*J. Trop. Agric. and Fd. Sc. 35(2)(2007): 221–230*

# Effects of kacangma herb *(Leonurus sibiricus)* intake on blood chemistry, clinical pathology, body and organ weight changes in rabbit

[Kesan pengambilan herba kacangma *(Leonurus sibiricus)* pada kimia darah, patologi klinikal, serta perubahan berat badan dan organ arnab]

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Key words: *Leonurus sibiricus*, toxicity evaluation, blood chemistry, body and organ weight changes, *New Zealand White* rabbit

**Abstract**

The toxicity of Sarawak traditional herb, kacangma (*Leonurus sibiricus* L.) was evaluated through acute and subchronic studies on *New Zealand White* male and female rabbits. In the acute toxicity study, rabbits were given two dosages of kacangma i.e. 2.0 and 5.0 g/kg body weight. The rabbits were observed for any toxic signs and death for the first 24 h and continued up to 14 days. During the 14-day period, none of the animals died and no significant differences were observed in body weight gain, and food and water consumption. Subsequently the subchronic toxicity was studied for 90 days. The rabbits were fed kacangma at the rate of 0.5 (low dose), 5.0 (medium dose) and 25.0 (high dose) g/kg body weight. The control group received only the commercial pellet. The changes in body weight, organ relative weight, lipid profile, and clinical pathology on renal and liver function were observed. Some indications of renal and liver toxicities were evident in the medium and high dose groups when plasma creatinine and liver enzymes (alanine transaminase and alkaline phosphatase) concentrations were significantly different as compared to the control and low dose groups. In conclusion, kacangma herb had showed no signs of toxicity if consumed at the rate of 0.5 g/kg body weight (low dose) based on the 90-day subchronic study.

## Introduction

Substances that are intentionally added to food products should be studied to ensure they are safe for consumption. There are various internationally accepted standard approaches for the safety assessment of food products. Determination of the safe level of various food ingredients including medicinal and culinary herbs and spices, are based on a series of in vitro and in vivo studies in experimental animals (WHO 1987).

Many herbs have been used over the centuries and are generally considered mild and safe mainly due to their natural origin. However, a number of intoxication cases related with herbal products have raised the issue of their safety and triggered significant concerns among consumers, and also the

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scientific and regulatory communities (Schilter et al. 2003). Furthermore, it has been reported that prolonged period of traditional herb consumption such as ginkgo, St. John Wort, ginseng, echinaceae and ephedra was associated with toxic effects on kidney, liver, lung, cardiovascular and central nervous system (Alnaqeeb et al. 1996; Thomson et al. 1998; Kadiri et al. 1999; Haller and Benowitz 2000; Ernst 2002). Therefore, it is very important to understand the potential toxicity of medicinal plants besides their health benefits.

Kacangma (*Leonurus sibiricus* Linn.) is a popular traditional herb that has been consumed for decades by the people of Sarawak as a herbal medicine or culinary ingredient (Chai et al. 1989; Teo and Chua 2001). The role of kacangma as an underutilized herb with potential economic value has been recognized (MOA 1995; Paulus and Lau 2004). Subsequently, efforts are made to increase the utilization by developing kacangma herb into various special herbal products with commercial significance such as mechanical dried kacangma, canned chicken in kacangma herbal soup, paste, spread and confectionery jelly (Chua 2005).

However, there was not much assessment data on its side effect and toxicity that could verify the safe use of kacangma herb. Since safety is regarded as one of the three important aspects in herbal products besides quality and efficacy, the toxicity of kacangma herb was evaluated on *New Zealand White* male and female rabbits through acute and subchronic studies as substantial to the previous study on *Sprague Dawley* rats (Chua et al. 2006).

## Materials and methods

### *Preparation of formulated kacangma pellet*

Formulated kacangma pellet was prepared by mixing the dried kacangma powder at certain fixed ratios with a commercial rabbit pellet [Gold Coin Feedmills (M) Sdn. Bhd.]. Dried kacangma leaves were processed by drying the freshly harvested 2-month-old kacangma herb *(Plate 1)* at 45 °C in a force-air oven (Chua et al. 2006). Dried kacangma was added to the rabbit feed and water was used to bind the mixture. The homogenised paste-like mixture was then reformed into pellets of 0.5 g average weight before drying in the oven at 45 °C until final moisture content was below 6% (w/w). The formulated kacangma pellets were stored at chilled temperature in airtight containers to prevent mould growth. The ratio of dried herb calculated for each group was 0.5 (low dose), 5.0 (medium dose) and 25.0 (high dose) g/kg of animal body weight. Original rabbit feed and formulated pellets are as shown in *Plate 2*.

*Plate 1. Harvesting of kacangma herb (**Leonurus sibiricus** L.) at 2-month maturity*

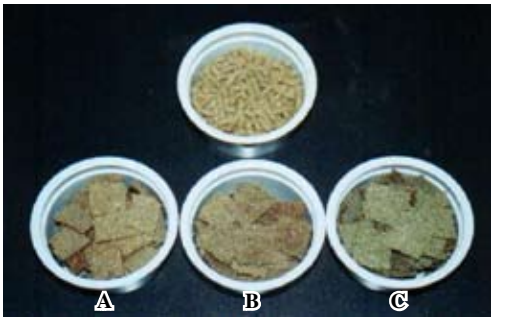


*Plate 2. Original rabbit feed (top) and formulated kacangma pellet with different contents of dried kacangma (below) (A) 0 .5, (B) 5.0 and (C) 25.0 g/kg body weight*

***Experimental animals***

A total of 40 *New Zealand White* rabbits (4 males and 4 females for acute oral toxicity, 16 males and 16 females for subchronic toxicity) each weighing 750 g (average) were quarantined for two weeks prior to initiation of the experiment. According to the guidelines for the toxicity investigation of herbal products using rabbits (non-rodent animals) as experimental animals, at least two animals per sex per group for acute oral toxicity test, and three animals per sex per group for long-term (subchronic and chronic) toxicity test should be used to be statistically validated (WHO 1993).

The rabbits were housed individually in elevated stainless steel cages and kept at temperature of 25 °C with a 12-h light/dark cycle. The rabbits were provided with formulated kacangma pellets and water *ad libitum* (free access for 24 h). Animal identification was via cages with colour-coded cards indicating the animal and treatment groups. All rabbits were climatized for a week before starting the study as stated in WHO (1993).

At the end of the experiment, all the rabbits were fasted overnight for at least 15 h and euthanasied with chloroform. The gross examination included the external surfaces, all orifices, all visceral organs, the cranial, thoracic, abdominal and pelvic cavities.

***Acute oral toxicity***

A single-dose acute oral toxicity (in-vivo limit dose test) as described by Greene (2000) was conducted on rabbits to evaluate the potential toxicity of high dose exposure of kacangma herb. The rabbits were divided into two groups (4 rabbits per group; 2 males and 2 females). Each group was fed with kacangma at the rate of 2 and 5 g/kg of body weight, respectively. Rabbits were then observed daily for mortality, signs of gross toxicity (such as fur loss, frequent urination, diarrhoea) and behavioural changes for the first 24 h until the 14th day.

***Subchronic toxicity***

In subchronic toxicity study, a 90-day repeat dose oral study was conducted to evaluate the potential toxicity of kacangma herb. A total of 32 rabbits (16 males and 16 females) were equally distributed into four groups (8 rabbits per group; 4 males and 4 females). Group A, B and C were fed formulated kacangma pellets each day with dried kacangma contents of 0.5 (low dose group), 5.0 (medium dose group) and 25.0 (high dose group) g/kg of body weight, respectively, for 90 days. Group D served as a control and was fed only commercial rabbit pellet. Individual food consumption and water intake were recorded weekly. Blood was collected in plain and EDTA coated vacuminated tubes from all rabbits at the end of the 90-day study prior to sacrifice. Blood was then evaluated for the clinical biochemistry analysis.

**Body weight** Body weights of all rabbits were recorded every 5 days during the experiment which included the initial and final stages of the experiment.

**Organ relative weight** At autopsy, the five main visceral organs viz. heart, kidneys, liver, lungs and pancreas were quickly excised of all excess tissues and fats, and weighed immediately after rinsing in 0.9% cold saline to remove any blood. The organ relative weight (% body weight) was obtained by dividing the final weight of organs to final body weight of the rabbit. Organ relative weight needs to be determined due to the fact that animal body weight will normally vary within group.

**Clinical biochemistry** 2.0 ml of blood was collected from each rabbit via intracardiac puncture. The blood was transferred into plain and EDTA coated vacuminated tubes and centrifuged at 3,000 rpm, 4 °C for 10 min to obtain the serum fraction. The serum was analysed for total protein, albumin, and enzyme activities: aspartate transaminase (AST),

alanine transaminase (ALT) and alkaline phosphatase (ALP). Cholesterol, high density lipoprotein (HDL) and triglycerides levels were analysed for lipid profile; while plasma creatinine and urea concentrations as indication for renal function test. All analyses were performed using the AGII Chemical Analyser (Landmark Scientific Inc., North Carolina, USA).

***Statistical analysis***

The significant differences between the control and kacangma herb-treated rabbits were determined using Analysis of Variance (ANOVA) at 5% level ($p$ <0.05) followed by Duncan Multiple Range Test (DMRT). All values are expressed as group mean ± standard error of mean (SEM).

## Results and discussion

***Acute oral toxicity***

Intake of dried kacangma herb did not induce any mortality even up to the highest dose, which was 5 g/kg body weight. All the treated rabbits also did not reveal any sign of gross toxicity, adverse pharmacological effect or abnormal behaviour throughout the observation period of 14 days. Under the conditions of this test, the acute oral toxicity dose of kacangma herb for rabbit was greater than 5 g/kg.

Acute oral toxicity in the form of limit dose test as used in this study was developed as replacement for the traditional median lethal dose test (classic $LD_{50}$) to reduce experiment time and cost as well as for humane reasons. It estimates whether the $LD_{50}$ is greater or less than a certain value i.e. the limit. According to the procedure, the limit dose test can conclude with as few as one animal, if the first animal dies; or involve as many as five animals, if survivals and deaths alternate (Rispin et al. 2002).

***Subchronic toxicity***

The 90-day repeat dose oral study was conducted with daily administration of formulated kacangma pellet. The lowest dose 0.5 g/kg body weight in this study was formulated based on the normal dose use of kacangma herb in human consumption, as well as the safe level of active constituents (alkaloid leonurine and stachydrine) in most *Leonurus* species as reported by Yeung et al. (1977) and Bradley (1992). Hence, dried kacangma at dose levels of 0.5, 5.0 and 25.0 g/kg body weight were selected for the study. Similar feed preparation method was used by Suhaila et al. (2001) in pegaga *(Centella asiatica)* efficacy test on rats.

**Body weight** All rabbits subjected to different kacangma administration showed an overall significant increase in body weight ($p$ <0.05) as compared to the initial stage *(Figure 1)*. This result was as expected because the rabbits were in growing stage. Average overall body weight indicated that the treated rabbits regardless of dose level were comparable to the controls. At final stage, high dose treated rabbits generally showed lower average body weight as compared to control rabbits but there was no significant difference. This treatment-related effect could be due to the presence of bitter substances in kacangma pellet that could have limited the food intake by this group of rabbits and it did not appear to be of toxicological significance. Increment in body weight is an important indication for health status of the experimental animals (Heywood 1983). Therefore, the result indicated a positive health status and no side effects observed in both treated and control rabbits.

**Organ relative weight** There was no significant difference ($p$ >0.05) in organ relative weight between male and female rabbits as well as for treated and control groups *(Table 1)*. This indicated that the organ relative weight was not affected by the administration of kacangma herb. Organ weight measurement is another important guide to assess general toxicity. In theory, changes in organ weight are indicator of toxicity since organ weight will be

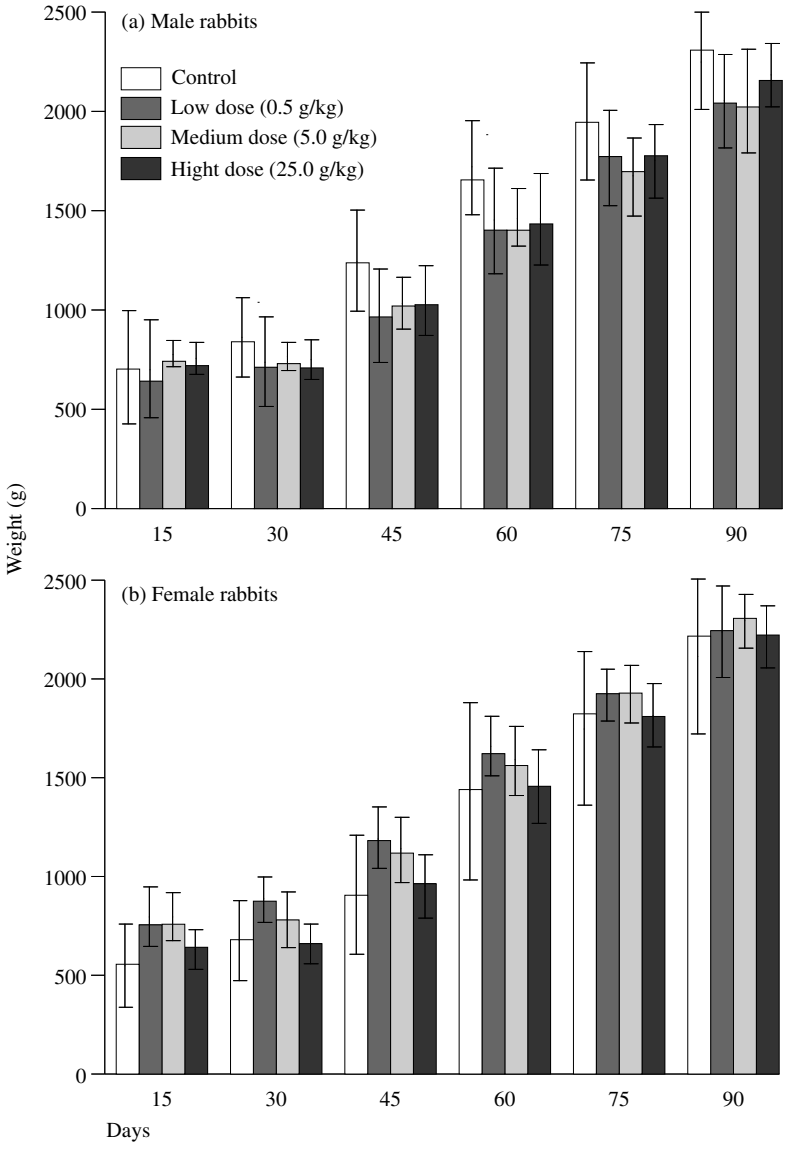


*Figure 1. Effect of kacangma on body weight of male rabbits and female rabbits*

affected by the suppression of body weight (Heywood 1983; Frank 1996).

**Clinical pathology** There were no mortalities, signs of gross toxicity and behavioural changes in all treated rabbits during subchronic toxicity study. No significant gross abnormalities (such as lesion, bleeding or enlargement of the visceral organs) were observed in the five main visceral organs.

**Effects of kacangma on renal function** Renal glomerular functions are assessable by measuring the plasma creatinine and urea concentrations (Moshi et al. 2001). Creatinine is a by-product from muscle as its concentration in blood will be affected by any changes in muscle mass. Whereas, urea is synthesized in the liver as the primary by-product of deamination of amino acids (Vaughn 1999). Both plasma creatinine and urea concentrations will be

Table 1. Effects of kacangma on organ relative weights in male and female rabbits (n = 4)

| | Control | | Low dose (0.5 g/kg) | | Medium dose (5.0 g/kg) | | High dose (25.0 g/kg) | |
|---|---|---|---|---|---|---|---|---|
| | Male | Female | Male | Female | Male | Female | Male | Female |
| Heart | | | | | | | | |
| Weight | 5.58 ± 0.45 | 4.95 ± 0.59 | 4.96 ± 1.57 | 5.17 ± 0.31 | 4.61 ± 1.14 | 5.46 ± 0.57 | 4.82 ± 0.85 | 4.85 ± 0.49 |
| % Body weight | 0.23 ± 0.01a | 0.22 ± 0.02a | 0.23 ± 0.05a | 0.22 ± 0.02a | 0.21 ± 0.04a | 0.22 ± 0.03a | 0.21 ± 0.04a | 0.21 ± 0.03a |
| Kidney | | | | | | | | |
| Weight | 11.11 ± 0.12 | 10.83 ± 1.87 | 10.75 ± 1.17 | 11.22 ± 1.65 | 11.15 ± 2.38 | 11.60 ± 1.47 | 11.23 ± 0.04 | 11.33 ± 0.50 |
| % Body weight | 0.47 ± 0.05a | 0.47 ± 0.01a | 0.50 ± 0.01a | 0.48 ± 0.02a | 0.51 ± 0.06a | 0.48 ± 0.05a | 0.48 ± 0.02a | 0.49 ± 0.03a |
| Liver | | | | | | | | |
| Weight | 40.55 ± 4.12 | 48.99 ± 6.67 | 39.20 ± 7.04 | 43.78 ± 3.30 | 45.27 ± 11.07 | 48.81 ± 7.15 | 45.64 ± 1.85 | 50.77 ± 9.47 |
| % Body weight | 1.96 ± 0.03a | 2.14 ± 0.11a | 1.82 ± 0.15a | 1.89 ± 0.14a | 2.07 ± 0.29a | 2.00 ± 0.24a | 1.94 ± 0.14a | 2.18 ± 0.37a |
| Lung | | | | | | | | |
| Weight | 11.68 ± 4.24 | 11.34 ± 2.01 | 12.60 ± 0.76 | 9.66 ± 2.15 | 10.46 ± 0.47 | 11.55 ± 2.62 | 10.19 ± 1.42 | 10.53 ± 1.08 |
| % Body weight | 0.48 ± 0.12a | 0.49 ± 0.02a | 0.49 ± 0.02a | 0.46 ± 0.09a | 0.49 ± 0.10a | 0.48 ± 0.11a | 0.41 ± 0.12a | 0.45 ± 0.06a |
| Pancreas | | | | | | | | |
| Weight | 0.72 ± 0.18 | 0.89 ± 0.40 | 1.01 ± 0.35 | 1.01 ± 0.22 | 0.89 ± 0.03 | 1.12 ± 0.13 | 0.99 ± 0.43 | 0.79 ± 0.17 |
| % Body weight | 0.03 ± 0.01a | 0.04 ± 0.01a | 0.05 ± 0.01a | 0.04 ± 0.01a | 0.03 ± 0.01a | 0.05 ± 0.01a | 0.04 ± 0.01a | 0.03 ± 0.01a |

*Mean values in the same row with the same letter are not significantly different ($p > 0.05$)

Table 2. Effects of kacangma feed on renal function (plasma creatinine and urea concentrations) in male and female rabbits (n = 4)

| | Control | | Low dose (0.5 g/kg) | | Medium dose (5.0 g/kg) | | High dose (25.0 g/kg) | |
|---|---|---|---|---|---|---|---|---|
| | Male | Female | Male | Female | Male | Female | Male | Female |
| Creatinine (mmol/litre) | 256.50 ± 70.50a | 240.67 ± 78.24a | 267.00 ± 66.25a | 263.50 ± 1.50a | 330.00 ± 129.38b | 318.33 ± 52.22b | 322.50 ± 48.50b | 304.75 ± 97.18b |
| Urea (mmol/litre) | 10.58 ± 1.42a | 9.89 ± 0.82a | 11.66 ± 1.50a | 10.33 ± 0.89a | 12.72 ± 0.90a | 11.83 ± 0.98a | 11.42 ± 0.09a | 10.62 ± 1.45a |

*Mean values in the same row with the same letter are not significantly different ($p > 0.05$)

increased in renal injuries. There were no significant differences in urea concentrations between all groups of rabbits *(Table 2)*. However, the creatinine concentrations were significantly higher ($p$ <0.05) in rabbits treated with medium and high doses of kacangma as compared to control and low dose treated rabbits. This indicates some injuries to the kidneys especially in the glomerular renal functions as a result of feeding with medium and high dose of kacangma to the rats. Similar results have been found in the previous study on toxicology evaluation of kacangma herb in *Sprague Dawley* rats (Chua et al. 2006). Since there was no significant gross abnormalities observed on kidneys of the rabbits from these groups, further microscopic histopathological examination needs to be carried out to verify the toxicity effects of kacangma herb.

**Effects of kacangma on plasma lipid profile** There were no significant differences ($p$ >0.05) in cholesterol, HDL and triglycerides levels for all the groups of rabbits *(Table 3)*. This indicates that the plasma lipid profile was not affected by the consumption of kacangma in all rabbits.

**Effects of kacangma on liver function** Concentration of total bilirubin, protein, albumin, globulin and AST were not affected by the administration of kacangma in all rabbits *(Table 4)*. This may indicate that synthesis of protein in rabbit's liver was not influenced by the administraton of kacangma. However, the ALT level was significantly higher in medium and high dose groups when compared to the control and the low dose groups. On the other hand, there was a significant decrease ($p$ <0.05) in ALP levels in the medium and the high dose groups. Alteration in ALT and ALP are indicator of liver affection in small mammals (Cornelius 1989) and this may indicate the liver toxicity in the medium and high dose groups. Toxicology evaluation of kacangma in *Sprague Dawley* rats showed

Table 3. Effects of kacangma feed on plasma lipid profile (cholesterol, HDL & triglycerides) in male and female rabbits (n = 4)

| | Control | | Low dose (0.5 g/kg) | | Medium dose (5.0 g/kg) | | High dose (25.0 g/kg) | |
|---|---|---|---|---|---|---|---|---|
| | Male | Female | Male | Female | Male | Female | Male | Female |
| Cholesterol (mmol/litre) | 2.80 ± 0.05a | 2.96 ± 0.46a | 2.58 ± 0.11a | 2.73 ± 0.37a | 3.06 ± 0.92a | 2.69 ± 0.67a | 3.05 ± 1.02a | 3.07 ± 1.12a |
| HDL (mmol/litre) | 1.14 ± 0.13a | 1.20 ± 0.04a | 1.24 ± 0.29a | 1.33 ± 0.05a | 1.26 ± 0.29a | 1.10 ± 0.16a | 1.19 ± 0.03a | 1.28 ± 0.39a |
| Triglycerides (mmol/litre) | 0.68 ± 0.06a | 0.70 ± 0.02a | 0.78 ± 0.10a | 0.69 ± 0.05a | 0.73 ± 0.27a | 0.65 ± 0.08a | 0.68 ± 0.15a | 0.77 ± 0.46a |

*Mean values in the same row with the same letter are not significantly different ($p$ >0.05)

Table 4. Effects of kacangma feed on liver function (serum chemistry and enzymes activities) in male and female rabbits (n = 4)

| | Control | | Low dose (0.5 g/kg) | | Medium dose (5 g/kg) | | High dose (25 g/kg) | |
|---|---|---|---|---|---|---|---|---|
| | Male | Female | Male | Female | Male | Female | Male | Female |
| Total bilirubin (mmol/litre) | 4.28 ± 0.86a | 3.76 ± 0.76a | 3.42 ± 1.15a | 3.42 ± 0.54a | 3.99 ± 0.81a | 3.42 ± 1.39a | 5.13 ± 1.71a | 3.99 ± 1.40a |
| Protein (g/dl) | 6.80 ± 0.60a | 6.57 ± 0.49a | 7.65 ± 0.05a | 6.90 ± 0.36a | 7.03 ± 0.56a | 6.90 ± 0.94a | 6.35 ± 1.15a | 6.23 ± 0.38a |
| Albumin (g/dl) | 4.25 ± 0.35a | 3.97 ± 0.29a | 4.38 ± 0.25a | 4.23 ± 0.17a | 4.40 ± 0.14a | 4.20 ± 0.14a | 3.30 ± 1.20a | 3.90 ± 0.16a |
| Globulin (g/dl) | 2.55 ± 0.25a | 2.07 ± 0.09a | 3.05 ± 0.05a | 2.67 ± 0.33a | 2.63 ± 0.61a | 2.37 ± 0.37a | 3.05 ± 0.05a | 2.33 ± 0.43a |
| A/G Ratio | 1.67 ± 0.03a | 1.92 ± 0.08a | 1.51 ± 0.03a | 1.61 ± 0.22a | 1.76 ± 0.38a | 1.81 ± 0.25a | 1.09 ± 0.41a | 1.76 ± 0.44a |
| Aspartate transaminase AST (u/litre) | 58 ± 11.00a | 48.67 ± 7.32a | 93 ± 22.00a | 51 ± 2.16a | 70 ± 11.58a | 56.33 ± 6.13a | 72.5 ± 13.50a | 64.75 ± 5.12a |
| Alanine transaminase ALT (u/litre) | 64.33 ± 8.96a | 58.67 ± 12.68a | 63 ± 17.22a | 62.67 ± 4.92a | 80.17 ± 30.79b | 80.5 ± 1.50b | 83 ± 9.00b | 78.8 ± 12.83b |
| Alkaline phosphatase ALP (u/litre) | 179.5 ± 47.50a | 201 ± 37.26a | 186.17 ± 24.51a | 180.5 ± 125.66a | 165.33 ± 20.50b | 164.75 ± 20.53b | 165.6 ± 47.06b | 161 ± 20.00b |

*Mean values in the same row with the same letter are not significantly different ($p > 0.05$)

similar results (Chua et al. 2006). However, results obtained from ALT and ALP will not be accurate enough to confirm the toxicity of kacangma since no significant gross abnormalities were observed on the livers of the rabbits from these groups. Further study on histopathology needs to be carried out to verify these hepatotoxicity effects of kacangma herb.

## Conclusion

Kacangma showed no noticeable gross toxicity in acute oral test, indicating that even at high dose, it did not cause death in the rabbits. There were no mortalities, signs of gross toxicity and behavioural changes in all treated rabbits during the subchronic toxicity study. No significant differences in plasma lipid profile for all the groups of rabbits. Minor treatment-related effects were observed for body weights, but these did not appear to be of toxicological significance. Some indications of renal and liver toxicities were evident in the medium and high dose groups when plasma creatinine and liver enzymes concentrations were significantly different as compared to the control and low dose groups. In conclusion, kacangma herb showed no signs of toxicity if consumed at 0.5 g/kg body weight (low dose) based on the 90-day subchronic study in rabbits.

## Acknowledgement

This study was funded by IRPA (Research grant No. 03-03-03-064 EA 001). Thanks are due to the support given by the staff of the MARDI Kuching, Sarawak.

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**Abstrak**

Ketoksikan herba ubatan tradisional Sarawak, kacangma *(Leonurus sibiricus* L.) telah dinilai melalui kajian akut dan subkronik terhadap arnab *New Zealand White*. Dalam ujian ketoksikan akut, arnab telah diberi makan dua dos kacangma iaitu 2.0 dan 5.0 g/kg berat badan. Pelbagai tanda ketoksikan dan kematian arnab dalam masa 24 jam sehingga 14 hari diperhatikan. Dalam tempoh 14 hari, tiada kematian dan tiada perbezaan bererti diperhatikan pada berat badan, pengambilan makanan dan air. Berikutan ini, kajian subkronik dikaji selama 90 hari. Arnab diberikan makanan yang mengandungi kacangma pada kadar 0.5 (dos rendah), 5.0 (dos sederhana) dan 25.0 (dos tinggi) g/kg berat badan. Arnab kawalan hanya diberi pelet komersial. Haiwan ini diperhatikan dari segi perubahan berat badan, berat organ relatif, profil lipid, dan patologi klinikal pada fungsi ginjal serta hati. Sedikit petanda ketoksikan telah dikesan pada ginjal dan hati pada kumpulan dos sederhana dan dos tinggi apabila aras kreatinin plasma dan pelbagai enzim hepar (alanin transaminase dan alkalin fosfatase) didapati berbeza secara bererti berbanding dengan kumpulan dos rendah dan kumpulan kawalan. Sebagai kesimpulan, herba kacangma tidak menunjukkan kesan ketoksikan apabila diambil pada aras 0.5 g/kg berat badan (dos rendah) berdasarkan kajian subkronik selama 90 hari.

*Accepted for publication on 28 August 2007*