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TOXICOLOGICAL STUDY ON TRADITIONAL KOREAN HERBAL DRUGS (V)

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ABSTRACT:*Water extracts of 21 traditional Korean herbal drugs were prepared, and a dose range of 100 mg/kg to 400 mg/kg was administered orally into mice once a day for five days. Changes of serum enzyme activities of glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), blood urea nitrogen (BUN), alkaline phosphatase, body weight changes and histo pathological examination of various organs were investigated. Water extract of Ephedra Herba caused severe body weight loss at a dose of 100 mg/kg and death from a dose level of 200 mg/kg by oral administration. Angelica koreanae Radix and Anthrisci Radix showed a slight body weight loss and damages to liver and kidney.*

Keywords:*Toxicity of traditional Korean herbal drugs, Water extract of herbal drugs, Toxicity of Ephedra Herba, Angelica koreanae Radix, Anthrisci Radix.*

INTRODUCTION

Herbal therapy has been in existence more than a thousand years and is still practiced in almost every part of the world. Korea is a country that has legally adopted two medicare system in tandem; one is the western medicine and the other is its own traditional medicine which has originated essentially from the traditional Chinese medicine. Herbal drugs used for the traditional medicine are usually prepared as a form of water extract after decocting a single or multiple number of medicinal plants, depending on the prescription made by the traditional practitioner. Those herbal preparations are essentially a crude drug unlike the western drugs which are usually in the pure state of active chemicals. A herbal preparation, therefore, can contain literally hundreds of natural constitutents, including the active ingredients and many other constitutents may cause some adverse effects to humans. However, it is interesting to note that the majority of public sector believes that traditional herbal drugs/remedies are very safe and virtually non-toxic, since they have used those drugs for humans for a thousand years. But such a stereo-typed concept may not be true. (Chang, 1986) Our previous studies on herbal drugs indicate that many medicinal plants used frequently in traditional prescriptions exhibited severe toxic effects to experimental animals. (Chang, 1979, 1981, 1982, 1983, 1986) In addition, a recent medical report showed that a number of Chinese herbal preparations cause various side-effects to human patients, e.g. hepatotoxicity, neurotoxicity, allergic reactions and cardiovascular toxicities, etc. (Wang, 1985). So it is needed that safety assessment on traditional herbal drugs should be conducted by using modern scientific means such as toxicology and natural product chemistry, etc.

Present study aims to conduct some toxicological experiments on medicinal plants used for traditional Korean medicine with water decocted herbal extract and the following critieria were observed. changes of serum enzyme activities body weight, and histo–pathologic states.

MATERIALS AND METHODS

Selection of Herbal Drugs: Recently the ministry of public health and social affairs, Republic of Korea announced that 98 traditional herbal drugs will be subjected to medical insurance coverage in the medicare system. Twenty one herbal drugs among 98 were selected for this study..

Preparation of Herbal Drug Extracts: All herbal drugs were purchased from the local dealer and their taxonomical identities were examined by a systemic botanist in the Natural Products Research Institute, Seoul National University. From each plant sample 300 g was taken and then extracted with water under reflux at 55–60°C for 3 hrs. After the extraction ceased, total solution was filtered off. The remaining residue was again subjected to re–extraction. All fitrate was collected and evaporated in vacuum at 55–60°C. Then the extract was mixed with 70% ethanol and evaporated under reduced pressure into dryness. Scheme 1 shows a brief procedure of extract preparation. And Table 1 shows the weights obtained from each sample.

Experimental Animals: Four weeks old ICR male mice (average wt. 20 ± 2 g) were supplied by the Experimental Animal Laboratory, Seoul National University. All mice were maintained on a commercial diet and water ad libitum in a climatized room with an alternating 12 hr. light cycle.

Toxicity Studies: Body weight changes, assay of serum enzyme activities and histopathological examinatiion of various organs were carried out.

Body Weight Changes: On day 1 the weight of each mouse in control and test groups was measured. Then a dose of 100 mg/kg, 200 mg/kg and 400 mg/kg of each dried herbal extract was administered orally once a day for 5 days. On day 6 the weight of each mouse again was measured and compared with that of day 1.

Assay of Serum Enzyme Activities: Blood was withdrawn from jugular vein and was centrifuged at 1,800x g for 10 min. Assay of Glutamin Oxaloacetic Transaminase (EC.

TABLE 1, THE AMOUT OF DRIED EXTRACT OBTAINED FROM 300 G HERBAL DRUGS.

NAME OF HERBAL DRUG	WEIGHT	NAME OF HERBAL DRUG	WEIGHT
Agastachis Herba	*51.4 g*	*Lycii Fructus*	*90.0 g*
Amomi Semen	*21.1 g*	*Moutan cortex Radicis*	*57.0 g*
Angelica gigantis Semen	*125.0 g*	*Paeoniae Radix*	*116.8 g*
Angelica koreanae Radix	*85.0 g*	*Persicae Semen*	*70.8 g*
Anthrisci Radix	*71.0 g*	*Platycodi Radix*	*115.4 g*
Arecae semen	*32.3 g*	*Pueraiae Radix*	*38.0 g*
Cnidii Rhizoma	*105.0 g*	*Scrophulariae Radix*	*142.0 g*
Curcuma Rhizoma	*42.0 g*	*Sileris Radix*	*95.0 g*
Dioscoreae Radix	*123.0 g*	*Viticis Fructus*	*48.2 g*
Ephedra Herba	*50.2 g*	*Zizyphis Semen*	*138.7 g*
Glycyrrhizae Radix	*100.0 g*		

藿香, 砂仁, 當歸, 羌活, 前胡, 嬪瑯子, 川芎, 鬱金, 山藥, 麻黃, 甘草, 枸杞子, 牡丹及, 菊藥, 桃仁, 桔梗, 葛根, 玄蔘, 防風, 蔓荊子, 酸棗仁.

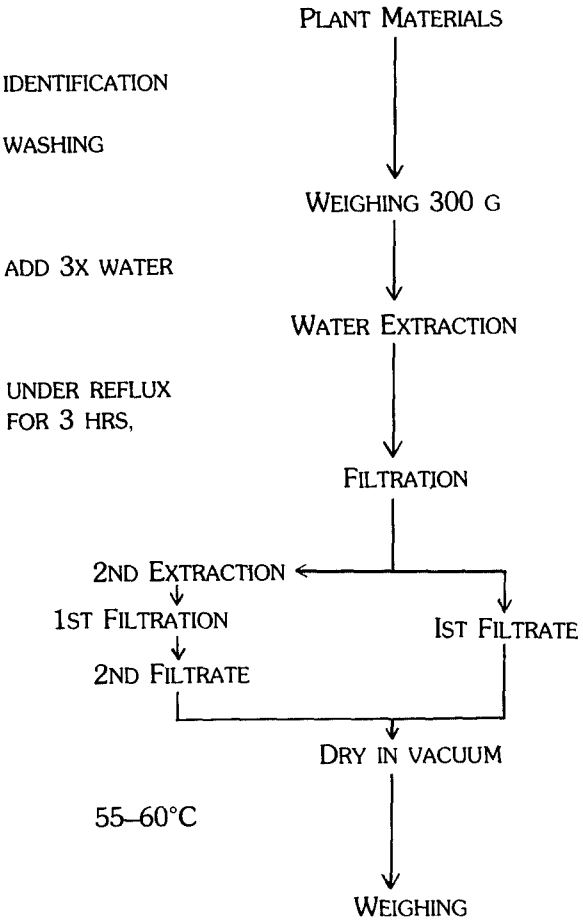
2.6.1.1), Glutamic Pyruvic Transaminase (EC. 2.6.1.2). Alkaline phosphatase (EC. 3.1.3.1) and Blood Urea Nitrogen were carried out by using ABA 200 autoanalyzer (Abbott Laboratory, U.S.A.).

Histopathological Observations: On day 6 all mice were sacrificed by cervical dislocation and various organs like liver, heart, spleen, kidney and stomach were removed. biopsy samples were fixed in formalin solution and stained with hematoxylin–eosin. All specimens were examined under optical microscope.

RESULTS AND DISCUSSION

Korean people have used traditional herbal drugs for centuries. From 1987, the government will extend its medical insurance coverage to the traditional medicine; ubsequently the herbal drug consumption is anticipated to increase.

Herbal drugs are a crude drug and they can contain numbers of natural constitutents, obviously including active ingredients but also some toxic substances which are generally the

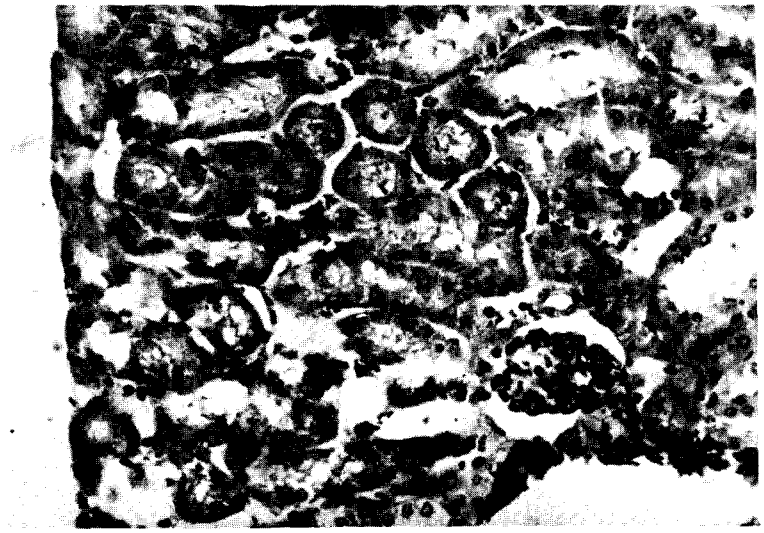


SCHEME 1. Preparation of herbal extract.

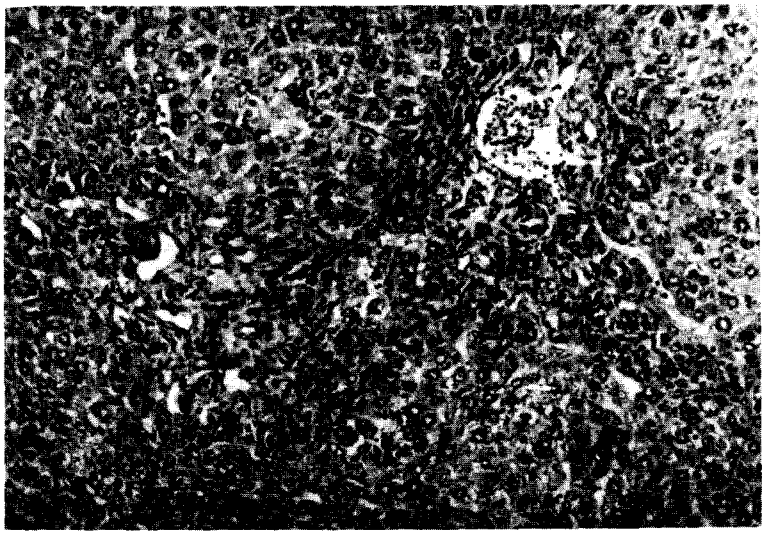
second metabolites of the plant. It is desirable to assess the safety of herbal drug (efficacy *vs* toxicity) by using modern sciences like pharmacology and toxicology, even though the public has used those herbal drugs for a thousand years.

To investigate possible toxicity of herbal drugs, we chose 21 kinds of traditional herbal drugs which have been frequently prescribed. Water decocted extracts were prepared in the way of the traditional medical practitioners, as shown in Scheme 1.

In Table 1, the amounts of each extract yield are shown and they are in a range of 21.1 g (*Amomi Semen* extract) to 142.0 g (*Scrophulariae Radix* extract). Experimental mice



400 mg/kg, Angelica koreanae Radix (Kidney)



400 mg/kg, Anthrisci Radix (Liver)

Fig. 1. Examples of liver and kidney damages.

Table 2. Toxicological evalulation of herbal drugs (Water extracts).

Name of Herbal Drugs	Dose (mg/kg) QD 1×5	Control body Wt. Change(g)	Body Wt. Change (T−C)	GOT (IU/L)	GPT (IU/L)	Alkaline Phosphatase (IU/L)	BUN (mg/dL)	Histological Observation				
								Liver	Stomach	Kidney	Spleen	Heart
Agastachis Herba	0	4.8		87.2±11.2	42.2± 9.8	338.1±33.0	31.4± 7.3					
	100		−0.7	84.0±13.4	40.8± 7.5	377.0±64.4	34.5± 5.0					
	200		−0.1	80.2±11.4	36.9± 6.6	373.5±46.0	34.1± 2.1					
	400		−0.1	99.0±18.1	46.6± 5.9	316.2±30.7	29.2± 4.0	NA	NA	−	−	NA
Amoi Semen	0	5.9		87.4±14.7	33.1± 6.0		37.6± 3.8					
	100		0.5	87.5± 7.7	33.1± 7.7		33.1± 7.1					
	200		−0.9	75.3±12.2	24.1± 6.1		34.1± 6.1					
	400		−0.2	93.8±15.2	42.4±19.2		42.4± 9.2	NA	NA	NA	−	NA
Angelica gigantis Semen	0	3.8		95.4±13.2	36.6± 6.4	327±72.6	25.6± 5.7					
	100		0	90.9±15.9	39.3± 8.1	336.0±60.0	28.7± 4.0					
	200		0.3	96.1±17.3	40.5±10.6	344.7±67.4	34.4± 4.6					
	400		1.0	101.6±28.1	42.1±10.4	331.5±37.9	30.8± 6.9	NA	NA	NA	NA	NA
Angelica koreanae Radix	0	2.2		91.3±17.1	42.7±13.3	388.2±53.0	31.4± 7.3					
	100		−0.6	112.8±29.1	45.9±12.6	335.4±16.9	35.5±16.9					
	200		0.1	113.6±29.2	53.2±14.3	474.0±66.3	35.8± 2.9					
	400		−0.7	112.4±28.5	54.9±12.5	498.5±52.9	32.8± 3.6	−	NA	NA	NA	NA
Anthrisci Radix	0	5.3		83.6±18.3	38.0±10.3	334.1±43.8	33.2±4.1					
	100		−1.2	91.3± 8.6	41.4±10.6	404.0±59.8	43.8± 7.1					
	200		−1.0	112.2±12.1	43.4± 9.1	414.8±36.3	40.2± 3.7					
	400		0.3	90.3±11.3	40.4± 2.2	408.8±22.7	45.6± 8.6	−	NA	−	NA	NA
Areace Semen	0	4.8		91.6± 8.7	38.2± 8.0	300.5±18.3	27.9± 4.0					
	100		−0.6	86.6± 9.8	43.0±17.4	343.2±22.9	34.0± 6.0					
	200		0.2	93.9± 9.8	54.3±13.3	296.9±21.2	36.4± 8.3					
	400		0.7	79.9±11.3	40.6± 7.8	298.5±21.8	33.0± 2.0	NA	NA	NA	NA	NA
Cnidii Rhizoma	0	2.1	−0.7	92.7±18.3	43.3± 7.9	327.0±28.0	33.4± 4.6					
	100		−0.5	93.7±17.6	36.6± 1.7	385.4±25.7	36.3± 6.3					
	200		−0.6	124.8±22.9	51.4± 7.6	359.2±33.8	32.8± 4.6					
	400			108.3±16.2	52.6± 7.0	359.8±12.8	36.8± 6.9	NA	NA	−	−	NA

Table 2. Toxicological evalulation of herbal drugs (Water extracts).

Name of Herbal Drugs	Dose (mg/kg) QD 1×5	Control Body Wt. Change(g)	Body Wt. Change (T−C)	GOT (IU/L)	GPT (IU/L)	Alkaline Phosphatase (IU/L)	BUN (mg/dL)	Histological Observation				
								Liver	Stomach	Kidney	Spleen	Heart
Curcuma rhizoma	0	6.1		85.4± 4.9	42.6± 3.9	336.5±54.2	29.8± 2.3					
	100		−0.5	90.9± 8.8	40.3± 7.5	346.7±32.9	25.8± 4.2					
	200		−0.8	88.9± 7.8	43.2±13.1	326.8±16.2	26.3± 2.5					
	400		−0.8	87.1± 7.5	47.8±13.3	342.3± 5.9	28.5± 4.7	NA	NA	NA	NA	NA
Dioscoreae Radix	0	4.9		84.6± 8.5	30.5± 3.1	311.3±22.8	40.8±5.8					
	100		−0.4	88.6± 4.6	31.2± 5.2	303.3±12.7	32.0±2.4					
	200		0.4	88.3±13.6	35.2± 6.7	303.6±10.8	31.6±3.8					
	400		−1.0	84.4±16.6	31.5± 3.9	296.3±19.4	30.8±3.6	NA	NA	−	NA	NA
Ehedra Herba	0	5.6	−4	80.0± 0.8	36.4± 5.9		36.5±5.1					
	100			100.8± 7.1	44.1± 5.1		32.3±1.4					
	200	Death		Toxic	Toxic							
	400	Death		Toxic	Toxic			NA	NA	NA	NA	NA
Glycyrrhizae Radix	0	2.7		89.1±18.3	42.0±12.6	302.3±23.1	26.9±2.5					
	100		1.1	85.6± 4.3	40.4± 5.8	298.7±18.4	25.5±1.5					
	200		1.2	84.5± 6.5	40.8± 8.5	312.3±15.2	26.0±3.0					
	400		1.1	86.7±15.3	41.9±10.8	288.0±20.2	25.4±4.3	NA	NA	NA	NA	NA
	0	4.3		89.8±19.2	50.0±12.1	329.8±24.6	28.7±5.1					
Lycii Fructus	100		0.3	87.7± 9.6	49.0± 8.9	346.2±30.6	27.8±2.9					
	200		−1.8	97.9± 9.7	55.9± 5.8	340.6±15.4	25.3±6.8					
	400		−1.1	98.9± 6.7	62.3± 8.7	295.6±21.3	28.7±5.1	NA	NA	NA	NA	NA
Moutan Cortex Radix	0	5.3			39.5± 6.9	298.9±30.0	28.5±4.1					
	100		−1.0		39.6± 9.3	306.2±22.8	31.6±6.8					
	200		−1.0		39.2± 5.9	298.5±24.1	29.2±2.4					
	400		−1.5		43.1± 4.7	314.2±19.8	28.9±5.2	NA	NA	NA	NA	NA
Paeonia Radix	0	5.5		89.9± 5.8	38.2±8.6	296.8±18.3	34.7±4.6					
	100		−1.4	87.5± 8.6	43.7± 9.8	298.8±22.7	29.8±2.9					
	200		−0.1	90.5± 7.8	42.9±12.7	294.5±25.4	29.8±3.1					
	400		−1.0	109.8±11.3	52.9± 8.4	299.9±24.4	36.5±5.3	NA	NA	NA	NA	NA

Table 2. Toxicological evalulation of herbal drugs (Water extracts).

Name of Herbal Drugs	Dose (mg/kg) OD 1×5	Control body Wt. Body Wt. Change(g)	Change (T–C)	GOT (IU/L)	GPT (IU/L)	Alkaline Phosphatase (IU/L)	BUN (mg/dL)	Histological Observatio Liver	Stomach	Kidney	Spleen	Heart
Persicae Semen	0	5.5		82.6±12.6	38.8±11.2	289.9±16.2	38.8±3.8					
	100		1.2	87.4± 5.3	35.0± 9.7	312.4±21.5	35.5±2.3					
	200		0.7	89.6± 9.0	35.4± 6.0	346.7±15.8	35.4±5.3					
	400		0.7	87.9± 8.9	33.0± 7.2	326.9±21.5	33.0±3.6	NA	NA	NA	–	NA
Platycodi Radix	0	4.4		90.5± 5.7	47.5± 9.2	298.6±12.5	30.8±2.8					
	100		–0.1	89.1± 7.4		307.2±22.5	29.7±3.7					
	200		0.7	91.6± 4.6	38.9± 5.9	287.0±18.9	27.9±3.2					
	400		–0.5	95.1± 8.7	46.2± 7.9	283.9±20.9	29.8±2.5	NA	NA	NA	NA	NA
Pueraiae Radix	0	3.4		90.3± 6.5	42.5± 6.2	301.3±14.8	28.3±2.4					
	100		0.4	92.1± 9.3	39.7± 4.8	314.6±20.8	26.5±3.5					
	200		0.2	87.6± 9.8	46.8± 7.3	295.9±22.5	25.8±1.8					
	400		0.0	90.5±10.8	42.1± 9.7	295.3±30.2	24.8±3.2	NA	NA	NA	NA	NA
Scrophulariae Radix	0	5.3		87.8± 9.5	47.2± 8.3	298.9±11.6	26.9±2.2					
	100		–0.1	92.8± 6.6	50.6± 3.8	304.6±15.7	26.2±3.1					
	200		–0.8	95.9±10.2	55.9± 4.9	314.6±18.2	25.9±2.6					
	400		–0.4	97.6± 9.6	53.2± 9.6	328.5±11.5	26.9±1.6	NA	NA	NA	NA	NA
Silerius Radix	0	2.5		86.9±10.7	39.9±10.7	296.4±14.0	26.1±2.8					
	100		–0.7	91.6± 8.5	42.8± 6.3	315.4±22.7	27.7±4.2					
	200		0.1	90.6± 8.3	40.9± 8.1	288.7±12.7	27.8±3.7					
	400		0.2	86.9±11.8	46.6± 4.2	285.9±18.3	26.9±2.5	NA	NA	NA	NA	NA
Viticis Fructus	0	7.0		92.3± 6.9	42.0±5.9		27.2±2.0					
	100		–0.2	96.4± 8.6	48.9± 9.7							
	200		–0.1	98.3± 8.9	47.2± 3.2		28.9±2.1					
	400		–0.1	95.7±10.8	53.1± 7.2		26.1±2.6	NA	NA	–	NA	NA
Zizyphis Semen	0	4.2		85.3± 7.3	47.2± 6.5	308.5±23.8	33.2±3.6					
	100		0.9	90.6± 7.5	41.4± 3.3	289.2±18.5	34.3±5.0					
	200		0.5	89.3± 3.8	43.6± 6.8	315.3±26.3	36.2±4.5					
	400		0.3	92.7± 7.8	46.6± 5.8	318.6±26.2	35.4+4.9	NA	NA	NA	NA	NA

NA: Not significant

received a dose in a range of 100 mg/kg to 400 mg/kg once a day for five days. The differences of body weight (T–C), changes of serum enzyme activities and histo pathological examination were observed.

As the data shown in Table 2 and Fig. 1, most of herbal extracts revealed relatively mild toxicities; even no significant toxicity was noted at a dose level of 100/kg except *Ephedra Herba* extract.

Ephedra Herba among 21 herbal extracts showed most potent acute toxicity resulting in severe body weight loss with a dose of 100 mg/kg. Death of mice was caused by a higher dose ($>$ 300 mg/kg). A slight body weight loss and minute damages in liver, kidney and spleen were produced by the administration of *Agastachis Herba, Angelika koreanae Radix* and *Anthrisci Radix* extracts.

It is interesting to note our previous report in which *Angelica koreanae Radix* and Anthrisci Radix exhibited much more potent toxicity when their extract were prepared with organic solvents (ethanol extraction, then chloroform–water partition) (Chang, 1982, 1986).

In this regard, it is worthwhile to mention that most therapeutically effective and/or toxic natural constitutents are the second metabolites of the plant and they generally have a molecular weight of less than 1000 and so are more easily extractable by organic solvents rather than water. In this connection, it is suggested that water extracts of *Angelica koreanae Radix* and *Anthrisci Radix* may contain a small amount of toxic substances; consequently they showed very mild toxicity at high dose levels.

Cnidii Rhixoma, Lycii Fructur, Moutan Cortex Radix, Paeonia Radix and *Scrophulariae Radix* exhibited either slight loss of body weight or a minor changes of organ, but no significant alteration of serum enzyme activities was noted.

In considering the water extract preparation of traditional herbal drugs, we could observe no significant acute toxicity at a dose level of 100 mg/kg. Only *Ephedra Herba* exhibited severe acute toxicity at a dose of 100 mg/kg. However, the dose 100 mg/kg appears to be much higher (5–10 times) than ordinary human dose recommended by traditional practitioners (When we approximate the conversion of the animal dose, 100 mg/kg, to human dose as follows; 300 g (*Ephedra Herba* sample used) $\times$ 100 mg/kg (a dose) $\div$ 50.2 g (total yield of the extract) $\times$ 60 Kg (adult human body weight) $\fallingdotseq$ 36 g, this is much higher amount than for a single administration for human). Therefore, the results imply that the old traditional way of herbal drug preparation, that is, water decoction, appears to be a wisdom by which much of the toxic second metabolite constitutents are not dissolved out into water extract. However, these results should not exclude sub–chronic, chronic and systemic toxicity studies for further safety assessment of herbal drugs.

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