Extramedullary Hematopoiesis in Rat Spleen after Exposure to High Doses of *Alpha*-Mangostin

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Background: *The pericarp extract of mangosteen (Garicinia mangostana) Linn, alpha-mangostin, is known to have beneficial effects on the body which includes anti-inflammatory, as well as anti-diabetic properties. Extramedullary hematopoiesis is the process whereby blood cellular components are formed outside the bone marrow under stressful conditions.*
Objective: *To evaluate the effects of subacute toxicity induced by alpha-mangostin in rat spleen.*
Material and Method: *A total of 40 Wistar rats were used to study histopathological changes in the spleen after being exposed to alpha-mangostin for one month. The rats were equally divided into four groups: treated male (n = 10); treated female (n = 10); control male (n = 10); and control female (n = 10). The treated group received alpha-mangostin pericarp extract diluted in 0.1% carboxymethylcellulose (0.1% CMC) in a concentration of 100 mg/5 ml, and 100 mg/kg/day alpha-mangostin was introduced to the rats via intra-peritoneal injection. The control group received 0.1% CMC five days per week for one month as standard treatment. Splenic tissues were collected at the end of the study period. Paraffin sections were examined by H&E and immunohistochemical stainings. Body weight was measured before and after the intervention for all groups.*
Results: *After exposure to alpha-mangostin, the treated groups showed increased platelet formation, myeloid progenitor cells, and megakaryocyte in the spleen as well as decrease in the body weight of male rats when compared to the control groups. Immunohistochemical study confirmed that the newly formed blood cells were from myeloid and erythroid precursor cells.*
Conclusion: *Exposure to high dose of alpha-mangostin marked the presence of extramedullary hematopoiesis which is the formation of blood cellular components outside the bone marrow.*

Keywords: *Extramedullary hematopoiesis, Alpha-mangostin, Spleen, Subacute toxicity*

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The spleen is the site for lymphocyte recirculation which includes the removal and filtration of aged red blood cells, circulating bacteria and particles away from the blood circulation[1]. The spleen also produces antibodies to function as a line of defense against blood-borne bacteria and phagocytose opsonized particles[2]. Containing hematopoietic and lymphoid elements, the spleen is the main site of extramedullary hematopoiesis (EMH)[3]. EMH is the process whereby the body tries to maintain red blood cell production in response to changes in the regular activity of erythropoiesis[4]. It is the increase in hematopoietic cell numbers above the normal background marked by formation of blood cellular components outside the bone marrow; this includes the presence of erythroid precursors, myeloid precursors, megakaryocytes or concoction of three cell types in the splenic red pulp. Any disruption to the regular hematopoiesis including systemic anemia, hematotoxic insult and infection can lead to the formation of blood cellular components outside the bone marrow[1]. EMH is considered as an epiphenomenon meaning that the process occurs secondary or as an accessory to underlying primary disease. Moreover, EMH in animals displays very minimal clinical signs which make it very difficult to diagnose[3].

Natural extracts from plants and fruits containing biologically active compounds, are currently used as the fundamental ingredients in developing new lead chemicals for pharmaceuticals[5,6]. Mangosteen (*Garicinia mangostana*) Linn is a fruit commonly grown in the Southeast Asia region such as Thailand, Malaysia, and Philippines. Unique and delectable,

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mangosteen has been named "the queen of fruits" marked by its tropical flavor[7]. The pericarps of mangosteen have been used to treat sickness such as abdominal pain, dysentery, skin infection and wounds as a form of traditional medicine[8]. In the recent years, the xanthones contained within the pericarps of the fruit had been isolated; including alpha-mangostin. Studies both *in vivo* and *in vitro* revealed a wide range of biological properties of this compound in anti-inflammatory, anticancer and antibacterial aspects[6,9].

However, the adverse effects of alpha-mangostin have not yet been investigated extensively. A study revealed toxicological properties of alpha-mangostin induced by oral administration in animals when compared to the control group; there were no hematological abnormalities or histopathological lesions found in the visceral organs in the experimental group[10]. Nonetheless, there were cases reported increasing aspartate aminotransferase (AST), alanine transaminase (ALT) and blood urea nitrogen (BUN), creatinine (Cr) levels which indicates impaired liver and kidney functions after administration of alpha-mangostin[10].

Current studies on the effects of chronic toxicity of alpha-mangostin on rats exhibited little acute adverse effects. None of the subjects from either treated or control groups were found to be dehydrated, overly stressed, or unresponsive. Moreover, the survival rates for both groups were 100 percent and that there was no change in the body weight[11]. However, it has been reported that increasing levels of AST and ALT were directly proportional to increasing concentration of alpha-mangostin[12]. Moreover, when compared to rats treated with paracetamol whose amount of total hepatic protein decreased significantly, those treated with alpha-mangostin did not change[13]. Nonetheless, another finding conducted a chronic toxicity study of alpha-mangostin pericarp extract *in vivo*, using varying concentrations from 10 to 1,000 mg/kg/day for six months[10]. Results showed no significant histopathological lesions in any of the visceral organs, however, there was a significant decrease in the body weight of rats that have been treated with 1,000 mg/kg/day alpha-mangostin in both sexes as well as lower glucose levels in comparison to their corresponding control groups. The alpha-mangostin pericarps extract has recently and increasingly become recognized by various research fields. The present study aims to identify the effects of subacute toxicity induced by exposure to high dose of alpha-mangostin with emphasis on histopathological changes in rat spleen.

Material and Method

Animals

All animals were obtained at six weeks of age from the Animal Center, Mahidol University, Thailand. The study was performed in accordance to the Thai guidelines for the handling of experimental animals and was approved by the Animal Ethics Committee of the Faculty of Medicine, Srinakharinwirot University under license No. 2/2558. The rats received the standard rat chow and necessary hydration. In a total of forty individuals, the rats were equally divided into 4 major groups of varying treatment conditions: male control, female control, treated male and treated female. Preliminary subacute toxicity study showed that alpha-mangostin at 200 mg/kg/day induced all animal death within 2 days after intraperitoneal administration. Hence this study has chosen to decrease the concentration of the substance to be at 100 mg/kg/day in order to demonstrate the effects of high doses of the substance. Prior injection of the substance into the body cavity of animals, alpha-mangostin pericarp extract was diluted in 0.1% carboxymethylcellulose (0.1% CMC) in a concentration of 100 mg/5 ml. The treatment group received alpha-mangostin pericarp extract 100 mg/5 ml/kg via intraperitoneal injection into the body cavity five days per week for a month. The substance was given from Monday to Friday consecutively during the experimental period. After four weeks of treatment, the rats were sacrificed via immediate decapitation under an O_2/CO_2 gas inhalation, the spleen was then removed from the abdominal cavity. Body weight changes of pre-and post-treatments of all animal groups were recorded. 96% of purified alpha-mangostin, extracted using ethyl alcohol and assessed by HPLC, was obtained from Associate Professor Primchanien Mongkarndi, Faculty of Pharmacy, Mahidol University, Thailand[14].

Tissue fixation and processing

Splenic tissues were fixed with 4% formaldehyde solution and dehydrated with ascending graded series of ethanol concentrations. Samples were embedded in paraffin, sectioned into thicknesses between 5 to 7 μm and transferred onto poly-L-lysine coated slides which were then left dried overnight in an oven with a temperature of 40°C.

Histological techniques

Tissue sections on poly-L-lysine coated slides were deparaffinized and hydrated with decreasing graded ethanol series, stained with hematoxylin and

eosin and mounted in Enthallan. Then, immunohistochemical staining technique was used to confirm whether the series of newly formed blood cells derived from the myeloid or erythroid series and the bone marrow was used as a positive control. Four main antibodies were purchased from BioLegend in San Diego, California and the four antibodies were subsequently used to distinguish cell lines. Antibodies to myeloperoxidase at ratio of 1: 500 (for myeloid series detection), CD61 at ratio 1: 100 (for megakaryocytes or platelets marker), and glycophorin A and C at ratio of 1: 100 (for erythroid series evaluation) were used. The procedure for immunoperoxidase staining then was performed later. This included an overnight incubation of HRP-conjugated primary antibody at 4°C, the specimens were then washed with PBS for three cycles of 5 minutes. Peroxidase substrate and chromogen mixture compose of hydrogen peroxide and DAB were combined in 0.1M Tris-HCl until the desired stain intensity appeared, sections were then deionized in water. The immuno-stained slides then undergone histopathological analysis by the pathologists at Department of Pathology, Faculty of Medicine, Srinakharinwirot University and results were classified according to the histopathological severity of the findings; mild (+1), moderate (+2) and severe (+3). In cases where there was very little damage including presence in small number of inflammatory cells observed on the tissue sample, it would be categorized as "Few", and if any foreign matter was observed in spleen its histopathological value was classified as "Presence" or "P". However, if there was no morphological change in the tissues, it was graded as "Unremarkable" or "UR".

Statistical analysis

The mean body weights of each gender were expressed as means $\pm$ SEM and statistical comparisons between the control and treated group were made by using student's paired t-test. The level of significance was set at $p<0.01$.

Results

Body weight changes

After intra-peritoneal injection of 100 mg/kg/day alpha-mangostin 5 days/week for 4 consecutive weeks, there was a statistically significant decrease in the growth of the body weight in male rats when compared to the male control group (Fig. 1). To the contrary in female rats: the growth of the body weight after treatment significantly increased when compared to the female control group (Fig. 2).

Controls

The normal histology of the spleen under controlled conditions was well-integrated (Fig. 3A), which consisted of mild sinusoidal congestion which could be found as a normal component of the spleen, lymphocyte accumulation around the red pulp, moreover, the marginal zone was prominent and easily identified (Fig. 3B). As for the stained section of control male splenic tissue, it exhibited mild extramedullary hematopoiesis marked by the presence of few scattering megakaryocytes (Figs. 4A, 4B). This was also consistent with histopathological analysis as mentioned in Table 1 and 2.

Little extramedullary hematopoiesis from subacute toxicity of alpha-mangostin could be observed in the spleens of the control groups of both male and female; in male control group 80% (8/10) experienced mild hematopoiesis, while 10% (1/10) experienced few hematopoiesis. Similarly, 70% (7/10) of female controls experienced very little extramedullary hematopoiesis.

Treatment with alpha-mangostin

At low magnification (Fig. 5A) splenic white pulp of the treated rats in both male and female groups appeared to be disintegrated when compared to the round shaped white pulp of the control group.

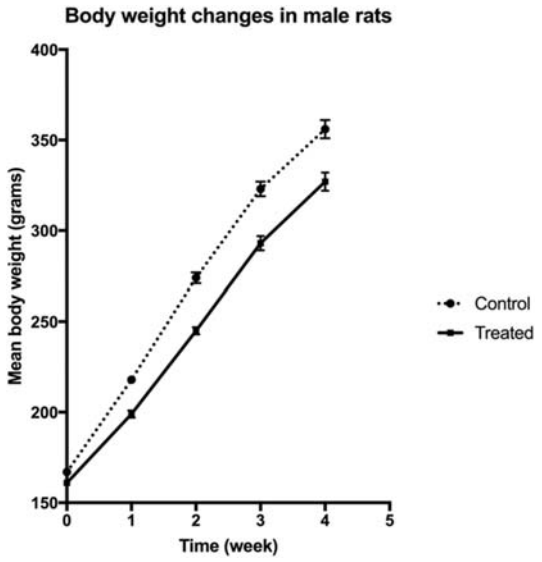

Fig. 1 Mean body weight changes after intraperitoneal administration with 100 mg/kg/day of alpha-mangostin in male rats for four weeks of treatment. Compared to control group at given period of time * ($p<0.01$).

Furthermore, the marginal zone was less distinct and there was an increased in the red pulp (Figs. 5B, 5C). Presence of inflammatory neutrophils suggested that there had been an injury to the red pulp of splenic tissue. Myeloid progenitor cells, markers for new white blood cells, were found in the splenic tissue (Fig. 6B). Regardless of gender, results from the spleen of the treated female group were also found in male splenic tissue stained with H&E (Figs. 7A, 7B). Platelet formation could be observed which marked the undergoing process of extramedullary hematopoiesis. The most distinct structure that was easily observed in all treated tissues was megakaryocytes. High occurrence of extramedullary hematopoiesis was found in all treated female rats (10/10). Furthermore, little sinusoidal congestion was also found in all members of the treated group (10/10). Same results were observed in male rats of the treated group.

Immunohistochemical staining confirmed that after treated with 100 mg/kg/day alpha-mangostin the newly formed cells in the rat spleens expressed both glycophorin A (Fig. 8B) and glycophorin C (Fig. 8D) indicating that the stained cells were from erythroid series. Furthermore, positive MPO staining (Fig. 9B) showed in the splenic tissues, meaning that the cells belonged to myeloid series. Lastly, CD61 antibody (Fig. 9D) was also tested as a positive marker for megakaryocytes and platelets, which was detected in the splenic tissue of the treated group. The presence of these cells indicated extramedullary hematopoiesis in the spleen.

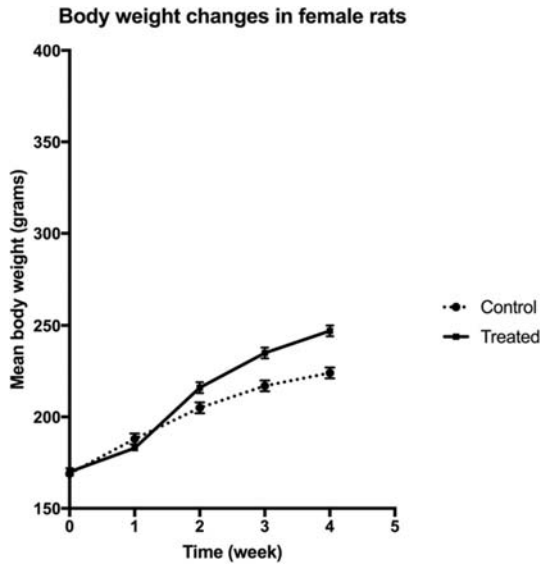

Fig. 2 Mean body weight changes after intraperitoneal administration with 100 mg/kg/day of alpha-mangostin in female rats for four weeks of treatment. Compared to control group at given period of time *(p<0.01).

Discussion

Results obtained from this study indicated that the spleen was the organ affected by alpha-mangostin via intra-peritoneal injection. Marked increase of erythroid cells and myeloid cells in the red pulp, it revealed that the histological morphology of the treated group of this study was consistent with other experiments that claimed the presence of extramedullary hematopoiesis in the spleen[15,16]. Hence, mature rat spleen can reverse the hematopoietic function after exposure to high dose of alpha-mangostin. Although some degree of extramedullary hematopoiesis was observed as a normal component of the splenic red pulp of rodents, mature rat spleen would not perform such function[1]. Extramedullary

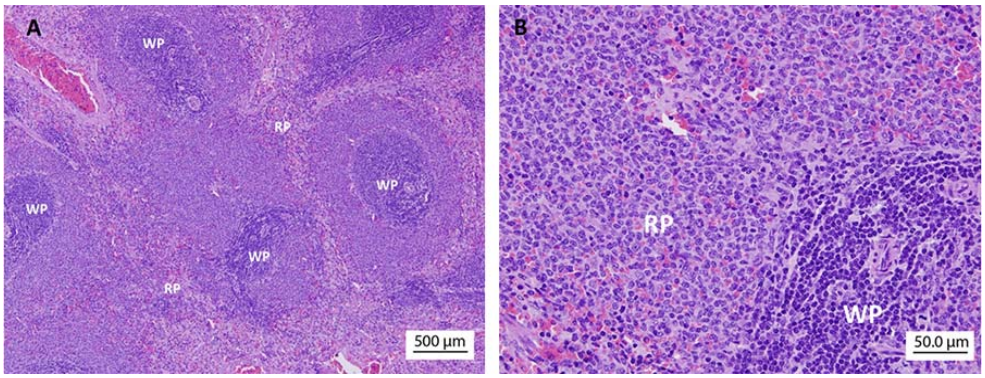

Fig. 3 Female control spleens undergone H&E staining from the control group. A) 100x magnification, B) 400x magnification. WP = white pulp, RP = red pulp.

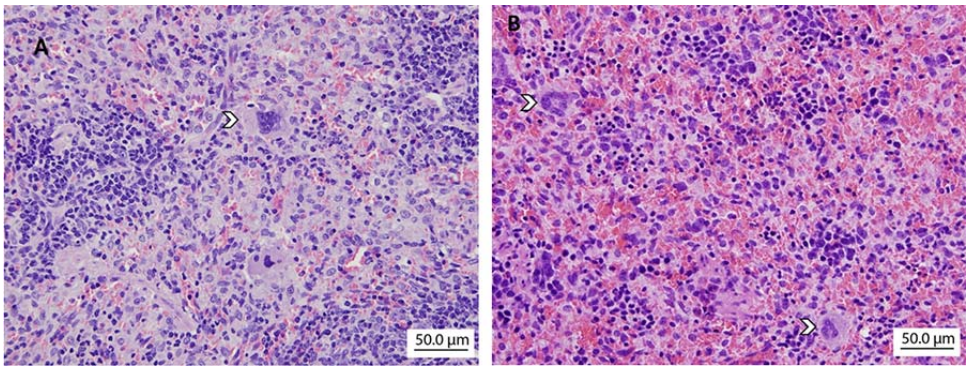

Fig. 4 A-B) Male control spleen executed with H&E staining, 400x magnification.

Table 1. Histopathological analysis of female rat splenic tissues

No.	Control Female – 0.1% CMC 5 mg/kg/day	Treated Female – alpha-mangostin 100 mg/kg/day
1	Extramedullary hematopoiesis (2+) Sinus congestion (2+)	Extramedullary hematopoiesis (3+) Sinus congestion (1+)
2	Extramedullary hematopoiesis (Few) Sinus congestion (1+)	Extramedullary hematopoiesis (3+) Sinus congestion (1+)
3	Extramedullary hematopoiesis (Few) Sinus congestion (1+)	Extramedullary hematopoiesis (3+) Sinus congestion (1+)
4	Extramedullary hematopoiesis (Few) Sinus congestion (2+)	Extramedullary hematopoiesis (3+) Sinus congestion (1+)
5	Extramedullary hematopoiesis (Few) Sinus congestion (2+)	Extramedullary hematopoiesis (3+) Sinus congestion (1+)
6	Extramedullary hematopoiesis (Few) Sinus congestion (1+)	Extramedullary hematopoiesis (3+) Sinus congestion (1+)
7	Extramedullary hematopoiesis (1+) Sinus congestion (1+)	Extramedullary hematopoiesis (3+) Sinus congestion (1+)
8	Extramedullary hematopoiesis (1+) Sinus congestion (1+)	Extramedullary hematopoiesis (3+) Sinus congestion (1+)
9	Extramedullary hematopoiesis (Few) Sinus congestion (1+)	Extramedullary hematopoiesis (3+) Sinus congestion (1+)
10	Extramedullary hematopoiesis (Few) Sinus congestion (1+)	Extramedullary hematopoiesis (3+) Sinus congestion (1+)

Table 2. Histopathological analysis of male rat splenic tissues

No.	Control Male – 0.1% CMC 5 mg/kg/day	Treated Male – alpha-mangostin 100 mg/kg/day
1	Extramedullary hematopoiesis (2+) Sinus congestion (1+)	Extramedullary hematopoiesis (3+) Sinus congestion (1+)
2	Extramedullary hematopoiesis (Few) Sinus congestion (2+)	Extramedullary hematopoiesis (3+) Sinus congestion (1+)
3	Extramedullary hematopoiesis (1+) Sinus congestion (2+)	Extramedullary hematopoiesis (3+) Sinus congestion (1+)
4	Extramedullary hematopoiesis (1+) Sinus congestion (1+)	Extramedullary hematopoiesis (3+) Sinus congestion (1+)
5	Extramedullary hematopoiesis (1+) Sinus congestion (1+)	Extramedullary hematopoiesis (3+) Sinus congestion (1+)
6	Extramedullary hematopoiesis (1+) Sinus congestion (1+)	Extramedullary hematopoiesis (3+) Sinus congestion (1+)
7	Extramedullary hematopoiesis (1+) Sinus congestion (1+)	Extramedullary hematopoiesis (3+) Sinus congestion (1+)
8	Extramedullary hematopoiesis (1+) Sinus congestion (1+)	Extramedullary hematopoiesis (3+) Sinus congestion (1+)
9	Extramedullary hematopoiesis (1+) Sinus congestion (1+)	Extramedullary hematopoiesis (3+) Sinus congestion (1+)
10	Extramedullary hematopoiesis (1+) Sinus congestion (1+)	Extramedullary hematopoiesis (3+) Sinus congestion (1+)

hematopoietic functions need to happen after high dose of alpha-mangostin possibly because the substance could lead to hematotoxic insult, systemic anemia or infections in the body[1]. There are several benefits in the presence of EMH, early diagnosis of diseases such as severe bone marrow failure, myelostimulation, tissue inflammation and abnormal chemokine production[3]. Nonetheless, our study did not investigate the mechanism of alpha-mangostin at molecular level hence we cannot determine its pathogenesis at this time.

In this study, it was found that male rats of the treated group lost more weight than female rats at the end of the experimental period. A similar study on the chronic effects of alpha-mangostin toxicity via oral administration has shown comparable results in the weight change of rodents; male rats were more vulnerable to weight loss than female[10]. Mice fed with diet containing tannic acid had shown retarded

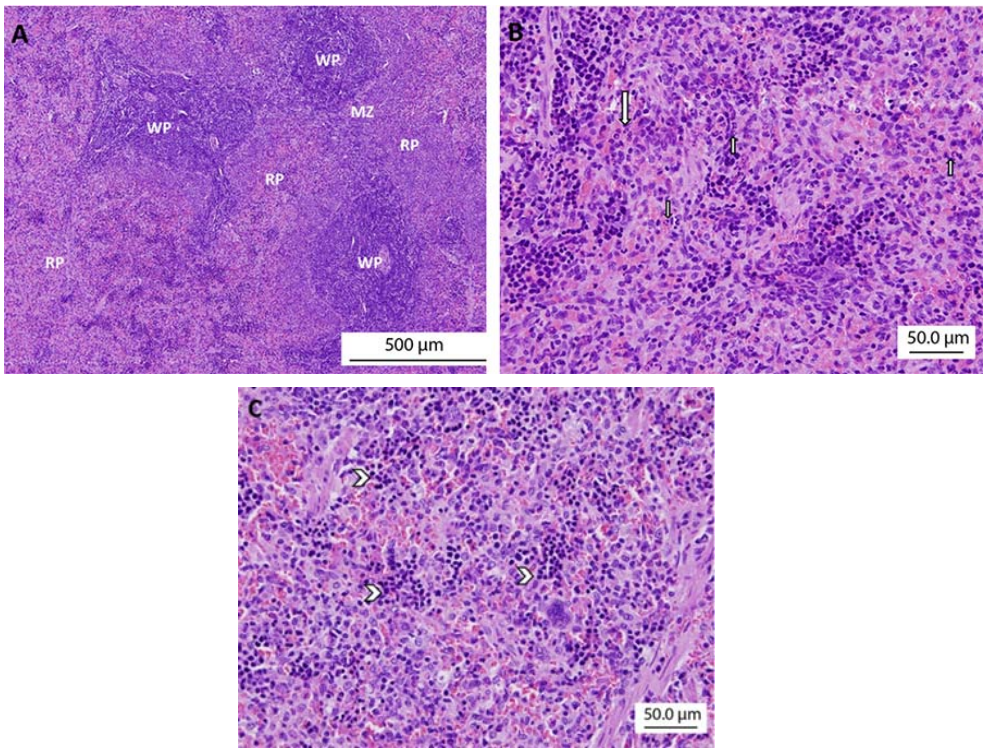

Fig. 5 Treated female spleen stained with H&E. A) 100x magnification, B-C) 400x magnification. Red pulp (RP), white pulp (WP), marginal zone (MZ), inflammatory neutrophils (arrows) and erythroid cells (arrowheads).

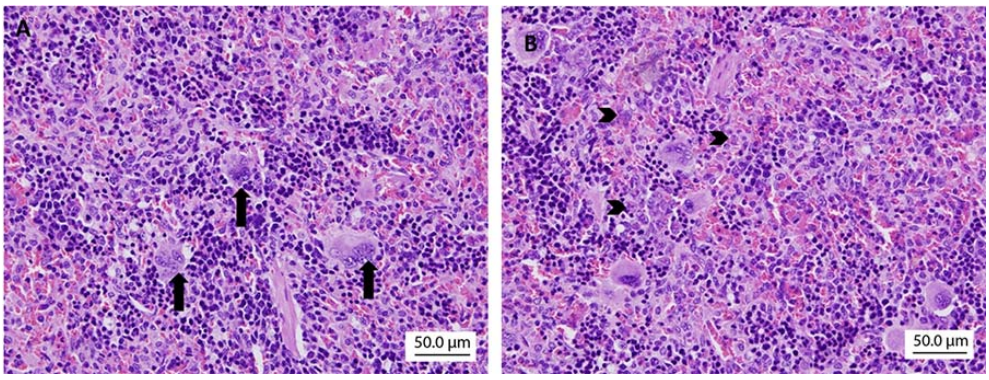

Fig. 6 Female rodent spleen treated with alpha-mangostin, H&E staining. A-B) 400x magnification. Extramedullary hematopoiesis with megakaryocytes (arrows) and myeloid precursors with intracytoplasmic granules.

growth[16], similarly a group of rats who received high tannin varieties of Sorghum which had also shown retarded growth in comparison to those with low tannin varieties[17]. Hence, the lower body weight in the male group treated with 100 mg/kg/day alpha-mangostin could be due to the effects of tannins. Another possible explanation for decrease in the body weight of rodents introduced to alpha-mangostin could be the induction of apoptosis and suppression of differentiation in preadipocytes by inhibiting fatty acid synthase[9]; it is proposed in the study that cytotoxicity of alpha-mangostin is involved in apoptotic events such as nuclear chromatin condensation and increase in cell membrane permeability, hence the decreased activity of fatty acid synthase in cells[9]. As a result, preadipocytes cannot differentiate into mature

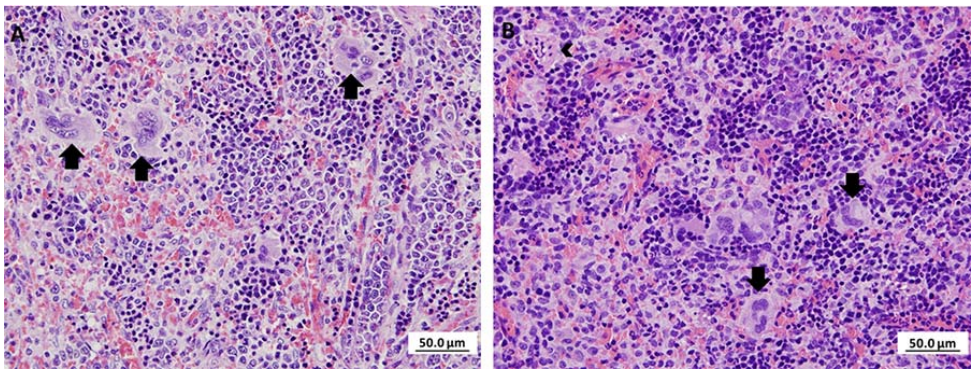

Fig. 7 Male rodent spleen treated with alpha-mangostin, H&E staining. A-B) 400x magnification. Megakaryocytes (arrows) and formation of platelets (arrowhead).

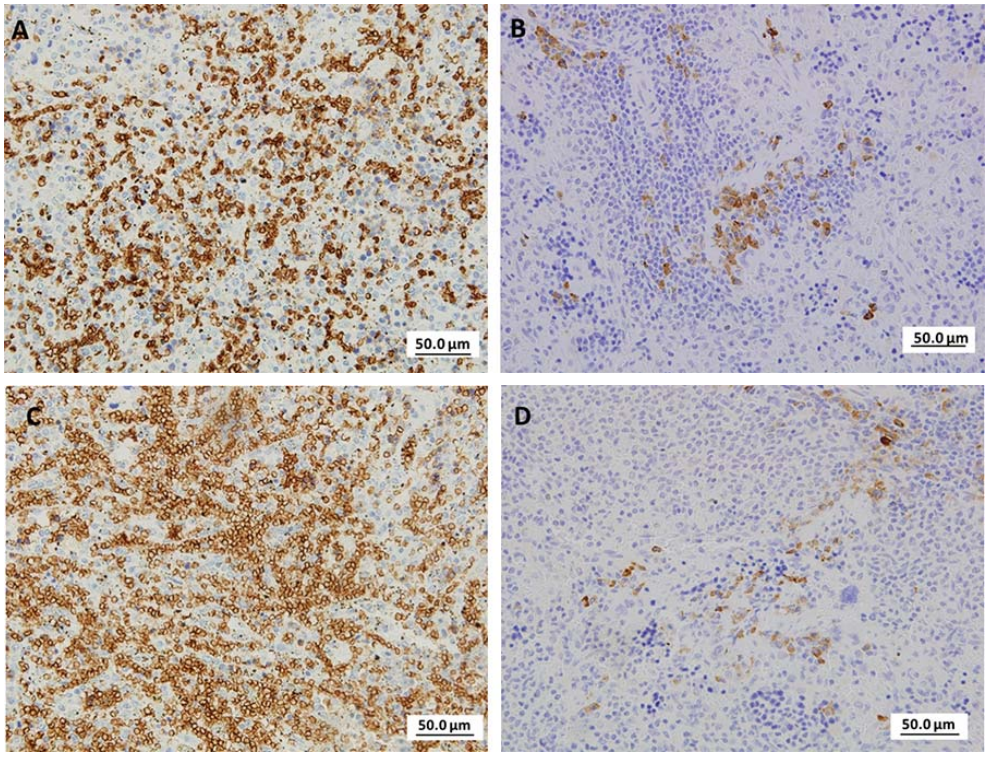

Fig. 8 Immunohistochemical staining. A) Glycophorin A, positive control, B) Glycophorin A, splenic tissue of treated group, C) Glycophorin C, positive control, D) Glycophorin C, splenic tissue of treated group.

adipocyte, impeding cytoplasmic lipid accumulation and hence preventing the development of obesity. Furthermore, alpha-mangostin also increases the released amount of free fatty acids[18].

Conclusion

Results from the subacute toxicity as shown in this study suggests that high dose alpha-mangostin may not be safe for long-term use and the target of alpha-mangostin is the hematopoietic system in the spleen. Exposure to high dose alpha-mangostin marked the presence of extramedullary hematopoiesis which is the formation of blood cellular components outside the bonw marrow. Hence, further studies are needed to confirm the mechanism of extramedullary hematopoiesis by alpha-mangostin via intra-peritoneal injection for

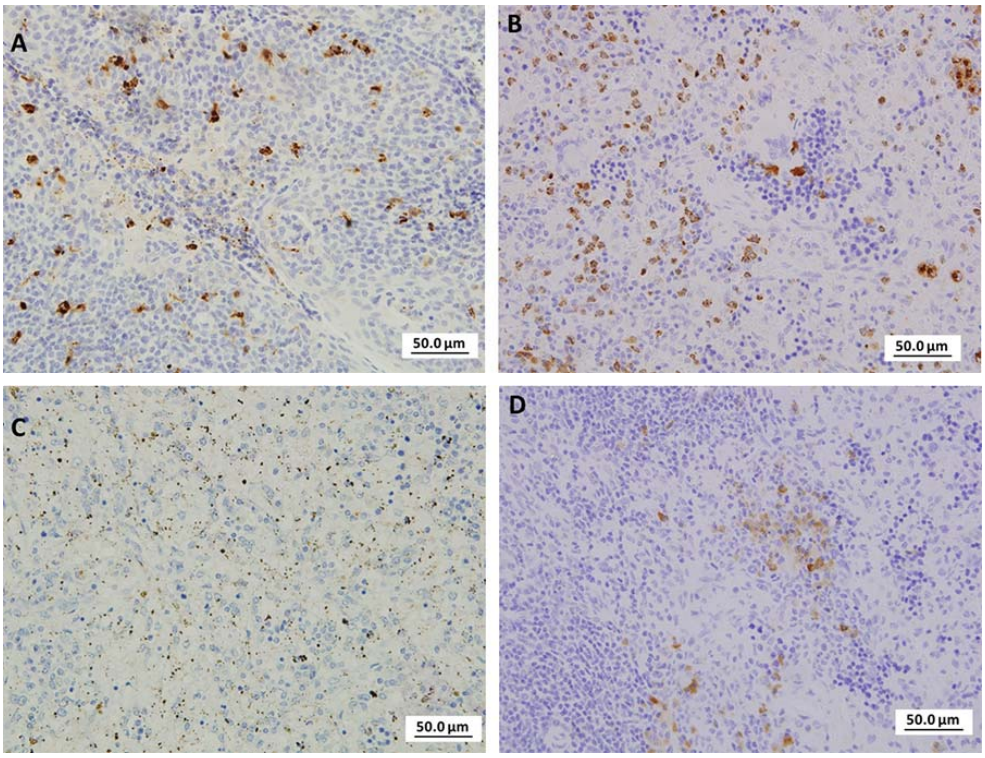

Fig. 9 Immunohistochemical staining. A) MPO, positive control, B) MPO, splenic tissue of treated group, C) CD61, positive control, D) CD61, splenic tissue of treated group.

the safe assessment as well as health product development derived from mangosteen pericarp extract.

What is already known on this topic?

In vivo and *in vitro* studies revealed that low dose of alpha-mangostin has a wide range of biological properties including anti-inflammation, anticancer and antibacteria. But it has not yet been documented regarding the effects of this compound at high doses.

What this study adds?

The findings from this experiment contribute to the existing knowledge of the properties of alpha-mangostin and show the adverse effects of high-dose alpha-mangostin, particularly on the spleen.

Acknowledgements

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Potential conflicts of interest

None.

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การสร้างเม็ดเลือดนอกไขกระดูกในหนูที่ได้รับสารแอลฟาแมงโกสตินความเข้มข้นสูง

สุริยา ผ่องสวัสดิ์, นฎาสิณีย์ จารุโชติรัตนสกุล, เฉง นิลบุหงา, วิสุทธิ์ ประดิษฐ์อาชีพ

ภูมิหลัง: สารแอลฟาแมงโกสตินที่สกัดจากเปลือกมังคุดมีคุณสมบัติในการต้านการอักเสบและต้านภาวะเบาหวานได้ เซลล์เม็ดเลือดปกติ เริ่มสร้างมาจากม้าม ตับ และในที่สุดย้ายไปสร้างที่ไขกระดูก ในกรณีที่ไขกระดูกถูกรบกวนการสร้างเม็ดเลือดนอกไขกระดูกสามารถเกิดขึ้นได้

วัตถุประสงค์: เพื่อศึกษาถึงผลของสารแอลฟาแมงโกสตินความเข้มข้นสูงต่อม้ามหนูแรท

วัสดุและวิธีการ: หนูแรท 40 ตัวได้นำมาใช้ในการศึกษาการเปลี่ยนแปลงทางพยาธิวิทยาของม้ามหลังจากฉีดสารแอลฟาแมงโกสตินเข้มข้นสูงเป็นเวลา 4 สัปดาห์ กลุ่มที่ 1 หนูกลุ่มทดลองเพศผู้จำนวน 10 ตัว กลุ่มที่ 2 หนูกลุ่มทดลองเพศเมียจำนวน 10 ตัว กลุ่มที่ 3 หนูกลุ่มควบคุมเพศผู้จำนวน 10 ตัว และกลุ่มที่ 4 หนูกลุ่มควบคุมเพศเมียจำนวน 10 ตัว โดยที่หนูแรทกลุ่มทดลองได้รับการฉีดสารแอลฟาแมงโกสตินที่ละลายใน 0.1% คาร์บอกซีเมททิวเซลลูโลสขนาด 100 มก./5 มล. และสารแอลฟาแมงโกสตินขนาด 100 มก./กก./วัน ได้ทำการฉีดเข้าช่องท้องของหนูแรทกลุ่มทดลองเป็นเวลา 4 สัปดาห์ ส่วนหนูแรทกลุ่มควบคุมได้รับสาร 0.1% คาร์บอกซีเมททิวเซลลูโลสเป็นเวลา 4 สัปดาห์ หลังจากนั้นทำการชั่งน้ำหนักและการการุณฆาตหนู ตัดเอาม้ามออกมาผ่านกระบวนการเตรียมสไลด์เนื้อเยื่อ และย้อมด้วยสีฮีมาทอกไซลีนกับสีอีโอซีนและสไลด์เนื้อเยื่อสำหรับย้อมทางอิมมูโนฮีสโตเคมิสตรี

ผลการศึกษา: ม้ามของหนูในกลุ่มที่ได้รับสารแอลฟาแมงโกสตินเข้มข้นสูงเมื่อย้อมด้วยสีฮีมาทอกไซลีนกับสีอีโอซีน พบมีการสร้างเกล็ดเลือดปริมาณมาก มีปริมาณเซลล์ตั้งต้นของกลุ่มไมอิลอยด์และเมกาคาริโอไซต์มากขึ้น เมื่อย้อมอิมมูโนฮีสโตเคมิสตรีพบว่ามีปริมาณเซลล์ตั้งต้นของกลุ่มไมอิลอยด์และต้นกำเนิดของเม็ดเลือดแดงจริง หนูเพศผู้ที่ได้รับสารแอลฟาแมงโกสตินมีน้ำหนักตัวน้อยกว่ากลุ่มควบคุมอย่างมีนัยสำคัญ

สรุป: การได้รับสารแอลฟาแมงโกสตินเข้มข้นสูงเป็นเวลา 4 สัปดาห์ชักนำทำให้มีการสร้างเม็ดเลือดนอกไขกระดูก