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Effect of phytol following single dose oral and intravenous administration in healthy rats

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Abstract
Phytol is a component of chlorophyll and is abundantly present in nature. Chemically, it is a diterpene and a branched-chain unsaturated acyclic fatty alcohol. Phytol is converted to phytanic acid and pristanic acid through α-oxidation and β-oxidation respectively. Its significant diverse bioactivities have recently drawn attention for their possible application in the pharmaceutical and biotechnological fields. Phytol had large variety of pharmacological actions and its metabolites had an influence in eliciting these actions. Literature search has revealed that phytol and its metabolites had an antidiabetic action and it can be used for the treatment of metabolism related disorders. The present study was undertaken to assess the effect of orally and intravenously administered phytol in healthy rats. Single dose of phytol was given orally and intravenously to separate groups of rats at a dose rate of 250 mg/kg and 25 mg/kg respectively. From the study, it was noted that all the animals were apparently healthy and showed normal ratty behaviour. Phytol as a single oral dose caused a significant increase in the weekly body weight with no significant effect on the feed and water intake. On the contrary, there was an increase in the feed intake of rats with no significant change in the weekly body weight following administration of phytol intravenously. However, administration of phytol through either route did not affect the water intake of rats. The relative organ weights of liver, kidney and small intestine were significantly increased after oral administration. Whereas, the relative organ weight of liver, lung and reproductive organ of rats showed a significant increase following intravenous administration of phytol when compared to that of control rats. Gross pathological lesions were not observed in any of the organs examined. Phytol is safe for therapeutic use by both oral and intravenous routes at the dose administered.

Keywords: Phytol, body weight, feed intake, water intake, relative organ weight

1. Introduction
History reveals that plants are sources of successful drugs. They can be a source of chemical compounds of biological and pharmacological importance. A large number of active constituents obtained from plants are used as drugs. Among such constituents, essential oils play a major role. Terpenes are one of the broadly investigated essential oil components.
Phytol (3, 7, 11, 15-tetramethylhexadec-2-en-1-ol), an acyclic monounsaturated diterpene alcohol is a constituent of chlorophyll and found abundantly in nature. Phytol is released during ruminal digestion of the green plants in ruminants (Van den Brink and Wanders, 2006) [1] and thus is present at significant levels in meat and dairy products. Phytol is present in vitamin K, vitamin E, and other tocopherols (Kim *et al.*, 2015) [2]. Phytol is used as an aromatic ingredient in many fragrant compounds and also found in some cosmetic and non-cosmetic products (McGinty *et al.*, 2010) [3]. The reported biological activities of phytol *viz.*, antimicrobial, anxiolytic, metabolism-modulating, cytotoxic, antioxidant, autophagy- and apoptosis inducing, antinociceptive, anti-inflammatory, immune-modulating and neuroprotective effects revealed its potential as drug entity for wide variety of pharmaceutical and biomedical applications (Islam *et al*., 2018) [4].
Additionally, the major metabolic derivatives of phytol *viz.*, phytanic acid (3, 7, 11, 15-tetramethylhexadecanoic acid) and pristanic acid (2, 6, 10, 14-tetramethylpentadecanoic acid) play a significant role in the biological effects (Gloerich *et al*., 2007) [5]. Phytol was first converted to phytanic acid by β-oxidation and further converted to pristanic acid by α-oxidation (Wanders *et al*., 2011) [6]. Phytol and its metabolites increased the transcriptional activity of nuclear receptors, such as the retinoic acid receptor and the peroxisome

proliferator–activated receptors (PPAR)/ retinoid X receptor (RXR) heterodimers (McGinty *et al.*, (2010) [3]. Thus, phytol also imparted a potential effect in the management of insulin resistance and metabolic disorders that accompany diabetes and/or obesity (Elmazar *et al.*, 2013) [7]. Further, literature search also revealed that much research has been directed on the effects of branched chain fatty acid derivatives of phytol on lipid metabolism in rats fed with phytol at different concentrations in diet.

Since, phytol has a great potential to be developed as a therapeutic drug, the current study was undertaken to study the effects in healthy rats administered phytol as a single dose orally and intravenously.

2. Materials and Methods

2.1 Chemicals

All the chemicals and solvents used in the research work were procured from M/S Merck India Ltd., Mumbai and M/s Sigma-Aldrich India Ltd., Bengaluru. The pure standard of analytical grade phytol was purchased from M/s Sigma Aldrich India Ltd., Bengaluru and used without further purification. The purity of the standards were ≥ 97%. Glycerol formal (≥98%), carboxy methyl cellulose were also purchased from M/s Merck Life Science Private Ltd, Mumbai.

2.2 Animal

The study was conducted on healthy adult Wistar rats with an average body weight of 200-250 g. The rats were procured from Small Animal Breeding Station, College of Veterinary and Animal Science, Mannuthy. The experiment was approved in the Institutional Animal Ethics Committee (IAEC) of College of Veterinary and Animal Sciences, Wayanad (IAEC/COVAS/PKD/22/2019) and conformed to the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines. All the rats were maintained in well ventilated cages (polypropylene rat cages) at 24 °C temperature and relative humidity ranging at 50-60%. The rats were fed with standard feed diet as per Bureau of Indian Standards (BIS) and had access to water *ad libitum*. The animals are kept under standard management conditions for one week, to get acclimatized to new laboratory environment, before the commencement of the experimental setup.

2.3 Experiment

The study group rats were divided into two groups i.e., oral section and intravenous section.

Group I: Twenty-four adult healthy rats of either sex was taken for single dose oral administration of phytol. Rats were fasted overnight and phytol was administered at the dose of 250 mg/kg body weight orally in one per cent (1%) carboxymethyl cellulose in water. Water was given *ad libitum* during the experiment. The quantity of feed and water intake of each rat was recorded daily. Weekly body weight change was noted for four weeks. After seventh day, fourteenth day, twenty first day and twenty-eighth day of oral administration of phytol, one rat from each set was humanely sacrificed as per ethical guidelines and organs such as brain, heart, lungs, liver, spleen, stomach, small intestine, large intestine, kidney, adrenal glands, reproductive organs, muscle, fat, bone, skin were collected immediately and organ weights were recorded.

Group II: Twenty four adult healthy rats of either sex were taken for the study of single dose intravenous administration of phytol. Phytol was administered at the dose of 25 mg/kg body weight intravenously in glycerine formol (98 percent pure without dilution) solution. Water was given *ad libitum* during the experiment. The quantity of feed and water intake of each rat was recorded daily. Weekly body weight change was noted for four weeks. After seventh day of intravenous administration of phytol, one rat from each set was humanely sacrificed as per ethical guidelines and organs such as brain, heart, lungs, liver, spleen, stomach, small intestine, large intestine, kidney, adrenal glands, reproductive organs, muscle, fat, bone, skin were collected immediately and organ weights were recorded.

2.4 Statistical analysis

All the analysis were performed using one way analysis of variance (ANOVA) followed Duncan multiple range test by using SPSS version 17.0. Significance was determined at $P < 0.05$.

3. Results

3.1 Mean weekly change in body weight of rats after oral and intravenous administration of phytol

Body weight of rats after single oral and intravenous administration of phytol were measured weekly and change in body weight was calculated and is depicted in table 1 and fig. 1. Rats received phytol orally (250 mg/kg) showed a significant increase in the change in weekly body weight from third week onwards. Whereas those rats received phytol intravenously (25 mg/kg) had no significant difference in change in weekly body weight.

Table 1: Mean of change in weekly body weight (g) of rats **A**) Group I after single oral administration of phytol @250 mg/kg, n=6; B) Group II after single intravenous administration of phytol @25mg/kg, n=6 (Mean ±SEM)

Week	Body weight (g) Mean ± SEM	
	Group I	Group II
0	177.25 ± 13.52^{b}	266.42 ± 12.59
1	197.15 ± 12.50^{ab}	276.96 ± 15.58
2	216.53 ± 12.17^{ab}	286.33 ± 16.98
3	234.92 ± 10.71^{a}	294.33 ± 15.41
4	233.2 ± 21.32^{a}	288.50 ± 21.07
F-value (P-value)	3.109* (0.034)	0.438^{ns} (0.780)

NS non-significant; * Significant at 0.05 level. Means having different letter as superscript differ significantly

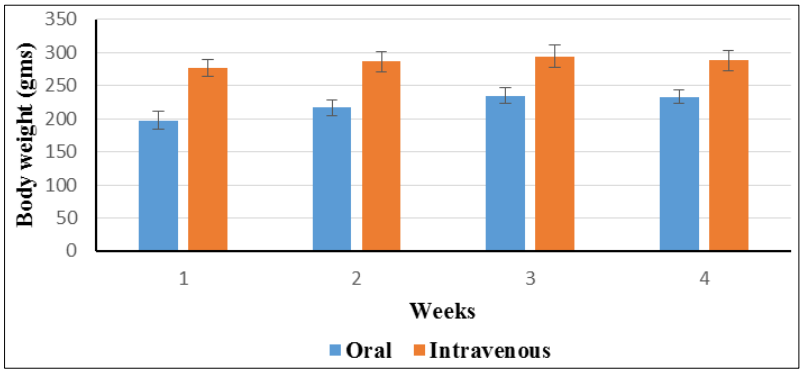

Fig 1: Weekly change in body weight (Mean ±SEM) of rats after oral and intravenous administration of phytol

3.2 Mean weekly change in feed and water intake of rats after oral and intravenous administration of phytol

Feed intake of rats after oral and intravenous administration of phytol were measured weekly and change in feed intake was calculated and is depicted in table 2 and fig. 2. There was no significant difference observed in the weekly feed intake of group I rats administered phytol orally. On the other hand, the rats in group II administered phytol intravenously showed a significance increase in the feed intake in the third week compared to first two weeks. Further the intake was reduced in the fourth week.

Table 2: Mean weekly feed intake (g) of rats A) Group I after single oral administration of phytol @250 mg/kg, n=6; B) Group II after single intravenous administration of phytol @25mg/kg, n=6 (Mean ±SEM)

Week	Feed intake (g) Mean ± SEM	
	Group I	Group II
Week 1	19.37 ± 1.28	22.45 ± 1.34^{b}
Week 2	19.61 ± 1.36	20.87 ± 1.77^{b}
Week 3	20.05 ± 1.45	26.37 ± 0.85^{a}
Week 4	19.00 ± 1.30	22.35 ± 1.17^{b}
F-value (P-value)	0.239^{ns} (0.867)	9.473** (0.001)

NS non-significant; ** Significant at 0.01 level. Means having different letter as superscript differ significantly

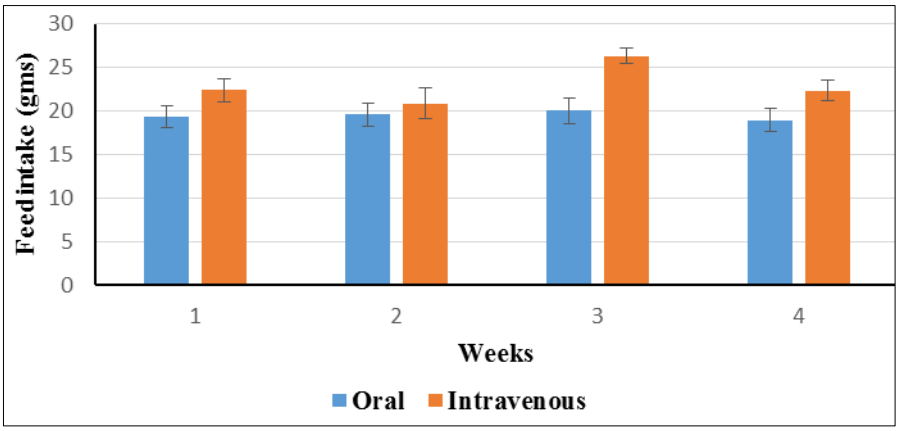

Fig 2: Weekly mean (±SEM) feed intake of rats after oral and intravenous administration of phytol

Water intake of rats after oral and intravenous administration of phytol were measured weekly and change in water intake was calculated and is depicted in table 3 and fig. 3. There were no significant difference in weekly water intake of rats administered with phytol either oral or intravenous route of administration.

Table 3: Mean weekly water intake (mL) of rats A) Group I after single oral administration of phytol @250 mg/kg, n=6; B) Group II after single intravenous administration of phytol @25mg/kg, n=6 (Mean ±SEM)

Weeks	Water intake (mL) Mean ± SEM	
	Group I	Group II
Week 1	22.05 ± 1.95	28.55 ± 2.49
Week 2	23.82 ± 2.08	28.95 ± 2.64
Week 3	23.12 ± 1.62	34.26 ± 1.24
Week 4	25.19 ± 2.41	27.60 ± 1.82
F-value (P-value)	0.239^{ns} (0.867)	2.671^{ns} (0.085)

ns non-significant

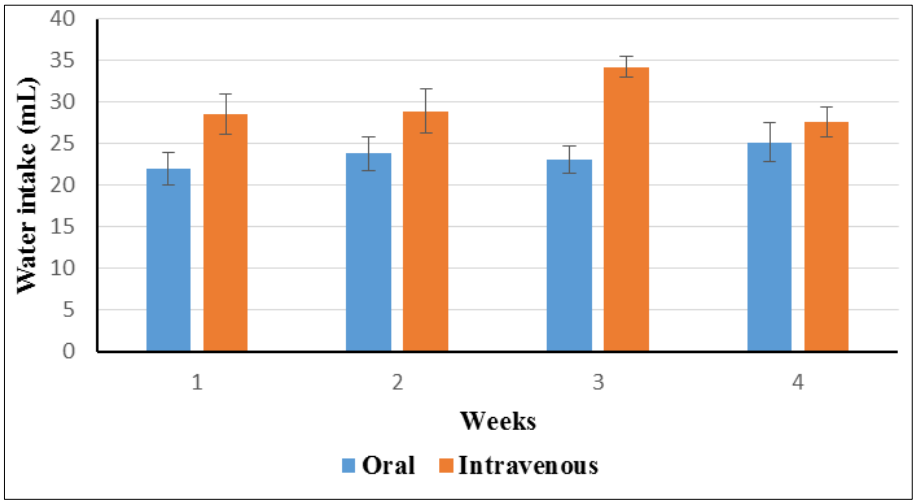

Fig 3: Weekly mean (±SEM) water intake of rats after oral and intravenous administration of phytol

3.3 Mean relative organ weight of rats after oral and intravenous administration of phytol

Relative organ weight of rats after oral and intravenous administration of phytol were measured weekly after humane slaughter. The weekly mean relative organ weight of rats after single oral administration of phytol at a dose of 250 mg/kg is shown in table 4 and fig. 4. Relative organ weight of group I rats scarified at weekly intervals were compared with that of control rats. There was no significant decrease in the relative organ weight of heart, spleen, lung, brain, adrenal gland, reproductive organ and caecum except liver, stomach, kidney and small intestine when compared with relative organ weight of control rats. The relative organ weight of liver exhibited a significant increase in the first, second, third and fourth week respectively. Whereas, the relative organ weight of stomach decreased significantly from second week onwards and was decreased in the fourth week. There was also a significant increase in the relative organ weights of kidney and small intestine in the third week when compared to control. None of the organs showed any gross pathological lesions.

The weekly mean relative organ weight of rats after single intravenous administration of phytol at a dose of 25 mg/kg is shown in table 5 and fig. 5. There was no significant change in the relative organ weight of heart, spleen, adrenal gland, kidney, small intestine and caecum except liver, lung, stomach, brain and reproductive organ when compared with relative organ weight of control rat. Relative organ weight of liver, lung and reproductive organ of rats showed a significant increase whereas stomach and brain showed a significant decrease when compared to that of control rats. None of the organs showed any gross pathological lesions.

Table 6: Weekly mean relative organ weight of rats after oral administration of phytol at a dose of 250 mg/kg (Mean ±SEM; n=6)

Organ	Control	1st Week	2nd Week	3rd Week	4th Week
Stomach	1.02 ± 0.07	0.83 ± 0.05^{ns}	0.76 ± 0.03**	0.78 ± 0.04*	0.7 ± 0.08*
Liver	2.79 ± 0.03	4.07 ± 0.17**	3.96 ± 0.27**	4.17 ± 0.18**	3.92 ± 0.18**
Heart	0.34 ± 0.01	0.42 ± 0.07^{ns}	0.36 ± 0.03^{ns}	0.39 ± 0.02^{ns}	0.35 ± 0.01^{ns}
Kidney	0.8 ± 0.01	0.86 ± 0.01^{ns}	0.86 ± 0.05^{ns}	0.98 ± 0.04*	0.83 ± 0.03^{ns}
Spleen	0.28 ± 0.01	0.31 ± 0.03^{ns}	0.27 ± 0.01^{ns}	0.25 ± 0.02^{ns}	0.3 ± 0.08^{ns}
Lung	0.71 ± 0.01	1.21 ± 0.15^{ns}	1.49 ± 0.43^{ns}	2.04 ± 1.05^{ns}	1.04 ± 0.17^{ns}
Brain	0.75 ± 0.01	0.83 ± 0.04^{ns}	0.79 ± 0.03^{ns}	0.75 ± 0.05^{ns}	0.71 ± 0.06^{ns}
RPO	0.48 ± 0.03	0.63 ± 0.24^{ns}	0.89 ± 0.32^{ns}	1.02 ± 0.34^{ns}	0.66 ± 0.23^{ns}
SI	2.33 ± 0.13	2.01 ± 0.64^{ns}	2.32 ± 0.47^{ns}	2.84 ± 0.09*	2.80 ± 0.19^{ns}
Caecum	0.65 ± 0.05	0.72 ± 0.04^{ns}	0.68 ± 0.04^{ns}	0.66 ± 0.01^{ns}	0.69 ± 0.08^{ns}
Adrenal	0.03 ± 0.005	0.03 ± 0.004^{ns}	0.02 ± 0.004^{ns}	0.02 ± 0.005^{ns}	0.02 ± 0.003^{ns}

** Significant at 0.01 level; * Significant at 0.05 level; ns non-significant

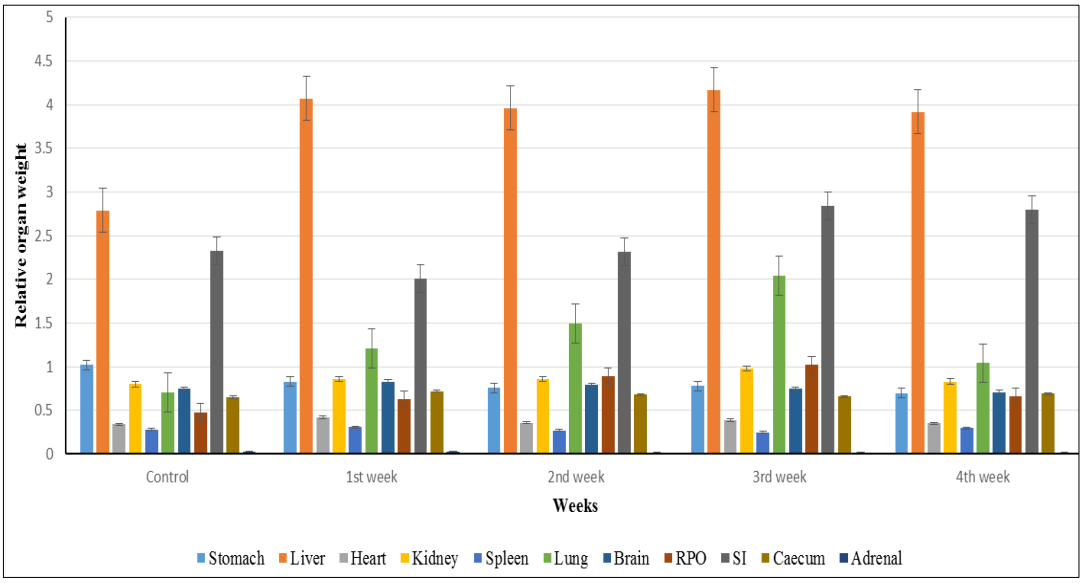

Fig 8: Weekly mean relative organ weight of rats after oral administration of phytol at a dose of 250 mg/kg (Mean ±SEM; n=6)

Table 7: Weekly mean relative organ weight of rats after intravenous administration of phytol at a dose of 25 mg/kg (Mean±SEM; n=6)

Organ	Control	1st Week
Stomach	1.02 ± 0.07	0.69 ± 0.04**
Liver	2.79 ± 0.03	3.78 ± 0.09**
Heart	0.34 ± 0.01	0.35 ± 0.01ns
Kidney	0.80 ± 0.01	0.81 ± 0.02ns
Spleen	0.28 ± 0.01	0.26 ± 0.02ns
Lung	0.71 ± 0.01	0.88 ± 0.04*
Brain	0.75 ± 0.01	0.62 ± 0.02**
RPO	0.48 ± 0.03	1.36 ± 0.23*
SI	2.33 ± 0.13	2.59 ± 0.11ns
Caecum	0.65 ± 0.05	0.66 ± 0.05ns
Adrenal	0.03 ± 0.005	0.02 ± 0.003ns

** Significant at 0.01 level; * Significant at 0.05 level; ns non-significant

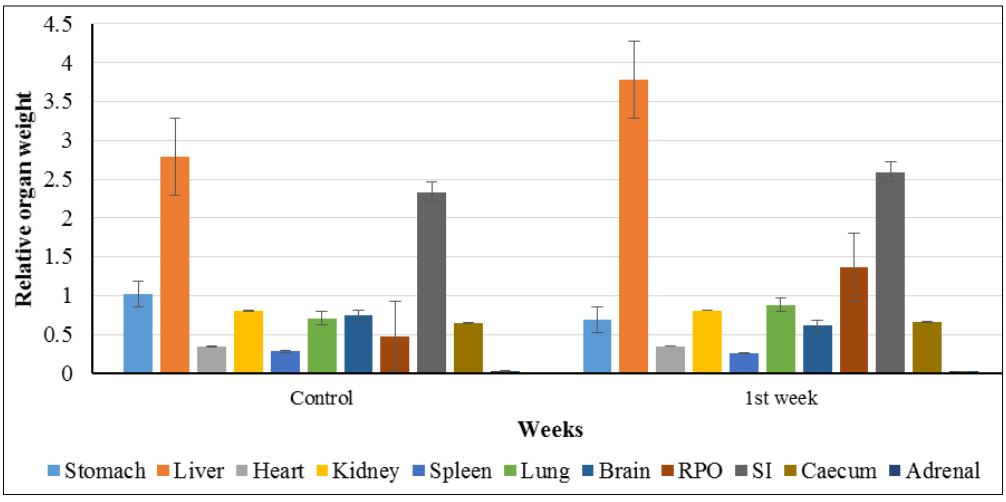

Fig 9: Weekly mean relative organ weight of rats after intravenous administration of phytol at a dose of 25 mg/kg (Mean ± SEM; n=6)

4. Discussion

During the experiment no abnormal behavior and mortality of the rats were recorded. According to Steinberg *et al.* (1966) [8] phytol at a high dosage (5%) fed in the feed, inhibited the growth of mice and caused death within 1-4 weeks. In the present study, there was a significant difference in the weekly body weight of group I rats administered phytol at 250 mg/kg body weight orally as a single dose. Comparison of the weekly body weight also revealed a significant increase from third week onwards. On the contrary, no significant difference in the weekly body weight was noted in group II rats administered phytol intravenously at the dose rate of 25 mg/kg body weight. This could be due to the lower concentration used for intravenous route when compared to the oral dose administered in the present study. However, the increase in body weight following the oral administration in the present study was contradictory to the findings of many workers following dietary supplementation of phytol at different concentrations ranging from 0.1 to 5%. Besides, in all these studies, phytol enriched diet was given for prolonged

periods. (Steinberg *et al.*, 1966, Zhang *et al.*, 2018) [8, 9].
No significant difference was observed in the weekly feed intake of rats administered phytol orally at 250 mg/kg (group I). Zhang *et al.* (2018) [9]. Reported no apparent change in the average weekly food intake in the mice administered phytol at 500 mg/kg every alternate day for seven weeks. On the other hand, the rats administered phytol intravenously at 25 mg/kg (group II) showed significant increase in the feed intake in the third week compared to first two weeks and then it was reduced in the fourth week. Moreover, the group I and II rats showed no significant difference in weekly water intake.
Relative organ weights of group I and group II rats showed significant differences when compared with that of control rats. Liver showed a consistently significant increase in organ weight. Significant increase in the organ weights of kidney and small intestine was also noted. On the other hand, there was a significant decrease in the relative stomach weight. The relative organ weights of liver, lung, and reproductive organ significantly increased whereas, the relative organ weights of stomach and brain, showed a significant decrease in group II rats compared with that of control rats. It is also reported that the protein level and activity of all of the peroxisomal-oxidation enzymes increased in mice after phytol feeding (Gloerich *et al.*, 2005) [10]. Thus, the increase in the relative organ weights could be correlated with the organs with highest expression of enzymes involved in the phytol metabolism (Gloerich *et al.*, 2007) [5]. Selkala *et al.* (2015) [11]. reported that the α-methylacyl-C_OA racemase (Amacr) deficient mice fed with 5% of phytol in diet for two weeks showed an increase in the relative organ weight of liver indicating hepatomegaly. On the contrary, Landrock *et al.* (2017) [12]. Reported a decrease in the relative organ weight of liver of *Fabp 1/Scp-2/Scp-x* gene ablated mouse fed with diet containing 0.5% phytol compared to the wild-type mouse.

5. Conclusion
The result of the current study reveals that single dose of phytol when given orally caused slight increase in the body weight only after two weeks whereas single intravenous dose had no effect in the body weight. Intravenously administered phytol had an effect in the feed intake of rats but phytol had no effect in the daily water intake of rats. Relative organ weight of liver, kidney and small intestine showed a significant increase and stomach showed significant decrease after oral phytol administration. Following intravenous administration of phytol relative organ weights of liver, lung and reproductive organ of rats showed a significant increase whereas stomach and brain showed a significant decrease when compared to that of control rats. Phytol is safe for therapeutic use by both oral and intravenous routes at the dose administered.

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7. Conflicts of interest
The authors declare that there are not any conflicts of interests

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