EVALUATION OF ACUTE AND SUBCHRONIC TOXICITIES OF DEHEMA PRODUCT IN EXPERIMENTAL ANIMALS

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This research was conducted to evaluate the acute and sub-chronic toxicities of the DEHEMA product through oral administration using experimental animal models. The acute toxicity of DEHEMA was determined in Swiss mice using the Litchfield-Wilcoxon method. The subchronic toxicity of DEHEMA was assessed in Wistar rats according to WHO and OECD's recommendations with oral doses of 10 mL/kg b.w./day (equivalent to the recommended human dose with conversion ratio 6) and 30 mL/kg b.w./day (3 times of the recommended human dose) for 30 consecutive days. In terms of acute toxicity, the DEHEMA product did not show acute toxicity in mice at the highest dose used (100 mL/kg b.w). In terms of subchronic toxicity, after oral administration of aqueous extract form of DEHEMA at 5.2 g/kg b.w./day and 15.6 g/kg b.w./day, the overall condition, weight, hematological parameters, liver and renal functions, and microscopic images of liver and kidney were unchanged in the treatment groups compared to those of the control group. In conclusion, DEHEMA did not produce acute and subchronic toxicities in Swiss mice and Wistar rats.

Keywords: DEHEMA, acute toxicity, subchronic toxicity, experimental animals.

I. INTRODUCTION

The World Health Organization (WHO) has defined herbal medicines as "herbs, herbal materials, herbal preparations and finished herbal products that contain, as active ingredients, parts of plants, other plant materials or combinations thereof".[1] Plant-based drugs and products have been widely used in many countries worldwide to treat human diseases or prevent ailments and maintain healthy condition.[1] Herbal medicines represent an important component in the healthcare system, especially in Asian countries.[1] According to WHO, approximately 80% of Member States use these types of remedies, with more than 90% of Member States in the Eastern Mediterranean, South-East Asia, and Western Pacific regions.[1] However, the evidence-based safety and toxicity profiling of herbal medicines is insufficient and although herbals products are considered to be safe, some might have potentially detrimental effect after prolonged use, or even be toxic. Therefore, studies conducted to evaluate the toxicity of herbal medications or products are needed to reveal the features, effects on general condition, and targeted organs. Results from these studies are useful for evaluating their detrimental effect on humans and proposing measures to minimize the risk, especially in early clinical trials.[1]

Toxicity is defined as harmful effects on biological systems.[2] Based on time of exposure, toxicity is categorized into acute, subchronic, and chronic toxicity. An acute toxicity test is designed to investigate the adverse effects occurring within a short interval after a single high dose of the reagent or after consecutive

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doses administered within 24 hours.[2-5] Since some plant's components exhibit their toxicity after repeated doses or long-term usage, a subchronic toxicity study is required to assess the clinical adverse effects on targeted organs or systems, the dose-response and time-response relationships, and to predict the safe dose range for repeated usage. Subchronic toxicity is defined as adverse effects from repeated exposure to up to 12 weeks but not exceeding 10% of the animal's life span.[2-5]

DEHEMA aqueous extract is prepared from seven medicinal herbs, including *Radix Angelica sinensis*, *Radix Rehmanniae glutinosae*, *Radix Paeoniae*, *Rhizoma Ligustici wallichii*, *Gummi resina Olibanu*m, *Myrrha*, and *Flos Carthami tinctorii*, originated from the ancient remedy "Tao Hong Si Wu Tang". This remedy has been clinically used to treat swelling, trauma, bruising, and blood stasis conditions. DEHEMA product was developed in the aqueous extracting preparation to be more convenient for patients' usage and storage. There has been no study on the safety of this product; thus, this study aimed to investigate the acute and subchronic toxicities of DEHEMA in experimental animals.

II. MATERIALS AND METHODS

1. Subjects

Research material

The DEHEMA product was manufactured by Medzavy Pharmaceutical Joint Stock Company, with the preparation form of 100 mL-bottled aqueous extract.

Each 100mL bottle of the product contained the extract of 10g *Radix Angelica sinensis*, 10g *Radix Rehmanniae glutinosae*, 8g *Radix Paeoniae*, 8gx *Rhizoma Ligustici wallichii*, 6g *Gummi resina Olibanu*m, 6g *Myrrha*, and 4g *Flos Carthami tinctorii*.

According to the product disclosure, DEHEMA promotes blood circulation, clears channels, disperses blood stasis and relieves pain. It can be prescribed for people with swelling, trauma, bruising and blood stasis. The recommended oral dosage for humans is 100mL per day, divided into 2 - 3 times, taken after meals (equivalent to 52g of herbs per day).

Experimental animals

Healthy male and female *Swiss* white mice (weighing from 18 to 22g) and *Wistar* rats (weighing from 180 to 220g) used in this study were provided by the National Hygiene and Epidemiology Institute. The mice and rats were housed at the laboratory of the Department of Pharmacology, Hanoi Medical University, for 5 – 10 days before the respective study and during the entire study with access to a standard certified rodent diet (supplied by the National Hygiene and Epidemiology Institute) and water *ad libitum*.

2. Methods

Acute toxicity study

The experiments investigating DEHEMA's acute toxicity and LD_{50} were carried out according to WHO Guidance and Organization for Economic Cooperation and Development guidelines (OECD guidelines).[6,7]

Mice were fasted overnight and randomly designated into groups of 10. Each group was orally administered with DEHEMA at ascending doses in the same volume that mice could tolerate, to identify the lowest dose causing 100% deaths and the highest dose causing 0% death. Mice's general condition, health status from the first sign of toxicity, and mortality rate in each group were observed within 72 hours. The median lethal dose (LD_{50}) was detected using the Litchfield-Wilcoxon method.[8] Animals that survived after 72 hours were further monitored for seven days in total after DEHEMA administration for signs of delayed toxicity.

Subchronic toxicity study

The subchronic toxicity study was carried out according to the WHO Guidance and OECD Guidelines.[6,7]

30 *Wistar* rats were divided into three groups of ten:

The control group (group 1) was orally administered distilled water 10 mL/kg b.w./day.

The low treatment dose group (group 2) was orally administered DEHEMA at 10 mL/kg b.w./day (equivalent to the recommended human dose, conversion ratio 6).

The high treatment dose group (group 3) was orally administered DEHEMA at 30 mL/kg b.w./day (3 times the dose administered for group 2).

Animals were given the oral administration of distilled water or DEHEMA once a day in the morning, for thirty consecutive days.

The study parameters at the baseline and during the study included:

General condition, body weight.

Hematopoietic function: Serum levels of red blood cells (RBC), hemoglobin (HGB), hematocrit, MCV (mean corpuscular volume), white blood cells (WBC), WBC differentials, platelet count (PLT).

Liver and kidney functions: Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, albumin, total cholesterol, and creatinine. These indicators were tested at the baseline(D0), after 15 days (D15), and after 30 days (D30) of DEHEMA administration.

- After 30 days, all rats were sacrificed to observe a full gross anatomy. 30% of rats' livers and kidneys in each group were randomly selected for histopathology examination. The histological evaluations were assessed at the Department of Pathology, E Hospital.

Statistical analysis

Data from the acute toxicity study were analyzed by Microsoft Excel 2019 software using the Student's T-test.

Data from the subchronic toxicity study were analyzed by Microsoft Excel 2019 software using the Student's T-test and paired-samples T-test. Comparisons between the control group and the two treatment groups were made. Data were reported as Mean ± Standard Deviation (SD). Results with a p-value of less than 0.05 were considered statistically significant.

III. RESULTS

1. Acute toxicity study

In the acute toxicity study of DEHEMA, white mice were administered DEHEMA from the lowest dose (50 mL of the original concentrated aqueous extract/kg b.w./day) to the highest dose (100 mL/kg b.w./day), QID. No abnormal sign and mortality was observed in mice treated with the highest dose of DEHEMA after 72 hours and 7 days of DEHEMA administration. Table 1 shows that no acute toxicity was exhibited in the studied mice. The maximum tolerated dose (always less than the LD_{50}) of the DEHEMA preparation was 100 mL/kg b.w./day.

Table 1. Acute toxicity study of DEHEMA

Group	n	Dose (mL of concentrated DEHEMA/kg b.w.)	Mortality rate (%)	Abnormal signs
Group 1	10	50	0	No
Group 2	10	75	0	No
Group 3	10	100	0	No

2. Subchronic toxicity study

Changes in general condition and body weight

General condition

During the subchronic toxicity study, rats were divided into the biological control group and two treatment groups. All rats had normal movements, agile, bright eyes, silky fur, good eating habits and dry normal stools.

Body weight

Table 2. The effect of DEHEMA on body weight

Time	Group 1		Group 2		Group 3		p
	Body weight (g)	% increase	Body weight (g)	% increase	Body weight (g))	% increase	
Before treatment (D0)	197.00 ± 49.68	-	200.00 ± 33.67	-	195.00 ± 34.72	-	> 0.05
After 15 days (D15)	227.00 ± 44.23	15.2	232.00 ± 26.16	16.0	236.00 ± 40.06	21.0	> 0.05
After 30 days (D30)	230.00 ± 36.82	16.8	234.00 ± 47.89	17.0	242.00 ± 41.58	24.1	> 0.05
p_{D0-D15}	*< 0.05*		*< 0.05*		*< 0.05*		
p_{D0-D30}	*< 0.05*		*< 0.05*		*< 0.05*		

Table 2 shows that after 15 and 30 days, the body weights of mice in each group increased significantly compared to baseline ($p < 0.05$).

The increases in weight of DEHEMA-treated mice tended to be higher than those of the control group, but the difference was not statistically significant ($p > 0.05$).

Effect on the hematopoietic functions

There were no significant difference in RBC count, hematocrit, hemoglobin level, MCV; WBC count, WBC differentials and platelet count between two DEHEMA-treated groups and group 1 (control group) ($p > 0.05$) (Table 3).

Table 3. The effect of DEHEMA on red blood cell parameters and platelet

Parameters	Group	Before treatment	After treatment	
			15 days	30 days
RBC (T/L)	Group 1	8.97 ± 1.14	8.21 ± 1.06	9.64 ± 0.87
	Group 2	9.36 ± 0.64	8.63 ± 0.85	8.69 ± 1.24
	Group 3	8.52 ± 1.54	8.21 ± 1.05	8.80 ± 1.08
	p	> 0.05	> 0.05	> 0.05
Hemoglobin level (g/dL)	Group 1	10.54 ± 2.63	10.56 ± 1.38	11.98 ± 1.04
	Group 2	11.66 ± 0.71	11.35 ± 0.82	11.04 ± 1.11
	Group 3	10.72 ± 2.17	10.93 ± 1.53	11.20 ± 0.75
	p	> 0.05	> 0.05	> 0.05

Parameters	Group	Before treatment	After treatment	
			15 days	30 days
Hematocrit (%)	Group 1	41.69 ± 4.07	38.24 ± 5.94	44.96 ± 4.54
	Group 2	44.50 ± 2.78	40.66 ± 3.69	43.02 ± 4.23
	Group 3	40.26 ± 7.45	38.62 ± 5.33	41.86 ± 5.52
	p	> 0.05	> 0.05	> 0.05
MCV (fL)	Group 1	47.20 ± 1.81	46.50 ± 1.96	46.70 ± 1.83
	Group 2	46.80 ± 2.35	46.00 ± 1.41	46.00 ± 1.63
	Group 3	47.20 ± 1.14	47.00 ± 1.15	47.30 ± 0.48
	p	> 0.05	> 0.05	> 0.05
WBC (G/L)	Group 1	8.46 ± 1.52	8.83 ± 2.05	8.00 ± 1.71
	Group 2	8.92 ± 1.98	8.43 ± 2.63	7.53 ± 2.38
	Group 3	8.20 ± 2.46	9.68 ± 2.33	7.14 ± 1.24
	p	> 0.05	> 0.05	> 0.05
Neutrophils (%)	Group 1	10.39 ± 3.09	11.75 ± 3.27	10.26 ± 3.33
	Group 2	13.08 ± 4.32	14.00 ± 4.48	11.38 ± 2.93
	Group 3	11.95 ± 3.13	11.55 ± 3.61	10.20 ± 2.28
	p	> 0.05	> 0.05	> 0.05
Lymphocytes (%)	Group 1	74.49 ± 6.38	73.53 ± 9.32	75.94 ± 3.88
	Group 2	71.70 ± 8.61	73.71 ± 6.61	73.11 ± 4.31
	Group 3	74.74 ± 5.11	77.46 ± 5.15	76.42 ± 3.82
	p	> 0.05	> 0.05	> 0.05
Platelet (G/L)	Group 1	569.60 ± 149.74	579.00 ± 112.89	621.80 ± 95.56
	Group 2	656.30 ± 128.35	659.10 ± 183.09	670.70 ± 128.88
	Group 3	569.90 ± 151.30	648.70 ± 129.98	678.00 ± 92.38
	p	> 0.05	> 0.05	> 0.05

Effect on liver and kidney functions

There were no significant differencein serum liver enzymes (AST, ALT), total bilirubin, albumin, total cholesterol, and creatinine levels between the two DEHEMA treatment groups (DEHEMA 10 mL/kg b.w./day and 30 mL/kg b.w./day) and the control group (p > 0.05). The results are shown in Table 4.

Table 4. The effect of DEHEMA on liver and kidney functions

Parameters	Group	Before treatment	After treatment	
			15 days	30 days
AST level (UI/L)	Group 1	63.20 ± 11.31	67.40 ± 19.47	76.40 ± 14.22
	Group 2	70.90 ± 11.40	59.30 ± 17.62	70.40 ± 15.30
	Group 3	73.40 ± 13.03	69.40 ± 11.49	77.90 ± 12.89
	p	> 0.05	> 0.05	> 0.05
ALT level (UI/L)	Group 1	43.10 ± 11.55	34.60 ± 8.14	41.10 ± 6.92
	Group 2	39.30 ± 11.19	33.70 ± 7.86	35.80 ± 5.41
	Group 3	35.10 ± 5.95	39.40 ± 7.72	37.80 ± 4.44
	p	> 0.05	> 0.05	> 0.05
Total bilirubin (mmol/L)	Group 1	8.05 ± 0.57	7.88 ± 0.54	8.43 ± 0.55
	Group 2	8.02 ± 0.44	8.49 ± 0.85	8.43 ± 0.57
	Group 3	8.14 ± 0.71	8.29 ± 0.52	8.18 ± 0.71
	p	> 0.05	> 0.05	> 0.05
Albumin concentration (g/dL)	Group 1	2.73 ± 0.33	2.75 ± 0.33	3.00 ± 0.27
	Group 2	2.89 ± 0.27	2.72 ± 0.17	2.74 ± 0.39
	Group 3	2.81 ± 0.32	2.69 ± 0.37	2.81 ± 0.19
	p	> 0.05	> 0.05	> 0.05
Total cholesterol concentration (mmol/L)	Group 1	1.07 ± 0.23	1.00 ± 0.28	1.26 ± 0.16
	Group 2	1.13 ± 0.17	1.00 ± 0.12	1.11 ± 0.17
	Group 3	1.08 ± 0.13	0.98 ± 0.15	1.20 ± 0.17
	p	> 0.05	> 0.05	> 0.05
Creatinine (mg/dL)	Group 1	78.90 ± 5.92	76.80 ± 6.11	81.00 ± 6.75
	Group 2	76.70 ± 4.52	77.60 ± 5.85	82.20 ± 7.79
	Group 3	80.60 ± 7.93	80.30 ± 5.03	79.00 ±6.46
	p	> 0.05	> 0.05	> 0.05

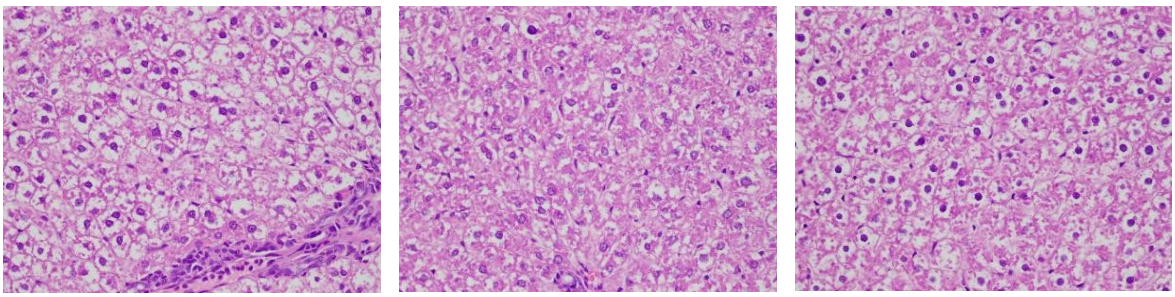
Effect of DEHEMA on histopathological evaluation

Macroscopic evaluation

The histopathological evaluation was conducted after 30 days of DEHEMA administration. All rats of the 3 groups were sacrificed to observe the macroscopic changes of the organs including heart, lungs, liver, spleen, pancreas, kidneys and digestive systems. No histopathological abnormality was found.

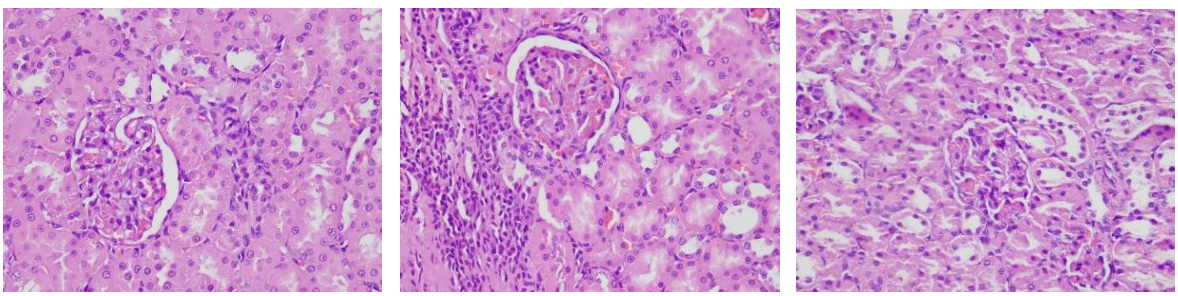
There were no significant difference in histopathological evaluations of the livers and kidneys between DEHEMA-treated mice group

2 (DEHEMA 10 mL/kg b.w./day, equivalent to 5.2g herbals/kg b.w./day), group 3 (DEHEMA 30 ml/kg b.w./day, equivalent to 15.6g herbals/kg b.w./day), and the control group after 30 days (Figures 1 and 2). The microscopic images of livers and kidneys in rats of three groups showed normal structures, no significant lesion was noted found.



Group 1 (Rat number 101) | Group 2 (Rat number 128) | Group 3 (Rat number 119)

Figure 1. Histopathological morphology of liver (HE X 400)



Group 1 (Rat number 110) | Group 2 (Rat number 125) | Group 3 (Rat number 119)

Figure 2. Histopathological morphology of kidney (HE X 400)

I. DISCUSSION

Toxicity is the degree to which a substance can harm humans or animals.[2,6,7] Toxicity can refer to the effect on a cell (cytotoxicity), an organ (e.g., renal or liver toxicity), or the whole organism.[2,6] To determine the safety of herbal drugs and products for human use, studying toxicity in various experimental animal models is essential to detect toxicity and provide guidelines for selecting 'safe' therapeutic doses in humans.[6,7]

The result of the acute toxicity study of DEHEMA showed that *Swiss* mice could tolerate DEHEMA up to a dose of 100 mL/kg b.w., approximately 4.2 times the recommended dose for human. During the study, no sign of acute toxicity and no mortality were observed in seven consecutive days after DEHEMA administration. LD_{50} of DEHEMA could not be determined in the studied mice. As defined by WHO, DEHEMA was a safe herbal product in experimental animals.[9]

The subchronic toxicity study of DEHEMA was identified by evaluating the changes in general conditions, body weight, hematopoietic function, liver function, kidney function, and histopathology examinations of rats' livers and kidneys.

Body weight change is the most basic

parameter indicating and reflecting xenobiotics' toxicity on experimental animals' general conditions as well as organ systems.[6,7] Daily observation of general signs and periodical measurement of body weight should be assessed.[6,7] In our study, DEHEMA administration did not significantly alter the animals' normal metabolism; the differences in rats' biological parameters of the kidneys and liver between the control group and the two treatment groups were not statistically significant.

The hematopoietic system is an important system responsible for blood cell production in the body, which is vital for maintaining a healthy blood supply and supporting the body's functions.[7,9] This system is one of the most sensitive targets of toxic compounds, and therefore, evaluating the changes in hematopoietic parameters is essential for studying the detrimental effects of xenobiotics on humans and animals' physiological and pathological status.[7,9] The changes of hematopoiesis in experimental studies can be used to predict the potential harmful effects on humans. After 15 and 30 days of DEHEMA administration, there were no significant difference in the RBC count, hematocrit percentage, hemoglobin concentration, MCV, platelet count, WBC count, and WBC differentials between the two DEHEMA treatment groups and the control group, suggesting that DEHEMA did not detrimentally affect the hematopoietic system in experimental animals.

Analysis of the kidney and liver is a fundamental part of the toxicity study evaluating the safety of drugs and plant extracts, as they are both vital for humans and animals' survival.[6,7,10] Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are two enzymes primarily found in the liver, which play a crucial role in metabolizing the amino acids.[10] When the liver is damaged, AST and ALT are released into the bloodstream; therefore, changes in the serum AST and/or ALT can suggest liver diseases or hepatoxicity.[10] Bilirubin, albumin, and cholesterol are three key indicators reflecting the liver's functions, including the liver's capacities of metabolizing lipids and producing bile, synthesizing protein, and processing RBC's breakdown products.[10] There were no significant change in serum ALT, AST, total bilirubin, albumin, and cholesterol concentrations in rats administered DEHEMA at two studied doses when compared to those of the control group; all values were within the normal physiological range. Creatinine is filtered by the kidneys and excreted in urine; thus, serum creatinine level is used to indicate kidney function.[11] There was no significant difference in serum creatinine level of DEHEMA-treated rats at two doses compared to the control group ($p > 0.05$). These results exhibited that DEHEMA did not affect liver and kidney function parameters.

To further investigate the potential damage of drugs or plant products on the cell structure level of animals, histopathological evaluations are carried out to reveal the alterations in the liver and kidney by using a microscope. These organs are vital because of their roles in metabolizing substances, eliminating, and filtering foreign substances from the body... The histopathological examination showed that there were no significant difference in the structure of rats' livers and kidneys in DEHEMA treatment groups compared to the control group, suggesting that DEHEMA did not affect the structure of the studied rats' livers and kidneys.

Our results were consistent with previous studies on single components of DEHEMA. Omar (2005) studied and compared the

genotoxicity, hepatotoxicity, and carcinogenic outcomes of Myrrh extract (Mirazid formulation) and praziquantel (standard drug) in rats using various markers such as bilirubin, ALT, and AST in the serum, liver histopathology, and bone marrow cell cytogenetic studies. Myrrh administration at 500 mg/kg daily for 6 weeks was observed to be safe, showing no sign of hepatotoxicity, genotoxicity, or carcinogenic effects while praziquantel at 1500 mg/kg weekly for 6 weeks had hepatotoxic, genotoxic, and carcinogenic effects. This study corroborates prior findings on the safety of myrrh even after prolonged usage.[12]

Singh (2012) conducted a 90-day toxicity study to evaluate the safety assessment of *Boswellia serrata* in rats, using repeated different doses of 100, 500, and 1000 mg/kg b.w./day. The results indicated that *Boswellia serrata* is relatively safe in rats up to the dose of 500 mg/kg b.w., as no adverse impact on health factors was reported.[13]

V. CONCLUSION

No sign of acute toxicity and mortality were observed in DEHEMA-treated mice at the highest dose of 100 mL/kg b.w/day (equivalent to 4.2 times the recommended human dose of 100 mL/day for a 50-kg adult, with the mouse ratio of 12). Oral LD50 of DEHEMA could not be determined in *Swiss* mice.

During 30 days of the subchronic toxicity study, the aqueous extract of DEHEMA at two doses of 10 mL/kg b.w./day (equivalent to 5.2 g herbals/kg b.w./day) and 30 mL/kg b.w./day (equivalent to 15.6 g herbals/kg b.w./day) did not cause any toxicity or abnormal signs or symptoms in hematopoietic parameters, biochemistry parameters, and histopathological observations of liver and kidney tissues between the DEHEMA-treated groups and the control group.

REFERENCES

1. World Health Organization. WHO global report on traditional and complementary medicine 2019. Geneva. 2019. License: CC BY-NC-SA 3.0 IGO.

2. Jităreanu A, Trifan A, Vieriu M, et al. Current Trends in Toxicity Assessment of Herbal Medicines: A Narrative Review. *Processes*. 2023; 11(1):83. https://doi.org/10.3390/pr11010083

3. Saganuwan S. Toxicity studies of drugs and chemicals in animals: An overview. *Bulg J Vet Med*. 2017; 20:291-318. doi:10.15547/bjvm.983.

4. Jong WH, Carraway J, Re G. In vivo and in vitro testing for the biological safety evaluation of biomaterials and medical devices. *Biocompat Perform Med Devices*. 2012;120-158. doi:10.1016/ B978-0-85709-070-6.50007-9.

5. Zhao Y-L, Su M, Shang J-H, et al. Acute and Chronic Toxicity of Indole Alkaloids from Leaves of Alstonia scholaris (L.) R. Br. in Mice and Rats. *Nat Prod Bioprospecting*. 2020;10(2):77-88. doi:10.1007/s13659-020-00237-1.

6. OECD. *Guidelines for the testing of chemicals repeated dose oral toxicity study in rodents*. Environmental Health and Safety Monograph Series on Testing and Assessment No 407; 2008.

7. World Health Organization. *Guidelines for Assessing Quality of Herbal Medicines with Reference to Contaminants and Residues*. World Health Organization. Geneva; 2007.

8. Litchfield JT, Wilcoxon FA. A simplified method of evaluating dose-effect experiments. *J. Pharmacol. Exp. Ther*. 1949; 96: 99-113.

9. OECD. Guidance Document on Acute Oral Toxicity Testing. OECD. 2002. doi:10.1787/9789264078413-en

10. Ramaiah SK. Preclinical safety

assessment: current gaps. challenges. and approaches in identifying translatable biomarkers of drug-induced liver injury. *Clin Lab Med*. 2011;31(1):161-172. doi:10.1016/j.cll.2010.10.004

11. Saganuwan SA. Toxicity studies of drugs and chemicals in animals: an overview. *Bulgarian Journal of Veterinary Medicine*. 2017; 4(20): 291-318.

12. Omar A, Elmesallamy Gel-S, Eassa S. Comparative study of the hepatotoxic. genotoxic and carcinogenic effects of praziquantel distocide & the natural myrrh extract Mirazid on adult male albino rats. *J Egypt Soc Parasitol*. 2005;35(1):313-329.

13. Singh P, Chacko KM, Aggarwal ML, et al. A-90 Day Gavage Safety Assessment of Boswellia serrata in Rats. *Toxicol Int*. 2012;19(3):273-278. doi:10.4103/0971-6580.103668