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The study of acute toxity and efficacy evaluation of bioactive compounds for constipation

Nufuzakhan Adilova
Tashkent Medical Academy, Tashkent, Uzbekistan

Malika Foziljonova
Pharmaceutical Education and Research Institute, Tashkent, Uzbekistan

Zilola Abdujalilova
Pharmaceutical Education and Research Institute, Tashkent, Uzbekistan

Abdusattor Tojiboyev
Tashkent Medical Academy, Tashkent, Uzbekistan

Jasurbek Kholmatov
Tashkent Medical Academy, Tashkent, Uzbekistan

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Abstract: Constipation is a prevalent gastrointestinal disorder that significantly impacts patients' quality of life. The present study aims to evaluate the acute toxicity and efficacy of selected bioactive compounds for the treatment of constipation. Acute toxicity was assessed using standardized in vivo models to determine the safety profile of the bioactive compounds. The therapeutic efficacy was evaluated through pharmacodynamic and biochemical analyses, focusing on bowel motility, stool frequency, and intestinal microbiota modulation. Preliminary findings suggest that the tested compounds exhibit favorable safety margins and potent laxative effects, potentially offering a novel approach for constipation management. Further clinical studies are required to validate their long-term safety and effectiveness.

Keywords: Garcinia cambogia, senna, chitosan, green coffee, constipation, bioactive compounds, acute toxicity, subchronic toxicity,white mice.

Introduction: The World Health Organisation is currently facing a global problem with the increasing number of pathological conditions in the human body due to metabolic disorders. Bioactive substances derived from natural plants have become a popular treatment for improving metabolism in the human body. As we know, in recent years, the number of types of drugs derived from bioactive substances obtained from plants has increased in the pharmaceutical market. The primary reason for this is the widespread awareness of the long-term health benefits of natural ingredients by consumers. As demand for plant-derived medicines grows worldwide, many countries are increasingly concentrating on producing new types of plant-based medicines.

Senna (Cassia angustifolia) is a plant of the bean family. This branched shrub, which is abundant throughout southern India, can reach a height of 1.8 m. Extracts of this plant are used in folk medicine to treat some gastrointestinal disorders. hydroxyanthrazine

glycosides, also known as sennosids, have been reported to stimulate the peristalsis of the colon and change the absorption and secretion of the colon resulting in fluid accumulation and excretion.b Researchers 2 have suggested that a normal daily dose of senna for adults consists of two tablets containing 18 mg of sennoside per 90 mg tablet. Other studies 4 have shown that sennosids cause diarrhea due to changes in the intestinal tract. The laxative effect of this natural product is due to its anthraquinone glycosides. [1,2,3,4,5]

Garcinia cambogia extract is quite promising for the correction of serum and tissue cortisol levels. It is known that the fruit of Garcinia cambogia includes organic acids, benzophenones, pectins, polyphenolic compounds, xanthocymol and isooxantocimol, cambonine, kamboginol, carbohydrates, molds and other biologically active substances; The content of hydroxylic acid in fruits reaches 65%. Numerous studies have shown that Garcinia cambogia drugs can prevent obesity, having hypolipidemic, antidiabetic, anti-inflammatory and antioxidant activity. [6,7,8].

Chitosan is a natural cationic polysaccharide obtained by the deacetylation of chitin [9]. The chemical reaction occurs as a result of the substitution of parts of the N-acetic groups in chitin, which are β- (1-4)-2-amino-2-deoxy-D-glycopyranose and β- (1-4)-Acetamide-2-deoxy-D-glicopyranosis [10]. Chitosan demonstrates good biocompatibility, biodegradability, permeability, low cell toxicity [11 ,12], anti-inflammatory, analgesic and blood-stopping action [13,14]. In addition, chitosan exhibits antibacterial activity by interacting protonated amino groups with the negative charges of bacterial cell membrane and cell wall [15 ,16] and binding to bacterial DNA, which avoids transcription and gene translation. These properties secrete chitosan among other biomaterials in wound healing [17, 18]. The antibacterial activity of chitosan can be improved by chemical modification of its structure, such as inclusion of amino groups [19, 20, 21, 22].

The composition of compounds in the following ratio was considered as a bioactive additive against constipation:

Composition of biologically active substance No. 1:

- Garcinia Cambodia – 400 mg
- Chitosan – 150 mg
- Senna – 50 mg
- Green coffee – 10 mg

Composition of biologically active substance 2:

- Garcinia Cambodia – 350mg
- Chitosan – 200 mg
- Senna – 40 mg
- Green coffee – 20 mg

Composition of biologically active substance 3:

- Garcinia Cambodia – 450 mg
- Chitosan – 100 mg
- Senna – 55 mg
- Green coffee – 5 mg

Composition of biologically active substance 4:

- Garcinia Cambodia – 400 mg
- Chitosan – 100 mg
- Senna – 70 mg
- Green coffee – 40 mg

METHODS

The study of acute toxic interaction described in the literature with the general method adopted, disposable into the stomach by sending special zond and toxic studied by determining the class was [23].

Type and number of animals: 72 white sterile male mice weighing 19-21 g, quarantined for 14 days, were used in the experiment.

Preparation of aqueous solutions: 12.2% aqueous solution of tested biologically active substances (1 capsule + 5 ml H2O) was prepared for acute toxicity study and determination of LD50.

The laxative effect of biologically active substances 1, 2, 3, 4 was studied on 24 white rats with a mass of 190-210 g.

RESULTS

The following information was obtained for biologically active substance №1:

1-group (dose 2440 mg/kg): biologically active substances for a day on the slopes remained active after being introduced, if it did not track changes in conduct. The usual mode of wool and skin, o'zgarishlarsiz, denial of food and water, not a day, diarrhea in mice were observed during the four slopes of the death did not take place. On the second day and the next tracking and pathological changes in physiological indicators during the period in the conduct of the slopes aredi. Stay on track by those behind the normal growth and development water and feed consumption ofdi. The slopes of the death of 14 days for the quality isadi.

2-group (dose 3660 mg/kg): substance is active after being introduced for a day on the slopes, track changes in the conduct did not. The usual mode of wool and skin, no changes, diarrhea were observed for 3 days, food and wateris to reject, the slopes of death did not take place. On the fourth day and the next tracking and

pathological changes in physiological indicators during the period in the conduct of the slopes aredi. Stay on track by those behind the normal growth and development water and feed consumption ofdi. The slopes of death for 14 days did not monitor the quality. Table № 1shows that mice did not die within 14 days.

Biologically active substances №1 of acute toxic

Table 1

Number of animals	Biologically active substance №1			
	Size		Sending way	Results
	mg/kg	ml		
1	2440	0.4	os	0/6
2	3660	0,6	os	0/6
3	4880	0.8	os	0/6
LD**50**	>4880 mg/kg			

Group 3 was treated with a biologically active substance (dose 4880 mg/kg) which caused short-term flaccidity and immobility in mice, but it disappeared after 60-90 minutes. 3-4 hours prior to the first day of the experiment, the animals did not consume any food or water. All animals had diarrhea for 3 days, despite the active behavior and normal physiological indicators. For the fourth day and period of observation, no changes in behavior and other physiological indicators were observed, mice consumed food and water willingly, their reactions to light and sound exposure remained normal, no mouse death was observed for 14 days.

The following information is gathered for substance №2.

The biologically active substance administered to mice in Group 1 (2440 mg/kg dose) remained active for 24 hours without any behavioral changes observed. The wool and skin were in a normal condition without any changes, food and water were not denied, and four mice had diarrhea for one day, but they did not die. No pathological changes in the mice' behavior or physiological indicators were observed during the second day and throughout the observation period. Normal water and food consumption did not cause growth and development delays. There were no mice deaths within 14 days.

Group 2 (dose 3660 mg/kg): mice were active within 24 hours of administration, no behavioural changes were observed. The condition of the wool and skin was normal without any changes. For three days, there was diarrhea, but food and water were not refused, and mice did not die. The behavioral and physiological indicators of mice did not change on the fourth day and during the observation period. The absence of normal water and food intake, growth, and developmental delays was observed. Table № 2 shows that mice did not die within 14 days.

Biologically active substances №2 of acute toxic

Table 2

Number of animals	Biologically active substances №2			
	Size		Sending way	Results
	mg/kg	ml		
1	2440	0.4	os	0/6
2	3660	0,6	os	0/6
3	4880	0.8	os	0/6
LD**50**	>4880 mg/kg			

Group 3 was given a biologically active substance (dose 4880 mg/kg) which caused short-term flaccidity and immobility in the mice, but it disappeared within 60 to 120 minutes. Before the first day of the experiment, the animals did not eat or drink for 4-5 hours. All animals had diarrhea for 3 days, despite the active behavior and normal physiological indicators. For the fourth day and during the observation period, no changes in behavior and other physiological indicators of mice were observed, mice willingly ate food and water, their reactions to light and sound exposure remained normal, no mouse death was observed for 14 days.

The following information is gathered for substance №3.

Group 1 (2440 mg/kg dose): Mice maintained activity for 24 hours after administering the biologically active substance, no behavioural changes were observed. The condition of the wool and skin was normal, without changes, food and water were not refused, four mice had diarrhea for one day, there was no mouse death. During the second day and throughout the observation period, no pathological changes in the behavior and physiological indicators of the mice were observed. Normal water and food consumption, growth and development delays were not observed. There was no death of mice within 14 days.

Group 2 (dose 3660 mg/kg): mice were active within 24 hours of administration, no behavioural changes were observed. The condition of the wool and skin was normal, without changes, for 3 days there was diarrhea, food and water were not refused, mice did not die. Pathological changes in the behavior and physiological indicators of mice for the fourth day and during the observation period were not detected. Normal water and food intake, growth and development delays were not observed. Mortality of mice within 14 days was not observed.

Group 3 (dose 4880 mg/kg): Following the administration of a biologically active substance, the mice exhibited temporary flaccidity and immobility, which resolved within 60 to 90 minutes. Prior to the commencement of the experiment, the animals refrained from consuming food and water for a duration of 2 to 4 hours. Their behavior was characterized as active, and physiological parameters remained within normal ranges; however, all subjects experienced diarrhea for a period of 4 days. By the fourth day and throughout the subsequent observation period, no alterations in behavior or other physiological parameters were noted. The mice resumed normal

feeding and drinking habits, their responses to light and sound stimuli remained unaffected, and no fatalities were recorded over the 14-day observation period. Table 1 indicates that the mice survived for a duration of 14 days without any fatalities

Biologically active substances №3 of acute toxic

Table 3

Number of animals	Biologically active substances №3			
	Size		Sending way	Results
	mg/kg	ml		
1	2440	0.4	os	0/6
2	3660	0,6	os	0/6
3	4880	0.8	os	0/6
LD**50**	>4880 mg/kg			

The following information is gathered for substance №4.

In Group 1, which received a dosage of 2440 mg/kg, the mice exhibited sustained activity for a full 24 hours following the administration of the biologically active substance, with no notable behavioral alterations recorded. The condition of their fur and skin remained normal, and there were no changes in their eating or drinking habits. Although four mice experienced diarrhea for a single day, there were no fatalities. Throughout the second day and the entire observation period, no pathological changes in behavior or physiological parameters were noted. Additionally, there were no delays in food and water consumption, growth, or development, and no mouse deaths occurred over the 14-day period.

In Group 2, which was administered a dose of 3660 mg/kg, the mice displayed activity for 24 hours post-

administration, with no behavioral changes detected. Their fur and skin condition remained stable, and they did not refuse food or water. Diarrhea was observed in the mice for a duration of three days, yet there were no instances of mortality. No pathological changes in behavior or physiological indicators were identified by the fourth day or throughout the observation period. Furthermore, normal consumption of food and water was maintained, and there were no delays in growth or development, with no recorded deaths among the mice after 14 days.

In Group 3 (dose 4880 mg/kg), the administration of a biologically active substance resulted in a temporary state of flaccidity and immobility in the mice, which resolved within 60 to 90 minutes. Prior to the commencement of the experiment, the animals refrained from consuming food and water for a duration of 3 to 4 hours. During the initial phase, the mice exhibited active behavior, and their physiological parameters remained within normal limits; however, all subjects experienced diarrhea for a period of three days. From the fourth day onward and throughout the observation period, no alterations in behavior or other physiological parameters were noted. The mice resumed normal consumption of food and water, and their responses to light and sound stimuli remained unaffected. Notably, there were no recorded fatalities among the mice over the 14-day observation period. These findings indicate that the acute toxic dose of the biologically active substance exceeds the LD50 threshold of 4880 mg/kg. Table 4 indicates that the mice survived for a duration of 14 days without any fatalities.

Biologically active substances №4 of acute toxic

Table 4

Number of animals	Biologically active substances №4			
	Size		Sending way	Results
	mg/kg	ml		
1	2440	0.4	os	0/6
2	3660	0,6	os	0/6
3	4880	0.8	os	0/6
LD**50**	>4880 mg/kg			

Efficiencies evaluation

Research on the laxative effects of biologically active substance-1 indicated that the stool mass was elevated by 1.92 times relative to the control group. Meanwhile, animals treated with biologically active substance-2 showed a 1.73-fold increase in stool mass. Additionally, those receiving biologically active substance-3 experienced a 1.6 times increase. In the fourth group, the content of the biologically active substance was found to have increased by 1.4 times. These findings are summarized in table 5.

Laxative activity of the analysed biologically active substances 1, 2, 3, 4

Table 5

	Weight, g	Dose		Feces of the mass, g,
		mg/kg	1 l/100g	
Control group + purified water				
1	189,3± 3.7	-	2	1,91 ± 0,14
Biologically active substance-1				
2	186,6 ± 6.7	140	2	3,68± 0,3 R<0.05 up to
Biologically active substance-2				
3	185,3 ± 4,9	140	2	3,31 ± 0,34 R<0.05 up to
Biological active ingredients-3				
4	187 ± 5,4	140	2	3 ± 0,27 R<0.05 up to
Biologically active substance-4				

5	189,8 ± 6.1	140	2	2,68 ± 0,36 R<0.05 up to

The experimental animals were categorized into five groups, each consisting of six individuals. The administration of biologically active substances occurred in the following sequence:

Control group: A single oral dose of 2 ml of purified water was provided;

Experimental group: A single oral dose of 50 mg/kg of a 1.0% solution of biologically active substance-1 (Uzbekistan) was administered;

Experimental group: A single oral dose of 50 mg/kg of a 1.0% solution of biologically active substance-2 (Uzbekistan) was administered;

Experimental group: A single oral dose of 50 mg/kg of a 1.0% solution of biologically active substance-3 (Uzbekistan) was administered;

Experimental group: A single oral dose of 50 mg/kg of a 1.0% solution of biologically active substance-4 (Uzbekistan) was administered.

The experimental animals in each group were housed in specialized containers, and fecal samples were collected twice, with an interval of eight hours. The weight of the fecal mass was determined by calculating the difference between the weight of the empty container and that of the container filled with feces. The results obtained were analyzed using the "STATISTICA" software in accordance with Student's paired t-test

DISCUSSION

The acute toxicity experiment of the biologically active substance 1,2,3,4 was conducted in four series. In the first series, white mice were divided into 3 groups of 6 individuals. The mice in each group were fed 12.2% of the biologically active solution into their stomachs as follows:

1 group (6 mice) - per os 2440 mg/kg (0.4 ml);

Group 2 (6 mice) - per os 3660 mg/kg (0.6 ml);

Group 3 (6 mice) - at os4880 mg/kg (0.8 ml).

In the second series, the mice in each group were injected with 12.2% of a biologically active solution into their stomachs as follows:

1 group (6 mice) - per os 2440 mg/kg (0.4 ml);

Group 2 (6 mice) - per os 3660 mg/kg (0.6 ml);

Group 3 (6 mice) - at os4880 mg/kg (0.8 ml).

In the third series, mice in each group were fed 12.2% aqueous solution of biologically active substance 3 into the stomach as follows:

1 group (6 mice) - per os 2440 mg/kg (0.4 ml);

Group 2 (6 mice) - per os 3660 mg/kg (0.6 ml);

Group 3 (6 mice) - per os 4880 mg/kg (0.8 ml).

In the fourth series, the mice in each group were injected with 12.2% of the aqueous solution of a biologically active substance into their stomachs as follows:

Group 1 (6 mice) - per os 2440 mg/kg (0.4 ml);

Group 2 (6 mice) - per os 3660 mg/kg (0.6 ml);

Group 3 (6 mice) - per os 4880 mg/kg (0.8 ml).

Observation: on the first day of the experiment animals in the experimental group were observed hourly, in laboratory conditions, by appearance (state of feathers, mucous membranes and so on). .k.; functional state (survival in the experiment, general state, coordination and death) and record of behavior. In the following days and daily for 2 weeks under vivarium conditions, changes in the general state and activity of animals of all groups, behavior characteristics, pain reactions, sound and light effects, frequency and depth of breathing movements, heartbeat, feather and skin condition, fecal mass quantity and consistency, urine, body mass and other indicators.[24]

The experimental animals were categorized into five groups, each consisting of six individuals. The administration of biologically active substances occurred in the following sequence:

Control group: A single oral dose of 2 ml of purified water was provided;

Experimental group: A single oral dose of 50 mg/kg of a 1.0% solution of biologically active substance-1 (Uzbekistan) was administered;

Experimental group: A single oral dose of 50 mg/kg of a 1.0% solution of biologically active substance-2 (Uzbekistan) was administered;

Experimental group: A single oral dose of 50 mg/kg of a 1.0% solution of biologically active substance-3 (Uzbekistan) was administered;

Experimental group: A single oral dose of 50 mg/kg of a 1.0% solution of biologically active substance-4 (Uzbekistan) was administered.

The experimental animals in each group were housed in specialized containers, and fecal samples were collected twice, with an interval of eight hours. The weight of the fecal mass was determined by calculating the difference between the weight of the empty container and that of the container filled with feces.

The results obtained were analyzed using the "STATISTICA" software in accordance with Student's paired t-test [25]

CONCLUSION

The analysis of the specific activities of biological active substances numbered 1, 2, 3, and 4 has determined that biological active substance No. 1 has a high degree of intravascular activity. It is recommended to keep using this substance as the primary laxative.

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