer diagnosis appeared to be a highly stressful time for all patients (15). As a result, patients who received a cancer diagnosis presented with increased risks of suicide compared with cancer-free individuals (15). Therefore, pharmacological interventions to reduce stress may help improve cancer outcomes.

Table I. *The antiproliferative effect of piceatannol on LLC cells.*

	Cell viability (% of the vehicle)
Vehicle	100.0±1.11
Piceatannol (10 μM)	106.2±3.57
Piceatannol (100 μM)	71.1±5.37**

Data are shown as the mean±SEM of three independent experiments; $^{**}p<0.001$ *versus* vehicle.

This is the first study to demonstrate the anxiolytic effects of the putative Glo1 inhibitor piceatannol in mice. Our results are consistent with those of a previous report, which demonstrated the anxiolytic-like effects of the Glo1 inhibitor BrBzGCp2 in mice (16). The anxiolytic effects of piceatannol may be associated with an increase in the levels

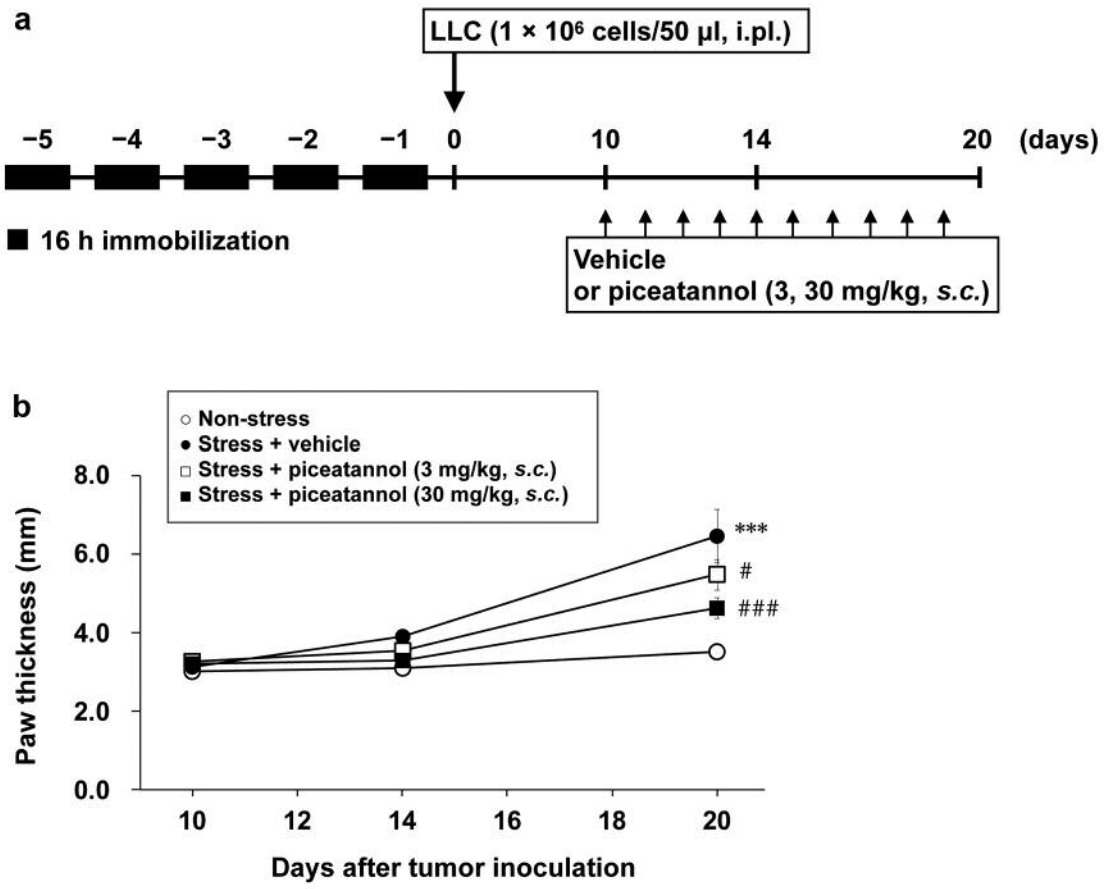

Figure 2. *Figure showing the experimental timeline (a). The effect of piceatannol on LLC growth after immobilization stress (b; n=6 mice per group). Paw thickness was measured at 10, 14, and 20 days using a Vernier caliper. Each point represents the mean±SEM of the paw thickness. ***p<0.005 versus the non-stress group; #p<0.05, ###p<0.005 versus the stress + vehicle group.*

of methylglyoxal. The glyoxalase system catalyzes the conversion of cytotoxic methylglyoxal to non-toxic D-lactate via the intermediate S-D-lactoylglutathione (1). Therefore, the inhibition of glyoxalases results in a decrease in D-lactate release leading to an increase in methylglyoxal levels. Piceatannol-induced anxiolytic effects are likely mediated through the regulation of methylglyoxal by Glo1 because methylglyoxal acts as a competitive partial agonist of the gamma-aminobutyric acid $(GABA)_A$ receptors (16). Contrary to piceatannol, previous reports (11) and this study have demonstrated that the administration of sodium lactate produces anxiety-like behaviors in rodents. We did not determine whether piceatannol increases the level of methylglyoxal or decreases the level of lactate in this study.

In this study, piceatannol demonstrated not only anxiolytic effects but also antitumor effects. As shown in Table I, piceatannol (100 µM) treatment suppressed the proliferation of LLC cells although it is not known whether these cells have high expression levels of Glo1. Furthermore, this study confirmed that piceatannol (3 mg/kg), which showed anxiolytic effects, slightly suppressed the stress-induced enhancement of tumor growth in LLC-bearing mice. At higher doses, piceatannol (30 mg/kg) significantly suppressed the stress-induced enhancement of tumor growth. According to a previous report, the concentration of piceatannol (10 mg/kg) administered intravenously in rats was approximately 40 µM (17). These results indicate that repeated administrations of piceatannol (3 mg/kg) are not sufficient for the exertion of antitumor effects. However, the anxiolytic effect of piceatannol appears to have contributed to the attenuation of the stress-induced enhancement of tumor growth in the animals.

Methylglyoxal is a byproduct of tumor-specific aerobic glycolysis (1). Methylglyoxal is highly reactive with DNA, RNA, and proteins, and it is believed to induce apoptosis in tumor cells (18). Therefore, the antitumor effect of piceatannol might be due, at least in part, to an increase in the level of methylglyoxal via Glo1 inhibition. Alternatively, several mechanisms leading to piceatannol-induced apoptosis

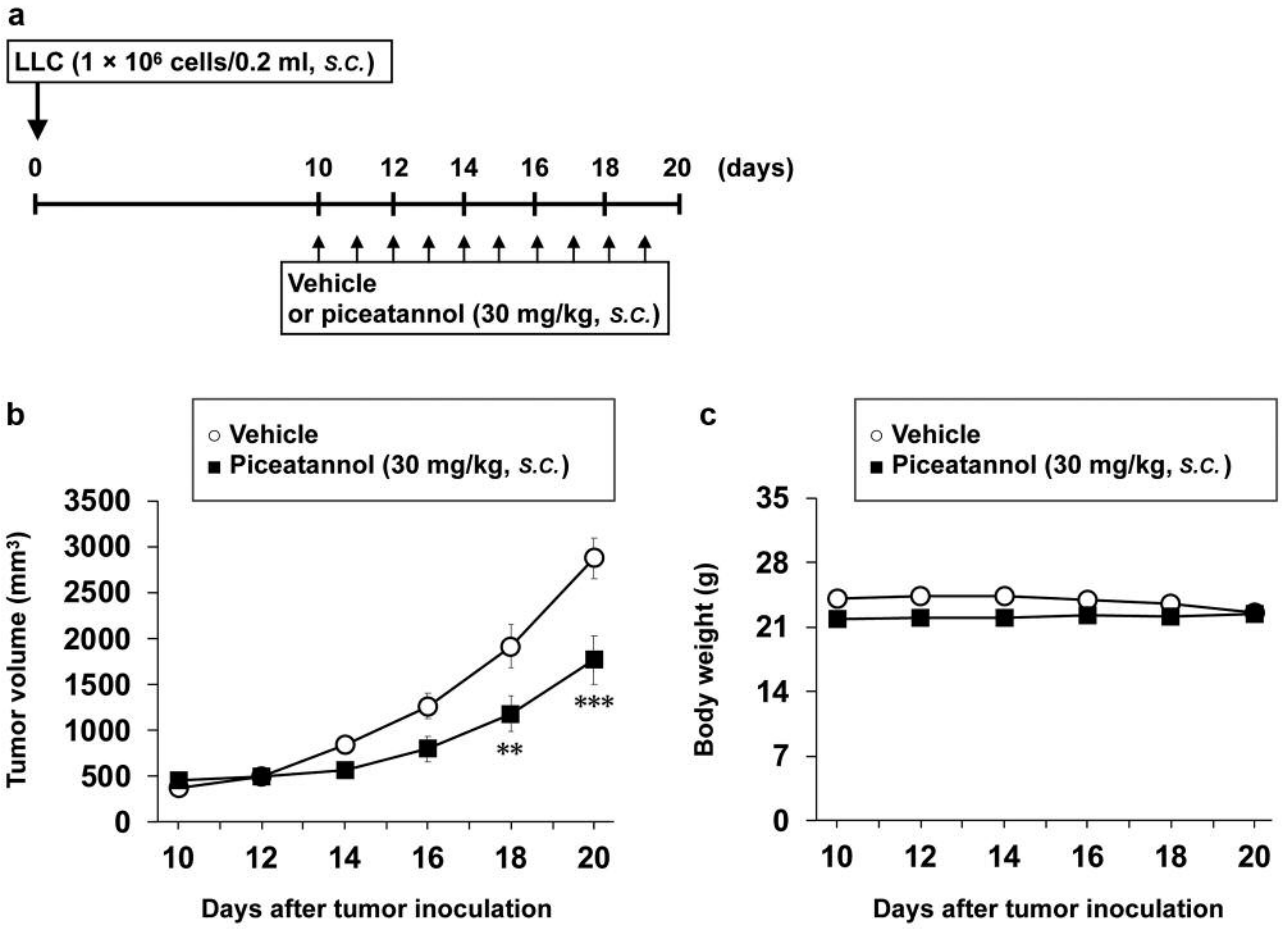

Figure 3. *Figure showing the experimental timeline (a). The effect of piceatannol on LLC-bearing mice (b; n=6 mice per group). Tumor volume was measured at 10, 12, 14, 16, 18, and 20 days using a Vernier caliper. Tumor volume=length × width × width/2. Each point represents the mean±SEM of the tumor volume. **p<0.01, ***p<0.005 versus the vehicle group.*

have already been suggested (8) including the phosphatidylinositol-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR), cyclooxygenase-2 (COX-2), and interleukin-6 (IL-6)/signal transducer and activator of transcription 3 (STAT3) pathways (8). Interestingly, the stress model mice (12), referenced in this study, demonstrated that stress induces the accumulation of myeloid-derived suppressor cells (MDSCs), which can contribute to immunosuppression. Furthermore, the COX-2-prostaglandinE2 (PGE2) loop has been shown to mediate the accumulation of MDSCs (12). Taken together, the antitumor effects of piceatannol on stress-induced tumor growth might also be partly related to the inhibition of COX-2. In other words, the stress-induced enhancement of tumor growth observed in this study is complicated by cancer cell growth and inflammation. Therefore, it was necessary to determine whether 30 mg/kg of piceatannol had antitumor and/or anti-inflammatory effects. It has been demonstrated that piceatannol exerts antitumorigenic activities in several cell lines and animal models (8). In this study, we confirmed that tumor growth was markedly suppressed in piceatannol (30 mg/kg)-treated LLC-bearing mice compared with the controls, thus indicating that a high dose of piceatannol has antitumor activities. These results indicate that the anti-inflammatory effect of piceatannol is unlikely to be involved in the suppression of stress-induced tumor growth.

In conclusion, we have demonstrated that low doses of piceatannol exert anxiolytic-like effects, whereas at high doses this agent can exert antitumor effects. Moreover, the anxiolytic activity of piceatannol was found to attenuate the stress-induced enhancement of tumor growth in the LLC-bearing mice.

Conflicts of Interest

The Authors declare that they have no conflicts of interest regarding this study.

Authors' Contributions

K.Y. and R.T. designed the experiments and wrote the manuscript. M.T. and S.U. conducted some of the *in vivo* and the *in vitro* experiments. H.S. and Y.K. provided scientific and technical advice. K.Y. supervised the overall project and contributed towards the design of the protocol and the writing of the manuscript. All of the Authors discussed the results and commented on the manuscript. All Authors have critically reviewed content and approved the final version submitted for publication.

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