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Original Article

Genotoxicity and subchronic toxicity studies of *Taiwanofungus camphoratus* extract

Jian-Yu Lin, Mei-Chun Chen and Emerson Chiu

Level Biotechnology Inc. CRO-Preclinical Testing Center, No. 80, Lane 169, Kangning St., Hsi-Chih Dist., New Taipei City 221, Taiwan R.O.C.

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ABSTRACT — *Taiwanofungus camphoratus* is an edible and medicinal mushroom originating in Taiwan. Several researches have revealed *T. camphoratus* possessed various biological activities, including anti-cancer, immunomodulation, liver protection and anti-inflammation. Recently, it has been widely used in food supplements and drug development for its health benefits and medicinal properties. Therefore, the safety issue is the primary concern for consumers. The aim of this study was to evaluate the toxicological effects of *T. camphoratus* extract that was composed of extracts from cut-log cultivated fruiting body and solid-state culture of *T. camphoratus*. The genotoxicity tests, rodent and non-rodent repeated dose toxicity studies were performed. The results of the genetic toxicology tests including *in vitro* bacterial reverse mutation assay, *in vitro* chromosomal aberration test, and *in vivo* mouse bone marrow micronucleus assay were all negative that indicated neither mutagenicity nor clastogenicity was caused by *T. camphoratus* extract. Moreover, 13-week and 26-week repeated dose oral toxicity studies in rats showed that no significant adverse effects of *T. camphoratus* extract were found up to dosages of 3400 mg/kg and 1700 mg/kg for male and female rats, respectively. The results of 28-day repeated dose oral toxicity study in beagle dogs showed no-observed-adverse-effect-level (NOAEL) of *T. camphoratus* extract up to dosage of 1500 mg/kg for male and female dogs. Accordingly, these results provided the safety information of *T. camphoratus* extract that supported for using in food supplements or medicinal usage.

Key words: *T. camphoratus*, Genotoxicity, Mutagenicity, Rat toxicity study, Beagle dog toxicity study

INTRODUCTION

Taiwanofungus camphoratus, also known as ”Niu-chang-chih”, is a rare and precious medicinal fungus originating in Taiwan. *Cinnamomum kanehirae* Hayata (Lauraceae), a native tree of Taiwan, is the only natural host of *T. camphoratus*. *T. camphoratus* has been used as traditional medicine by the aboriginals in Taiwan to promote health, treat liver disease, drug and food intoxication, hangover, exhaustion and cancers (Geethangili and Tzeng, 2011; Wu, 1997). Many active components of *T. camphoratus* have been identified, such as polysaccharides, terpenoids, benzenoids, nucleic acid, benzoquinone derivatives, steroids, and maleic/succinic acid derivatives (Geethangili and Tzeng, 2011; Lu *et al*., 2013). Triterpenoids are the most abundant compounds in fruiting body of *T. camphoratus*, but is much less in mycelium. Besides, several researches have revealed that *T. camphoratus* possessed a variety of pharmacological activities, including immune regulation (Chen *et al*., 2018; Lin *et al*., 2010; Lin *et al*., 2018), anti-cancer (Chang *et al*., 2013; Hseu *et al*., 2017; Shang *et al*., 2017), hepatoprotection (Chiu and Hua, 2016; Li *et al*., 2017; Wu *et al*., 2011), and anti-inflammation (Chen *et al*., 2017; Huang *et al*., 2014; Shie *et*

Correspondence: Emerson Chiu (E-mail: emerson@mail.level.com.tw)

al., 2016).

The growth rate of wild *T. camphoratus* is very slow, therefore, different artificial cultivation methods have been developed to produce *T. camphoratus* to meet the increasingly market demand. It can be classified as cut-log culture, solid-state culture, submerged fermentation and dish culture. Culture medium and methods significantly affect the quality and quantity of components in *T. camphoratus*, thus pharmacological or toxicity effects of *T. camphoratus* products predominantly depends on cultivation techniques (Chung *et al*., 2016; Lu *et al*., 2013). Due to its multiple health benefits and medicinal properties, *T. camphoratus* has been wildly used in nutritional supplements, health food products and drug development. However, there is still no sufficient information regarding the toxicity properties of *T. camphoratus*. Currently, some toxicology studies have demonstrated the safety of *T. camphoratus*, but mostly focus on mycelium products. The 90 days repeated toxicity study showed the no-observed-adverse-effect-level (NOAEL) value of submerged fermentation and solid-state cultivation *T. camphoratus* mycelium is 3000 mg/kg and up to the dosage of 7.6 g/kg in rats (Chen *et al*., 2010; Lo *et al*., 2016). The previous study also showed no adverse effects found in rats treated with mycelium of solid-state cultivation of *T. camphoratus* and no genotoxicity and mutagenic effects were observed (Lo *et al*., 2016; Lin *et al*., 2016).

This study aimed to investigate the toxicological effects of *T. camphoratus* extract that was composed of extracts from cut-log cultivated fruiting body and solid-state culture of *T. camphoratus*. Results from genotoxicity studies including bacterial reverse mutation test, mammalian chromosome aberration test and mammalian erythrocyte micronucleus test showed *T. camphoratus* extract did not induce genotoxic and mutagenic effects. Furthermore, the repeated dose oral toxicity tests in rats and beagle dogs demonstrated that no significant adverse effects of *T. camphoratus* extract were found up to dosage of 3400 mg/kg in male rats, 1700 mg/kg in female rats and 1500 mg/kg in both genders of beagle dogs. Taken together, these results support the safe use of *T. camphoratus* for human consumption.

MATERIALS AND METHODS

All studies were performed at Level Biotechnology Inc. Preclinical Testing Center in compliance with the Good Laboratory Practice for Non-clinical Laboratory Studies (FDA, 21 CFR, Part 58), Good Laboratory Practice for Non-clinical Laboratory Studies (Ministry of Health and Welfare, R.O.C., 3rd ed., 2006) and OECD Principles of Good Laboratory Practice (as revised in 1997). These studies were also conducted in accordance with ICH (2009) M3 (R2) Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (CPMP/ICH/286/95).

Test substance

The test article, *T. camphoratus* extract (named as LEAC-102), was composed of ethanol and water extracts from cut-log cultivated fruiting body (FB) and solid-state culture (SC) of *T. camphoratus* that provided by Taiwan Leader Biotech Corp. (Taipei, Taiwan). The cut-log cultivated FB and solid-state culture of *T. camphoratus* were manufactured by R&D Center of Taiwan Leader Biotech Corp. (Taichung, Taiwan). The dry powders of FB and SC were mixed in the ratio of 1:10 (w/w) and were extracted with 10 volumes of 95% ethanol for 2 hr twice, followed by extraction with 10 volumes of boiled water for 2 hr twice. The ethanol and water extracts from FB and SC were combined and concentrated to obtain LEAC-102. 1 gram of *T. camphoratus* extract equivalent to the extract from dried raw material of 0.22 g of fruit body and 2.2 g of solid-state culture.

Bacterial reverse mutation test

The histidine-dependent *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537 (Moltox Inc., Boone, NC) were used to evaluate the genotoxicity of *T. camphoratus* extract. *T. camphoratus* extract was dissolved in DMSO to obtain the dosing solution and the highest dose of this study was set at 5 mg/plate based on the results of dose range finding test in TA100. Hence, five concentrations, 0.050, 0.158, 0.50, 1.58, 5 mg/plate, were used in this study. Positive controls, negative control (sterile water), vehicle control (dimethylfloxide, DMSO) and test solutions with or without metabolic activation (S9 mixture, Aroclor 1254-induced; Moltox, BOONE, NC) were included in study. Positive controls are as follows (all reagents were from Sigma Aldrich, St. Louis, MO), (1) without S9: 2-nitrofluorene for TA98, sodium azide for TA100 and TA1535, mitomycin C for TA102, and 9-aminoacridine for TA1537, (2) with S9: 2-aminoanthracene for TA98, TA102, TA1535 and TA1537, benzo[a]pyrene for TA100. 0.05 mL of test solutions, 0.1 mL of bacterial broth and 0.5 mL phosphate buffer (0.2 M, pH 7.4) (without S9 metabolic activation) or 0.5 mL S9 mixture were mixed with the molten top agar and poured onto the surface of a minimal glucose agar plate. The plates were incubated at 37°C for 48-72 hr then the number of revertant colonies per plate was counted. The data of revertant colonies count on triplicate plates was represented with Mean ± S.D., and its coefficient of variation (CV.) was calculated as well. If an increase in revertants of *T. camphoratus* extract treated plates (more than 2-fold in TA98, TA100 and TA102 or 3-fold in TA1535 and TA1537) were noted, statistical analysis by ANOVA and Dunnett's test would be performed. Besides, an additional dose-related response analysis will be used if the ANOVA results are statistically significant. Probability of 0.05 ($p < 0.05$) was used as the criterion of significance.

In vitro **Mammalian Chromosome Aberration Test**

Chinese Hamster Ovary (CHO-K1) cell line was obtained from Bioresource Collection and Research Center (BCRC, Hsinchu, Taiwan). CHO-K1 cell was cultured in HAM's F12 medium with 2 mM of L-glutamine, 100 U/mL of penicillin and streptomycin, 10% of heat-inactivated FBS (all supplements were from Biological industries, Grand Island, NY) in a humidified atmosphere containing 5% CO_2 at 37°C. *T. camphoratus* extract was dissolved in DMSO to obtain the test solution of 6.2, 18.5, 55.6, 166.7, 500 and 1500 µg/mL that used in dose range finding cytotoxicity test for selecting the high dose used in main study. CHO-K1 cells (3-5 x 10^5 cells/dish) were seeded in 6 cm culture dishes and culture for 24 hr before treatment. For short-term treatment with or without S9 activation, cells were treated with *T. camphoratus* extract (18.5, 55.6, 166.7 µg/mL), 0.5 µg/mL mitomycin C (positive control for without S9) or 25 µg/mL benzo(a)pyrene (positive control for with S9) for 3-6 hr. For long-term treatment without S9 activation, cells were treated with *T. camphoratus* extract (6.2, 18.5, 55.6 µg/mL), 0.5 µg/mL mitomycin C (positive control) for 18-22 hr. The 1% DMSO solution and culture medium were used as vehicle control and negative control, respectively. After treatment, 0.1 µg/mL Colcemid solution was added into culture medium for 1-3 hr. Cells were harvested and treated with hypotonic solution (0.075 M KCl) and fixed with a mixture of methanol/acetic acid (3:1, v/v). Cells were placed on clean slides and stained with Giemsa solution. The chromosome aberration was evaluated by examination of at least 300 well-spread metaphase cells with a number of centromeres equal to the modal number (20 ± 2) for each dose in duplicate. The structural chromosome aberrations, including chromatid breakage (ctb) and exchange (cte), chromosome breakage (csb) and exchange (cse), and other abnormalities, such as polyploidy, shall be scored and recorded by photographing. The statistical evaluation was analyzed by Poisson distribution. The statistical significance level was defined at $p < 0.05$. The number of cells with chromosome aberration in positive control should be significantly increased comparing with that in negative control. If more than two testing dosages show significant increase in number of cells with chromosome aberration, it was considered that the test article would induce structural chromosome aberration in CHO-K1 cells. If only one testing dosage shows significant increase in number of cells with chromosome aberration, the Cochran-Armitage trend test (C-A test) will be performed for dose-dependent analysis. Only if there is a dose dependent trend in number of cells with chromosome aberration, the test article would be considered genotoxic in CHO-K1 cells.

Mammalian erythrocyte micronucleus test

The micronucleus test was performed using 7-8 weeks old ICR mice (BioLASCO Taiwan Co. Ltd) and the test article, *T. camphoratus* extract, was prepared in sterile water at the designated concentration. Animals were housed in the SPF grade animal room in the AAALAC International accredited facility of Level Biotech. Inc. under 12 hr light/12 hr dark cycle at 19-23°C with relative humidity 35-75%. The highest dosage was determined based on the result of preliminary dose range finding. The mice were randomly divided into 5 groups, including negative control, positive control and three treatment groups, 10 mice in each group of 5 male and 5 female. Mice were orally administered *T. camphoratus* extract at doses of 1700, 3400 and 6800 mg/kg bw. The positive control group was intraperitoneally injected with 80 mg/kg bw cyclophosphamide and negative control group was given sterile water orally. The daily dosing volume for oral dosing was 20 mL/kg bw and BID dosing was conducted at 2-3 hr interval (10 mL/kg bw per dosing time). The mortality of animals was observed once daily during study period and peripheral blood samples were collected from tail vein at 48 ± 2 and 72 ± 2 hr after dosing. The positive control group was sampled only at 48 ± 2 hr after dosing. The peripheral blood was smeared on the acridine orange coated slide, and the staining was performed in room temperature for 2-3 hr. The fluorescent microscopes (Zeiss AXIO Scope.A1 and Zeiss AXIO Imager.A1) with 460-490 nm exciting and 515 nm long pass filter were used for polychromatic erythrocytes (PCE) and micronucleus identification and counting. The proportion of PCE in erythrocytes was determined by counting at least 2000 erythrocytes. At least 4000 PCE per animal were scored for frequency of micronucleated cells (MN ‰PCE). The data was presented with mean ± S.D. The micronucleus frequency was analyzed by Poisson distribution. Probability of 0.05 ($p < 0.05$) was used as the criterion of significance. If significant difference has shown in testing group comparing with concurrent negative control, the Cochran-Armitage trend test (C-A test) will be used for dose dependent analysis. Furthermore, the test article will be considered to display genotoxic if the dose dependent response has existed. In addition, if the PCE percentage of testing group was 50% less than the negative control, it indicated that the test article inhibit erythropoiesis. The study was approved by the Institutional Animal Care and Use Committee (IACUC number 160101-C1).

13-week repeated dose oral toxicity test in rats with a 4-week recovery

The 6 weeks old Sprague Dawley (SD) rats (BioLASCO Taiwan Co. Ltd.) were randomly divided into four groups, 12 rats per sex in each group with additional recovery groups (6 animals/sex/vehicle control and high dose group). The animals were housed in the AAALAC International accredited facility of Level Biotech. Inc. under 12 hr light/12 hr dark cycle and the temperature of animal room was at 19-23°C with relative humidity 35-75%. The rats received *T. camphoratus* extract orally at doses of 425, 850 and 1700 mg/kg once daily for 13 weeks and the recovery animals in vehicle control and high dose groups were allowed a 4 weeks treatment free period. The animals had free access to diet and the clinical signs were observed during the experiment period. The body weight and food consumption were measured weekly. Hematology, serum biochemistry, urinalysis and gross necropsy were conducted on all surviving animals at scheduled sacrifice. Organs and tissues were collected, weighed and examined microscopically. The data was presented with mean ± S.D. and analyzed by one-way ANOVA followed by Dunnett's method (SPSS, Ver. 12.0 or Ver. 22.0). In addition, student's *t*-test was used to analyze the data of recovery groups. The statistical significance level was defined at $p < 0.05$. The study was approved by the Institutional Animal Care and Use Committee (IACUC number 151101).

26-week repeated dose oral toxicity test in rats with a 4-week recovery

The 6 weeks old Sprague Dawley (SD) rats (BioLASCO Taiwan Co. Ltd) were randomly divided into four groups, 22 rats per sex in each group with additional recovery groups (12 animals/sex/vehicle control and high dose group). The animals were housed in the AAALAC International accredited facility of Level Biotech. Inc. under 12 hr light/12 hr dark cycle and the temperature of animal room was at 19-23°C with relative humidity 35-75%. The male rats received *T. camphoratus* extract orally at doses of 850, 1700 and 3400 mg/kg and female rats received 425, 850 and 1700 mg/kg once daily for 26 weeks and the recovery animals in vehicle control and high dose groups were allowed a 4 weeks treatment free period. The animals had free access to diet and the clinical sings were observed during the experiment period. The body weight and food consumption were measured weekly. Hematology, serum biochemistry, urinalysis were conducted on all surviving animals on week 13 and at the end of the study. Organs and tissues were collected, weighed and examined microscopically. The data was presented with mean ± S.D. and analyzed by one-way ANOVA followed by Dunnett's method (SPSS, Ver. 12.0 or Ver. 22.0). In addition, student's *t*-test was used to analyze the data of recovery groups. The statistical significance level was defined at $p < 0.05$. The study was approved by the Institutional Animal Care and Use Committee (IACUC number 160202 and 160202-C1).

28-day repeated dose oral toxicity test with a 14-Day recovery in beagle dogs

The 6-7 months old male and female beagle dogs were purchased from Covance Inc. (Cumberland, VA). The animals were housed individually by using stainless cage in the AAALAC International accredited facility of Level Biotech. Inc. under 12 hr light/12 hr dark cycle and the temperature of animal room was at 19.2-22.3°C with relative humidity 43.7-67.4%. The diet (400 g/animal/day) was applied once daily for approximately 1 week and twice daily (200 g/animals/time) thereafter. Naïve beagle dogs were randomly assigned to four groups (vehicle control, 540, 900 and 1500 mg/kg/day groups, 3 animals/sex/group) with additional recovery groups (2 animals/sex/vehicle control and 1500 mg/kg/day groups). The animals were orally administered with *T. camphoratus* extract in gelatin capsules (Empty Porcine Hard Gelatin Capsules, Torpac Inc., Fairfield, NJ) or empty capsules (vehicle control) three times daily that a quantity of one-third total daily dose was given at 2 hr interval for consecutive 28 days with designated doses. At the end of treatment period, the recovery animals of vehicle control and high dose groups were maintained for a 14 days treatment free period. The mortality, body weight, food consumption and clinical signs were observed during the study period. Electrocardiographic (ECG) examination was performed on animals during pre-dose period, Day 28 (end of treatment) and Day 42 (end of recovery). Ophthalmologic examinations were performed for all animals at the grouping day and before terminal sacrifice. Hematology, serum chemistry and urinalysis were performed for all animals at pre-dose and at the end of treatment and recovery periods. Gross necropsy and histopathology examination are performed at the end of study. The study was approved by the Institutional Animal Care and Use Committee (IACUC number 171104-C1 and 171104-C2).

RESULTS AND DISCUSSION

Bacterial reverse mutation test

The genotypes of five *Salmonella typhimurium* strains (TA98, TA100, TA102, TA1535, and TA1537) for this study were identified and met the criteria as described in Table S1-S2. The results of dose range finding test in TA100 showed *T. camphoratus* extract had no cytotoxic and mutagenic effect (Table S3), therefore, 5 doses (0.050, 0.158, 0.50, 1.58 and 5 mg/plate) of *T. camphoratus* extract were chosen in this test. The test results were summarized in Table 1. The revertant colonies in positive control group were over two-fold (in TA98, TA100, and TA102) and three-fold (in TA1535 and TA1537) compared to negative control groups.

T. camphoratus extract at all testing doses (0.050-5 mg/plate) did not cause significant increase in revertant colony number under both with and without S9 metabolic activation conditions. Thus it's indicated that no mutagenic effect of *T. camphoratus* extract was noted on five *S. typhimurium* strains in all testing groups.

Mammalian Chromosome Aberration Test

Three analyzable concentrations used in the chromosome aberration test were selected by cytotoxicity test that produced greater than 50% cell viability. The cell viability of testing concentrations at 18.5, 55.6, 166.7 μg/mL for 3 hr treatment without S9 metabolic activation were 80.26 ± 8.72%, 88.19 ± 11.98% and 89.71 ± 10.08%, respectively. Of 3 hr treatment in the presence of S9, the cell viability of testing concentrations at 18.5, 55.6, 166.7 μg/mL were 92.55 ± 7.03%, 91.95 ± 10.94% and 97.32 ± 9.02%, respectively. In long term (18 hr) treatment without S9, the cell viability of testing concentrations at 6.2, 18.5, 55.6 μg/mL were 146.82 ± 8.95%, 110.18 ± 17.80% and 51.64 ± 7.41%, respectively (Table S4). The result of chromosome aberration was summarized in Table 3. Clear positive responses in positive control group were observed that the cell numbers of chromosome aberration were 22, 35 and 50 in short term with or without S9 and long term without S9, respectively. The chromosome aberrations in *T. camphoratus* extract treated cells were 1, 1 and 0 at 166.7, 55.6 and 18.5 μg/mL, respectively under 3 hr without S9 and 1, 0 and 3 at 166.7, 55.6 and 18.5 μg/mL, respectively under 3 hr with S9. Moreover, the chromosome aberrations were 2, 2 and 2 at 55.6, 18.5 and 6.2 μg/mL, respectively under 18 hr without S9. The results showed that no significant increase in chromosome aberrations at all tested dosages under the test conditions and indicated that *T. camphoratus* extract could be considered nonmutagenic in this system.

Mammalian erythrocyte micronucleus test

According to the dose range finding test in ICR mice, animals were found no abnormal symptoms and mortality at the highest dose (6800 mg/kg). Therefore, the doses of *T. camphoratus* extract were set as 80, 1700, 3400 and 6800 mg/kg bw in micronucleus test. As shown in Table 2, the PCE percentage of negative control group at 48 and 72 hr were 3.28 ± 0.04% and 3.34 ± 0.05% in male, 3.44 ± 0.11% and 3.46 ± 0.11% in female, respectively. The PCE percentage of positive control group at 48 hr was 1.02 ± 0.04% in male and 1.40 ± 0.38% in female. As expected, the inhibition of erythropoiesis by cyclophosphamide was noted based on the decreased PCE percentage, while no significant decrease in PCE percentage was observed in all testing groups which is indicated that *T. camphoratus* extract did not inhibit erythropoiesis. The micronucleus frequency of 1700, 3400 and 6800 mg/kg *T. camphoratus* extract at 48 hr after dosing in male was 0.72 ± 0.41‰PCE, 0.42 ± 0.11‰PCE and 0.44 ± 0.22‰PCE and that at 72 hr after dosing in male was 0.66 ± 0.23‰PCE, 0.50 ± 0.27‰PCE and 0.34 ± 0.09‰PCE respectively. The micronucleus frequency of 1700, 3400 and 6800 mg/kg *T. camphoratus* extract at 48 hr after dosing in female was 0.42 ± 0.29‰PCE, 0.48 ± 0.20‰PCE and 0.56 ± 0.26‰PCE and that at 72 hr after dosing in female was 0.48 ± 0.30‰PCE, 0.52 ± 0.18‰PCE and 0.48 ± 0.34‰PCE respectively. There was no significant difference in the micronucleus frequency between negative control and all testing groups of *T. camphoratus* extract in both genders under Poison distribution analysis. Accordingly, *T. camphoratus* extract was considered negative in inducing micronucleus formation. The micronucleus frequency of positive control was more than double of that in negative controls, thereby confirming this study was authentic and valid. In conclusion, *T. camphoratus* extract was non-genotoxic and would not affect erythropoiesis in mice under the test condition.

13-week repeated dose oral toxicity study with a 4-week recovery in rats

In the study, 13-week daily oral administered of *T. camphoratus* extract in rats, there was no test article-related death or ophthalmologic abnormality (Table S5) and no significant changes in body weight (Fig. 1) and food consumption were observed. Only female rats in 1700 mg/kg recovery group had a higher mean body

Table 1. Results of bacterial reverse mutation test.

Treatment groups (mg/plate)		Number of revertants/plate (without S9)					Number of revertants/plate (with S9)				
		TA98	TA100	TA102	TA1535	TA1537	TA98	TA100	TA102	TA1535	TA1537
T. camphoratus extract	5	29.3 ± 13.7	116.7 ± 11.0	340.7 ± 21.2	9.3 ± 2.9	5.0 ± 1.0	43.7 ± 7.1	137.0 ± 4.4	381.3 ± 11.0	16.0 ± 2.6	12.3 ± 3.5
	1.58	22.0 ± 1.7	112.0 ± 12.5	320.7 ± 12.9	10.0 ± 1.0	5.0 ± 0.0	34.7 ± 6.4	130.0 ± 8.9	342.7 ± 14.0	13.7 ± 2.1	9.7 ± 1.5
	0.50	23.7 ± 1.5	126.7 ± 15.9	318.7 ± 11.5	12.7 ± 1.2	7.3 ± 1.5	29.7 ± 4.0	161.7 ± 9.3	404.0 ± 11.1	15.3 ± 2.3	7.0 ± 2.0
	0.158	22.3 ± 2.5	150.7 ± 3.2	299.3 ± 19.6	10.0 ± 1.0	6.0 ± 1.0	31.7 ± 2.5	162.3 ± 6.8	405.3 ± 20.2	10.0 ± 2.0	7.3 ± 1.5
	0.050	21.7 ± 1.5	148.3 ± 7.6	290.0 ± 6.9	9.0 ± 1.7	8.7 ± 2.9	32.7 ± 2.5	151.3 ± 13.3	383.3 ± 15.3	9.7 ± 1.5	7.7 ± 1.5
Negative control		24.0 ± 1.0	159.7 ± 4.2	334.7 ± 12.2	7.0 ± 1.0	11.3 ± 3.5	32.0 ± 5.2	171.3 ± 6.4	362.0 ± 12.2	8.3 ± 0.6	8.7 ± 2.1
Positive control[a]		285.3 ± 9.0*	546.0 ± 8.7*	3357.3 ± 113.2*	441.3 ± 9.2*	234.7 ± 5.0*	788.7 ± 26.0*	468.7 ± 22.7*	924.7 ± 12.1*	248.7 ± 3.1*	453.0 ± 11.3*
Vehicle control		22.7 ± 0.6	134.0 ± 11.0	320.7 ± 31.8	6.7 ± 0.6	8.3 ± 1.5	29.7 ± 2.5	164.0 ± 7.5	384.7 ± 10.3	9.0 ± 0.0	10.0 ± 1.0

All data presented as mean ± S.D.
[a] The use of positive control substance for each strains was listed as follows:
(1) Without S9: 2-nitrofluorene for TA98, Sodium azide for TA100 and TA1535, Mitomycin C for TA102, and 9-aminoacridine for TA1537.
(2) With S9: 2-aminoanthracene for TA98, Benzo[a]pyrene for TA100, 2-aminoanthracene for TA102, TA1535 and TA1537.
*more than two or three-fold increase in revertants over the vehicle control

Table 2. Results of *in vivo* micronucleus test.

Group	Dose (g/kg b.w)	PCE/RBC (%)				MN ‰ PCE			
		Male		Female		Male		Female	
		48 hr	72 hr	48 hr	72 hr	48 hr	72 hr	48 hr	72 hr
Negative control		3.28 ± 0.04	3.34 ± 0.05	3.44 ± 0.11	3.46 ± 0.11	0.54 ± 0.25	0.42 ± 0.11	0.50 ± 0.35	0.38 ± 0.11
Cyclophosphamide[a]	80	1.02 ± 0.04	--	1.40 ± 0.38	--	16.52 ± 1.69*	--	21.12 ± 1.94*	--
T. camphoratus extract	1700	3.34 ± 0.11	3.44 ± 0.05	3.02 ± 0.52	3.30 ± 0.35	0.72 ± 0.41	0.66 ± 0.23	0.42 ± 0.29	0.48 ± 0.30
	3400	3.36 ± 0.05	3.38 ± 0.11	3.36 ± 0.29	3.40 ± 0.14	0.42 ± 0.11	0.50 ± 0.27	0.48 ± 0.20	0.52 ± 0.18
	6800	3.40 ± 0.07	3.44 ± 0.05	3.44 ± 0.23	3.38 ± 0.29	0.44 ± 0.22	0.34 ± 0.09	0.56 ± 0.26	0.48 ± 0.34

All data presented as mean ± S.D. *$p < 0.05$ compared to negative control. [a] Positive control.
At least two thousand erythrocytes were observed per animal. Four thousand PCEs were observed per animal.

Table 3. The Result of Chromosome Aberration Test.

Treatment period	S9 Mixture	Test article	Dosage	Aberration Frequency#1	*p* value
Short-term 3~6 hr	-S9	Negative control	NA	2 /300	--
		Vehicle control: DMSO	1%	0 /300	1.0000#4
		T. camphoratus extract	166.7 g/mL	1 /300	0.7358#2
			55.6 mg/mL	1 /300	0.7358#2
			18.5 mg/mL	0 /300	1.0000#2
		Positive: Mitomycin C	0.5 μg/mL	22 /300	0.0000#4*
	S9	Negative control	NA	2 /300	--
		Vehicle control: DMSO	1%	1 /300	0.9197#4
		T. camphoratus extract	166.7 g/mL	1 /300	0.7358#3
			55.6 mg/mL	0 /300	1.0000#3
			18.5 mg/mL	3 /300	0.1991#3
		Positive: Benzo(a)pyrene	25 μg/mL	35 /300	0.0000#4*
Long-term 18~22 hr	-S9	Negative control	NA	2 /300	--
		Vehicle control: DMSO	1%	1 /300	0.9197#4
		T. camphoratus extract	55.6 g/mL	2 /300	0.4060#3
			18.5 mg/mL	2 /300	0.4060#3
			6.2 mg/mL	2 /300	0.4060#3
		Positive: Mitomycin C	0.5 μg/mL	50 /300	0.0000#4*

All data presented as mean ± S.D. *$p < 0.05$ compared to vehicle control.
#1The aberration frequency was displayed in the manner of number of cells with chromosome aberration in 300 metaphase cells observed.
#2The statistical evaluation was analyzed by Poisson distribution in comparison with historical data of negative control because the aberration frequency of concurrent vehicle control is zero.
#3The statistical evaluation was analyzed by Poisson distribution in comparison with concurrent vehicle control.
#4The statistical evaluation was analyzed by Poisson distribution in comparison with concurrent negative control.

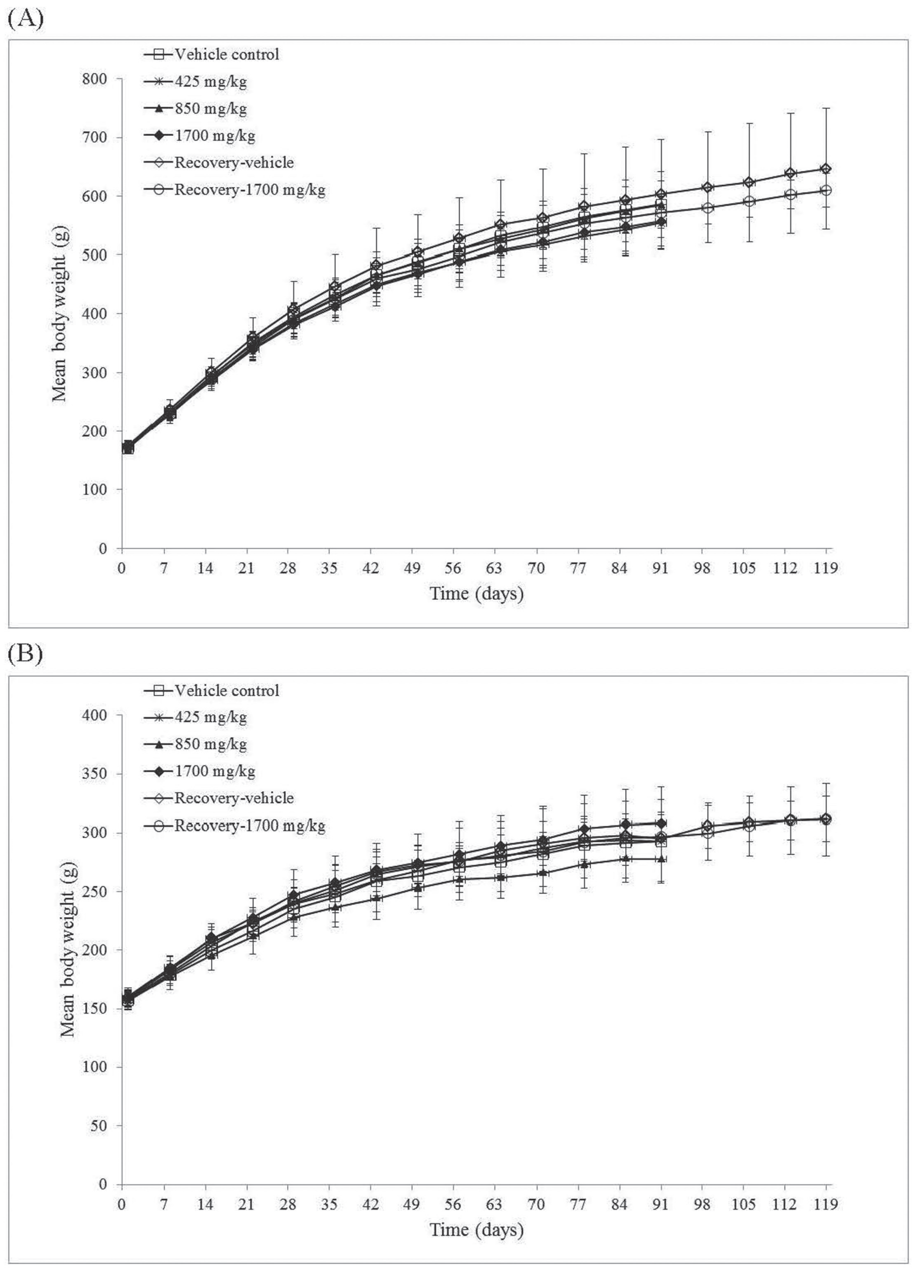


Fig. 1. Effects of repeated oral dose (13 weeks) of *T. camphoratus* extract on body weight in rats. Results of body weight in (A) male rats and (B) female rats treated with *T. camphoratus* extract for 13 weeks with additional 4 recovery weeks. No significant changes in body weight were observed in *T. camphoratus* extract treated animals. All data presented as mean ± S.D.

weight gains in week 3 and a lower mean body weight gains in week 14 (Table S6), and male rats in high-dose main study group had lower average food consumption in week 1 when compared to vehicle control (Table S7). However, the values were within the range of historical control data and the changes were infrequent and sporadic, thus it was considered as non-treatment related. One female rat from 425 mg/kg group showed corneal opacity in left eye before necropsy that it was considered incidental and unrelated to treatment due to lack of dose responses and/or microscopic correlations. Additionally, no treatment related clinical signs were observed on all animals although, several signs including hair loss, wounds and teeth damage were still observed in few animals due to housing-related behavior (Table S8). One female rat in 850 mg/kg group developed dyspnea, audible respiration and soft feces from study day 78 through the study termination, following macropiscally and microscopically evaluation, the spontaneous lesion in large intestine, megacolon, was observed. Therefore, the data (body weight, food consumption, clinical pathology parameters and organ weights) from this female rat was not included in statistic evaluation.

In clinical pathology evaluation, no significant toxicity evidences were found among all treatment groups. Some statistical differences were noted when compared to vehicle control. However, all values were within normal physiological ranges. The results of hematology and serum biochemistry parameters were summarized in Table 4-5. The female rats in 1700 mg/kg recovery group showed lower mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) compared to vehicle control recovery group. The male rats in 850 mg/kg group showed higher phosphorus (P) and the female rats in 1700 mg/kg main study group showed higher glucose and cholesterol compared to vehicle control. The male rats in 1700 mg/kg recovery group showed lower albumin and higher chloride (Cl) and female rats in 1700 mg/kg recovery group showed lower sodium (Na) and chloride (Cl) compared to vehicle control (Table 5). Moreover, there were no *T. camphoratus* extract-related changes in urinalysis after 13 weeks of administration (data not shown). As shown in table 6, the heart weight of male rats at 425 mg/kg group and pituitary weight of male rats at 1700 mg/kg recovery group were statistical lower than respective control groups. In females, statistical higher liver weight was noted in 1700 mg/kg main study group and higher adrenal weights were noted in all three treatment groups (425, 850 and 1700 mg/kg) compared to vehicle control, but all values were within the historical control data. Additionally, no significant difference was noted between control and 1700 mg/kg recovery groups in the organ weight data of female recovery group, and the significant differences in organ weight data described above, including adrenal and liver, were not seen. All organ weight changes noted above were considered incidental and unrelated to *T. camphoratus* extract treatment, due to lack of dose responses and/or microscopic correlations. Macroscopically, no treatment related abnormality was found in all animals. A spontaneous thymic atrophy was noted only in one female rat in vehicle control recovery group. Furthermore, there were no *T. camphoratus* extract-related histopathological lesions in all animals at 1700 mg/kg group (Table S9). Base on the results, the NOAEL of *T. camphoratus* extract in this study is 1700 mg/kg.

26-week repeated dose oral toxicity study with a 4-week recovery in rats

T. camphoratus extract were administered in rat orally, daily for 26 weeks and the results showed no mortality, no ophthalmologic abnormality and no significant differences in mean body weight. *T. camphoratus* extract were daily oral administered in rats for 26 weeks and the results showed no mortality, no ophthalmologic abnormality and no significant differences in mean body weights (Fig. 2). In body weight gain evaluation, some statistical differences were observed (Table S10-11), but all values were within the range of historical control data. Only the body weight gain of male rats in 3400 mg/kg recovery group was out of the lower limit of historical control range, however, this finding was not correlated to body weight and food consumption. Thus, the body weight changes were considered incidental and unrelated to treatment. There were no *T. camphoratus* extract related effects on food consumption, but some statistical changes were also noted in male rats (Table S12). Some clinical signs such as hail loss, wounds, teeth damage and swelling were observed during the study period and the results were summarized in Table S13. These findings might be caused by housing behavior or individual variation and were considered unrelated to *T. camphoratus* extract.

There was no toxicity evidences were noted for hematology, serum chemistry and urinalysis parameters among the vehicle control group and *T. camphoratus* extract treatment groups, whereas some statistical difference were observed in both male and female rats. The interim analysis results of hematology analysis in male rats showed higher neutrophil in 3400 mg/kg main group and lower red blood cell (RBC) in 3400 mg/kg recovery group when compared to vehicle control. In female rats, white blood cell (WBC) in 1700 mg/kg main group was lower than vehicle control and WBC, RBC, hemoglobin (Hb) and hematocrit (Hct) in 1700 mg/kg recovery group was lower than vehicle control recovery group. In terminal analysis, there was no statistical difference in all *T. camphoratus* extract treated male rats when compared to vehicle control /vehicle control recovery groups. In female rats, there was no statistical difference among vehicle control and all test article treatment groups in the data of main study groups. Lower RBC, Hb, Hct and platelet were noted in 1700 mg/kg recovery group when compared to vehicle control recovery group (Table 7).

Table 4. Results of hematological parameters in rats administered with *T. camphoratus* extract for 13 weeks.

	Gender	Dose (mg/kg)	WBC ($10^3/\mu L$)	RBC ($10^6/\mu L$)	Hb (g/dL)	Hct (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	
Main	Male	0	9.497 ± 2.937	9.089 ± 0.348	16.43 ± 0.59	44.46 ± 1.53	48.98 ± 2.72	18.09 ± 0.85	36.96 ± 0.61	
		425	7.981 ± 3.357	8.782 ± 0.465	16.12 ± 0.76	43.71 ± 1.97	49.88 ± 2.75	18.35 ± 0.73	36.88 ± 0.90	
		850	9.200 ± 2.144	8.887 ± 0.393	16.01 ± 0.86	43.17 ± 2.17	48.56 ± 0.88	18.02 ± 0.35	37.08 ± 0.44	
		1700	10.597 ± 2.058	8.903 ± 0.291	16.13 ± 0.55	43.73 ± 1.48	49.13 ± 1.20	18.10 ± 0.42	36.88 ± 0.25	
	Female	0	6.023 ± 1.329	8.000 ± 0.321	15.70 ± 0.56	42.50 ± 1.66	53.18 ± 2.03	19.64 ± 0.51	36.95 ± 0.73	
		425	6.422 ± 1.272	8.140 ± 0.351	15.68 ± 0.55	42.03 ± 1.28	51.68 ± 1.98	19.28 ± 0.59	37.30 ± 0.61	
		850[a]	5.438 ± 1.930	8.163 ± 0.695	15.90 ± 1.46	43.23 ± 4.36	52.91 ± 1.36	19.48 ± 0.36	36.82 ± 0.44	
		1700	6.768 ± 2.041	8.048 ± 0.363	15.58 ± 0.62	42.32 ± 1.35	52.63 ± 1.60	19.37 ± 0.52	36.82 ± 0.61	
Recovery	Male	0	8.065 ± 1.657	9.160 ± 0.353	16.47 ± 0.67	44.73 ± 2.02	48.93 ± 3.48	18.00 ± 0.99	36.82 ± 0.66	
		1700	9.578 ± 1.799	9.430 ± 0.326	16.55 ± 0.34	44.45 ± 0.72	47.18 ± 1.72	17.57 ± 0.67	37.23 ± 0.53	
	Female	0	5.668 ± 1.421	7.988 ± 0.597	15.62 ± 0.70	42.63 ± 1.59	53.50 ± 2.22	19.58 ± 0.59	36.62 ± 0.73	
		1700[b]	4.942 ± 1.784	7.980 ± 0.464	14.86 ± 0.72	40.48 ± 1.58	50.76 ± 1.25 *	18.64 ± 0.30 *	36.70 ± 0.41	
	Gender	Dose (mg/kg)	Platelet ($10^3/\mu L$)	Neutrophil (%)	Lymphocyte (%)	Monocyte (%)	Eosinophil (%)	Basophil (%)	PT (sec)	APTT (sec)
Main	Male	0	1176.9 ± 94.1	21.36 ± 6.49	73.40 ± 7.22	4.97 ± 0.90	0.24 ± 0.14	0.03 ± 0.05	13.48 ± 1.23	19.08 ± 0.88
		425	1031.3 ± 317.2	25.34 ± 6.00	68.90 ± 6.75	4.83 ± 1.65	0.80 ± 1.35	0.13 ± 0.20	13.36 ± 1.03	18.59 ± 2.07
		850	1155.3 ± 110.7	22.74 ± 7.43	72.42 ± 7.38	4.49 ± 0.98	0.29 ± 0.14	0.06 ± 0.05	13.67 ± 2.17	18.44 ± 1.40
		1700	1184.8 ± 122.7	19.05 ± 6.38	76.39 ± 6.90	4.14 ± 1.04	0.36 ± 0.31	0.06 ± 0.05	14.81 ± 1.43	19.58 ± 1.48
	Female	0	1008.7 ± 74.7	19.03 ± 6.55	76.28 ± 7.00	4.37 ± 0.93	0.33 ± 0.26	0.00 ± 0.00	9.86 ± 0.18	16.36 ± 1.29
		425	1050.1 ± 121.9	16.08 ± 4.42	79.39 ± 4.73	4.19 ± 0.66	0.33 ± 0.20	0.00 ± 0.00	9.69 ± 0.18	17.06 ± 1.24
		850[a]	905.3 ± 135.2	17.83 ± 7.46	77.73 ± 8.68	4.04 ± 1.24	0.36 ± 0.30	0.05 ± 0.12	9.91 ± 0.37	15.74 ± 2.06
		1700	1049.3 ± 97.6	18.98 ± 10.43	76.70 ± 10.73	3.98 ± 0.92	0.33 ± 0.24	0.01 ± 0.03	9.99 ± 0.31	17.76 ± 1.12
Recovery	Male	0	1229.2 ± 104.8	21.08 ± 4.23	73.90 ± 4.94	4.80 ± 0.88	0.20 ± 0.15	0.02 ± 0.04	12.90 ± 1.18	18.12 ± 1.79
		1700	1205.5 ± 153.2	20.90 ± 8.16	74.20 ± 8.70	4.58 ± 1.11	0.27 ± 0.16	0.05 ± 0.05	12.75 ± 2.14	17.50 ± 1.73
	Female	0	1002.2 ± 92.7	15.02 ± 5.20	80.55 ± 6.57	4.12 ± 1.27	0.28 ± 0.50	0.03 ± 0.05	9.82 ± 0.24	16.50 ± 2.35
		1700[b]	985.6 ± 97.0	20.80 ± 10.58	74.54 ± 10.53	4.00 ± 1.27	0.66 ± 0.83	0.00 ± 0.00	9.66 ± 0.09	16.22 ± 1.30

All data presented as mean ± S.D. *$p < 0.05$ compared to vehicle control. [a]n = 11; [b]n =5 (One female rat was found dead due to gavage error.)
Historical control data for female rats: MCV (fL): 48.24 ~ 56.40; MCH (pg): 17.35 ~ 19.82

Table 5. Results of serum biochemical parameters in rats administered with *T. camphoratus* extract for 13 weeks.

	Gender	Dose (mg/kg)	AST (U/L)	ALT (U/L)	Glucose (mg/dL)	Total protein (g/dL)	Albumin (g/dL)	Total bilirubin (mg/dL)	BUN (mg/dL)	Creatinine (mg/dL)	γ-GT (U/L)
Main	Male	0	146.82 ± 29.03	28.97 ± 5.94	190.57 ± 40.69	5.95 ± 0.27	4.20 ± 0.17	< 0.04	16.55 ± 1.70	0.37 ± 0.07	< 2.0
		425	160.51 ± 24.01	29.03 ± 3.98	181.85 ± 30.50	5.78 ± 0.28	4.14 ± 0.22	< 0.04	15.52 ± 1.42	0.33 ± 0.07	< 2.0
		850	178.17 ± 146.81	33.84 ± 13.67	211.38 ± 44.51	5.88 ± 0.33	4.20 ± 0.22	< 0.04	15.70 ± 2.03	0.35 ± 0.05	< 2.0
		1700	132.74 ± 29.94	29.43 ± 6.74	220.26 ± 41.96	5.77 ± 0.29	4.21 ± 0.21	< 0.04	15.94 ± 1.32	0.37 ± 0.05	< 2.0
	Female	0	135.29 ± 35.81	29.08 ± 16.06	168.31 ± 25.80	6.49 ± 0.33	4.99 ± 0.41	< 0.11	17.28 ± 3.21	0.45 ± 0.09	< 2.0
		425	125.08 ± 32.59	27.04 ± 6.08	187.97 ± 29.32	6.46 ± 0.32	5.00 ± 0.25	< 0.04	15.89 ± 2.42	0.42 ± 0.06	< 2.0
		850[a]	141.23 ± 67.62	34.13 ± 24.83	155.01 ± 36.78	6.15 ± 0.31	4.83 ± 0.28	< 0.05	17.80 ± 3.65	0.45 ± 0.08	< 3.6
		1700	122.03 ± 21.37	26.55 ± 7.40	199.72 ± 38.47 *	6.53 ± 0.37	5.20 ± 0.35	< 0.04	15.08 ± 2.85	0.40 ± 0.06	< 2.0
Recovery	Male	0	114.77 ± 19.87	30.73 ± 4.29	214.75 ± 42.76	6.35 ± 0.28	4.50 ± 0.06	< 0.05	16.93 ± 1.28	0.43 ± 0.08	< 2.0
		1700	113.35 ± 19.95	30.38 ± 3.09	187.08 ± 21.65	6.32 ± 0.25	4.28 ± 0.18 *	< 0.05	17.77 ± 2.13	0.48 ± 0.12	< 2.0
	Female	0	109.25 ± 26.89	28.18 ± 9.95	192.73 ± 14.84	7.02 ± 0.37	5.33 ± 0.25	< 0.10	17.12 ± 2.50	0.53 ± 0.08	< 2.0
		1700[b]	119.34 ± 29.77	31.62 ± 10.05	206.78 ± 26.22	7.14 ± 0.85	5.50 ± 0.67	< 0.11	19.24 ± 1.42	0.58 ± 0.04	< 2.4

	Gender	Dose (mg/kg)	ALP (U/L)	Cholesterol (mg/dL)	TG (mg/dL)	Ca2+ (mg/dL)	P (mg/dL)	Creatine kinase (U/L)	Amylase (U/L)	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)
Main	Male	0	273.58 ± 75.75	60.33 ± 12.86	35.04 ± 19.66	9.93 ± 0.32	6.69 ± 0.52	806.17 ± 254.53	1471.8 ± 235.1	144.30 ± 1.61	4.537 ± 0.234	104.48 ± 2.30
		425	260.31 ± 48.90	56.04 ± 11.56	36.93 ± 16.54	9.74 ± 0.37	6.80 ± 0.56	948.10 ± 238.36	1381.8 ± 211.7	145.19 ± 1.43	4.531 ± 0.252	103.55 ± 1.57
		850	295.23 ± 42.36	69.19 ± 12.68	46.22 ± 26.99	10.11 ± 0.25	7.33 ± 0.65 *	963.13 ± 785.94	1422.1 ± 226.2	144.77 ± 1.54	4.782 ± 0.376	102.60 ± 1.63
		1700	293.52 ± 39.80	69.18 ± 14.76	32.39 ± 10.70	9.84 ± 0.28	7.16 ± 0.48	756.45 ± 366.72	1383.8 ± 196.9	144.73 ± 1.37	4.721 ± 0.359	103.53 ± 1.24
	Female	0	150.53 ± 39.92	65.05 ± 14.58	22.62 ± 8.98	10.25 ± 0.35	6.14 ± 1.01	597.57 ± 242.35	999.6 ± 205.2	143.54 ± 1.15	4.380 ± 0.231	102.03 ± 1.85
		425	149.03 ± 28.13	71.28 ± 11.64	23.14 ± 10.23	10.30 ± 0.42	6.05 ± 0.57	535.78 ± 238.91	1038.1 ± 120.8	143.23 ± 0.95	4.385 ± 0.346	101.86 ± 0.99
		850[a]	159.97 ± 44.24	73.83 ± 8.05	19.97 ± 6.10	10.28 ± 0.31	6.79 ± 1.08	511.77 ± 214.77	1041.6 ± 348.6	144.64 ± 2.48	4.580 ± 0.396	102.63 ± 1.49
		1700	143.21 ± 51.63	84.73 ± 10.64 *	21.73 ± 7.22	10.39 ± 0.40	6.01 ± 0.62	605.19 ± 158.55	1079.9 ± 240.9	142.79 ± 0.86	4.435 ± 0.265	102.21 ± 1.22
Recovery	Male	0	242.60 ± 35.94	61.65 ± 13.37	60.32 ± 50.81	10.87 ± 0.43	6.75 ± 0.85	460.52 ± 212.35	1484.7 ± 108.7	149.35 ± 1.68	4.577 ± 0.180	111.67 ± 1.88
		1700	233.02 ± 50.50	58.50 ± 13.00	44.32 ± 23.30	10.78 ± 0.29	7.73 ± 1.92	508.85 ± 270.02	1516.8 ± 151.1	150.78 ± 0.79	4.618 ± 0.469	115.92 ± 1.57 *
	Female	0	109.08 ± 26.63	55.60 ± 12.05	22.07 ± 7.03	11.13 ± 0.38	5.03 ± 0.68	407.92 ± 169.91	1246.7 ± 629.1	149.22 ± 0.52	4.185 ± 0.290	112.83 ± 2.07
		1700[b]	99.66 ± 12.78	77.20 ± 19.82	49.52 ± 34.15	11.26 ± 0.54	5.52 ± 0.83	442.38 ± 325.75	1302.8 ± 594.6	147.86 ± 1.19 *	4.518 ± 0.921	108.18 ± 2.22 *

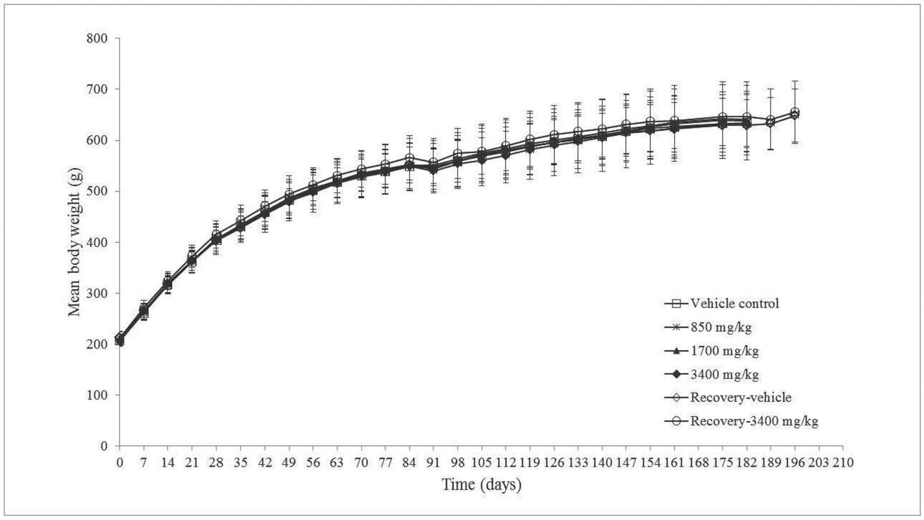
All data presented as mean ± S.D. *$p < 0.05$ compared to vehicle control. [a]n = 11; [b]n =5 (One female rat was found dead due to gavage error.)
Historical control data for male rats: P (mg/dL): 5.42 ~ 8.52; Albumin (g/dL): 3.49 ~ 4.54; Cl (mmol/L): 97.23 ~ 117.11
Historical control data for female rats: Na (mmol/L): 136.48-150.37; Cl (mmol/L): 93.71-114.46; Glucose (mg/dL): 96.58-210.32; Cholesterol (mg/dL): 31.28-126.31

Table 6. Results of absolute organ weights in rats administered with *T. camphoratus* extract for 13 weeks.

	Male					
	Main (mg/kg)				Recovery (mg/kg)	
Organ (g)	0	425	850	1700	0	1700
Adrenals (Paired)	0.05674 ± 0.00588	0.05715 ± 0.00651	0.05633 ± 0.00806	0.05853 ± 0.01006	0.04717 ± 0.00709	0.05183 ± 0.00927
Pituitary	0.01465 ± 0.00152	0.01411 ± 0.00177	0.01570 ± 0.00198	0.01511 ± 0.00129	0.01550 ± 0.00079	0.01490 ± 0.00204*
Brain	2.198 ± 0.076	2.234 ± 0.092	2.221 ± 0.093	2.216 ± 0.101	2.327 ± 0.055	2.213 ± 0.092
Heart	1.681 ± 0.099	1.533 ± 0.117*	1.675 ± 0.185	1.573 ± 0.100	1.765 ± 0.191	1.738 ± 0.175
Thymus	0.424 ± 0.114	0.409 ± 0.095	0.396 ± 0.114	0.384 ± 0.093	0.407 ± 0.149	0.342 ± 0.066
Liver	15.878 ± 2.102	15.248 ± 2.229	16.720 ± 2.350	16.279 ± 1.625	16.883 ± 3.649	15.828 ± 0.994
Spleen	0.935 ± 0.141	0.845 ± 0.107	0.897 ± 0.139	0.816 ± 0.084	0.933 ± 0.158	0.862 ± 0.107
Kidneys (Paired)	3.633 ± 0.253	3.412 ± 0.284	3.547 ± 0.433	3.541 ± 0.261	3.778 ± 0.347	3.732 ± 0.378
Testes (Paired)	3.512 ± 0.265	3.470 ± 0.410	3.478 ± 0.261	3.557 ± 0.244	3.518 ± 0.305	3.583 ± 0.247
Epididymides (Paired)	1.371 ± 0.086	1.307 ± 0.114	1.329 ± 0.119	1.318 ± 0.105	1.472 ± 0.077	1.387 ± 0.098
Prostates and seminal[b]	3.519 ± 0.413	3.368 ± 0.511	3.349 ± 0.508	3.495 ± 0.365	3.628 ± 0.377	3.535 ± 0.667
	Female					
	Main (mg/kg)				Recovery (mg/kg)	
Organ (g)	0	425	850[a]	1700	0	1700[b]
Ovaries with oviducts	0.12738 ± 0.02520	0.13354 ± 0.02045	0.13382 ± 0.01534	0.13278 ± 0.01830	0.12550 ± 0.00989	0.10182 ± 0.02962
Adrenals (Paired)	0.06510 ± 0.00739	0.07858 ± 0.01328*	0.07837 ± 0.01080*	0.08966 ± 0.01061*	0.06770 ± 0.00457	0.07116 ± 0.01051
Pituitary	0.01873 ± 0.00230	0.01958 ± 0.00192	0.01867 ± 0.00327	0.01914 ± 0.00275	0.01642 ± 0.00294	0.01970 ± 0.00384
Brain	1.964 ± 0.079	2.019 ± 0.059	1.995 ± 0.088	2.000 ± 0.097	2.022 ± 0.063	2.052 ± 0.036
Heart	0.942 ± 0.078	0.950 ± 0.092	0.924 ± 0.084	0.970 ± 0.083	1.042 ± 0.093	1.022 ± 0.053
Thymus	0.294 ± 0.052	0.258 ± 0.037	0.270 ± 0.070	0.301 ± 0.076	0.247 ± 0.091	0.200 ± 0.043
Liver	7.867 ± 0.476	8.137 ± 0.991	7.951 ± 0.956	9.569 ± 0.994*	8.297 ± 0.908	8.450 ± 1.092
Spleen	0.492 ± 0.056	0.517 ± 0.090	0.505 ± 0.085	0.533 ± 0.059	0.597 ± 0.050	0.540 ± 0.094
Kidneys (Paired)	1.848 ± 0.159	1.936 ± 0.197	1.740 ± 0.137	1.964 ± 0.231	1.958 ± 0.197	2.100 ± 0.202
Uterus with cervix	0.687 ± 0.216	0.628 ± 0.212	0.605 ± 0.268	0.780 ± 0.444	0.793 ± 0.245	0.670 ± 0.173

All data presented as mean ± S.D. *$p < 0.05$ compared to vehicle control. [a]n = 11; [b]n =5 (One female rat was found dead due to gavage error.)
[b]Prostates and seminal: Prostates and seminal vesicles with coagulating glands
Historical control data for male rats: Heart (g): 1.256-1.930; Pituitary (g): 0.00938-0.01631
Historical control data for female rats: Adrenals (g): 0.04933-0.08974; Liver (g): 6.137-9.955

(A)



(B)

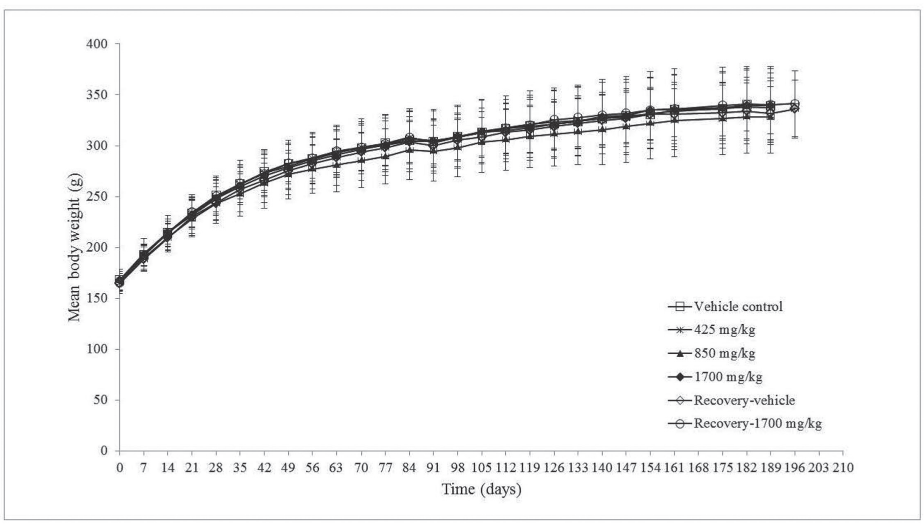


Fig. 2. Effects of repeated oral dose (26 weeks) of *T. camphoratus* extract on body weight in rats. Results of body weight in (A) male rats and (B) female rats treated with *T. camphoratus* extract for 26 weeks with additional 4 recovery weeks. No significant changes in body weight were observed in *T. camphoratus* extract treated animals. All data presented as mean ± S.D.

In interim analysis of serum biochemistry analysis, the results of male rats in main study groups showed higher values in glucose (3400 mg/kg), albumin (in 1700 and 3400 mg/kg), alkaline phosphatase (ALP) (3400 mg/kg), cholesterol (3400 mg/kg), calcium (850, 1700 and 3400 mg/kg), phosphorus (3400 mg/kg), amylase (3400 mg/kg), sodium (1700 and 3400 mg/kg), potassium (1700 and 3400 mg/kg) and chloride (850, 1700 and 3400 mg/kg) as compared to vehicle control. In male recovery rats, statistical higher glucose, albumin, ALP, amylase, sodium and chloride and lower potassium were noted in 3400 mg/kg recovery group when compared to vehicle recovery group. In female main study groups, lower aspartate aminotransferase (AST) (425, 850 and 1700 mg/kg), higher glucose (1700 mg/kg), lower blood urea nitrogen (BUN) (1700 mg/kg), lower creatinine (850 mg/kg), higher cholesterol (850 and 1700 mg/kg) and lower sodium (425 and 850 mg/kg) were noted. In female recovery rats, higher total protein, albumin, cholesterol, calcium and amylase were noted in 1700 mg/kg recovery group. In terminal

Table7. Results of hematological parameters in rats administered with *T. camphoratus* extract for 26 weeks.

	Gender	Dose (mg/kg)	WBC ($10^3/\mu L$)	RBC ($10^6/\mu L$)	Hb (g/dL)	Hct (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)
Main-interim analysis at week 13	Male	0	13.800 ± 2.584	9.400 ± 0.410	16.89 ± 0.48	46.24 ± 1.08	49.25 ± 1.77	17.97 ± 0.56	36.51 ± 0.52
		850	12.791 ± 2.565	9.495 ± 0.485	16.95 ± 0.60	47.18 ± 2.10	49.75 ± 2.50	17.87 ± 0.61	35.94 ± 0.99
		1700	13.757 ± 2.593	9.474 ± 0.453	17.06 ± 0.60	47.22 ± 1.38	49.91 ± 2.03	18.03 ± 0.50	36.12 ± 0.78
		3400	14.413 ± 3.058	9.388 ± 0.434	16.67 ± 0.70	45.97 ± 1.77	49.00 ± 1.56	17.76 ± 0.47	36.26 ± 0.47
	Female	0	9.652 ± 2.585	8.735 ± 0.376	16.64 ± 0.62	45.53 ± 1.79	52.15 ± 1.54	19.06 ± 0.55	36.55 ± 0.46
		425	9.109 ± 2.108	8.749 ± 0.411	16.61 ± 0.56	45.24 ± 1.44	51.77 ± 1.66	19.02 ± 0.60	36.72 ± 0.35
		850	8.475 ± 2.717	8.685 ± 0.314	16.44 ± 0.50	45.03 ± 1.45	51.88 ± 1.56	18.95 ± 0.51	36.51 ± 0.33
		1700	7.605 ± 2.397 *	8.662 ± 0.293	16.31 ± 0.52	44.76 ± 1.57	51.70 ± 1.75	18.83 ± 0.56	36.43 ± 0.52
Main-terminal analysis	Male	0	8.556 ± 2.553	8.899 ± 0.435	15.75 ± 0.72	43.78 ± 1.95	49.23 ± 1.85	17.70 ± 0.58	35.99 ± 0.59
		850	8.452 ± 1.941	9.092 ± 0.556	16.00 ± 0.71	44.24 ± 1.89	48.74 ± 1.94	17.62 ± 0.66	36.17 ± 0.37
		1700	8.203 ± 1.707	8.959 ± 0.487	15.90 ± 0.60	44.32 ± 1.63	49.54 ± 1.95	17.76 ± 0.55	35.87 ± 0.57
		3400	8.463 ± 2.373	8.919 ± 0.415	15.68 ± 0.74	43.66 ± 1.85	49.01 ± 1.74	17.58 ± 0.53	35.89 ± 0.49
	Female	0	4.540 ± 1.466	7.952 ± 0.393	15.26 ± 0.69	42.61 ± 1.82	53.61 ± 1.52	19.19 ± 0.56	35.81 ± 0.53
		425	4.527 ± 1.383	7.795 ± 0.708	14.92 ± 0.90	41.70 ± 2.45	53.73 ± 2.91	19.23 ± 0.97	35.79 ± 0.41
		850	4.167 ± 1.163	7.741 ± 0.443	14.75 ± 0.73	41.33 ± 1.73	53.46 ± 1.78	19.06 ± 0.56	35.67 ± 0.48
		1700	4.376 ± 1.247	7.533 ± 1.472	14.22 ± 2.87	39.85 ± 7.64	53.08 ± 1.96	18.74 ± 1.06	35.32 ± 2.01
Recovery-interim analysis at week 13	Male	0	15.503 ± 3.095	9.426 ± 0.311	17.03 ± 0.63	46.83 ± 1.56	49.72 ± 1.92	18.08 ± 0.66	36.38 ± 0.53
		3400	13.797 ± 2.800	9.161 ± 0.311*	16.79 ± 0.43	46.73 ± 1.54	51.07 ± 2.52	18.35 ± 0.71	35.95 ± 0.54
	Female	0	9.448 ± 2.173	8.892 ± 0.315	16.97 ± 0.46	46.40 ± 1.40	52.23 ± 1.78	19.10 ± 0.60	36.57 ± 0.53
		1700	7.787 ± 1.552 *	8.503 ± 0.333 *	16.21 ± 0.45 *	44.49 ± 1.24 *	52.35 ± 1.14	19.08 ± 0.37	36.43 ± 0.44
Recovery-terminal analysis	Male	0	6.134 ± 1.454	8.813 ± 0.319	15.60 ± 0.49	43.36 ± 1.23	49.24 ± 1.70	17.70 ± 0.55	35.97 ± 0.50
		3400	5.155 ± 1.597	8.569 ± 0.410	15.58 ± 0.54	43.74 ± 1.55	51.14 ± 2.95	18.21 ± 0.73	35.63 ± 0.76
	Female	0	3.533 ± 1.263	7.931 ± 0.301	15.18 ± 0.67	42.17 ± 1.83	53.18 ± 1.69	19.13 ± 0.61	35.99 ± 0.21
		1700	3.331 ± 1.032	7.542 ± 0.443 *	14.24 ± 0.66 *	39.89 ± 1.59 *	52.96 ± 1.56	18.90 ± 0.41	35.69 ± 0.59

	Gender	Dose (mg/kg)	Platelet ($10^3/\mu L$)	Neutrophil (%)	Lymphocyte (%)	Monocyte (%)	Eosinophil (%)	Basophil (%)	PT (sec)	APTT (sec)
Main-interim analysis at week 13	Male	0	1144.5 ± 167.6	16.72 ± 4.44	76.47 ± 5.46	5.22 ± 1.33	1.50 ± 0.46	0.09 ± 0.03		
		850	1094.1 ± 134.1	20.99 ± 5.28	72.30 ± 5.67	5.22 ± 0.99	1.40 ± 0.39	0.09 ± 0.04		
		1700	1162.9 ± 149.6	20.39 ± 6.06	73.11 ± 6.78	5.00 ± 1.07	1.41 ± 0.43	0.08 ± 0.04		
		3400	1193.5 ± 98.3	22.75 ± 9.97 *	70.90 ± 10.42	4.90 ± 0.97	1.36 ± 0.53	0.09 ± 0.03		
	Female	0	1072.5 ± 154.6	13.83 ± 6.53	79.67 ± 7.54	4.54 ± 1.38	1.91 ± 0.54	0.06 ± 0.07		
		425	1090.5 ± 119.2[a]	14.58 ± 5.08	79.81 ± 5.85	3.87 ± 1.09	1.68 ± 0.64	0.10 ± 0.21		
		850	1066.0 ± 108.9	14.41 ± 3.98	80.19 ± 4.40	3.70 ± 1.01	1.66 ± 0.50	0.04 ± 0.05		
		1700	1049.2 ± 149.8	17.45 ± 5.91	76.26 ± 7.09	3.96 ± 1.12	2.25 ± 0.85	0.07 ± 0.09		
Main-terminal analysis	Male	0	1122.3 ± 135.9	22.48 ± 7.75	71.63 ± 7.84	5.42 ± 1.08	0.43 ± 0.30	0.04 ± 0.06	13.38 ± 1.56	18.07 ± 1.77
		850	1142.5 ± 127.4	27.03 ± 6.66	66.26 ± 6.77	6.27 ± 1.12	0.40 ± 0.19	0.04 ± 0.06	13.79 ± 1.88	18.22 ± 1.89
		1700	1125.3 ± 131.5	25.02 ± 6.45	68.70 ± 7.25	5.85 ± 1.42	0.38 ± 0.34	0.05 ± 0.06	14.22 ± 1.69	17.99 ± 1.43
		3400	1156.6 ± 123	23.71 ± 6.42	70.39 ± 6.77	5.50 ± 1.20	0.36 ± 0.22	0.04 ± 0.06	13.44 ± 1.91	17.62 ± 1.39
	Female	0	922.5 ± 87.1	16.92 ± 4.70	77.53 ± 4.92	5.00 ± 1.12	0.51 ± 0.32	0.04 ± 0.10	9.98 ± 0.16	16.81 ± 1.39
		425	914.9 ± 227.2	19.41 ± 5.07	74.44 ± 5.85	5.51 ± 1.37	0.64 ± 0.47	0.00 ± 0.00	9.98 ± 0.24	17.37 ± 0.88
		850	993.4 ± 102.2	18.31 ± 6.77	76.58 ± 7.41	4.60 ± 1.22	0.51 ± 0.32	0.00 ± 0.00	9.92 ± 0.29	17.24 ± 1.15
		1700	888.9 ± 218.7	19.66 ± 5.70	74.80 ± 6.73	5.01 ± 1.35	0.50 ± 0.42	0.03 ± 0.08	10.01 ± 0.25[a]	17.46 ± 1.03[a]

Table 7. (Continued).

	Gender	Dose (mg/kg)	Platelet ($10^3/\mu L$)	Neutrophil (%)	Lymphocyte (%)	Monocyte (%)	Eosinophil (%)	Basophil (%)	PT (sec)	APTT (sec)
Recovery-interim analysis at week 13	Male	0	1175.6 ± 120.7	23.33 ± 9.51	68.91 ± 9.77	5.87 ± 0.89	1.82 ± 0.61	0.08 ± 0.04		
		3400	1205.5 ± 109.9	23.38 ± 4.44	69.65 ± 5.34	5.33 ± 1.54	1.56 ± 0.49	0.08 ± 0.05		
	Female	0	1075.7 ± 137.6	14.42 ± 4.95	80.21 ± 5.55	3.68 ± 0.95	1.65 ± 0.64	0.04 ± 0.05		
		1700	1059.3 ± 58.2	15.08 ± 4.14	79.95 ± 5.11	3.40 ± 1.19	1.51 ± 0.34	0.06 ± 0.08		
Recovery-terminal analysis	Male	0	1170.2 ± 121.6	27.33 ± 5.62	67.29 ± 5.45	4.89 ± 0.94	0.48 ± 0.24	0.02 ± 0.06	12.95 ± 0.94	18.31 ± 1.41
		3400	1167.2 ± 127.6	28.08 ± 7.37	66.93 ± 7.39	4.55 ± 0.93	0.43 ± 0.38	0.01 ± 0.03	13.10 ± 1.21	18.33 ± 0.80
	Female	0	1037.5 ± 188.8	23.05 ± 7.32	71.23 ± 7.57	4.93 ± 1.42	0.80 ± 0.50	0.00 ± 0.00	9.82 ± 0.16	16.05 ± 1.07
		1700	865.0 ± 108.2 *	22.82 ± 6.27	71.68 ± 6.95	4.63 ± 1.54	0.88 ± 0.56	0.00 ± 0.00	10.05 ± 0.46 [b]	15.34 ± 1.29 [b]

All data presented as mean ± S.D. *$p < 0.05$ compared to vehicle control. [a]n = 21; [b]n = 11
Historical control data for male rats: Neutrophil (%): 4.38-34.70; RBC ($10^6/\mu L$): 8.723-10.163;
Historical control data for female rats (interim analysis): WBC ($10^3/\mu L$): 4.293-13.579; RBC ($10^6/\mu L$): 8.050-9.534; Hemoglobin (g/dL): 15.17-17.88; Hematocrit (%): 41.17-48.94
Historical control data for female rats (terminal analysis): RBC ($10^6/\mu L$): 7.176-8.704; Hemoglobin (g/dL): 13.84-16.49; Hematocrit (%): 38.57-45.79; Platelet ($10^3/\mu L$): 755.1-1095.8

Table 8. Results of serum biochemical parameters in rats administered with *T. camphoratus* extract for 26 weeks.

	Gender	Dose (mg/kg)	AST (U/L)	ALT (U/L)	Glucose (mg/dL)	Total protein (g/dL)	Albumin (g/dL)	Total bilirubin (mg/dL)	BUN (mg/dL)	Creatinine (mg/dL)	γ-GT (U/L)
Main-interim analysis at week 13	Male	0	184.03 ± 42.13	33.99 ± 3.76	102.38 ± 23.46	6.90 ± 0.41	4.92 ± 0.25	< 0.04	16.45 ± 1.94	0.25 ± 0.09	< 3.3
		850	185.25 ± 53.31	34.69 ± 5.56	106.68 ± 24.64	7.02 ± 0.38	5.08 ± 0.28	< 0.04	15.76 ± 2.14	0.29 ± 0.10	< 2.0
		1700	168.13 ± 47.11	33.38 ± 4.78	103.10 ± 19.40	7.20 ± 0.39	5.28 ± 0.24*	< 0.04	15.38 ± 2.01	0.25 ± 0.09	< 2.0
		3400	170.08 ± 50.66	34.47 ± 6.13	123.84 ± 24.38*	7.19 ± 0.47	5.41 ± 0.30*	< 0.04	15.77 ± 2.28	0.28 ± 0.10	< 2.0
	Female	0	197.97 ± 29.93	34.79 ± 9.51	97.15 ± 12.89	7.73 ± 0.65	5.98 ± 0.55	< 0.04	17.00 ± 2.68	0.30 ± 0.10	< 3.7
		425	169.11 ± 36.98*	27.91 ± 5.92	102.43 ± 12.14	7.70 ± 0.59	6.07 ± 0.54	< 0.04	15.63 ± 1.86	0.30 ± 0.12	< 2.0
		850	173.70 ± 33.15*	31.67 ± 18.07	106.54 ± 16.85	7.68 ± 0.50	6.15 ± 0.42	< 0.04	15.56 ± 2.34	0.23 ± 0.09*	< 2.0
		1700	167.22 ± 24.42*	27.27 ± 6.85	109.00 ± 13.80*	7.87 ± 0.47	6.25 ± 0.47	< 0.04	14.77 ± 2.42*	0.24 ± 0.08	< 2.0
Main-terminal analysis	Male	0	142.69 ± 29.75	40.05 ± 24.67	160.35 ± 28.03	5.90 ± 0.25	3.98 ± 0.18	< 0.05	17.25 ± 1.87	0.50 ± 0.09	< 2.0
		850	137.99 ± 22.15	33.70 ± 6.09	166.86 ± 31.84	5.99 ± 0.25	4.11 ± 0.24	<0.06	16.50 ± 1.97	0.47 ± 0.07	< 2.0
		1700	142.05 ± 37.16	31.16 ± 5.26	171.27 ± 28.63	6.00 ± 0.32	4.21 ± 0.19*	< 0.04	16.26 ± 1.87	0.46 ± 0.07	< 2.0
		3400	143.72 ± 33.94	37.06 ± 32.69	179.18 ± 49.15	5.89 ± 0.28	4.21 ± 0.19*	< 0.04	16.98 ± 1.91	0.45 ± 0.07	< 2.0
	Female	0	134.76 ± 31.49	35.14 ± 12.24	163.72 ± 29.16	6.77 ± 0.37	5.14 ± 0.34	< 0.10	17.05 ± 2.31	0.50 ± 0.05	< 2.0
		425	120.19 ± 28.65	34.89 ± 15.72	183.99 ± 38.81	6.91 ± 0.52	5.35 ± 0.48	< 0.07	17.47 ± 3.04	0.55 ± 0.07	< 2.0
		850	128.89 ± 52.60	40.01 ± 27.44	178.53 ± 31.87	7.03 ± 0.59	5.42 ± 0.45	< 0.06	16.74 ± 2.44	0.51 ± 0.07	< 2.0
		1700	108.09 ± 14.24	26.26 ± 5.33	188.15 ± 35.10	7.17 ± 0.48	5.42 ± 0.47	< 0.06	16.01 ± 2.33	0.48 ± 0.06	< 2.0
Recovery-interim analysis at week 13	Male	0	199.72 ± 26.61	32.70 ± 6.02	93.80 ± 22.59	7.43 ± 0.32	5.15 ± 0.23	< 0.04	16.63 ± 1.49	0.28 ± 0.10	< 2.0
		3400	174.52 ± 45.69	31.90 ± 2.87	112.92 ± 22.41*	7.30 ± 0.22	5.47 ± 0.16*	< 0.04	15.73 ± 1.30	0.27 ± 0.10	< 2.0
	Female	0	135.07 ± 16.74	29.07 ± 5.98	120.20 ± 14.71	7.65 ± 0.51	6.03 ± 0.35	< 0.04	15.42 ± 2.17	0.28 ± 0.10	<2.0
		1700	138.47 ± 17.21	29.65 ± 7.34	127.88 ± 10.23	8.07 ± 0.36*	6.45 ± 0.27*	< 0.04	14.90 ± 2.21	0.25 ± 0.09	< 5.2
Recovery-terminal analysis	Male	0	114.12 ± 26.99	32.57 ± 5.62	172.99 ± 59.44	6.03 ± 0.24	3.94 ± 0.14	< 0.05	13.78 ± 1.89	0.36 ± 0.05	< 2.0
		3400	109.27 ± 27.15	30.90 ± 3.34	171.49 ± 21.85	5.98 ± 0.20	3.97 ± 0.13	<0.05	14.51 ± 1.86	0.38 ± 0.05	< 2.0
	Female	0	127.53 ± 53.47	53.43 ± 22.02	165.35 ± 23.67	7.14 ± 0.47	5.57 ± 0.39	0.067 ± 0.014 [b]	17.62 ± 1.91	0.52 ± 0.07	< 2.0
		1700	90.60 ± 20.03*	40.46 ± 17.33	194.33 ± 35.61*	7.35 ± 0.32	5.67 ± 0.27	0.062 ± 0.010 [c]	17.03 ± 2.02	0.50 ± 0.06	< 2.0

Table 8. (Continued).

	Gender	Dose (mg/kg)	ALP (U/L)	Cholesterol (mg/dL)	TG (mg/dL)	Ca2+ (mg/dL)	P (mg/dL)	Creatine kinase (U/L)	Amylase (U/L)	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)
Main-interim analysis at week 13	Male	0	253.98 ± 67.48	63.84 ± 18.37	59.15 ± 35.81	9.75 ± 0.32	7.40 ± 0.71	1166.25 ± 480.52	1537.6 ± 258.5	148.54 ± 4.44	5.449 ± 0.334	86.00 ± 4.31
		850	275.19 ± 47.65	70.97 ± 17.61	56.50 ± 25.82	10.10 ± 0.37*	7.13 ± 0.76	1004.52 ± 450.94	1573.0 ± 207.6	150.42 ± 2.36	5.442 ± 0.425	89.21 ± 2.30*
		1700	293.42 ± 58.79	77.05 ± 15.11	51.69 ± 19.91	10.31 ± 0.35*	7.61 ± 0.83	965.23 ± 577.12	1664.6 ± 204.0	151.84 ± 2.74*	5.752 ± 0.364*	89.08 ± 2.38*
		3400	338.73 ± 79.57*	81.26 ± 22.74*	49.76 ± 36.21	10.45 ± 0.40*	8.26 ± 0.93*	937.81 ± 412.97	1718.5 ± 191.1 *	151.95 ± 2.20*	5.990 ± 0.511*	90.01 ± 1.81*
	Female	0	141.47 ± 39.63	70.68 ± 23.57	15.94 ± 8.41[a]	10.76 ± 0.51	6.63 ± 1.24	1227.30 ± 330.08	1085.2 ± 167.8	150.17 ± 4.11	5.410 ± 0.478	93.30 ± 4.06
		425	136.16 ± 39.54	72.75 ± 17.01	14.01 ± 6.04	10.65 ± 0.35	5.85 ± 0.67	1070.11 ± 387.76	1052.9 ± 155.2	147.16 ± 2.74*	5.265 ± 0.515	92.35 ± 2.23
		850	147.65 ± 41.72	84.47 ± 16.16*	15.52 ± 5.73	10.58 ± 0.44	6.10 ± 1.08	1057.75 ± 318.67	1070.5 ± 175.7	146.43 ± 4.13*	5.281 ± 0.462	91.98 ± 4.00
		1700	139.68 ± 45.74	99.65 ± 16.25*	16.72 ± 7.50	10.70 ± 0.39	6.04 ± 0.76	1052.70 ± 280.69	1116.5 ± 223.7	148.59 ± 4.28	5.385 ± 0.392	94.59 ± 3.57
Main-terminal analysis	Male	0	157.22 ± 37.24	64.39 ± 22.46	32.40 ± 17.41	9.85 ± 0.33	7.28 ± 1.02	624.33 ± 196.76	1364.4 ± 261.0	147.36 ± 1.19	4.726 ± 0.244	105.26 ± 1.20
		850	175.66 ± 30.57	69.91 ± 18.62	36.81 ± 19.48	9.90 ± 0.35	7.29 ± 0.97	584.40 ± 143.02	1356.0 ± 173.2	147.78 ± 1.44	4.730 ± 0.278	105.46 ± 1.37
		1700	189.91 ± 41.25*	73.39 ± 16.55	28.96 ± 12.19	9.93 ± 0.33	6.98 ± 1.18	681.96 ± 302.71	1422.6 ± 191.0	147.22 ± 1.54	4.873 ± 0.343	104.60 ± 1.64
		3400	215.87 ± 52.55*	74.63 ± 18.12	24.90 ± 15.25	9.78 ± 0.34	7.39 ± 1.19	701.43 ± 251.80	1484.0 ± 141.7	146.95 ± 1.53	4.965 ± 0.259 *	104.67 ± 1.45
	Female	0	79.15 ± 29.50	67.67 ± 21.97	23.66 ± 12.24	10.17 ± 0.26	5.90 ± 0.77	542.15 ± 175.36	1022.0 ± 182.9	144.18 ± 1.51	4.124 ± 0.281	94.34 ± 1.91
		425	71.71 ± 22.17	72.95 ± 18.39	28.54 ± 17.07	10.23 ± 0.33	5.64 ± 0.92	489.35 ± 190.74	1094.3 ± 237.2	143.72 ± 1.31	4.179 ± 0.260	94.09 ± 1.92
		850	74.06 ± 28.15	88.50 ± 19.45*	24.75 ± 9.41	10.21 ± 0.44	5.70 ± 0.81	460.97 ± 165.88	1161.4 ± 237.6	143.68 ± 1.37	4.120 ± 0.338	93.48 ± 1.98
		1700	72.30 ± 22.03	94.82 ± 21.34*	25.05 ± 9.16	10.25 ± 0.35	5.58 ± 0.60	480.73 ± 168.26	1181.8 ± 150.5 *	143.80 ± 1.23	4.300 ± 0.294	101.63 ± 4.59*
Recovery-interim analysis at week 13	Male	0	266.33 ± 37.77	81.20 ± 15.66	55.52 ± 25.83	10.28 ± 0.34	8.22 ± 0.94	1184.22 ± 288.45	1525.0 ± 236.1	151.47 ± 1.49	5.978 ± 0.391	91.92 ± 1.96
		3400	330.22 ± 63.80*	84.82 ± 17.94	47.33 ± 19.56	10.47 ± 0.26	7.78 ± 0.68	938.18 ± 354.96	1736.2 ± 160.1*	154.55 ± 2.01 *	5.675 ± 0.272 *	94.97 ± 2.19*
	Femal	0	152.50 ± 34.21	71.67 ± 15.39	9.33 ± 3.07	10.43 ± 0.48	6.78 ± 0.90	720.65 ± 268.18	1049.8 ± 186.4	148.78 ± 1.75	5.450 ± 0.424	92.75 ± 1.78
		1700	137.35 ± 37.30	93.33 ± 14.23*	10.30 ± 4.83	10.82 ± 0.38 *	6.43 ± 1.05	729.62 ± 168.02	1251.0 ± 190.5 *	149.93 ± 3.35	5.555 ± 0.244	93.97 ± 2.38
Recovery-terminal analysis	Male	0	181.78 ± 22.25	80.63 ± 12.95	41.38 ± 20.18	9.69 ± 0.26	5.88 ± 0.65	544.36 ± 278.99	1471.0 ± 244.7	145.56 ± 1.02	4.568 ± 0.205	106.87 ± 1.10
		3400	186.38 ± 49.90	75.95 ± 13.60	52.93 ± 30.21	9.58 ± 0.35	5.89 ± 0.28	598.67 ± 307.94	1480.4 ± 108.4	146.12 ± 0.58	4.529 ± 0.214	106.63 ± 1.00
	Female	0	86.92 ± 38.74	95.16 ± 10.93	22.82 ± 7.08	10.28 ± 0.39	4.93 ± 0.50	390.73 ± 181.33	1201.9 ± 230.5	144.28 ± 1.52	3.983 ± 0.238	105.30 ± 2.55
		1700	63.06 ± 14.54	100.27 ± 16.77	28.14 ± 13.16	10.63 ± 0.37 *	5.32 ± 0.68	279.58 ± 148.16	1340.8 ± 294.4	143.63 ± 0.88	4.095 ± 0.455	104.91 ± 1.83

All data presented as mean ± SD. **p* < 0.05 compared to vehicle control. [a]n = 11; [b]n = 9; [c]n = 10

Historical control data for male rats (interim analysis): Glucose (mg/dL): 55.51-191.63; Albumin (g/dL): 4.29-5.41; ALP (U/L): 147.56-457.63;Cholesterol (mg/dL): 33.84-99.54; Ca^{2+} (mg/dL): 9.20-10.71; P (mg/dL): 5.26-8.87; Amylase (U/L): 991.8-2284.8; Na (mmol/L): 142.63-155.12; K (mmol/L): 4.637-6.704; Cl (mmol/L): 80.21-111.09

Historical control data for male rats (terminal analysis): Albumin (g/dL): 3.53-4.43; ALP (U/L): 108.05-302.17; K (mmol/L): 3.989-5.337; Glucose (mg/dL): 55.51-191.63; Amylase (U/L): 991.8-2284.8; Na (mmol/L): 142.63-155.12; K (mmol/L): 4.637-6.704; Cl (mmol/L): 80.21-111.09

Historical control data for female rats (interim analysis): AST (U/L): 94.02-243.16; Glucose (mg/dL): 67.97-170.64; BUN (mg/dL): 11.66-24.38; Creatinine (mg/dL): 0.0-0.8; Cholesterol (mg/dL): 34.84-113.40; Na (mmol/L): 143.36-156.87; Total protein (g/dL): 6.49-8.69; Albumin (g/dL): 4.84-6.78; Ca^{2+} (mg/dL): 9.71-11.66; Amylase (U/L): 664.0-1574.6;

Historical control data for female rats (terminal analysis): AST (U/L): 66.48-186.27; Glucose (mg/dL): 111.57-240.39;
Ca^{2+} (mg/dL): 9.64-10.93; Cholesterol (mg/dL): 30.13-110.13; Amylase (U/L): 666.8-1482.9; Cl (mmol/L): 89.07-111.57

analysis, the main study male rats showed higher albumin (1700 and 3400 mg/kg), ALP (1700 and 3400 mg/kg) and potassium (3400 mg/kg) compared to vehicle control. There was no statistical difference between vehicle control recovery group and 3400 mg/kg recovery group of males. In main study female rats, the results showed higher cholesterol (850 and 1700 mg/kg), amylase (1700 mg/kg) and chloride (1700 mg/kg) compared to vehicle control. In female recovery rats, lower AST, higher glucose and calcium in 1700 mg/kg recovery group were noted (Table 8). To summarize, the values described above were all within normal physiological range except albumin (interim analysis results from male recovery group). According to the magnitude of change in serum albumin value, this difference was not considered to be of toxicological significance. In addition, the urine analysis results showed no *T. camphoratus* extract related effects were observed (data not shown).

The absolute and relative organ weight results of both genders showed no significant difference between *T. camphoratus* extract treated groups and vehicle control, except adrenal (Male: 850 and 3400 mg/kg; Female: 850 and 1700 mg/kg), liver (Male: 850, 1700 and 3400 mg/kg; Female: 850 and 1700 mg/kg), heart (Male: 3400 mg/kg) and pituitary (Female: 1700 mg/kg) (Table 9-10). The values of mean liver weight and mean liver / body weight ratio of high dose (3400 mg/kg) males were out of the upper limits of historical control range. Following histopathological examination of the liver samples, no test article related lesions were observed. In addition, the significant differences in absolute and relative organ weight data described above, including adrenal and liver, were not seen in the data of male recovery group. Though the values of mean adrenal weight and mean adrenal / body weight ratio of 1700 mg/kg females were out of the upper limits of historical control range, the histopathological findings in adrenal of 1700 mg/kg females were not significantly different from vehicle control females. Besides, there was no significant difference in relative adrenal weight data between vehicle control recovery group and 1700 mg/kg recovery group. Moreover, the significant differences in female liver weight data described above were not seen in high-dose recovery animals. All organ weight changes noted above were not considered to be of toxicological significance, due to lack of statistically significant evidence from microscopic evaluation. The gross necropsy findings showed spontaneous abnormalities found in two male vehicle control rats with atrophy in testes and epididymis and in one female rat (425 mg/kg group) with a focal mass (< 1 cm in diameter) in thorax. Following histopathological examination, minimal to moderate diffuse atrophy were noted in testes and epididymis of male rats and adenocarcinoma in focal mammary glands of female rat was observed. Of the histopathological examination in all animals in high-dose group, no *T. camphoratus* extract related histopathological lesions were observed (Table S14). The NOAEL in this study is 3400 mg/kg/day for male rats, and 1700 mg/kg/day for female rats.

28-days repeated dose oral toxicity study with a 14-Day recovery in beagle dogs

The beagle dogs received capsules containing *T. camphoratus* extract for consecutively 28 days and the results showed no *T. camphoratus* extract related mortality, ophthalmologic abnormality, clinical signs of toxicity and no significant differences on body weight (Fig. 3) and food consumption evaluation. In daily observation of clinical signs, several signs were noted and described as follow. As we know, dogs have a natural tendency to vomit. In this study, vomiting was observed mostly during the first week (adaptation period or affected due to over eating). Vomiting was mostly observed during the week 1-week 2 with one feeding of diet per day and the frequency of vomiting was reduced afterwards (twice daily feeding after week 2). In addition, un-dissolved capsule was vomited by one male dog of the 540 mg/kg group (Day 20) and one female dog of the 1500 mg/kg group (Day 9). The vomited capsules were re-administered to animal within 6 hr of the total times for dosing. Additionally, the vomitus-containing test article-like substance was noted in one female of the 900 mg/kg group and in three females of the 1500 mg/kg group. These findings were not considered to be of toxicological significance since they were sporadic and occurring with a mild severity in observed animals.

Some animals were also showed watery stool (male: all groups; female: control and 1500 mg/kg), soft stool (male: control and 900 mg/kg; female: 900 mg/kg) and poor appetite (male: all groups; female: control and 900 mg/kg).The gastrointestinal disturbances observed (soft stools and/or watery stool) were considered unrelated to the treatment since they were sporadic, not dose related and no pathologic findings were observed from microscopic evaluation. No correlated effects were noted between poor appetite and body weights.

Furthermore, one male dog of the 425 mg/kg group developed illness symptoms (hypoactivity, prostrate, salivation, lacrimation, yellow nose mucus secretion and poor appetite) on Day 20; anorexia and audible respiration were observed on Day 21; anorexia and poor appetite were observed on Day 22 and Day 23 to 24, respectively. A veterinarian's treatment was given to the animal dur-

Table 9. Results of absolute organ weights in rats administered with *T. camphoratus* extract for 26 weeks.

	Male					
	Main (mg/kg)				Recovery (mg/kg)	
Organ (g)	0	850	1700	3400	0	3400
Adrenals (Paired)	0.05391 ± 0.00414	0.06230 ± 0.01056 *	0.05882 ± 0.00782	0.06850 ± 0.00826 *	0.05343 ± 0.00758	0.05112 ± 0.00864
Pituitary	0.01490 ± 0.00211	0.01519 ± 0.00171	0.01559 ± 0.00187	0.01559 ± 0.00155	0.01528 ± 0.00228	0.01520 ± 0.00210
Brain	2.288 ± 0.087	2.261 ± 0.111	2.285 ± 0.071	2.285 ± 0.106	2.236 ± 0.070	2.308 ± 0.126
Heart	1.684 ± 0.160	1.721 ± 0.193	1.812 ± 0.341	1.778 ± 0.158	1.688 ± 0.150	1.850 ± 0.213 *
Thymus	0.331 ± 0.129	0.323 ± 0.106	0.360 ± 0.129	0.307 ± 0.117	0.258 ± 0.070	0.284 ± 0.088
Liver	15.457 ± 2.591	16.810 ± 2.235	17.901 ± 3.484 *	19.845 ± 3.009 *	16.368 ± 2.634	17.884 ± 3.217
Spleen	0.886 ± 0.098	0.919 ± 0.169	0.889 ± 0.126	0.855 ± 0.109	0.917 ± 0.157	0.932 ± 0.242
Kidneys (Paired)	3.674 ± 0.426	3.770 ± 0.383	3.811 ± 0.595	3.925 ± 0.415	3.672 ± 0.459	3.862 ± 0.472
Testes (Paired)	3.577 ± 0.290[b]	3.596 ± 0.296	3.698 ± 0.237	3.690 ± 0.237[b]	3.682 ± 0.252	3.617 ± 0.230
Epididymides (Paired)	1.414 ± 0.091[b]	1.449 ± 0.087	1.443 ± 0.155	1.450 ± 0.149[b]	1.484 ± 0.148	1.483 ± 0.118
Prostates and seminal[a]	4.155 ± 0.687	3.991 ± 0.507	3.741 ± 0.601	3.945 ± 0.439	3.616 ± 0.434	3.742 ± 0.538
	Female					
	Main (mg/kg)				Recovery (mg/kg)	
Organ (g)	0	425	850[a]	1700	0	1700[b]
Ovaries with oviducts	0.12793 ± 0.02774	0.12522 ± 0.02166	0.11751 ± 0.02124	0.12408 ± 0.02580	0.09652 ± 0.01187	0.09876 ± 0.01495
Adrenals (Paired)	0.07671 ± 0.01017	0.08061 ± 0.00783	0.08843 ± 0.01277 *	0.09632 ± 0.01968 *	0.06337 ± 0.00885	0.07069 ± 0.00762 *
Pituitary	0.02156 ± 0.00728	0.02193 ± 0.00528	0.02410 ± 0.00678	0.02375 ± 0.00559	0.02209 ± 0.00539	0.02657 ± 0.00511 *
Brain	2.052 ± 0.068	2.041 ± 0.069	2.076 ± 0.065	2.075 ± 0.098	2.087 ± 0.104	2.041 ± 0.095
Heart	1.072 ± 0.105	1.050 ± 0.093	1.035 ± 0.113	1.074 ± 0.122	1.046 ± 0.135	1.090 ± 0.082
Thymus	0.223 ± 0.039	0.215 ± 0.060	0.210 ± 0.050	0.194 ± 0.040	0.215 ± 0.055	0.193 ± 0.058
Liver	8.702 ± 1.289	9.052 ± 1.220	9.309 ± 1.558	10.470 ± 1.633 *	8.734 ± 1.078	9.199 ± 1.177
Spleen	0.585 ± 0.071	0.574 ± 0.067	0.538 ± 0.063	0.546 ± 0.091	0.562 ± 0.090	0.532 ± 0.069
Kidneys (Paired)	2.181 ± 0.237	2.120 ± 0.244	2.130 ± 0.234	2.170 ± 0.23	2.127 ± 0.225	2.208 ± 0.297
Uterus with cervix	0.716 ± 0.215	0.815 ± 0.259	0.825 ± 0.274	0.835 ± 0.35	0.752 ± 0.211	0.794 ± 0.111

All data presented as mean ± S.D. *$p < 0.05$ compared tovehicle control. [b]n = 21 (The spontaneous lesions, atrophy in testes and epididymis, were found in one male.)
[a]Prostates and seminal: Prostates and seminal vesicles with coagulating glands
Historical control data for male rats: Adrenals (g): 0.04063-0.06936; Liver (g): 11.385-19.367; Heart (g): 1.345-2.009
Historical control data for female rats: Adrenals (g): 0.04650-0.09503; Liver (g): 6.002-10.649; Pituitary (g): 0.00972-0.03241

Table 10. Results of relative organ weights in rats administered with *T. camphoratus* extract for 26 weeks.

	Male					
	Main (%, Mean ± SD)				Recovery (%, Mean ± SD)	
Organ (g)	0	850	1700	3400	0	3400
Adrenals (Paired)	0.00893 ± 0.00105	0.01019 ± 0.00183 *	0.00970 ± 0.00168	0.01128 ± 0.00144 *	0.00838 ± 0.00141	0.00786 ± 0.00096
Pituitary	0.00247 ± 0.00035	0.00247 ± 0.00028	0.00255 ± 0.00028	0.00256 ± 0.00031	0.00238 ± 0.00035	0.00233 ± 0.00029
Brain	0.378 ± 0.037	0.369 ± 0.028	0.377 ± 0.043	0.377 ± 0.035	0.349 ± 0.026	0.355 ± 0.024
Heart	0.277 ± 0.021	0.280 ± 0.023	0.293 ± 0.034	0.293 ± 0.024	0.263 ± 0.018	0.285 ± 0.014 *
Thymus	0.054 ± 0.019	0.052 ± 0.015	0.059 ± 0.018	0.050 ± 0.018	0.041 ± 0.011	0.043 ± 0.011
Liver	2.526 ± 0.227	2.722 ± 0.188 *	2.895 ± 0.264 *	3.238 ± 0.254 *	2.540 ± 0.255	2.731 ± 0.229
Spleen	0.145 ± 0.017	0.150 ± 0.024	0.145 ± 0.016	0.140 ± 0.016	0.143 ± 0.020	0.143 ± 0.028
Kidneys (Paired)	0.605 ± 0.053	0.612 ± 0.044	0.622 ± 0.076	0.644 ± 0.049	0.572 ± 0.046	0.594 ± 0.049
Testes (Paired)	0.592 ± 0.078[b]	0.588 ± 0.073	0.609 ± 0.070	0.612 ± 0.067[c]	0.577 ± 0.045	0.561 ± 0.065
Epididymides (Paired)	0.235 ± 0.028[b]	0.237 ± 0.030	0.239 ± 0.038	0.241 ± 0.030[c]	0.233 ± 0.024	0.230 ± 0.027
Prostates and seminal[a]	0.691 ± 0.140	0.656 ± 0.120	0.619 ± 0.139	0.652 ± 0.094	0.569 ± 0.097	0.578 ± 0.083
	Female					
	Main (%, Mean ± SD)				Recovery (%, Mean ± SD)	
Organ (g)	0	425	850	1700	0	1700
Ovaries with oviducts	0.04016 ± 0.00902	0.03966 ± 0.00731	0.03875 ± 0.00917	0.03949 ± 0.00983	0.02945 ± 0.00429	0.02995 ± 0.00555
Adrenals (Paired)	0.02401 ± 0.00288	0.02553 ± 0.00291	0.02880 ± 0.00363 *	0.03022 ± 0.00502 *	0.01932 ± 0.00274	0.02143 ± 0.00299
Pituitary	0.00680 ± 0.00240	0.00694 ± 0.00170	0.00781 ± 0.00193	0.00755 ± 0.00215	0.00671 ± 0.00161	0.00796 ± 0.00103 *
Brain	0.645 ± 0.053	0.647 ± 0.063	0.681 ± 0.068	0.657 ± 0.069	0.635 ± 0.051	0.619 ± 0.069
Heart	0.336 ± 0.032	0.331 ± 0.023	0.337 ± 0.029	0.338 ± 0.022	0.317 ± 0.035	0.330 ± 0.029
Thymus	0.070 ± 0.011	0.067 ± 0.016	0.067 ± 0.013	0.061 ± 0.010	0.065 ± 0.013	0.056 ± 0.014
Liver	2.726 ± 0.432	2.859 ± 0.352	3.015 ± 0.308 *	3.288 ± 0.407 *	2.653 ± 0.264	2.767 ± 0.197
Spleen	0.184 ± 0.021	0.181 ± 0.022	0.175 ± 0.017	0.172 ± 0.025	0.172 ± 0.024	0.161 ± 0.022
Kidneys (Paired)	0.685 ± 0.085	0.672 ± 0.089	0.697 ± 0.093	0.684 ± 0.072	0.649 ± 0.087	0.665 ± 0.062
Uterus with cervix	0.226 ± 0.073	0.260 ± 0.089	0.271 ± 0.096	0.267 ± 0.134	0.228 ± 0.056	0.239 ± 0.033

All data presented as mean ± SD. *$p < 0.05$ compared to vehicle control. [b]n = 21 (The spontaneous lesions, atrophy in testes and epididymis, were found in one male.)
[a]Prostates and seminal: Prostates and seminal vesicles with coagulating glands
Relative organ weight (%) = Absolute organ weight / Body weight of rat on the day of sacrifice (g) x 100
Historical control data for male rats: Relative adrenal weight (%): 0.00674-0.01140; Relative liver weight (%): 2.147-2.900; Relative heart weight (%): 0.231-0.297
Historical control data for female rats: Relative adrenal weight (%): 0.01562-0.03016; Relative liver weight (%): 2.024-3.354; Relative pituitary weight (%): 0.00348-0.00995

(A)

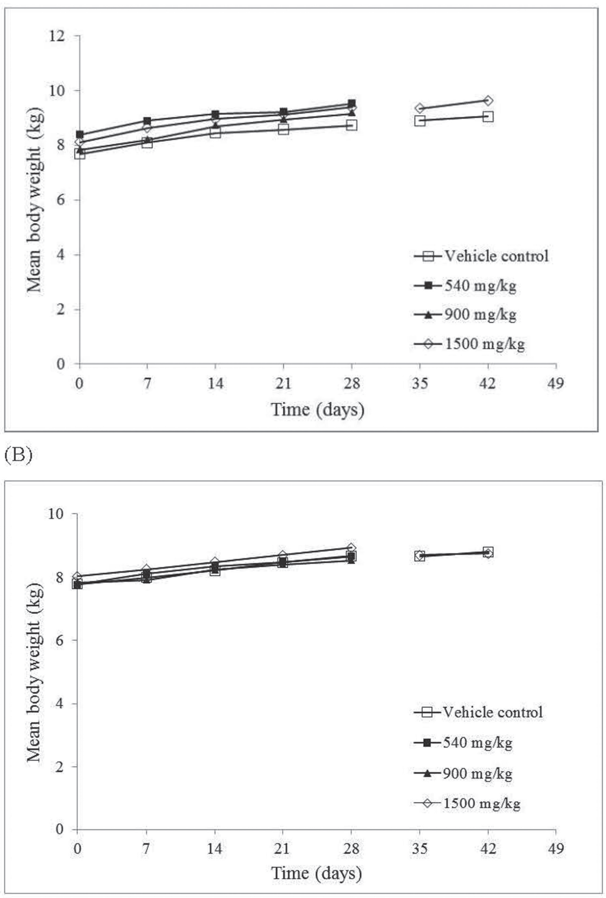


Fig. 3. Effects of repeated oral dose of *T. camphoratus* extract on body weight in beagle dogs. Results of body weight in (A) male dogs and (B) female dogs treated with *T. camphoratus* extract for 28 days with additional 14 recovery days. No significant changes in body weight were observed in *T. camphoratus* extract treated animals. All data presented as mean ± S.D.

ing Day 20 to 24 and its health condition was improved on Day 22. According to the diagnosis results, the animal condition deteriorated markedly due to aspiration of vomit or idiopathic reason, resulted in interstitial lung disease. These findings were considered unrelated to the test article because of lack of dose dependency.

In ECG examination, the waveform morphology was evaluated by a veterinary cardiologist and the measured parameters including heart rate, RR interval, PR interval, QRS interval, QT interval and QT interval corrected for heart rate using Fridericia's formula were examined in all animals at pre-dose, end of treatment and recovery stages. The evaluated results showed no test article related abnormalities in morphology and measured parameters. The only two statistical differences were found in female dogs: lower PR interval in 540 mg/kg group at pre-dose phase and higher PR interval in 900 mg/kg group at end of treatment (Table 11). These data was within the normal physiological range of dogs.

In clinical pathology evaluation (hematology, serum biochemistry and urine analysis), no significant toxicity effects were noted. Some statistical differences were observed when compared to vehicle control and described as follow. For hematology evaluation, higher activated partial thromboplastin time (APTT) in male rat of 540 mg/kg group at pre-dose phase was noted, but it was within normal physiological range (Table 12). For serum biochemistry evaluation, lower potassium in male rat of 900 mg/kg group at pre-dose phase, lower cholesterol in male rat of 1500 mg/kg group at end of treatment and higher triglyceride (TG) in male rat of 1500 mg/kg recovery group were noted. In addition, a minimal (about 2-fold) increase in ALT was observed in male rats of 1500 mg/kg group, but no other correlated parameters were affected and no pathologic findings were present from microscopic evaluation. This difference was not seen in recovery. Therefore, it was not considered to be of toxicological significance. In female rats, lower cholesterol in 1500 mg/kg group at end of treatment was noted. These values were within normal physiological range (Table 13).

There was no significant difference between control and each treatment groups in absolute and relative organ weight in main study animals (Table 14-15). Statistical lower spleen / body weight ratio in male (1500 mg/kg) recovery group and higher kidney weight and lower adrenal / body weight ratio in female (1500 mg/kg) recovery group were noted when compared to vehicle control (Table 14). All organ weight changes noted above were considered incidental and unrelated to treatment, due to individual variability and lack of microscopic correlations. The gross necropsy observation results showed that one male dog of 1500 mg/kg group had spontaneous unilateral absence of right epididymis (aplasia of right epididymis was confirmed by histopathological examination) (Table S15). In addition, the ill male dog of 425 mg/kg group developed illness symptoms on Day 20 showed diffuse yellow discoloration and diffuse firm abnormal consistency in lung at necropsy. Following histopathological examination, moderate diffuse interstitial mononuclear cell inflammation in lung was observed and it was considered unrelated to treatment. Moreover, there were no test article related histopathological changes in all animals at 1500 mg/kg (Table S16). This was the first study to explore the toxicity effect of *T. camphoratus* on beagle dogs. Based on the results, administration of *T. camphoratus* extract did not cause significant toxic effects in dogs at dose of 1500 mg/kg. The results would provide more safety evidences for further medical use.

The results from *in vitro* and *in vivo* genotoxicity studies showed *T. camphoratus* extract had no mutagenic activity and genotoxicity. Besides, the results of repeated dose toxicity studies in rodent and non-rodent showed no significant toxicity evidences with the dosages up to 3400 mg/kg for male rats, 1700 mg/kg for female rats, and 1500 mg/kg for both genders of beagle dogs. Tak-

Table 11. Effect of *T. camphoratus* extract on ECG parameters in beagle dogs.

Parameters	Gender	Dose (mg/kg)	Pre-dose	End of treatment	End of recovery
RR Interval (ms)	Male	0	572.096 ± 96.074	549.796 ± 79.307	502.165 ± 76.134
		540	534.130 ± 103.344	512.777 ± 30.754	
		900	607.943 ± 219.259	570.120 ± 190.645	
		1500	585.290 ± 183.822	453.714 ± 66.798	544.165 ± 111.391
	Female	0	494.982 ± 81.476	477.276 ± 39.240	471.375 ± 52.291
		540	580.820 ± 75.492	478.213 ± 29.666	
		900	641.343 ± 226.433	641.833 ± 139.448	
		1500	536.002 ± 105.932	539.928 ± 151.688	431.135 ± 86.232
PR Interval (ms)	Male	0	88.038 ± 8.141	90.890 ± 10.790	95.635 ± 10.953
		540	75.770 ± 8.670	76.493 ± 3.846	
		900	84.520 ± 3.918	87.307 ± 4.882	
		1500	86.410 ± 2.290	83.306 ± 7.614	84.665 ± 3.585
	Female	0	87.070 ± 7.389	86.062 ± 4.833	87.575 ± 7.389
		540	70.610 ± 10.345 *	76.347 ± 4.866	
		900	94.173 ± 4.795	98.503 ± 5.456 *	
		1500	87.798 ± 5.647	87.206 ± 6.535	89.240 ± 3.111
QRS interval (ms)	Male	0	36.614 ± 2.702	37.218 ± 1.574	37.515 ± 3.203
		540	36.120 ± 1.277	36.650 ± 2.498	
		900	36.350 ± 2.256	37.443 ± 1.250	
		1500	39.874 ± 2.043	37.618 ± 1.683	34.735 ± 0.092
	Female	0	36.900 ± 2.151	36.430 ± 1.277	37.170 ± 1.315
		540	37.870 ± 7.627	38.510 ± 3.071	
		900	38.127 ± 0.219	38.703 ± 1.377	
		1500	35.692 ± 1.686	35.960 ± 1.248	37.500 ± 3.536
QT Interval (ms)	Male	0	175.986 ± 16.989	173.488 ± 11.209	170.665 ± 10.373
		540	167.925 ± 7.129	172.467 ± 5.094	
		900	176.303 ± 14.200	169.293 ± 18.777	
		1500	176.258 ± 15.622	160.682 ± 9.831	166.985 ± 16.525
	Female	0	169.560 ± 6.008	168.272 ± 7.002	169.245 ± 0.064
		540	177.630 ± 5.818	169.067 ± 7.695	
		900	178.367 ± 13.214	183.157 ± 27.990	
		1500	173.466 ± 12.622	169.402 ± 9.077	160.250 ± 4.992
QTcF (ms)	Male	0	214.370 ± 14.378	213.078 ± 12.175	216.545 ± 1.902
		540	208.953 ± 13.323	217.240 ± 9.117	
		900	211.737 ± 8.273	206.927 ± 12.367	
		1500	214.406 ± 17.024	210.046 ± 8.322	206.090 ± 7.198
	Female	0	215.838 ± 9.780	216.076 ± 4.474	218.465 ± 8.450
		540	214.303 ± 11.095	216.790 ± 8.394	
		900	211.777 ± 6.865	214.923 ± 20.473	
		1500	216.196 ± 10.087	211.822 ± 10.407	212.875 ± 7.658
Heart Rate (bpm)	Male	0	107.108 ± 16.707	110.914 ± 15.487	120.870 ± 18.328
		540	115.268 ± 20.388	117.297 ± 7.137	
		900	106.347 ± 31.866	114.217 ± 40.990	
		1500	111.022 ± 34.515	134.678 ± 20.829	112.620 ± 23.052
	Female	0	123.814 ± 19.847	126.430 ± 10.874	128.075 ± 14.206
		540	104.557 ± 14.524	125.783 ± 7.613	
		900	100.687 ± 30.484	96.410 ± 20.372	
		1500	116.240 ± 27.488	119.328 ± 37.859	142.005 ± 28.404

All data presented as mean ± S.D. *$p < 0.05$ compared to vehicle control.

Table 12. Effect of *T. camphoratus* extract on hematological parameters in beagle dogs.

	Gender	Dose (mg/kg)	WBC (10^3/μL)	RBC (10^6/μL)	Hb (g/dL)	Hct (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)
Pre-dose	Male	0	12.008 ± 1.631	6.362 ± 0.291	15.02 ± 0.54	43.64 ± 1.43	68.66 ± 1.68	23.64 ± 0.34	34.42 ± 0.43
		540	10.758 ± 1.689	6.618 ± 0.162	14.73 ± 0.17	43.08 ± 0.43	65.13 ± 1.00	22.25 ± 0.40	34.20 ± 0.42
		900	13.017 ± 3.434	6.103 ± 0.757	14.13 ± 2.08	41.07 ± 4.46	67.50 ± 4.97	23.23 ± 2.42	34.33 ± 1.43
		1500	13.112 ± 4.019	6.530 ± 0.563	14.86 ± 1.24	43.16 ± 2.94	66.18 ± 1.19	22.78 ± 0.15	34.40 ± 0.57
	Female	0	10.644 ± 3.318	6.786 ± 0.550	15.76 ± 1.29	45.68 ± 3.43	67.36 ± 1.52	23.24 ± 0.47	34.50 ± 0.34
		540	11.293 ± 3.722	6.910 ± 0.607	15.60 ± 0.44	45.43 ± 1.93	65.93 ± 3.18	22.67 ± 1.42	34.37 ± 0.55
		900	12.690 ± 2.434	6.650 ± 0.433	15.73 ± 1.02	45.17 ± 2.72	67.90 ± 1.08	23.67 ± 0.55	34.83 ± 0.29
		1500	11.554 ± 1.752	6.426 ± 0.508	15.02 ± 0.59	43.48 ± 2.29	67.78 ± 1.78	23.42 ± 1.04	34.54 ± 0.71
End of treatment	Male	0	8.868 ± 1.956	6.742 ± 0.559	15.76 ± 1.30	45.76 ± 3.24	67.92 ± 1.18	23.38 ± 0.37	34.42 ± 0.47
		540	10.647 ± 1.380	6.653 ± 0.346	14.77 ± 1.10	43.43 ± 2.51	65.27 ± 0.65	22.17 ± 0.57	33.97 ± 0.55
		900	10.570 ± 1.780	6.070 ± 0.137	14.20 ± 1.41	41.20 ± 2.45	67.87 ± 3.23	23.37 ± 1.90	34.40 ± 1.37
		1500	11.106 ± 4.761	6.740 ± 0.447	15.08 ± 0.94	44.68 ± 2.67	66.34 ± 0.77	22.40 ± 0.28	33.76 ± 0.28
	Female	0	9.492 ± 1.788	6.960 ± 0.746	16.20 ± 1.54	47.10 ± 4.48	67.76 ± 1.16	23.30 ± 0.52	34.42 ± 0.18
		540	9.600 ± 0.709	6.777 ± 0.260	15.20 ± 1.01	44.70 ± 2.26	65.93 ± 2.49	22.43 ± 1.19	33.97 ± 0.55
		900	10.003 ± 1.753	6.890 ± 0.400	16.20 ± 1.11	46.97 ± 2.96	68.17 ± 1.01	23.53 ± 0.47	34.50 ± 0.26
		1500	9.792 ± 1.326	6.514 ± 0.594	15.08 ± 0.80	44.00 ± 2.85	67.66 ± 1.81	23.20 ± 0.84	34.30 ± 0.50
End of recovery	Male	0	10.125 ± 2.638	6.735 ± 0.120	15.40 ± 0.28	45.70 ± 0.71	67.90 ± 2.26	22.90 ± 0.85	33.70 ± 0.14
		1500	11.840 ± 3.833	7.185 ± 0.530	15.85 ± 1.34	46.50 ± 2.40	64.80 ± 1.41	22.05 ± 0.21	34.10 ± 1.13
	Female	0	14.365 ± 7.078	7.120 ± 0.467	16.65 ± 1.06	48.65 ± 3.04	68.35 ± 0.21	23.40 ± 0.00	34.25 ± 0.07
		1500	7.945 ± 1.223	7.220 ± 0.297	16.85 ± 0.49	48.55 ± 0.07	67.30 ± 2.69	23.35 ± 1.63	34.75 ± 1.06

	Gender	Dose (mg/kg)	Platelet (10^3/μL)	Neutrophil (%)	Lymphocyte (%)	Monocyte (%)	Eosinophil (%)	Basophil (%)	PT(sec)	APTT (sec)
Pre-dose	Male	0	377.4 ± 98.0	60.78 ± 4.45	30.32 ± 3.51	6.62 ± 0.42	1.96 ± 1.06	0.32 ± 0.08	7.66 ± 0.55	14.46 ± 0.61
		540	452.8 ± 52.2	56.35 ± 4.17	33.08 ± 5.56	7.98 ± 1.23	2.23 ± 1.02	0.38 ± 0.10	7.58 ± 0.22	15.75 ± 0.21*
		900	353.3 ± 121.8	59.13 ± 7.42	30.23 ± 4.02	7.83 ± 2.71	2.40 ± 1.54	0.40 ± 0.10	7.97 ± 0.50	15.33 ± 0.47
		1500	404.2 ± 90.3	63.84 ± 4.10	27.70 ± 3.53	7.02 ± 0.91	1.22 ± 0.57	0.22 ± 0.08	7.84 ± 0.51	14.94 ± 0.50
	Female	0	377.4 ± 54.5	61.80 ± 8.64	29.30 ± 7.57	6.72 ± 2.00	1.62 ± 1.70	0.56 ± 0.40	7.86 ± 0.29	14.96 ± 0.23
		540	375.0 ± 23.9	58.60 ± 8.78	30.93 ± 6.63	7.07 ± 2.00	3.03 ± 1.12	0.37 ± 0.15	8.03 ± 0.40	16.17 ± 1.76
		900	363.3 ± 62.5	59.23 ± 10.55	29.80 ± 10.44	7.57 ± 0.91	2.83 ± 1.11	0.57 ± 0.23	7.93 ± 0.29	14.77 ± 0.64
		1500	439.8 ± 29.4	61.56 ± 5.68	29.20 ± 5.14	7.22 ± 1.69	1.64 ± 0.92	0.38 ± 0.11	7.72 ± 0.22	15.52 ± 1.44
End of treatment	Male	0	307.2 ± 65.7	55.74 ± 3.55	35.00 ± 2.51	6.50 ± 0.51	2.32 ± 0.91	0.44 ± 0.17	7.86 ± 0.39	14.00 ± 0.35
		540	382.3 ± 113.0	55.13 ± 2.01	35.43 ± 1.76	7.13 ± 0.81	1.90 ± 0.87	0.40 ± 0.20	7.47 ± 0.15	14.33 ± 0.29
		900	291.7 ± 43.9	53.70 ± 3.47	36.47 ± 1.33	6.73 ± 1.85	2.70 ± 0.56	0.40 ± 0.10	8.33 ± 0.12	14.30 ± 0.66
		1500	333.8 ± 38.4	56.32 ± 9.07	35.16 ± 7.68	6.52 ± 1.32	1.74 ± 0.35	0.26 ± 0.11	8.22 ± 0.37	14.04 ± 0.34
	Female	0	305.2 ± 53.8	54.98 ± 5.08	34.88 ± 3.25	7.14 ± 1.83	2.42 ± 1.40	0.58 ± 0.48	7.92 ± 0.37	14.66 ± 0.25
		540	295.3 ± 76.8	55.33 ± 6.46	34.80 ± 3.97	6.63 ± 2.22	2.73 ± 0.23	0.50 ± 0.30	8.10 ± 0.78	15.17 ± 0.76
		900	311.7 ± 68.2	51.47 ± 3.15	37.33 ± 4.26	6.97 ± 1.05	3.70 ± 3.56	0.53 ± 0.06	8.00 ± 0.00	14.13 ± 0.75
		1500	354.6 ± 38.5	55.90 ± 4.64	34.76 ± 3.41	6.86 ± 1.87	2.06 ± 1.02	0.42 ± 0.16	7.82 ± 0.33	14.40 ± 1.07
End of recovery	Male	0	283.5 ± 92.6	54.85 ± 1.06	35.65 ± 3.32	6.60 ± 1.27	2.45 ± 0.78	0.45 ± 0.21	7.45 ± 0.07	14.25 ± 0.21
		1500	364.0 ± 17.0	52.70 ± 0.00	38.65 ± 1.34	5.30 ± 0.71	3.05 ± 0.64	0.30 ± 0.00	8.10 ± 0.85	14.00 ± 0.99
	Female	0	310.0 ± 65.1	59.55 ± 13.51	30.35 ± 11.81	7.15 ± 0.35	2.50 ± 0.99	0.45 ± 0.35	8.30 ± 0.28	14.30 ± 0.71
		1500	322.0 ± 60.8	55.50 ± 4.81	35.40 ± 4.53	6.45 ± 1.20	2.20 ± 0.71	0.45 ± 0.21	7.90 ± 0.14	14.00 ± 0.28

All data presented as mean ± S.D. *$p < 0.05$ compared to vehicle control.

Table 13. Effect of *T. camphoratus* extract on serum biochemical parameters in beagle dogs.

	Gender	Dose (mg/kg)	AST (U/L)	ALT (U/L)	Glucose (mg/dL)	Total protein (g/dL)	Albumin (g/dL)	Total bilirubin (mg/dL)	BUN (mg/dL)	Creatinine (mg/dL)	γ-GT (U/L)
Pre-dose	Male	0	37.60 ± 5.15	38.22 ± 7.59	103.04 ± 3.47	5.44 ± 0.19	3.34 ± 0.21	< 0.04	14.10 ± 6.75	0.60 ± 0.22	3.50 ± 0.63a
		540	45.15 ± 11.45	34.13 ± 3.12	97.60 ± 11.77	5.60 ± 0.27	3.35 ± 0.06	< 0.06	14.13 ± 3.61	0.48 ± 0.05	3.23 ± 0.74
		900	40.10 ± 1.73	30.13 ± 4.27	93.73 ± 20.95	5.47 ± 0.25	3.20 ± 0.10	< 0.04	12.87 ± 0.97	0.47 ± 0.06	4.10 ± 0.50
		1500	39.44 ± 9.34	34.06 ± 5.25	98.70 ± 9.09	5.66 ± 0.11	3.42 ± 0.04	< 0.07	12.84 ± 2.63	0.52 ± 0.04	3.86 ± 0.46
	Female	0	44.90 ± 9.25	31.94 ± 4.33	84.62 ± 6.37	5.68 ± 0.08	3.52 ± 0.18	< 0.04	14.48 ± 1.63	0.56 ± 0.05	3.95 ± 1.47[a]
		540	37.47 ± 2.55	36.37 ± 5.64	82.77 ± 0.12	5.77 ± 0.21	3.50 ± 0.00	< 0.07	11.97 ± 0.47	0.47 ± 0.06	3.60 ± 0.26
		900	38.10 ± 8.71	30.00 ± 5.17	86.33 ± 5.00	5.50 ± 0.26	3.37 ± 0.15	< 0.05	13.27 ± 1.77	0.57 ± 0.06	3.63 ± 0.55
		1500	45.16 ± 5.31	41.86 ± 25.85	85.64 ± 4.60	5.42 ± 0.18	3.38 ± 0.08	< 0.07	12.08 ± 2.38	0.52 ± 0.08	3.64 ± 0.28
End of treatment	Male	0	36.24 ± 6.05	41.40 ± 7.29	101.34 ± 4.69	5.54 ± 0.13	3.36 ± 0.17	< 0.04	13.94 ± 4.56	0.60 ± 0.17	2.80 ± 0.43
		540	49.97 ± 15.02	37.03 ± 7.27	97.17 ± 13.30	5.77 ± 0.29	3.33 ± 0.12	< 0.04	15.50 ± 1.47	0.53 ± 0.06	3.70 ± 0.56
		900	37.43 ± 2.75	45.23 ± 4.27	98.23 ± 16.89	5.53 ± 0.21	3.27 ± 0.15	< 0.04	13.90 ± 1.39	0.60 ± 0.10	4.80 ± 1.40
		1500	42.90 ± 8.13	81.20 ± 33.01*	104.18 ± 9.43	5.74 ± 0.09	3.54 ± 0.05	< 0.04	15.16 ± 2.49	0.58 ± 0.04	5.18 ± 2.60
	Female	0	46.98 ± 14.08	38.24 ± 6.10	104.90 ± 4.44	5.54 ± 0.11	3.50 ± 0.07	< 0.05	15.70 ± 2.19	0.66 ± 0.05	4.90 ± 0.80
		540	40.17 ± 5.83	39.93 ± 4.35	102.47 ± 6.03	5.87 ± 0.12	3.60 ± 0.17	< 0.05	15.83 ± 2.11	0.60 ± 0.00	4.73 ± 0.59
		900	36.33 ± 6.05	35.43 ± 9.21	104.77 ± 2.32	5.40 ± 0.36	3.50 ± 0.20	< 0.04	15.90 ± 2.00	0.67 ± 0.12	4.37 ± 0.96
		1500	49.06 ± 4.80	49.76 ± 19.64	109.60 ± 3.15	5.30 ± 0.22	3.38 ± 0.08	< 0.04	15.26 ± 2.29	0.64 ± 0.05	4.62 ± 1.14
End of recovery	Male	0	37.45 ± 2.05	43.80 ± 0.57	102.50 ± 7.50	5.50 ± 0.00	3.30 ± 0.14	< 0.04	15.60 ± 0.85	0.55 ± 0.07	3.55 ± 1.34
		1500	41.15 ± 5.59	53.00 ± 22.20	99.80 ± 14.85	5.70 ± 0.14	3.45 ± 0.07	< 0.04	14.25 ± 4.60	0.65 ± 0.07	5.40 ± 0.71
	Female	0	46.20 ± 12.02	40.55 ± 0.78	103.60 ± 0.99	5.50 ± 0.14	3.50 ± 0.14	< 0.04	14.15 ± 3.46	0.65 ± 0.07	4.30 ± 0.71
		1500	42.05 ± 1.20	43.45 ± 9.40	107.95 ± 7.28	5.35 ± 0.21	3.40 ± 0.00	< 0.04	13.80 ± 0.42	0.60 ± 0.00	4.60 ± 0.28

	Gender	Dose (mg/kg)	ALP (U/L)	Cholesterol (mg/dL)	TG (mg/dL)	Ca^{2+} (mg/dL)	P (mg/dL)	Creatine kinase (U/L)	Amylase (U/L)	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)
Pre-dose	Male	0	332.56 ± 43.98	181.96 ± 21.56	26.90 ± 0.71	11.20 ± 0.29	7.06 ± 0.39	272.04 ± 29.98	710.6 ± 96.7	147.00 ± 0.90	5.050 ± 0.142	109.38 ± 1.37
		540	495.15 ± 230.93	174.90 ± 14.87	28.70 ± 4.79	11.28 ± 0.21	7.05 ± 0.54	372.90 ± 214.08	847.3 ± 89.8	147.08 ± 1.17	5.120 ± 0.163	107.58 ± 1.42
		900	413.97 ± 107.15	156.97 ± 31.21	29.53 ± 1.46	11.30 ± 0.36	6.97 ± 0.67	269.53 ± 10.68	828.3 ± 119.4	146.03 ± 0.40	4.720 ± 0.191*	106.77 ± 2.08
		1500	371.50 ± 70.00	164.20 ± 17.58	24.58 ± 6.14	11.18 ± 0.19	7.18 ± 0.38	314.06 ± 105.53	750.4 ± 110.6	147.26 ± 1.41	4.822 ± 0.061	108.16 ± 1.47
	Female	0	420.14 ± 76.47	161.24 ± 15.81	25.22 ± 2.58	11.34 ± 0.23	6.86 ± 0.27	393.62 ± 213.52	743.2 ± 94.0	147.60 ± 1.57	5.000 ± 0.098	110.60 ± 4.73
		540	336.57 ± 82.56	147.03 ± 9.08	33.33 ± 1.36	11.40 ± 0.17	6.57 ± 0.42	266.53 ± 16.60	858.3 ± 256.7	147.47 ± 0.93	5.257 ± 0.191	113.70 ± 4.34
		900	337.07 ± 96.22	138.83 ± 4.54	29.87 ± 5.85	11.23 ± 0.25	7.30 ± 0.56	269.97 ± 20.08	676.0 ± 128.0	147.17 ± 1.99	5.183 ± 0.025	112.87 ± 1.88
		1500	426.16 ± 112.32	159.30 ± 30.70	31.98 ± 9.16	11.28 ± 0.28	7.32 ± 0.50	377.60 ± 149.35	708.0 ± 137.4	147.74 ± 0.87	5.030 ± 0.194	113.60 ± 4.79
End of treatment	Male	0	249.48 ± 44.39	174.62 ± 33.98	19.24 ± 3.35	11.06 ± 0.36	6.54 ± 0.55	245.16 ± 40.14	820.8 ± 144.1	147.14 ± 1.13	4.818 ± 0.186	108.56 ± 1.53
		540	341.50 ± 127.66	144.23 ± 4.90	19.87 ± 5.63	11.03 ± 0.15	6.07 ± 0.55	385.80 ± 229.49	1035.3 ± 99.2	144.93 ± 1.76	4.980 ± 0.271	107.80 ± 0.79
		900	326.77 ± 71.84	129.90 ± 22.55	15.27 ± 4.04	11.10 ± 0.10	6.07 ± 0.15	239.93 ± 39.74	938.0 ± 177.5	145.17 ± 1.05	4.790 ± 0.046	107.30 ± 2.13
		1500	399.56 ± 265.38	124.76 ± 17.00*	14.54 ± 3.50	11.06 ± 0.11	6.58 ± 0.28	297.36 ± 87.45	808.0 ± 175.5	146.22 ± 1.79	4.872 ± 0.144	107.58 ± 1.24
	Female	0	321.82 ± 63.70	146.28 ± 13.69	22.62 ± 4.88	11.12 ± 0.18	6.04 ± 0.28	398.28 ± 275.56	831.2 ± 124.0	146.08 ± 0.68	4.848 ± 0.279	107.48 ± 0.59
		540	269.27 ± 42.90	129.47 ± 5.62	20.43 ± 7.89	11.23 ± 0.21	5.77 ± 0.75	290.73 ± 28.81	894.3 ± 251.1	147.27 ± 1.17	4.470 ± 0.106	108.10 ± 1.08
		900	234.87 ± 68.31	115.47 ± 21.07	17.83 ± 2.61	11.03 ± 0.25	6.40 ± 0.40	212.63 ± 43.54	614.7 ± 66.9	146.13 ± 1.90	5.107 ± 0.272	108.40 ± 1.50
		1500	312.04 ± 71.78	113.48 ± 19.60*	19.38 ± 5.61	11.06 ± 0.15	6.14 ± 0.71	371.72 ± 129.86	664.4 ± 82.5	145.72 ± 1.17	4.762 ± 0.274	107.78 ± 1.04
End of recovery	Male	0	245.15 ± 55.93	162.75 ± 23.12	18.50 ± 1.41	10.80 ± 0.42	6.40 ± 0.00	209.30 ± 6.51	900.5 ± 222.7	146.55 ± 1.06	5.075 ± 0.106	108.90 ± 1.56
		1500	313.80 ± 120.35	164.75 ± 42.50	24.30 ± 1.13*	10.90 ± 0.28	6.75 ± 0.35	222.50 ± 47.66	761.5 ± 20.5	146.65 ± 0.21	4.875 ± 0.106	106.40 ± 1.13
	Female	0	232.60 ± 21.64	130.30 ± 19.09	21.50 ± 0.71	10.50 ± 0.42	5.85 ± 0.21	279.50 ± 175.93	742.0 ± 9.9	146.25 ± 0.35	4.770 ± 0.127	106.65 ± 0.49
		1500	292.65 ± 41.37	143.20 ± 7.78	26.45 ± 8.41	10.45 ± 0.07	5.75 ± 0.07	292.10 ± 10.89	760.0 ± 58.0	146.10 ± 2.12	4.870 ± 0.057	107.80 ± 1.13

All data presented as mean ± S.D. *$p < 0.05$ compared to vehicle control.
[a]n = 4 (Value from one animal was below detection limit.)

Table 14. Effect of *T. camphoratus* extract on absolute organ weights in beagle dogs.

	Male					
	Main (mg/kg)				Recovery (mg/kg)	
Organ (g)	0	450	900	1500	0	1500
Adrenals (Paired)	1.02640 ± 0.17918	0.88240 ± 0.03935	0.92973 ± 0.21160	0.87923 ± 0.05687	0.84505 ± 0.23257	0.93075 ± 0.25307
Pituitary	0.06120 ± 0.01185	0.05813 ± 0.00739	0.05810 ± 0.00690	0.05890 ± 0.00384	0.05990 ± 0.00820	0.05055 ± 0.00148
Thyroid with parathyroid	0.58033 ± 0.12742	0.82110 ± 0.17016	0.90517 ± 0.27018	0.67133 ± 0.21232	0.87415 ± 0.34938	0.84905 ± 0.39902
Salivary glands	8.210 ± 0.782	8.487 ± 2.097	8.853 ± 1.354	8.940 ± 1.019	7.050 ± 2.008	7.825 ± 0.290
Brain	73.33 ± 8.20	73.00 ± 6.00	72.27 ± 5.59	73.17 ± 3.29	77.20 ± 12.87	70.25 ± 9.55
Heart	71.47 ± 5.62	84.60 ± 12.95	72.30 ± 6.10	85.63 ± 7.72	82.00 ± 23.48	71.95 ± 1.34
Thymus	9.300 ± 2.245	11.647 ± 4.151	11.997 ± 4.901	9.640 ± 2.517	8.080 ± 1.131	7.965 ± 1.096
Liver	261.57 ± 45.95	284.20 ± 57.02	252.43 ± 38.08	266.90 ± 21.62	269.00 ± 70.71	270.75 ± 33.73
Spleen	63.80 ± 31.88	45.13 ± 6.29	48.57 ± 11.93	45.17 ± 10.43	58.80 ± 14.57	44.50 ± 3.11
Kidneys (Paired)	47.03 ± 5.41	46.57 ± 4.11	41.63 ± 3.44	48.07 ± 7.98	39.95 ± 10.82	44.75 ± 0.07
Testes (Paired)	10.367 ± 3.427	13.653 ± 2.896	10.370 ± 3.376	11.910 ± 2.602	12.025 ± 2.906	13.045 ± 0.516
Epididymides (Paired)	1.613 ± 0.627	1.980 ± 0.280	1.917 ± 0.326	1.753 ± 0.552	1.875 ± 0.361	2.035 ± 0.276
Prostates	2.300 ± 1.065	2.777 ± 0.930	2.780 ± 1.351	1.877 ± 0.501	2.280 ± 0.382	4.325 ± 2.694
	Female					
	Main (mg/kg)				Recovery (mg/kg)	
Organ (g)	0	450	900	1500	0	1500
Ovaries with oviducts	0.60533 ± 0.13804	0.74423 ± 0.19871	0.54120 ± 0.05895	0.63917 ± 0.07627	0.59450 ± 0.04808	0.60455 ± 0.17133
Adrenals (Paired)	0.95450 ± 0.13245	1.00477 ± 0.28472	0.84723 ± 0.01281	0.93997 ± 0.14129	0.77885 ± 0.00007	0.71415 ± 0.04929
Pituitary	0.05793 ± 0.00519	0.05423 ± 0.00625	0.05533 ± 0.00835	0.07000 ± 0.00577	0.05195 ± 0.00700	0.05295 ± 0.00361
Thyroid with parathyroid	0.71657 ± 0.07577	0.73537 ± 0.23597	0.65967 ± 0.05351	0.63217 ± 0.05634	0.60400 ± 0.01640	0.63825 ± 0.02751
Salivary glands	7.970 ± 0.384	7.870 ± 0.815	7.347 ± 1.138	8.437 ± 0.356	6.950 ± 0.085	7.805 ± 0.417
Brain	71.60 ± 5.92	73.33 ± 1.86	68.70 ± 6.30	79.63 ± 9.64	67.50 ± 2.30	71.65 ± 13.65
Heart	77.27 ± 4.70	72.43 ± 8.06	69.47 ± 7.07	73.10 ± 5.64	81.90 ± 2.90	83.80 ± 17.68
Thymus	9.087 ± 3.291	9.033 ± 1.782	9.047 ± 0.210	10.780 ± 2.361	10.210 ± 0.481	4.945 ± 2.722
Liver	229.83 ± 23.12	241.10 ± 10.79	224.70 ± 33.53	250.47 ± 18.12	212.55 ± 4.60	224.70 ± 4.24
Spleen	45.20 ± 3.56	43.30 ± 12.55	40.53 ± 13.94	41.40 ± 10.10	55.30 ± 7.64	57.25 ± 0.64
Kidneys (Paired)	41.77 ± 2.70	43.43 ± 5.99	37.80 ± 2.71	44.33 ± 5.16	35.85 ± 0.07	38.50 ± 0.14*
Uterus with cervix	1.473 ± 0.169	3.673 ± 2.950	3.247 ± 1.464	2.460 ± 1.067	3.110 ± 0.156	4.515 ± 3.147

All data presented as mean ± S.D. *$p < 0.05$ compared to vehicle control.

Table 15. Effect of *T. camphoratus* extract on relative organ weights in beagle dogs.

	Male					
	Main (mg/kg)				Recovery (mg/kg)	
Organ (%)	0	450	900	1500	0	1500
Adrenals (Paired)	0.01200 ± 0.00171	0.00977 ± 0.00177	0.01050 ± 0.00121	0.00963 ± 0.00006	0.00955 ± 0.00007	0.01000 ± 0.00170
Pituitary	0.00073 ± 0.00021	0.00063 ± 0.00006	0.00067 ± 0.00006	0.00063 ± 0.00006	0.00070 ± 0.00014	0.00055 ± 0.00007
Thyroid with parathyroid	0.00677 ± 0.00071	0.00887 ± 0.00051	0.01013 ± 0.00170	0.00733 ± 0.00214	0.00970 ± 0.00141	0.00905 ± 0.00332
Salivary glands	0.097 ± 0.006	0.090 ± 0.010	0.103 ± 0.012	0.097 ± 0.015	0.080 ± 0.000	0.085 ± 0.007
Brain	0.877 ± 0.191	0.800 ± 0.062	0.833 ± 0.080	0.800 ± 0.056	0.885 ± 0.092	0.765 ± 0.021
Heart	0.840 ± 0.046	0.920 ± 0.010	0.833 ± 0.076	0.940 ± 0.079	0.925 ± 0.021	0.790 ± 0.071
Thymus	0.110 ± 0.020	0.127 ± 0.040	0.137 ± 0.047	0.103 ± 0.035	0.090 ± 0.014	0.085 ± 0.007
Liver	3.053 ± 0.133	3.148 ± 0.213	2.900 ± 0.414	2.927 ± 0.156	3.040 ± 0.000	2.940 ± 0.057
Spleen	0.737 ± 0.359	0.497 ± 0.093	0.560 ± 0.149	0.493 ± 0.115	0.665 ± 0.007	0.485 ± 0.021 *
Kidneys (Paired)	0.550 ± 0.010	0.513 ± 0.087	0.480 ± 0.036	0.527 ± 0.072	0.450 ± 0.000	0.490 ± 0.057
Testes (Paired)	0.123 ± 0.040	0.147 ± 0.012	0.117 ± 0.032	0.130 ± 0.020	0.135 ± 0.007	0.145 ± 0.007
Epididymides (Paired)	0.020 ± 0.010	0.020 ± 0.000	0.023 ± 0.006	0.023 ± 0.006	0.020 ± 0.000	0.020 ± 0.000
Prostates	0.030 ± 0.017	0.033 ± 0.012	0.033 ± 0.021	0.023 ± 0.006	0.030 ± 0.014	0.045 ± 0.021
	Female					
	Main (mg/kg)				Recovery (mg/kg)	
Organ (%)	0	450	900	1500	0	1500
Ovaries with oviducts	0.00723 ± 0.00182	0.00887 ± 0.00227	0.00663 ± 0.00035	0.00733 ± 0.00097	0.00715 ± 0.00049	0.00710 ± 0.00141
Adrenals (Paired)	0.01137 ± 0.00137	0.01190 ± 0.00249	0.01040 ± 0.00121	0.01087 ± 0.00200	0.00935 ± 0.00007	0.00845 ± 0.00021*
Pituitary	0.00070 ± 0.00000	0.00067 ± 0.00006	0.00067 ± 0.00012	0.00080 ± 0.00010	0.00065 ± 0.00007	0.00060 ± 0.00000
Thyroid with parathyroid	0.00860 ± 0.00139	0.00870 ± 0.00218	0.00813 ± 0.00150	0.00727 ± 0.00086	0.00725 ± 0.00021	0.00755 ± 0.00035
Salivary glands	0.093 ± 0.012	0.093 ± 0.006	0.087 ± 0.012	0.097 ± 0.006	0.080 ± 0.000	0.095 ± 0.007
Brain	0.853 ± 0.081	0.877 ± 0.057	0.840 ± 0.044	0.910 ± 0.062	0.805 ± 0.021	0.860 ± 0.240
Heart	0.920 ± 0.040	0.867 ± 0.040	0.847 ± 0.045	0.843 ± 0.097	0.980 ± 0.028	0.985 ± 0.120
Thymus	0.110 ± 0.044	0.110 ± 0.017	0.110 ± 0.010	0.127 ± 0.023	0.125 ± 0.007	0.060 ± 0.028
Liver	2.733 ± 0.127	2.893 ± 0.248	2.730 ± 0.262	2.877 ± 0.076	2.545 ± 0.078	2.670 ± 0.198
Spleen	0.540 ± 0.046	0.513 ± 0.132	0.490 ± 0.161	0.473 ± 0.106	0.660 ± 0.099	0.680 ± 0.057
Kidneys (Paired)	0.493 ± 0.006	0.520 ± 0.046	0.463 ± 0.029	0.513 ± 0.068	0.430 ± 0.000	0.460 ± 0.042
Uterus with cervix	0.020 ± 0.000	0.043 ± 0.032	0.037 ± 0.015	0.027 ± 0.015	0.040 ± 0.000	0.050 ± 0.028

All data presented as mean ± S.D. *$p < 0.05$ compared to vehicle control.

en together, the present studies suggested *T. camphoratus* has highly safety properties for use in dietary supplements or medicinal products.

Conflict of interest---- The authors declare that there is no conflict of interest.

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