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The Evaluation of the Single-Dose Toxicity and Safety of 4-Carvomenthenol in ICR Mice

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Background: 4-carvomenthenol[4-methyl-1-(1-methylethyl)-3-cyclohexen-1-ol] is a main component of *Origanum vulgare* L., *Zanthoxylum piperitum* (L.) DC., and other plants. It has been reported to exhibit anti-inflammatory, antibacterial, and anti-tumor effects. Furthermore, it is necessary to conduct a toxicity test on 4-carvomenthenol to ensure its safety.

Methods: This study included 5-week-old Institute of Cancer Research mice that were categorized into 3 treatment groups (12, 25, and 50 mg/kg 4-carvomenthenol dose levels) and a control group (10% dimethyl sulfoxide, 40% polyethylene glycol 300, 5% Tween 80, and 45% normal saline injection of the final volume), with 5 male mice and 5 female mice per group. All groups were observed for clinical symptoms and body weight in a period of 14 days and were subjected to gross necropsy after euthanasia.

Results: No deaths were recorded. No test substance-related clinical signs in the female mice of the 12 mg/kg dose group were observed. Abnormal gait was observed in 1 male from day 1 to day 3 in the 12 mg/kg dose group; 1–3 males from day 1 to day 7 and 1–5 females from day 1 to day 15 in the 25 mg/kg dose group; and 2–5 males and 2–5 females from day 1 to day 15 in the 50 mg/kg dose group. No test substance-related effect on the body weight and necropsy findings was observed.

Conclusion: The results of this study suggested that the lethal dose of 4-carvomenthenol could be greater than 50 mg/kg. However, further research is needed, especially repeated-dose toxicity studies, to confirm the efficacy and safety of 4-carvomenthenol.

Keywords: 4-methyl-1-(1-methylethyl)-3-cyclohexen-1-ol; Medicinal herb; Toxicity test; Toxicology

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INTRODUCTION

Herbal medicine has consistently played an important role in health management. A great majority of the global population (approximately 80%) depends on the use of herbal medicine for their healthcare [1]. However, only a few studies have focused on the safety of herbal medicine [2], which raises a growing concern about the potential side effects of herbal medicine [3,4].

The appropriate drug dosage is highly crucial in the treatment process. This is because even though a drug has an anticipated beneficial effect at a particular dose, it can be toxic when administered at higher doses [5]. Therefore, conducting a toxicity test is crucial to ensure the safe use of herbal medicine.

4-carvomenthenol[4-methyl-1-(1-methylethyl)-3-cyclohexen-1-ol] is a main component of *Origanum vulgare* L. and *Zanthoxylum piperitum* (L.) DC. (*Z. piperitum* DC.) [6,7]. *Origanum vulgare* and *Z. piperitum* are used in various fields, including the food, medical, and cosmetic sectors [8,9].

A comprehensive investigation has been conducted to understand the effects of 4-carvomenthenol. Based on the findings of the literature, it has been shown that 4-carvomenthenol exhibits anti-inflammatory and immunomodulatory properties. Bezerra Barros et al. [10] found that 4-carvomenthenol alleviated the symptoms of allergic rhinitis and asthma by suppressing interleukin-13 and mucus production in mice. Previous studies also revealed its significant antibacterial effectiveness against both Gram-positive and Gram-negative bacteria [6,11]. Moreover, it also possesses anticancer properties by triggering apoptosis in the colorectal tumor cells of mice [12].

Considering the various effects and the wide range of uses of plants containing 4-carvomenthenol, it is important to ensure the safe use of 4-carvomenthenol. However, toxicity related to the dosage of 4-carvomenthenol has not been investigated. Therefore, the aim of this study is to evaluate the potential toxicity and approximate lethal dose of 4-carvomenthenol.

MATERIALS AND METHODS

1. Test substance

4-carvomenthenol (purit, 99.0%; conten, p-Menth-1-en-4-ol and 95–100%; molecular weight, 154.25 g/mol; Sigma-Aldrich) was suspended sequentially with 10% dimethyl sulfoxide (DMSO, Sigma-Aldrich), 40% polyethylene glycol (PEG) 300 (Sigma-Aldrich), 5% Tween 80 (Sigma-Aldrich) of the final volume. The dosing formulation was prepared to the desired concentration with the normal saline injection (JW Pharmaceutical Co., Ltd.). The dose was prepared on the same day of administration.

2. Experimental animals

This study employed Institute of Cancer Research (CRlOri: CD1 [ICR]) mice (Orient Bio Inc.) as they have abundant historical control data and are commonly used in toxicity studies. A total of 48 5-week-old mice were included in this study, which comprised 24 male mice weighing between 26.3 and 30.8 g and 24 female mice weighing between 22.1 and 25.1 g.

Throughout the quarantine-acclimation period, these mice were observed daily for any clinical signs. No abnormalities were observed in any of them. The experiment conditions are as follows: temperature, 20.2–23.4℃; relative humidity, 50.1–63.4%; ventilation, 10–15 times/h; and light, 7 AM to 7 PM (150–300 lux). Food and water were supplied without restrictions. On the last day of the quarantine-acclimation period, 20 males and 20 females with body weights close to the mean body weight were selected. Subsequently, they were randomly assigned to four groups, and each group had five subjects of the same sex.

This experiment was carried out at Biotoxtech Co., Ltd., complying with the regulations of the Animal Protection Act of the Republic of Korea (the Guide for the Care and Use of Laboratory Animals) [13]. Biotoxtech Co., Ltd., obtained full certification from the Association for Assessment and Accreditation of Laboratory Animal Care International in 2010.

Based on the Animal Protection Act of the Republic of Korea, the Institutional Animal Care and Use Committee (IACUC) of Biotoxtech Co., Ltd., thoroughly reviewed and approved this study (Enactment May 31, 1991, No. 4379, Revision Feb. 11, 2020, No.16977) (Approval No.: 220304).

3. Single-dose intramuscular toxicity study

This study was conducted in accordance with the Standards for Toxicity Studies of Drugs [14]. The dosing route was an intramuscular injection. The route was chosen to evaluate the toxicity of intramuscular exposure to the test substance. The dosage of each animal was determined by rounding up the third decimal of their body weight, which was recorded prior to the day of administration. The dosing formulation was administered once into the left thigh muscle via intramuscular injection us-

ing a disposable syringe.

The study comprised four groups: a control group and three treatment groups administered at dose levels of 12, 25, and 50 mg/kg, wherein each group consisted of 5 males and 5 females. The control group was administered with the vehicle (10% DMSO, 40% PEG 300, 5% Tween 80, and 45% normal saline injection of final volume) that has the same dose volume as the treatment group (Table 1).

4. Evaluated parameters

All subjects were monitored for clinical signs (type, severity, time of onset and recovery, etc.) and mortality at 30 minutes, 1, 2, 4, and 6 hours after administration (day 1) and once daily thereafter for 14 days (day 2 to day 15). The body weight measurements were taken once on the day of administration (prior to dosing) and subsequently on days 4, 8, and 15. On day 15, CO_2 gas inhalation was used to anesthetize all the subjects, followed by the exsanguination from the abdominal aorta. Subsequently, complete gross postmortem examinations were conducted on each subject in the study. Since no gross findings during the necropsy were recorded, a histopathological examination was not performed.

Table 1. Group designation

Group	Dose weight (mg/kg)	Dose volume (mg/kg)	No. of animals (ID)	
			Male	Female
G1 (control)	0	2	5 (1101–1105)	5 (2101–2105)
G2 (low dose)	12	2	5 (1201–1205)	5 (2201–2205)
G3 (mid dose)	25	2	5 (1301–1305)	5 (2301–2305)
G4 (high dose)	50	2	5 (1401–1405)	5 (2401–2405)

G1, 0 mg/kg dose group; G2, 12 mg/kg dose group; G3, 25 mg/kg dose group; G4, 50 mg/kg dose group.

5. Statistical analysis

The body weight data were analyzed using the SAS program version 9.4 (SAS Institute). The homoscedasticity of the measurement data was measured using Bartlett test (α = 0.05). When the homoscedasticity assumptions were met, one-way analysis of variance was conducted, and the level of significance was set at an α value of 0.05.

RESULTS

1. Mortality

During the observation period, no deaths of animals in both sexes were recorded in the control group and the 12, 25, and 50 mg/kg dose groups (Table 2).

2. Clinical signs

During the observation period, no abnormalities of clinical signs were recorded in both sexes in the control group and in the female mice of the 12 mg/kg dose group. In the 12 mg/kg dose group, abnormal gait (left hindlimb) was observed in one male from 30 minutes after treatment to day 3. In the 25 mg/kg dose group, abnormal gait (left hindlimb) was observed in 1–3 males from 30 minutes after treatment to day 7 and in 1–5 females from 30 minutes after treatment to day 15. In the 50 mg/kg dose group, abnormal gait (left hindlimb) was consistently observed in 2–5 males and 2–5 females from 30 minutes after treatment to day 15 (Table 3).

3. Body weights

Throughout the observation period, no significant changes were observed in the body weights of animals in both sexes in the 12, 25, and 50 mg/kg dose groups and the control group (Table 4).

Table 2. Summary of mortality

Sex	Group/dose (mg/kg)	No. of animals	Days after treatment															Mortality (dead/total)
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Male	G1/0	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5
	G2/12	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5
	G3/25	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5
	G4/50	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5
Female	G1/0	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5
	G2/12	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5
	G3/25	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5
	G4/50	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5

Table 3. Summary of clinical signs

Sex	Group/dose (mg/kg)	No. of animals	Clinical sign	Day 1 (h)				
				0.5	1	2	4	6
Male	G1/0	5	NOA	5	5	5	5	5
	G2/12	5	NOA	4	4	4	4	4
			Left hindlimb	1	1	1	1	1
	G3/25	5	NOA	2	2	2	2	4
			Left hindlimb	3	3	3	3	1
	G4/50	5	Left hindlimb	5	5	5	5	5
Female	G1/0	5	NOA	5	5	5	5	5
	G2/12	5	NOA	5	5	5	5	5
	G3/25	5	NOA	2	2	-	1	2
			Left hindlimb	3	3	5	4	3
	G4/50	5	Left hindlimb	5	5	5	5	5

				Day													
				2	3	4	5	6	7	8	9	10	11	12	13	14	15
Male	G1/0	5	NOA	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	G2/12	5	NOA	4	4	5	5	5	5	5	5	5	5	5	5	5	5
			Left hindlimb	1	1	-	-	-	-	-	-	-	-	-	-	-	-
	G3/25	5	NOA	4	4	4	4	4	4	5	5	5	5	5	5	5	5
			Left hindlimb	1	1	1	1	1	1	-	-	-	-	-	-	-	-
	G4/50	5	NOA	-	-	-	-	-	-	1	1	1	1	1	2	2	3
			Left hindlimb	5	5	5	5	5	5	4	4	4	4	4	3	3	2
Female	G1/0	5	NOA	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	G2/12	5	NOA	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	G3/25	5	NOA	2	2	2	2	2	2	3	3	3	3	3	3	3	4
			Left hindlimb	3	3	3	3	3	3	2	2	2	2	2	2	2	1
	G4/50	5	NOA	-	-	-	-	-	-	-	-	-	-	-	1	1	3
			Left hindlimb	5	5	5	5	5	5	5	5	5	5	5	4	4	2

NOA, no observable abnormality.

4. Necropsy findings

No abnormal gross findings were observed in both sexes in the 12, 25, and 50 mg/kg dose groups and control group at necropsy.

DISCUSSION

As the global demand for herbal medicine continues to rise remarkably, numerous studies have been conducted to emphasize its safe application [15]. However, only a few studies have confirmed the safety of traditional medicine [2], leading to misinformation [15]. Furthermore, several studies have revealed the toxic side effects resulting from the arbitrary and excessive use of herbal medicines without a prescription from medical professionals [3]. Using herbal medicine with the appropriate dosage is important. Furthermore, it is important to conduct toxicity studies regarding treatment dosage to ensure the safety and efficacy of the treatment method.

4-carvomenthenol is a main component of *O. vulgare*, *Z. piperitum*, and other plants [7,16]. According to the results of previous studies, it has a notable ability to inhibit the growth of colorectal, pancreatic, prostate, and gastric cancer cells [17]. It also possesses anti-inflammatory and antibacterial functions [6,10,11]. However, research data on the dose toxicity of 4-carvomenthenol is insufficient [16].

Zanthoxylum piperitum is found in traditional herbal medicine and is reported to possess antibacterial, anti-inflammatory, and antioxidant effects [18,19]. Previous studies also confirmed its therapeutic effects on osteoar-

Table 4. Mean body weight

Sex	Group/dose (mg/kg)	Days after administration				Day 1–15 weight gain (g)
		1	4	8	15	
Male	G1/0	32.0 ± 2.0	32.8 ± 1.8	34.3 ± 1.2	35.5 ± 1.9	3.5 ± 1.4
		5	5	5	5	5
	G2/12	32.7 ± 1.0	33.4 ± 1.4	35.2 ± 0.8	36.6 ± 0.6	3.9 ± 1.1
		5	5	5	5	5
	G3/25	31.8 ± 1.8	32.7 ± 1.9	34.7 ± 2.2	36.4 ± 2.5	4.6 ± 2.1
		5	5	5	5	5
	G4/50	32.5 ± 1.4	32.6 ± 1.3	33.8 ± 1.4	34.8 ± 2.4	2.3 ± 2.1
		5	5	5	5	5
Female	G1/0	26.6 ± 1.9	27.9 ± 2.0	28.9 ± 1.7	30.3 ± 1.9	3.7 ± 0.6
		5	5	5	5	5
	G2/12	26.4 ± 2.0	27.9 ± 1.8	28.7 ± 1.8	30.1 ± 2.5	3.7 ± 1.5
		5	5	5	5	5
	G3/25	26.6 ± 2.3	27.7 ± 2.8	29.0 ± 2.7	29.6 ± 2.3	3.0 ± 0.9
		5	5	5	5	5
	G4/50	26.7 ± 1.5	27.5 ± 1.1	28.2 ± 1.3	30.0 ± 1.1	3.2 ± 0.8
		5	5	5	5	5

Values are presented as mean±standard deviation or number only.
Significantly different from the control by Dunnett's t-test.

thritis and rheumatoid arthritis [20,21].

Due to the lack of toxicity test conducted on 4-carvomenthenol, this study aims to gather baseline data for long-term and repeated-dose toxicity, determine effective clinical dosages and appropriate administration volumes, and provide a basis for research on the maximum dosage by conducting a single intramuscular injection toxicity test.

A preliminary study investigated the plasma and dermal pharmacokinetics of 4-carvomenthenol in rats following intravenous administration at a dose of 2 mg/kg [22]. To investigate toxicity levels up to 25 times the dosage used in the preliminary study, 50 mg/kg was selected as the high dose of this study. The mid and low doses were selected at 25 and 12 mg/kg, respectively.

No fatalities were recorded in any groups. The test substance showed no significant impact on body weight and necropsy. The only clinical sign that was monitored during the observation period was the abnormal gait in the left hindlimb where the 4-carvomenthenol was administered. Since the clinical sign was observed only in the test substance dose groups, it is considered to be caused by the test substance.

Our findings revealed that the lethal dose of 4-carvomenthenol could be greater than 50 mg/kg in both male and female mice. Since these results are only based on a short-term, single-dose acute toxicity test, further research, such as long-term and multiple-dose toxicity studies, is needed to ensure the safety and efficacy of 4-carvomenthenol.

CONCLUSION

The results of this study revealed that the lethal dose of 4-carvomenthenol could be greater than 50 mg/kg in both male and female mice following a single intramuscular injection.

AUTHOR CONTRIBUTIONS

Conceptualization: LYG, KJH, LJW. Data curation: LYG. Funding acquisition: YTH. Investigation: LYG, KJH, LJW. Methodology: LYG, KJH, LJW, YGS, YTH. Project administration: YTH. Resources: KJH, LJW. Supervision: YGS, YTH. Validation: YGS, YTH. Writing – original draft: LYG. Writing – review & editing: LYG, YGS.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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ETHICAL STATEMENT

This experiment was carried out at Biotoxtech Co., Ltd., complying with the regulations of the Animal Protection Act of the Republic of Korea (the Guide for the Care and Use of Laboratory Animals) [13]. Biotoxtech Co., Ltd., obtained full certification from the Association for Assessment and Accreditation of Laboratory Animal Care International in 2010.

Based on the Animal Protection Act of the Republic of Korea, the Institutional Animal Care and Use Committee (IACUC) of Biotoxtech Co., Ltd., thoroughly reviewed and approved this study (Enactment May 31, 1991, No. 4379, Revision Feb. 11, 2020, No.16977) (Approval No.: 220304).

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