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Acute oral toxicity assessment of galbanic acid in albino rat according to OECD 425 TG

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ABSTRACT

In spite of the broad biological and also anticarcinogenic effects which have been reported for galbanic acid in various studies, its toxic effects are not still well characterized. The study was accomplished to evaluate the acute oral toxicity of galbanic acid pursuant to Organisation for Economic Co-operation and Development (OECD) TG No. 425. Female rats were received asafoetida extract and galbanic acid in distilled water by oral gavage. According to the existing information, limit test was done for aqueous extract of asafoetida and main test was done for galbanic acid. The animals were monitored for 2 weeks. Then under general anesthesia, the blood samples were obtained from the heart for biochemical and hematological assessment and the vital organs of rats were isolated for pathological evaluation. The results showed that although the Median lethal dose (LD50) of asafoetida extract was above the 2000 mg/kg body weight, the galbanic acid estimated LD50 was 310.2 mg/kg. There was no considerable change in body weight of vehicle and extract treated animals but in galbanic acid treated animals, the body weights were not normally increased. A significant rise was observed in high-density lipoprotein (HDL), (aspartate aminotransferase) AST and (alanine aminotransferase) ALT levels as well as in white blood cells (WBC), platelet and lymphocytes counts in galbanic acid group compared to vehicle and extract groups. Based on the obtained results, we suggest that although the asafoetida aqueous extract could be categorized as group 5 (LD50 > 2000 mg/kg), but galbanic acid estimated LD50 is about 310.2 mg/kg and toxicity signs also appeared in lung, liver enzymes and complete blood count (CBC) of galbanic acid treated animals.

1. Introduction

Cancer is one of the main reasons of death in the world, and 10 million deaths in 2020 were attributed to cancer. Non-developed countries undertake most of the cancer burden. Induction of the apoptosis by synthetic or natural compounds is an important way for cancer treatment. Since the very beginning, the recording of traditional information particularly about the medicinal applications of plants has provided numerous important drugs of the present-time [7]. Plants have been an endless origin of therapeutic agents, and in recent decades great attention has been paid to discovering new compounds from medicinal herbs.

Ferula is a genus of flowering plants in the subfamily of *Apioideae*, family of *Umbelliferae* which scattered all over the central Asia and Mediterranean region [33]. Asafoetida is the gum oleoresin emerged from the different parts of *Ferula* genus and has been used as a food seasoning and also as an indigenous medicine for treatment of different illness [4]. In indigenous medicine, it is exploited for the remedy of various ailment, including digestive problems, influenza, epilepsy and asthma [19]. Phytochemical evaluation of asafoetida revealed the presence of numerous active agents such as galbanic acid, farnesiferol B and C, karatavicinol and umbelliprenin [11]. Galbanic acid (GBA) which obtained from the gum resin of some *Ferula* genus has numerous reported pharmacological effects such as anticancer, antibacterial and antiplatelet activity [6,16,21,24,29,33].

Acute oral toxicity test by OECD guidelines is not needed for pharmaceuticals. However in special cases including anticarcinogenic agents, conducting acute oral toxicity test is required. The results of acute oral toxicity test are the backing of the single dose studies in human. Despite the fact that anticarcinogenic effects have been reported for galbanic acid in various in vitro and in vivo studies [2,6,17,21,22,24,29,33], there is a lack of information about its acute oral toxicity. Thus, we assessed the potential harmful effects of galbanic acid after acute oral exposure in rats and compared the results with the acute oral toxicity of asafoetida extract. Our results demonstrate that although the asafoetida aqueous extract was non-toxic (LD50 > 2000 mg/kg), galbanic acid

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induced toxic effects in lung, liver and blood cells in treated animals.

2. Materials and methods

2.1. Preparation of extract

Galbanic acid GBA was generously provided by Dr. Zohreh Abolhassanzadeh. The gum resin was purchased from the local store of Shahrekord city in May 2022 and grounded to fine powder, soaked and heated in distilled water for 4 h. The obtained extract was filtered and concentrated with the rotary evaporator. The concentrated extract was dried at 40 °C in oven for 48 h and finally freeze-dried.

2.2. Approval from animal's ethics committee

This study was performed in Shahrekord University of Medical Sciences and approved by Animals Ethics Committee of the university. Ref. no. IR.SKUMS.AEC.1400.023.

2.3. Acute oral toxicity

The acute oral toxicity test of galbanic acid and asafoetida extract was performed according to the OECD Guideline No. 425. Before conducting the study, we considered all the available information on the test substances include the results of any toxicity tests on the substances, structurally related substances or similar mixtures. Based on the existing information, asafoetida extract is non-toxic and the limit test was performed for aqueous extract of asafoetida as a sole dose at 2000 mg/kg p. o to a single female rat. Following survival of tested animal, 4 extra rats were treated sequentially with the same dose. Primary evaluation of the galbanic acid LD50 was 400 mg/kg according to the existing information. So, the main test was performed for galbanic acid and the 1st animal was received 175 mg/kg (a step below the best primary evaluation of the LD50) of galbanic acid as described in the Guideline No. 425. Galbanic acid and asafoetida extract were dissolved in distilled water, so distilled water was used as a vehicle. Non pregnant and nulliparous rats, having age 8–12 weeks (200 ± 20 g) were chosen arbitrarily and maintained in normal condition for at least 5 days for adaptation to the laboratory conditions. Food was withheld 3–4 h in advance of dosing and the animals were monitored individually for any toxic effect at regular intervals which were mentioned in the OECD guideline. The LD50 was calculated based on the maximum likelihood method using AOT425StatPgm software. Animal weights were also monitored and documented. Eventually, for assessment of hematological and biochemical parameters, blood samples were derived from the heart under ketamine (40 mg/kg)/xylazine (15 mg/kg) anesthesia. The main organs of humanely killed rats were isolated, weighted and conserved in 10 % buffered formalin for further study.

2.4. Hematological analysis

The blood samples were derived from all rats and stored in EDTA containing tubes for hematological assessments. Complete blood count (CBC) parameters; total RBC, hemoglobin (Hb), packed cell volume (PVC), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), white blood cells (WBC) count, monocytes (M), lymphocytes (L), neutrophils (N), eosinophils (E) and platelet count were determined with humalyzer.

2.5. Biochemical analysis

Urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphate, very low density lipoprotein (VLDL), low density lipoprotein (LDL), high density lipoprotein (HDL), cholesterol, triglyceride, bilirubin, globulins, albumin and total protein were assessed using Randox kits.

2.6. Histopathological assay

The internal organs collected from all groups were assessed macroscopically and the organs with gross pathological changes were fixed with 10 % buffered formalin for further microscopic assessment. After embedding in paraffin wax, sections of 5 μm thickness were prepared from the fixed organs. The slides were stained with hematoxylin and eosin and a light microscope was used for observing them.

2.7. Statistical analysis

Statistical analysis of experimental results was done by GraphPad Prism 5 (Graphpad Software, La Jolla, CA) using one way analysis of variance followed by post hoc Tukey test. P value ≤ 0.05 was considered as statistically significant and the results are presented as the mean ± standard error of the mean.

3. Results

3.1. Estimated LD50

When limit test was carried out for asafoetida extract at 2000 mg/kg body weight (b.w) using distilled water as a vehicle, no fatality was noticed. So, the LD50 of galbanic acid is more than 2000 mg/kg b.w. The main test was conducted for galbanic acid and the first animal received 175 mg/kg galbanic acid. The first animal was survived, so the 2st animal received 550 mg/kg galbanic acid. The 2st animal was died and dosing was continued as described in the Guideline No. 425 and show below. Stopping criteria was met with 5 reversals in 6 tests and the measured LD50 was 310.2 mg/kg.

Animal ID	AE dose (mg/kg)	Result
1st	2000	O
2st	2000	O
3st	2000	O
4st	2000	O
5st	2000	O

(AE = Asafoetida Extract) (X = Died, O = Survived).

Animal ID	GA dose (mg/kg)	Result
1st	175	O
2st	550	X
3st	175	O
4st	550	X
5st	175	O
6st	550	X

(GA = Galbanic Acid) (X = Died, O = Survived).

3.2. Body weight and behavior

The body weight (BW) of animals was elevated steadily in vehicle and asafoetida extract groups within the survey course (Table 1). In galbanic acid treated animals, the body weights were not normally

Table 1
Effects of the vehicle, asafoetida extract (2000 mg/kg) and galbanic acid (175 mg/kg) on body weight of rats in acute oral toxicity test.

Groups	1st day body weight (gm)	7th day body weight (gm)	14th day body weight (gm)
Vehicle control	208.5 ± 5	220.8 ± 8	241.9 ± 5
2000 mg/kg Asafoetida extract	210.3 ± 7	221.2 ± 5	243.1 ± 3
175 mg/kg Galbanic acid	209.7 ± 4	214.9 ± 3	225.2 ± 4

Values are presented as mean ± SEM; N = 6.

increased during the 2 weeks of study. Behavioral monitoring of the extract and galbanic acid treated animals demonstrated raised respiration rate and somatomotor activity for first hours in galbanic acid treated group. Subtle trembling was also detected in the galbanic acid treated rats repeatedly in 1st day. Sometimes itching was noticed in extract and galbanic acid treated groups in first days of this research. Behavioral changes are concised in Table 2.

3.3. Biochemical analysis

There was a non-significant increase in serum urea and creatinine levels in galbanic acid treated group (Table 3). The markers of liver function (ALT, AST) were significantly enhanced in galbanic acid treated group in comparison with extract and vehicle groups as summarized (Table 3). No remarkable difference in triglycerides, L.D.L and cholesterol were observed in different groups (Table 4). However, significant ($P < 0.05$) elevation in HDL level was found in extract and galbanic acid treated rats compared with control animals.

3.4. Hematological analysis

Table 5 presents the results of hematological assay following the acute oral toxicity test of asafoetida and galbanic acid in rats. No significant changes in monocytes, neutrophils, eosinophils, total RBC, MCV, MCHC and MCH levels were observed in extract and galbanic acid treated rats. However, significant ($P < 0.05$) raises in lymphocytes, platelet, WBC counts were detected in galbanic acid treated rats compared with extract and control groups.

3.5. Histopathological study

Gross (macroscopic) pathological assessment of vital organs was not shown any lesion in extract treated animals, but in galbanic acid treated group there were area with mild and severe lesions in lung. So, the microscopic pathological assessment was done for lung tissue and area with apoptosis, necrosis and infiltration was observed (Fig. 1). The ratio of organ weight to body weight in vehicle, extract and galbanic acid treated animals was also calculated (data not shown). The data demonstrate that there was no considerable difference present between the groups except for the lung to body weight that significantly ($p < 0.05$) reduced in galbanic acid treated group.

4. Discussion

Despite the fact that galbanic acid has a variety of reported pharmacological effects especially anticarcinogenic activities, there is a lack of information about its potential toxicity and adverse effects. Thus, the acute oral toxicity of galbanic acid was assessed in this study by following OECD Guideline 425 procedure [25]. Furthermore, we compared the acute oral toxicity of galbanic acid with the acute oral toxicity of asafetida aqueous extract. Acute oral toxicity test is required for determination of potential target organs of toxicity, toxic doses (LD50) and proper doses for conducting longer toxicity (sub-acute and sub-chronic) and future pharmacological studies.

Female rats were used in the current study [23]. Literature review of acute oral toxicity tests demonstrate that in those studies where differences are noticed, females are commonly a little bit more sensitive [20]. Clinical signs and symptoms which are the most important manifestations among numerous other toxicity criteria are the toxic consequences of test substances on the main body organs [15]. In vehicle and extract treated groups no animal was found dead, while in galbanic acid treated group animals were died with 550 mg/kg of galbanic acid. In galbanic acid treated group some alterations in behavioral pattern such as enhanced respiration, excess somatomotor activity, subtle tremor and

Table 3
Effect of acute oral administration of vehicle, asafoetida extract (2000 mg/kg) and galbanic acid (175 mg/kg) on renal and liver function test of rats. (mean ± SE).

Groups	Creatinine (mg/dL)	Urea (mg/dL)	ALT (IU/L)	AST (IU/L)	ALP (IU/L)
C	0.58 ± 0.18	26.6 ± 3.4	25.2 ± 2.4	145.30 ± 16.7	93.2 ± 8.5
AE	0.59 ± 0.11	24.9 ± 4.1	25.7 ± 4.1	148.10 ± 9.2	95.6 ± 3.4
GA	0.61 ± 0.32	27.2 ± 2.4	38.9 ± 3.8*	215.40 ± 14.4*	94.4 ± 4.7

Key: C = Vehicle Control group, AE = Asafoetida extract treated groups, GA = Galbanic acid treated group, ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, ALP = Alkaline phosphatase, SE = Standard error, * $p < 0.05$ when compared with the vehicle control group.

Table 4
Effects of acute oral administration of vehicle, asafoetida extract (2000 mg/kg) and galbanic acid (175 mg/kg) on lipid profile of rats.

Parameters	Unit	Vehicle control	Asafoetida extract	Galbanic acid
Cholesterol	mg/dl	115 ± 4.36	114 ± 3.42	111 ± 1.57
Triglycerides	mg/dl	71 ± 0.86	69 ± 1.15	68 ± 1.68
H.D.L (Cholesterol)	mg/dl	64 ± 0.56	68 ± 0. 92*	77 ± 0.36*
L.D.L (Cholesterol	mg/dl	36 ± 6.32	36 ± 3.52	33 ± 5. 23

Values are presented as mean ± SEM, N = 5. * $p < 0.05$ when compared with the control group.

Table 2
Behavioral patterns of rats in vehicle, asafoetida extract (2000 mg/kg) and galbanic acid (175 mg/kg) treated groups following acute oral toxicity test.

Parameters	30 min			4 h			24 h			48 h			7 days			14 days		
	C	AE	GA	C	AE	GA	C	AE	GA	C	AE	GA	C	AE	GA	C	AE	GA
Fur & skin	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Eyes	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Itching	N	p	p	N	p	p	N	N	N	N	N	N	N	N	N	N	N	N
salivation	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mucous membrane	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Urination(color)	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Somatomotor activity & behavior pattern	N	N	N	N	N	↑	N	N	N	N	N	N	N	N	N	N	N	N
Sleep	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Convulsions & tremors	N	N	N	N	N	p	N	N	p	N	N	N	N	N	N	N	N	N
Respiration	N	N	N	N	N	↑	N	N	N	N	N	N	N	N	N	N	N	N
Coma	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mortality	N	N	N	N	N	N	N	N	p	N	N	p	N	N	p	N	N	p

Key: C = Vehicle Control group, AE = Asafoetida extract treated groups, GA = Galbanic acid treated group, N = Normal, P = Present, ↑ = Increased, N.F = Not found.

Table 5
Effects of acute oral administration of vehicle, asafoetida extract (2000 mg/kg) and galbanic acid (175 mg/kg) on hematological parameters of rats.

Parameters	Unit	Vehicle control	Asafoetida extract	Galbanic acid
Hemoglobin	g/dl	14.6 ± 0.4	13.7 ± 0.7	14.5 ± 0.2
Total RBC	10^6/ul	7.53 ± 0.27	8.13 ± 0.34	7.93 ± 0.17
Hematocrit	%	41.47 ± 0.38	41.52 ± 0.46	40.97 ± 0.78
MCV	Fl	51 ± 2.42	52 ± 1.72	52 ± 3.67
MCH	Pg	18.2 ± 0.03	18.8 ± 0.12	18.4 ± 0.25
MCHC	g/dl	32.9 ± 2.29	33.2 ± 1.14	33.8 ± 1.73
Eosinophils	%	2.8 ± 0.43	2.9 ± 1.13	3.4 ± 0.95
Neutrophils	%	22.9 ± 0.31	22.8 ± 1.52	23.38 ± 0.42
Lymphocytes	%	72 ± 0.33	72 ± 0.82	83 ± 0.21*
Monocytes	%	2.3 ± 0.07	2.3 ± 0.34	2.2 ± 0.49
WBC Count (TLC)	10^6/ul	4.21 ± 0.28	4.98 ± 1.32	7.19 ± 0.73*
Platelet Count	10^6/ul	878 ± 5.68	883 ± 6.32	992 ± 8.64*

Values are presented as mean ± SEM. * $p < 0.05$ when compared with the vehicle control group.

itching were recorded in 1st day (Table 2). Within two weeks of acute oral toxicity test monitoring, normal water and food consume were observed in vehicle and extract treated groups, while in galbanic acid treated group food intake was reduced and as a consequence steadily increase in body weight was not observed. It indicates the abnormal processing of nutrients inside the body of galbanic acid treated rats, because nutrients have various basic functions in the animal's body [9,13]. Toxic substances metabolically affect vital organs like heart, lung, liver and kidney as the major targets [3]. Gross examination of vital organs at the end of study was demonstrated no lesions in liver, kidney and lung of extract treated animal in comparison with control group. However, macroscopic examination of vital organs was shown mild to severe lesions (apoptosis, necrosis, infiltration) in lung of galbanic acid treated rats. The lung to body weight index significantly ($p < 0.05$) diminished in galbanic acid treated animals when compared with control group (data not shown). According to the international harmonized system of classification, substances are categorized into 5 groups based on their Lethal Dose 50 [31]. The asafoetida aqueous extract could be categorized as group 5 (LD50 > 2000 mg/kg), and the galbanic acid could be assign to group 4 (LD50 > 300 mg/kg).

In acute oral toxicity test of asafoetida extract and galbanic acid, the healthiness of the animals was assessed with further biological indexes such as serum molecular markers evaluation. Hepatotoxicity induced by chemicals and drugs can give rise to elevation of total proteins, AST and ALT levels [26,27]. Statistically significant raise in ALT, AST levels were noticed in galbanic acid treated animals (Table 3). A previous study has also been reported such changes in AST and ALP levels with asafetida extract after acute and subchronic tests [10]. Cell membrane permeability due to hepatocellular injury can lead to release of transaminases into blood flow [8]. In line with previous studies [1,18], increased level of HDL (Table 4) was found in the extract and galbanic acid treated groups, suggesting the protective effects of asafoetida against heart disease and stroke [32]. Renal injury is demonstrated by raised amounts of serum creatinine and urea [30]. In the present investigation, serum creatinine and urea levels were slightly upraised (Table 4) which display that there is benign renal damage in galbanic acid treated animals. These results are in accordance with Goudah et al. [10] finding in the acute and subchronic toxicity study of *Ferula assa-foetida* gum in rodents.

Hematological factors are sensitive indicators of the physiological alterations in reaction to any toxic effects in animals [14]. Thrombocytes (Blood platelets) have a crucial role in the procedure of bleeding prevention. In the present study significant raise of platelet count was observed (Table 5) in galbanic acid treated group which indicates hemostatic activity of galbanic acid. Illuri et al. have also investigated the sub-acute and acute toxicity of *Ferula asafoetida* and *Silybum marianum* formulation and observed non-significant increase in platelet count [12]. Significant ($p < 0.05$) increase in WBC and lymphocytes counts (Table 5) indicates the potential activity of galbanic acid against the pathogens and also its capability to boost the innate immune response.

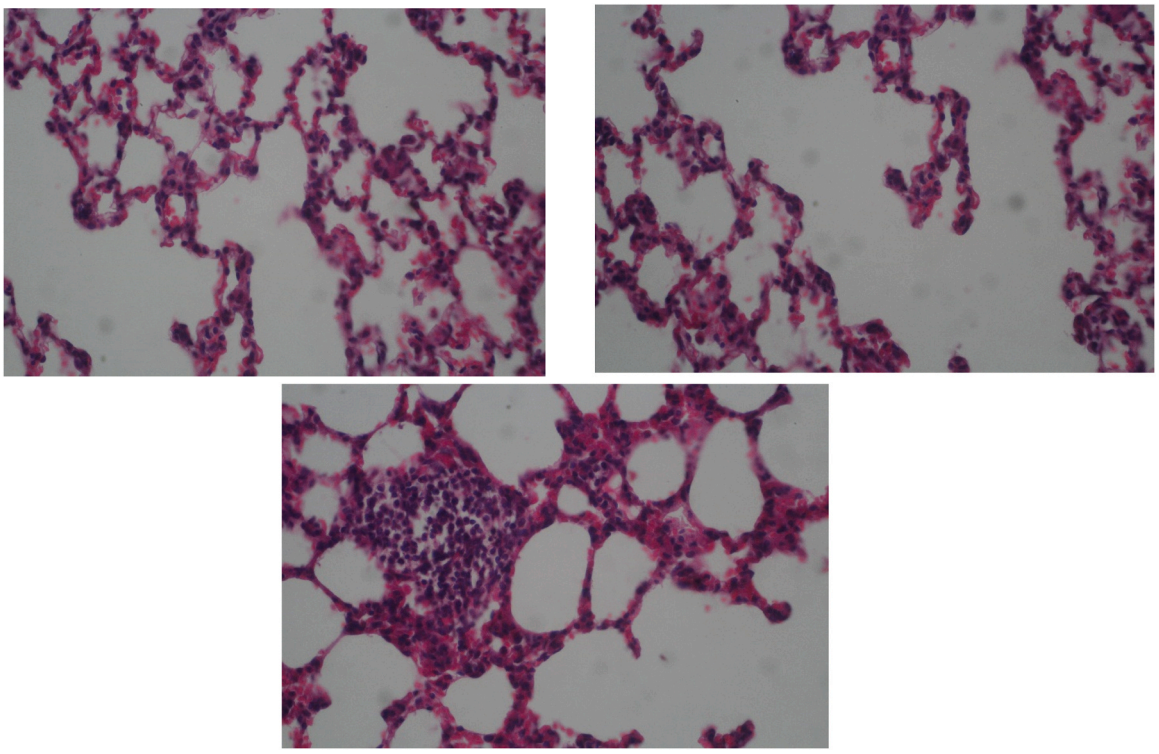

Fig. 1. Histopatological examination of lung in galbanic acid treated animals. Histopatological examination of vital organs in galbanic acid treated group there were area with mild to severe lesions (apoptosis, necrosis, infiltration) in lung.

These results are in accordance with other researches about the biological effects of asafoetida [5,28].

5. Conclusion

Based on our findings of acute oral toxicity testing, we can conclude that although the aqueous extract of asafoetida has subtle toxic effects as it elevates urea and creatinine, galbanic acid altered different biochemical, hematological and pathological parameters that showed the toxicity of this compound at doses that used in present study. Nevertheless, the early findings indicated that it should be moreover assessed for repeated dose toxicity and prolonged usage to find safe doses of this compound for further anticarcinogrnic studies.

CRediT authorship contribution statement

Mohammad Hadi Zarei: Project administration, Writing – review & editing, Methodology, study conception and design; **Zahra Loori Goini:** Writing – review & editing; **Hossein amini khoei:** Formal Analysis, Material preparation; **Elham Bijad:** Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

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