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The 100-Days Oral Toxicity of Tomato Pomace in Healthy Mice

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Abstract: Problem statement: Growing attention is being paid to functional food. The beneficial effect of functional food appears to relate to its bioactive ingredient such as substances containing antioxidant. Therefore, the information about the toxicity of the substances is very much essential to recommend the safety for the substances implication in both clinical and application trials. Herein, we have investigated for the possible sub-chronic toxicity of *Lycopersicon esculentum*, or commonly known as tomato (a source of antioxidants), was administered orally in the form of dried tomato pomace extract in healthy mice. **Approach:** Eighty mice (40 males and 40 females) were divided randomly into 4 groups. The first group was the control group and fed with equal volume of distilled water, while the other 3 groups were given a single daily dose of the dried tomato pomace per os at different doses (10, 100 and 500 mg kg^{-1} BW) for 100 days. **Results:** No toxicity was detected with reference to clinical signs, hematology and serum biochemistry data and organ weights. However, the female mice which received the dried tomato pomace at a dose of 10 mg kg^{-1} BW showed the reduction of body weight higher than that of the control treated group but female mice were treated with the extract at a dose of 500 mg kg^{-1} BW reversed these parameters significantly. **Conclusion:** This study indicates that tomato pomace consumption has no sub-acute adverse effects and the No-Observed-Adverse-Effect Level (NOAEL) doses in mice were 500 mg kg^{-1} BW. However, the reduction of body weight after the exact consumption needs further studies.

Key words: *Lycopersicon esculentum*, sub-chronic toxicity, tomato pomace, functional food, antioxidant

INTRODUCTION

To date, foods are no longer appreciated by consumers only in terms of its taste and immediate nutritional needs, but also in terms of its ability to provide specific health benefits. Functional foods became an important food sector promoting the health benefits and reduce the risk of chronic disease via functional ingredients in these products (Verschuren, 2002; Phachonpai *et al*., 2012; Abushita *et al*., 2000). Abundant evidence suggests that the beneficial effect of functional food appears to relate to its bioactive ingredient such as substances containing antioxidant (Raghuveer and Tandon, 2009).

Lycopersicon esculentum, commonly known as tomato, a plant in the family of Solanaceae, is a good source of antioxidants (Wang *et al*., 1996). It contains nutrients that prevent illness, e.g., by detoxification (Nguyen, 1999), promoting growth (Shi and Maguer, 2000) and proper immune system functioning (Sandhu *et al*., 2000). In addition, tomato also contains valuable phytochemicals, including carotenoids such as lycopene and beta-carotene (Canene-Adams *et al*., 2005). It had been reported that lycopene, waste product or tomato pomace obtained from food industry processing contained skin, pulp and crushed seeds of tomato. This tomato waste product still contains lycopene and beta-carotene (Sabio *et al*., 2003). Our previous studied reported that dried tomato pomace exhibited the cognitive enhancing effect in normal and cognitive impairment conditions (Thukhammee *et al*., 2012). Therefore, the development tomato pomace as functional food is very much interesting. However, little is known about its side effects when continuously administered via the oral route.

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This study was conducted in response to recent interest in the nutritional and health benefits of tomato pomace. Another driving force was research and development of functional foods from local crops aimed at the worldwide vegetable market. The objectives of this study were to investigate the general toxicity of tomato pomace administered in the diet for 100 days in healthy mice.

MATERIALS AND METHODS

Preparation of dried tomato pomace powder: Tomato pomace is consisting of tomato skins, pulp and crushed seeds that remain after the processing of tomatoes in juice. Wet tomato pomace was dried with oven at 50°C for 2 h. The %yield of tomato pomace is 12.75. The dried tomato pomace was grinded as a powder and determined both lycopene level and total phenolic compound and used as markers for quality control. It was found that the dried tomato pomace contained lycopene 160.94 mg/100 g sample while contained total phenolic compound 413.07±34.45 mg of Gallic acid equivalent/mg. The dried tomato pomace was kept in an airtight container at room temperature until use. The administration of dried tomato pomace was performed using distilled water as the vehicle.

Animals: Healthy 5 weeks old mice (40 males and 40 females) were obtained from National Laboratory Animal Center, Salaya, Nakorn Pathom. They were housed in groups of 5 per cage in standard metal cages at 2 ± 22°C on 12:12 h light-dark cycle. All animals were given access to food and water *ad libitum*. Experiments were performed to minimize animal suffering in accordance with the internationally accepted principles for laboratory use and care of the European Community (EEC directive of 1986; 86/609/EEC) and approved by the Ethical Committee of the Khon Kaen University.

Experimental design: All mice were randomly assigned to 4 groups (n = 10 in each group). The dried tomato pomace was administrated per os to mice of groups 2-4 in a single dose/day of 10, 100 and 500 mg kg^{-1} BW respectively by intragastric gavages using a feeding needle. The control treated group (group 1) received an equal volume of distilled water as the vehicle. All treatments lasted 100 days. All mice were observed daily for clinical signs and mortality. Body weight and food consumption were measured weekly.

Collection and analyses of blood: At the end of the experiment, all animals were sacrificed. Blood samples were collected by cardiac puncture into three sets of plain (no-additive), EDTA treated and sodium citrate tubes for hematology and serum biochemistry analyses. Hematological examinations included the following parameters: White Blood cell count (WBC), Red Blood Cell count (RBC), Hemoglobin concentration (Hb), Hematocrit (Ht), Platelet count (PLT), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH) and Mean Corpuscular Hemoglobin Concentration (MCHC). Serum biochemistry was performed to examine aspartate Aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline Phosphatase (ALP), Creatinine (CRN), Triglycerides (TG), Cholesterol (Cho), Total Bilirubin (T-Bil), Blood Urea Nitrogen (BUN) and Blood Sugar (BS). Analyses for hematology and serum biochemistry were conducted at the laboratory of Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand. At sacrifice, the lung, heart, liver, spleen, brain, kidneys, adrenals, ovaries, testes, thymus and salivary gland were excised and weighed.

Statistical analysis: The results were expressed as the mean value ± SEM. Statistical differences between groups were assessed using the SPSS software, version 16 and the Student's t-test was used to determine the difference between groups. A probability level less than 0.05 were accepted as significant.

RESULTS

In this study, the oral administrations of the dried tomato pomace at all dosages were given for 100 days did not produce any visible sign of sub-acute toxicity or instant death in mice tested during the period of observation.

Food consumption and body weight: Food consumption of animals in the treated groups and in the control group is shown in Table 1. There is no statistically significant difference between any groups. On the contrary, the female mice exposed to dried tomato pomace at a dose of 10 mg kg^{-1} BW intervention for 100 days showed the reduction of body weight higher than that of the control treated group ($p<0.01$) while the reduction of body weight in the extract at a dose of 500 mg kg^{-1} BW was significantly ($p<0.05$) lower than that of the control treated group (Table 1).

Organ weights: As shown in Table 2, the mean of each organ weights did not differ between the treated and the control groups.

Table 1: Effect of the dried tomato pomace on body weight and food consumption in mice

Sex	Group	Food consumption (g/day)	Initial weighs	Body weight (g) Final weight	Weight gain (%)
Male	Control	6.40 ± 0.90	39.13 ± 0.28	43.00 ± 0.51	9.89
	L. esculentum 10	6.10 ± 0.80	38.86 ± 0.27	41.33 ± 0.22	6.36
	L. esculentum 100	5.70 ± 0.90	39.57 ± 0.22	41.00 ± 0.18	3.61
	L. esculentum 500	6.50 ± 0.90	39.44 ± 0.12	42.45 ± 0.19	7.63
Female	Control	6.10 ± 0.50	33.30 ± 0.10	31.00 ± 0.21	-6.91
	L. esculentum 10	5.60 ± 0.80	33.88 ± 0.16	29.85 ± 0.18	-11.89**
	L. esculentum 100	5.90 ± 0.70	34.25 ± 0.14	32.00 ± 0.14	-6.57
	L. esculentum 500	5.90 ± 0.60	32.56 ± 0.15	31.40 ± 0.1	-3.56*

*: Values are statistically significant at $p<0.05$ when compared to control treated group; **: Values are statistically significant at $p<0.01$ when compared to control treated group

Table 2: Effect of the dried tomato pomace on organ weights in mice

Sex	Group	Heart (g kg^{-1} BW)	Lung (g kg^{-1} BW)	Liver (g kg^{-1} BW)	Spleen (g kg^{-1} BW)
Male	Control	4.65 ± 0.60	8.42 ± 0.27	55.50 ± 0.07	7.55 ± 0.63
	L. esculentum 10	4.78 ± 0.0	8.88 ± 0.48	54.12 ± 0.85	8.16 ± 0.24
	L. esculentum 100	5.05 ± 0.08	7.77 ± 0.12	53.53 ± 0.65	7.67 ± 0.12
	L. esculentum 500	4.74 ± 0.06	9.17 ± 0.25	49.53± 1.04	7.29 ± 0.20
Female	Control	5.14 ± 0.05	8.73 ± 0.09	52.57 ± 1.70	9.56 ± 0.50
	L. esculentum 10	4.78 ± 0.07	8.91 ± 0.62	49.31 ± 0.51	9.95 ± 0.25
	L. esculentum 100	4.92 ± 0.08	8.50 ± 0.11	49.89 ± 1.68	9.19 ± 0.36
	L. esculentum 500	4.97 ± 0.05	9.79 ± 0.59	50.52 ± 2.75	9.51 ± 0.37
		Brain (g kg^{-1} BW)	Ovary (g kg^{-1}BW)	Kidneys (g kg^{-1}BW)	Thymus (g kg^{-1} BW)
Male	Control	13.36 ± 0.31	-	8.24 ± 0.06	2.57 ± 0.40
	L. esculentum 10	14.09 ± 0.14	-	8.29 ± 0.21	2.50 ± 0.19
	L. esculentum 100	13.43 ± 0.19	-	8.45 ± 0.09	2.21 ± 0.05
	L. esculentum 500	14.54 ± 0.16	-	8.73 ± 0.13	1.74 ± 0.05
Female	Control	14.87 ± 0.15	3.42 ± 0.04	6.82 ± 0.09	2.36 ± 0.05
	L. esculentum 10	15.45 ± 0.10	3.20 ± 0.06	6.50 ± 0.09	2.68 ± 0.14
	L. esculentum 100	15.62 ± 0.34	3.27 ± 0.07	6.23 ± 0.12	2.85 ± 0.05
	L. esculentum 500	16.30 ± 0.16	3.52 ± 0.12	6.11 ± 0.08	2.89 ± 0.06
		Salivary gland (g kg^{-1} BW)	Adrenal gland (g kg^{-1}BW)	Testes (g kg^{-1}BW)	
Male	Control	1.57 ± 0.09	0.65 ± 0.06	3.79 ± 0.08	
	L. esculentum 10	1.60 ± 0.08	0.52 ± 0.02	3.57 ± 0.09	
	L. esculentum 100	1.56 ± 0.03	0.58 ± 0.03	3.82 ± 0.15	
	L. esculentum 500	1.44 ± 0.10	0.56 ± 0.02	3.98 ± 0.04	
Female	Control	0.56 ± 0.02	0.37 ± 0.01	-	
	L. esculentum 10	0.53 ± 0.06	0.38 ± 0.01	-	
	L. esculentum 100	0.58 ± 0.05	0.35 ± 0.01	-	
	L. esculentum 500	0.55 ± 0.05	0.38 ± 0.02	-	

Table 3: Effect of the dried tomato pomace on serum biochemical parameters of mice

Sex	Group	BS (mg/dL)	Chol (mg/dL)	TG (mg/dL)	BUN (mg/dL)
Male	Control	81.60 ± 1.89	64.40 ± 0.95	73.60 ± 1.76	21.61 ± 0.35
	L. esculentum 10	78.89 ± 1.20	65.22 ± 1.25	65.78 ± 1.02	22.26 ± 0.27
	L. esculentum 100	80.67 ± 0.70	63.33 ± 0.79	65.44 ± 1.49	20.71 ± 0.13
	L. esculentum 500	79.25 ± 0.75	63.00 ± 0.70	64.25 ± 1.73	20.06 ± 0.18
Female	Control	82.36 ± 1.35	61.18 ± 0.63	75.64 ± 1.88	22.67 ± 0.19
	L. esculentum 10	89.82 ± 0.83	61.09 ± 0.73	66.00 ± 1.23	23.09 ± 0.16
	L. esculentum 100	81.00 ± 0.48	59.27 ± 0.86	72.91 ± 1.07	23.64 ± 0.21
	L. esculentum 500	79.78 ± 0.67	60.67 ± 0.68	65.11 ± 0.86	23.44 ± 0.22
		CRN (mg/dl)	ALT (U/L)	AST (U/L)	ALP (U/L)
Male	Control	0.31 ± 0.00	37.70 ± 0.45	62.30 ± 1.41	48.70 ± 0.97
	L. esculentum 10	0.31 ± 0.01	38.11 ± 0.47	61.44 ± 1.00	47.67 ± 1.03
	L. esculentum 100	0.33 ± 0.01	38.31 ± 0.19	63.11 ± 0.71	46.89 ± 1.21
	L. esculentum 500	0.35 ± 0.01	39.88 ± 0.29	61.25 ± 1.35	45.38 ± 0.64
Female	Control	0.38 ± 0.01	44.00 ± 0.62	78.82 ± 1.35	40.73 ± 0.66
	L. esculentum 10	0.39 ± 0.01	43.18 ± 0.69	77.64 ± 1.07	41.06 ± 0.78
	L. esculentum 100	0.35 ± 0.01	39.09 ± 0.39	82.00 ± 0.76	41.18 ± 0.61
	L. esculentum 500	0.39 ± 0.01	45.11 ± 0.74	79.67 ± 1.75	41.56 ± 1.11
		T-Bil (mg/dL)			
Male	Control	0.11 ± 0.001			
	L. esculentum 10	0.09±0.001			
	L. esculentum 100	0.14 ± 0.001			
	L. esculentum 500	0.08 ± 0.001			
Female	Control	0.09 ± 0.001			
	L. esculentum 10	0.10 ± 0.001			
	L. esculentum 100	0.09 ± 0.001			
	L. esculentum 500	0.10 ± 0.010			

Table 4: Effect of the dried tomato pomace on blood hematology parameters of mice

Sex	Group	WBC ($\times 10^3$)	RBC ($\times 10^6$)	Hb (g/dL)	Hct (%)
Male	Control	5.32 ± 0.17	8.93 ± 0.16	13.29 ± 0.23	40.48 ± 0.59
	L. esculentum 10	5.32 ± 0.11	8.00 ± 0.17	12.18 ± 0.25	39.28 ± 0.49
	L. esculentum 100	5.42 ± 0.10	8.24 ± 0.15	12.06 ± 0.19	39.15 ± 0.48
	L. esculentum 500	5.11 ± 0.10	8.30 ± 0.19	12.39 ± 0.16	38.57 ± 0.49
Female	Control	5.99 ± 0.22	9.05 ± 0.10	12.83 ± 0.17	38.91 ± 0.45
	L. esculentum 10	4.54 ± 0.12	8.38 ± 0.25	12.83 ± 0.11	40.09 ± 0.35
	L. esculentum 100	4.44 ± 0.18	8.81 ± 0.17	11.59 ± 0.09	36.70 ± 0.30
	L. esculentum 500	5.19 ± 0.21	8.99 ± 0.19	12.26 ± 0.29	37.94 ± 0.81
		MCV (fL)	MCH (pg)	MCHC (pg/dL)	PLT (×103)
Male	Control	45.87 ± 0.53	14.93 ± 0.10	32.77 ± 0.21	16.21 ± 2.82
	L. esculentum 10	51.32 ± 1.22	15.33 ± 0.08	30.66 ± 0.39	16.94 ± 2.49
	L. esculentum 100	50.60 ± 1.00	15.31 ± 0.08	31.00 ± 0.27	16.71 ± 2.38
	L. esculentum 500	46.46 ± 0.29	14.93 ± 0.10	32.13 ± 0.03	16.67 ± 2.20
Female	Control	43.09 ± 0.36	14.16 ± 0.10	32.95 ± 0.15	15.26 ± 2.84
	L. esculentum 10	47.77 ± 0.20	15.29 ± 0.05	32.01 ± 0.09	15.84 ± 2.59
	L. esculentum 100	47.23 ± 0.40	14.86 ± 0.06	31.68 ± 0.20	15.30 ± 2.81
	L. esculentum 500	46.49 ± 0.15	15.33 ± 0.04	33.04 ± 0.14	15.27 ± 2.92

Hematological and the serum biochemical parameters: The serum biochemistry and blood hematology results for the mice are presented in Table 3 and 4 respectively. There is a tendency to decrease in ALP and TG was seen in a dose related manner in males. However, all values were within the normal physiological range. A comparison of hematological parameters indicated no significant difference between controls and the extract treated group.

DISCUSSION

Despite the widespread consumption, few scientific studies have been undertaken to ascertain the safety and efficacy of dried tomato pomace. The present investigation demonstrates that the dried tomato pomace powder is non toxic via the oral route in mice. In this study, no mortality and symptoms of pronounced behavior were noted after oral administration of the extract in mice. This finding is in accordance with the previous report of dried tomato pomace effect in rats (Thukhammee *et al*., 2012). However, the dose of the extract, the species of animals and the duration of treatment of the plant extract were different.

In the sub-chronic oral toxicity study, tomato pomace at the oral doses of 10 mg kg^{-1} BW produced significant reductions in the pattern of body weight gain higher than that of the control treated group. A reduction in body weight gain is simple but strong and sensitive indices of toxicity after exposure to toxic substances (Teo *et al*., 2002). Cumulative evidences reported that red and green tomato contains glycoalkaloids, is a natural toxin substance could reduce body weight gain in hamsters (Friedman and Levin, 1995; Friedman *et al*., 2000). On the contrary, the female mice which received the extract of dried tomato pomace at a dose of 500 mg kg^{-1} BW significantly decreased of body weight lower than that of control treated group. One possible explanation for this phenomenon may be due to the dried tomato pomace powder used in this study was the crude extract; therefore, increasing the dose of the extract might also increase the concentration of some ingredients which masked the effect of the active ingredients (glycoalkaloids). However, this study did not investigate about the possible active ingredients, gender differences and the precise underlying mechanisms of this extract on body weight gain; this is planned in future studies.

Measurement of the activities of 'marker' enzymes in tissues and body fluids can be used in assessing the degree of assault and the toxicity of a chemical compound on organs/tissues (Malomo, 2000; Akanji *et al*., 2008).

Alkaline Phosphatase (ALP) is generally considered as sensitive markers of liver function and their concentrations are increased in the serum because of their cytoplasmic nature and are thus released in blood by changing in the permeability of hepatocyte membranes. The primary importance of measuring ALP is to check the possibility of bone disease or liver disease. Since the mucosal cells that line the bile system of the liver are the source of the ALP, the free flow of bile through the liver and down into the biliary tract and gallbladder are responsible for maintaining the proper level of this enzyme in the blood. When the liver, bile ducts or gallbladder system are not functioning properly or are blocked, this enzyme is not excreted through the bile and ALP is released into the blood stream. Thus the serum ALP is a measure of the integrity of the hepato-biliary system and the flow of bile into the small intestine. Hepatic damage results in increased concentrations of serum Aspartate aminotransferase

(AST), alanine aminotransferase (ALT) and ALP (Nakanishi and Goto, 1975; Pastor *et al*., 1997). A tendency towards a decrease in ALP and Triglyceride (TG) were observed in the males. Therefore, the current results were in agreement with previous study which demonstrated the dried tomato powder consumption could reduce the Low-Density Lipoprotein (LDL) cholesterol and plasma triglyceride (Friedman *et al*., 2000). However, all values were within the normal physiological range.

To the best of our knowledge, this is the first report of the sub-acute effect of tomato pomace consumption and the reduction of body weight gain. At the present time, the precise underlying of this mechanism and active ingredient are yet to be verified and warrants further investigations.

CONCLUSION

The data of the present study do suggest that oral administration of dried tomato pomace for 100 days is not toxic and the No-Observed-Adverse Effect Level (NOAEL) for this extract to be 500 mg kg^{-1} BW under the conditions of the present study. Obviously, this work points to the need for additional studies to better define the roles of tomato consumption that may be responsible for the beneficial effects. No less challenging, but potentially beneficial for human health, would be an assessment whether the cited effects in mice parallel those in humans.

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