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RESEARCH ARTICLE

In vivo Antioxidant Potentials of Rambutan, Mangosteen, and *Langsat* Peel Extracts and Effects on Liver Enzymes in Experimental Rats

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Abstract Antioxidative potentials of peel extracts of rambutan (*Nephelium lappaceum*), mangosteen (*Garcinia mangostana*), and *langsat* (*Lansium domesticum*) in experimental rats were investigated. Antioxidant activities were evaluated using liver enzymatic and non-enzymatic systems. Rats were treated with fruit peel extracts for 14 and 30 days. Blood was collected on the final day of treatment and the liver was harvested for antioxidant assays. A significant decrease ($p<0.05$) in blood enzyme marker levels, compared with a control group, were observed. Oral administration of peel extracts for 14 and 30 days resulted in a significant increase ($p<0.05$) in superoxide dismutase, glutathione reductase, catalase, and lipid peroxidation levels, compared with a control group. Rambutan peel extracts exhibited a higher antioxidant potency than mangosteen and *langsat*. These fruit peels can be developed into functional foods with antioxidative properties.

Keywords: antioxidative potential, *Lansium domesticum*, *Garcinia mangostana*, *Nephelium lappaceum*

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Introduction

Many human diseases are caused by oxidative stress that results from an imbalance between formation and neutralization of pro-oxidants (1). Oxidative stress, which is associated with formation of lipid peroxides, contributes to pathological processes in aging and many diseases, including diabetes mellitus, atherosclerosis, myocardial infarction, arthritis, anemia, asthma, inflammation, neurodegenerative diseases, and carcinogenesis (2,3). Increased oxidative stress as a result of increased free radical formation has also been suggested as a contributor to vascular damage in many diseases (2,4).

Free radicals are atoms or molecules that bear unpaired electrons and are extremely reactive, capable of engaging in rapid reactions that destabilize other molecules and generate many free radicals. However, human cells have an array of protection mechanisms as natural defense systems involving antioxidant enzymes to prevent production of free radicals and oxidative damage (4). Antioxidants are the foremost part of defensive systems that limit the toxicity associated with free radicals and greatly reduce damage due to oxidants by neutralization of free radicals before attacks on cells, thus preventing damage to lipids, proteins, enzymes, and carbohydrates (5). Antioxidants can be classified into the 2 major classes of enzymic and non-enzymic antioxidants, including superoxide dismutase, catalase, glutathione reductase, ascorbic acid, and tocopherol (6).

Protective roles of the antioxidant defense system may be disrupted as a result of pathological processes, resulting in damage to cells. Antioxidant supplements of both natural and synthetic origin have been reported to reduce the effects of radicals. However, the commercially available synthetic antioxidants butylated hydroxytoluene (BHT)

and butylated hydroxyanisole (BHA) have been reported to be toxic to animals, including humans. Hence, natural products of plant origin are gaining importance as sources of natural antioxidants with strong activities (1,5).

Fruits are key ingredients in many processed foods. Consumption of fruits and vegetables has long been associated with health benefits. Epidemiological studies have shown that consumption of fruits with high phenolic contents correlates with reduced rates of cardio and cerebrovascular diseases, and with a reduction in the rate of cancer mortality (7). The most abundant antioxidants in fruits are polyphenols and vitamin C, whereas vitamins A, B, and E, and carotenoids are present to a lesser extent in some fruits. Studies have shown that a number of tropical fruits found in Malaysia possess high antioxidant activities (8). The seasonal fruits investigated in this study were rambutan (*Nephelium lappaceum*), mangosteen (*Garcinia mangostana*), and *langsat* (*Lansium domesticum*). Numerous studies have reported that these fruits possess high antioxidant activities (9,10). However, few studies have reported on the antioxidant properties of these tropical fruits *in vivo.* Peel portions of some fruits possess higher antioxidant activities than pulp portions (10). Arazo *et al.* (11) reported that mangosteen peel exhibited a higher antioxidant activity than pulp. Hence, in this study, the *in vivo* antioxidative potentials of rambutan, mangosteen and *langsat* peels were investigated.

Materials and Methods

Samples Rambutan, mangosteen, and *langsat* fruits were purchased from an orchard in Selangor, Malaysia in June 2012. These fruits have been registered with the Department of Agriculture, Malaysia (No. R161: rambutan; No. GA2: manggis; No. DL2: *langsat*) (12).

Preparation of extracts Fruits were washed under tap water and peels were separated from pulp manually. Peels were cut into small pieces of approximately 1 cm^3 before drying in a convection oven (UFB 500; Memmert, Schwabach, Germany) at 45°C. The initial drying and the final drying weights of the each sample are shown in Table 1. Dried samples were ground into a powdered form using a grinder. Dried powder was then subjected to extraction using a binary solvent extraction system of ethanol and water at a time and temperature from a previous study (13). The rambutan samples was extracted using 80% ethanol for 2 h and at 50°C, whereas mangosteen was extracted with 60% ethanol for 1 h at 25°C, and *langsat* was extracted using 80% ethanol for 2 h at 25°C. The extracts were then concentrated using a rotary evaporator at 40°C (Rotavapor R-200; Buchi, Switzerland), freeze dried (Alpha 1-4 LD Plus; Christ, Osterode, Germany), and stored at −20°C freezer (E388L; Fisher & Payker, Manukau, New Zealand) until further analysis.

Preparation of test compounds Fruit extracts and α-tocopherol (100 mg/kg each) were dissolved in 0.5 mL of absolute ethanol and suspended in a saline solution. Silymarin (50 mg/kg) was dissolved in a saline solution and was used as an antioxidant reference drug. All test solutions were freshly prepared on the day of experiments.

Animals Sprague-Dawley rats purchased from the animal house of Universiti Kebangsaan Malaysia (UKM) of both sexes weighing 200 g each were used in this study. Rats were screened and housed in standard polypropylene cages (3 rats per cage), maintained under standard laboratory conditions (a 12:12 h light and dark cycle at an ambient temperature of 25±5°C at a 50-70% relative humidity). Animals were fed with a standard rat pellet diet and water was available at all times. The study was approved by the Faculty of Applied Sciences Research Ethical Committee, UCSI University (Proj-FAS-EC-13-030).

Experimental design After 7 days of acclimatization, rats were divided into 6 groups (n=6). Treatments with rambutan, mangosteen and *langsat* peel extracts were performed for 14 and 30 days (Table 2). Blood was collected via cardiac puncture under anesthesia. The rats were given a mixture of ketamine-xylazine containing anesthesia before withdrawing blood from the heart. 24 h after the final treatment of each extracts, blood samples were sent to the UCSI University Pathology Laboratory for analysis of serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) activities, the alkaline phosphatase level, and total protein and total

Table 1. Yields of rambutan, mangosteen, and *langsat* peels

Sample	Weight (g)		Yield (%)[1)]
	Before drying	After drying	
Rambutan (*Nephelium lappaceum*)	1693.68±3.21	478.11±5.83	28.23
Mangosteen (*Garcinia mangostana*)	1637.60±18.77	627.44±11.05	38.31
Langsat (*Lansium domesticum*)	1558.18±2.08	443.75±11.70	28.58

[1)]Yield (%)=Weight $_{\text{after drying}}$ /Weight $_{\text{before drying}}$×100

Table 2. Experimental design for 14 and 30 day treatment periods

Group	14 and 30 days[1)]
Group I	Normal control (0.9% normal saline; 1 mL/kg orally)
Group II	Rambutan peel extract (100 mg/kg/day; orally)
Group III	Mangosteen peel extract (100 mg/kg/day; orally)
Group IV	*Langsat* peel extract (100 mg/kg/day; orally)
Group V	Standard drug, Silymarin (50 mg/kg/day; orally)
Group VI	α-Tocopherol (100 mg/kg/day; orally)

[1)]For each treatment period n=3 rats

bilirubin concentrations. All animals were then sacrificed by cervical dislocation and liver tissues were collected for *in vivo* antioxidant studies.

Tissue sample preparation for lipid peroxidation (LPO), GSH, and SOD assays Liver tissue (1 g) was collected, washed in normal saline, and soaked in filter paper. Tissues were then homogenized in 10 mL of 0.15 M tris buffer (pH 7.4) and centrifuged (Allegra X-22R; Beckman Coulter, Brea, CA, USA) at 1,970×g at 4ºC for 30 min. Collected supernatants were used for LPO, GSH, and SOD assays (6).

Tissue sample preparation for a CAT assay Liver tissue (900 mg) was collected, washed in normal saline, and soaked in filter paper. Tissues were then homogenized using a mortar and pestle in 3.0 mL of 0.15 M phosphate buffer (pH 7.0) and centrifuged (Allegra X-22R) at 1,970×g at 4ºC for 1 h. The collected supernatant was used for a CAT assay (6).

LPO assay LPO was assayed according to the method of Okhawa *et al.* (14). Amounts of 1 mL of normal saline (0.9% w/v) and 2.0 mL of 10% TCA were added to a sample of tissue homogenate (1 mL) and mixed well using a vortex. The mixture was then centrifuged (Allegra X-22R) at room temperature for 10 min at 1,970×g. Then, 2 mL of the supernatant was obtained and 0.5 mL 1.0% TBA was added, followed by heating at 95ºC using a water bath for 60 min to obtained a pink colored minimum detectable activity. Changes in the absorbance (Abs) values of samples were measured using a spectrophotometer (XTD 5; Secomam, Ales Gard, France) at 532 nm. The percentage of inhibition was calculated as:

$$\text{LPO inhibition (\%)}=[(\text{Abs}_{\text{normal activity}}-\text{Abs}_{\text{inhibited activity}})/\text{Abs}_{\text{normal activity}}]\times 100 \quad (1)$$

SOD assay The SOD activity was estimated using the method of Fridovich and Richard (15) with slight modification. A reaction mixture consisted of 0.5 mL of homogenized tissue, 1 mL of 50 mM sodium carbonate, 0.4 mL of 25 μM nitro blue tetrazolium (NBT) , and 0.2 mL of (0.1 mM) EDTA. The reaction was initiated by addition of 0.4 mL of 1 mM hydroxylamine-hydrochloride. Changes in the absorbance value by spectrophotometer (XTD 5) were recorded at 560 nm. The percentage inhibition was calculated as:

$$\text{SOD inhibition (\%)}=[(\text{Abs}_{\text{normal activity}}-\text{Abs}_{\text{inhibited activity}})/\text{Abs}_{\text{normal activity}}]\times 100 \quad (2)$$

CAT activity The CAT activity was assayed colorimetrically using spectrophotometer (XTD 5) at 620 nm as following the method of Sinha (16). A reaction mixture of 1.5 mL containing 1.0 mL of 0.01 M, pH 7.0 phosphate buffer, 0.1 mL of tissue homogenate (supernatant), and 0.4 mL of 2.0 M H_2O_2. The reaction was stopped using addition of 2.0 mL of dichromate-acetic acid reagent (5% potassium dichromate and glacial acetic acid mixed at a 1:3 ratio).

GSH activity The GSH activity was determined using the modified method of Ellman (17). An aliquot of 1.0 mL of liver homogenate supernatant was treated with 0.5 mL of Ellman's reagent (19.8 mg of 5,5'-dithiobisnitro benzoic acid (DTNB) in 100 mL of 0.1 % sodium nitrate), and 3.0 mL of phosphate buffer (0.2 M, pH 8.0). The absorbance value was measured using a spectrophotometer (XTD 5) at 412 nm. The percentage inhibition of GSH was calculated as:

$$\text{GSH inhibition (\%)}=[(\text{Abs}_{\text{normal activity}}-\text{Abs}_{\text{inhibited activity}})/\text{Abs}_{\text{normal activity}}]\times 100 \quad (3)$$

Statistical analysis All analyses were conducted using results from triplicate samples with Statistical Package for the Social Sciences (SPSS, version 19; SPSS, Inc., Chicago, IL, USA). A one-way analysis of variance (ANOVA) with Tukey's multiple comparisons and paired t-tests were performed. The significant level was defined as $p<0.05$.

Results and Discussion

Estimation of biochemical parameters The biochemical parameters SGOT, SGPT, ALP, total protein, and total bilirubin for 14 and 30 days treatment durations are shown in Fig. 1. For both treatment durations, the level of total proteins in groups (Table 2) treated with fruit peel extracts and standards were higher than that in the control group. There was a significant decrease ($p<0.05$) in the levels of

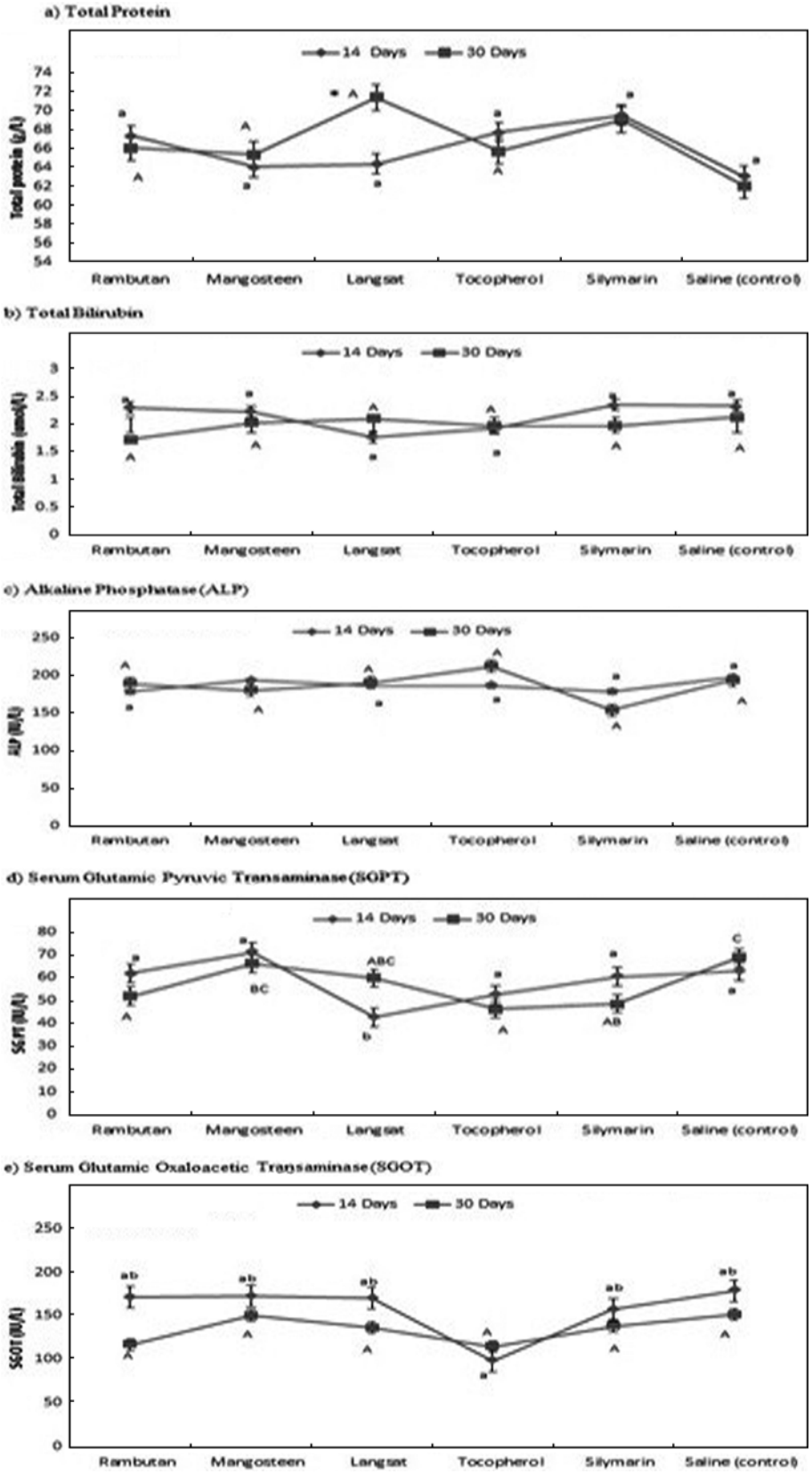

Fig. 1. The effects of tropical fruit peel extracts on total protein, total bilirubin, and serum enzyme levels of rats treated for 14 and 30 days. Values are presented as mean±standard deviation (SD). Values marked by lower and upper case letters (a-c and A-C) indicate significant differences ($p<0.05$) at 14 and 30 days, respectively. An asterisk (*) indicates significant differences ($p<0.05$) between the 2 treatment periods.

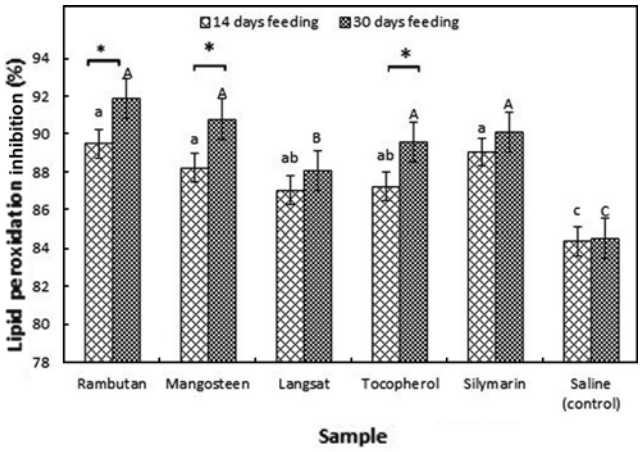

Fig. 2. Inhibition of liver lipid peroxidation in rats treated with different fruit peel extracts for 14 and 30 days. Values are presented as mean±SD. Values marked by lower and upper case letters (a-c and A-B) indicate significant differences ($p<0.05$) at 14 and 30 days, respectively. An asterisk (*) indicates significant differences ($p<0.05$) between the 2 treatment periods.

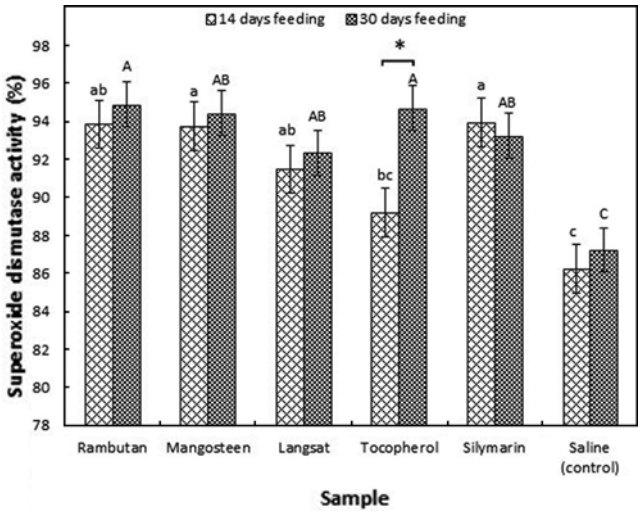

Fig. 3. The liver superoxide dismutase activity of rats treated with different fruit peel extracts for 14 and 30 days. Values are presented as mean±SD. Values marked by lower and upper case letters (a-c and A-C) indicate significant differences ($p<0.05$) at 14 and 30 days, respectively. An asterisk (*) indicates significant differences ($p<0.05$) between the 2 treatment periods.

the marker enzymes SGOT, SGPT, ALP, and in the total bilirubin level in groups treated with fruit peel extracts and standards, compared with the control group. The increase in total protein levels in groups treated with fruit extracts indicated stabilization of the endoplasmic reticulum leading to protein synthesis in treated groups (6). Sunil and Ignachimuthu (18) reported that rats treated with carbon tetrachloride (CCL_4) showed a significant degree of hepatic damage and oxidative stress, resulting in a substantial increase in the activities of the marker enzymes SGOT, SGPT, and ALP, and an increase in the total bilirubin level. In this study, a reduction in the level of these enzymes indicated stabilization of plasma membranes and repair of hepatic tissue damage. Fruit extracts preserved the structural integrity of the hepatocellular membrane evident from reductions in enzyme levels in treated rats.

Effects of lipid peroxidation (LPO), enzymic (SOD, CAT), and non-enzymic (GSH) antioxidant activities on the normal rat liver Effects of different types of tropical fruit peels on antioxidant enzyme activities of the normal rat liver were studied. Percentage inhibition values for LPO, enzymic CAT and SOD, and non-enzymic GSH antioxidant activities for liver homogenates for treatment durations of 14 and 30 days are shown in Fig. 1-4. Antioxidant enzyme activities were not significantly ($p>0.05$) different between experimental rats treated with different tropical fruit peel extracts for 30 days.

Inhibition activities of LPO in experimental rats treated for 14 and 30 days is shown in Fig. 2. After 14 days, rats treated with rambutan (89.50%) and mangosteen (88.20%) peel extracts exhibited the highest antioxidant activities. *Langsat* peel extract exhibited the lowest activity (86.57%). These peel extract inhibition values were significantly ($p<0.05$) higher when compared with the control group (84.34%). When compared with the standard drug, silymarin (89.04%), the rambutan peel extract exhibited the highest inhibition activity, followed by silymarin (89.04%), then mangosteen. However, no significant ($p>0.05$) differences were observed between the inhibitory activities of the 3 extracts at the 14 days treatment period. After 30 days of treatment, the inhibition activity increased and the rambutan extract showed the highest inhibition rate (91.85%) followed by mangosteen (90.78%), silymarin (90.11%) and α-tocopherol (89.55%) and all these extracts were not significantly different ($p<0.05$) from each other. The inhibitory activity of the *langsat* peel extract (88.04%) increased after 30 days of treatment. However, *langsat* still exhibited the least activity. Rats treated with rambutan, mangosteen, and tocopherol exhibited significant ($p<0.05$) differences between the treatment periods. However, there were no other significant ($p>0.05$) differences observed between the two treatment periods for any compound.

Lipid peroxidation is an oxidative alteration of poly-unsaturated fatty acids in cell membranes that generates a number of degradation products and is also an autocatalytic free radical chain propagating reaction associated with pathological conditions in cells (19). Malondialdehyde (MDA), one of the end products of lipid peroxidation, has been studied widely as an index of lipid peroxidation and as a marker of oxidative stress (17). Venkateshwarlu *et al.* (4) reported that the percentage inhibition of MDA production

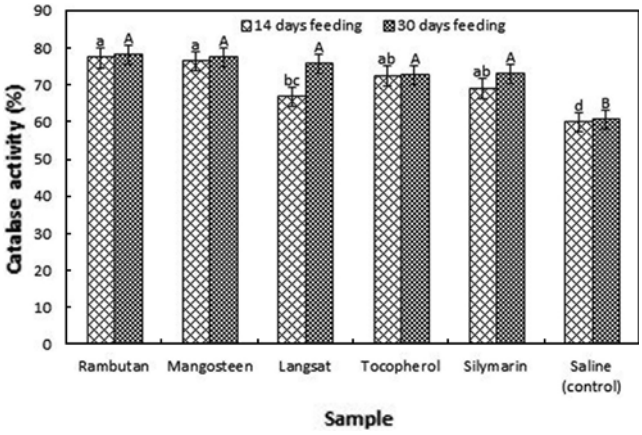

Fig. 4. The liver catalase activity of rats treated with different fruit peel extracts for 14 and 30 days. Values are presented as mean±SD. Values marked by lower and upper case letters (a-c and A-B) indicate significant differences ($p<0.05$) at 14 and 30 days, respectively.

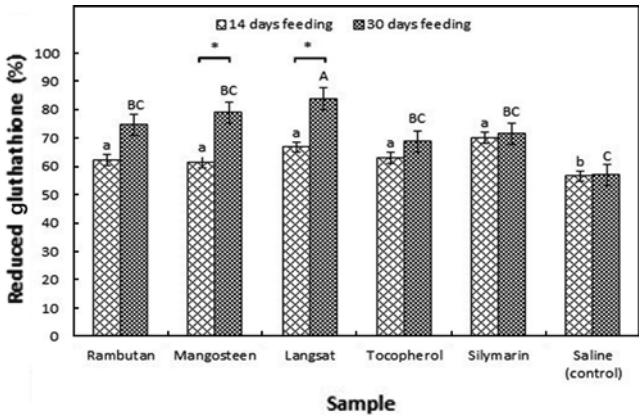

Fig. 5. Reduced gluthathione levels in liver activity of rats treated with different fruit extracts for 14 and 30 days. Values are presented as mean±SD. Values marked by lower and upper case letters (a-c and A-C) indicate significant differences ($p<0.05$) at 14 and 30 days, respectively. An asterisk (*) indicates significant differences ($p<0.05$) between the 2 treatment periods.

was low in a CCl_4 treated rats, implying enhanced lipid peroxidation leading to tissue damage of antioxidant defense systems against free radicals. Thus, in this study, selected tropical fruits peels and the standard drug silymarin exhibited higher inhibition activities than the control group, implying that all tested tropical fruit peels and silymarin possessed higher antioxidant activities than the natural antioxidants that exist in the natural body defense system. Rambutan peel exhibited higher antioxidant potency than mangosteen and *langsat* peels.

The effects of the SOD activity in experimental rats treated for 14 days and 30 days are shown in Fig. 3. After 14 days, rambutan showed the highest inhibition activity (93.85%), followed by mangosteen (93.74%), and *langsat* (91.49%). Silymarin, exhibited a higher inhibition activity rate (93.95%) than the fruit peel extracts, no significant difference was observed among them ($p<0.05$). For the 30 days treatment period, the inhibition rate of all tested compounds increased slightly with rambutan peel extract showing the highest inhibition rate (94.90%) followed (in decreasing order) by mangosteen peel>α-tocopeherol> silymarin>*langsat* peel. However, no significant ($p>0.05$) differences were observed between the inhibition activity rates of rambutan, mangosteen, *langsat*, α-tocopeherol and silymarin. A significant difference ($p<0.05$) was observed between the α-tocopherol treated groups for 14 and 30 day treatments.

The CAT activities in experimental rats treated for 14 and 30 days are shown in Fig. 4. Rambutan peel extract (77.34%) exhibited the highest inhibition activity, followed by mangosteen (76.42%), tocopherol (72.44%), and silymarin (69%) at 14 days of treatment, No significant ($p>0.05$) differences were found in CAT activities in experimental rats after 14 days of treatment. The *langsat* peel extract showed a significantly ($p<0.05$) lower CAT inhibition activity (66.88%) than the other tested compounds. After 30 days of treatment, the inhibition rate increased slightly with rambutan peel extract still being the highest with inhibition rate of 78.16% followed by mangosteen>*langsat* >silymarin>α-tocopherol. After 30 days of treatment, the inhibition rates between rambutan, mangosteen, *langsat*, silymarin, and α-tocopherol were not significantly ($p>0.05$) different. The CAT activity showed a significant ($p<0.05$) difference for rambutan, mangosteen, and *langsat* between the two treatment periods.

Both SOD and CAT are key antioxidant enzymes that protect against oxidative stress and tissue damage. These enzymes are known to be critical for defense against the harmful effects of reactive oxygen species and free radicals in biological systems (20). SOD scavenges the superoxide radical by conversion of the radical to hydrogen peroxide and molecular oxygen while CAT causes reduction of hydrogen peroxide and protects tissues from highly reactive hydroxyl radicals (5,20). In this study, both enzymes showed low levels of activity in the control group, indicating the natural level of the body defense mechanism. When fruit peel extracts were administered to treatment groups, both SOD and CAT activities were improved, reflecting the antioxidant potency of the fruits. Rambutan peel exhibited the highest antioxidant potency.

GSH levels in experimental rats treated for 14 and 30 days are shown in Fig. 5. Tested compounds did not show significantly ($p>0.05$) different activities in between the 2 treatment periods. However, activities of the compounds were all significantly ($p<0.05$) different compared with the control group. Silymarin exhibited the highest inhibition activity (70.11%), followed by *langsat*>rambutan>α-

tocopherol>mangosteen. The inhibition activities of silymarin, *langsat*, rambutan, α-tocopherol, and mangosteen were not significantly ($p>0.05$) different. After 30 days of treatment, the inhibition rate of *langsat* was significantly ($p<0.05$) higher than the rates of the other tested compounds.

GSH is a tripeptide, non-enzymatic biological antioxidant present in the liver that helps protect cells from reactive oxygen species, such as free radicals and peroxides. GSH is a potent inhibitor of the neoplastic process, and plays an important role in the endogenous anti-oxidant system. GSH is found in particularly high concentrations in the liver and is known to have a key function in the protective process against the toxic effects of lipid peroxidation (1,21). Oyedemi *et al.* (1) reported that a decreased level of GSH is associated with an increase in lipid peroxidation, and vice versa. In this study, a low GSH activity in the control group indicated a weak natural body antioxidant defense system. Both treatment groups administered fruit showed significant ($p<0.05$) increases in the levels of GSH, compared with the control group. The ability of fruit extracts to increase GSH activity was reflected by lower levels of lipid peroxidation.

In the present study, peel extracts of rambutan, mangosteen, and *langsat* showed *in vivo* antioxidant activities against liver enzymes in experimental rats. *In vivo* antioxidant potencies can be ascribed to antioxidants compounds contained in the peels. Ellagic acid and corilagin have been identified and quantified in peel extracts of rambutan and *langsat*, and α-mangostin in a peel extract of mangosteen using HPLC (22). Ellagic acid, corilagin and α-mangostin are natural antioxidants found in fruits and vegetables. *In vitro* antioxidant and antiproliferative effects of ellagic acid, corilagin, and α-mangostin have been reported previously (23-25).

The natural defense mechanism of the body is not sufficient to prevent damage caused by excessive levels of free radicals. Antioxidant supplementation is necessary to protect cells against oxidative stress-related diseases. Rambutan, mangosteen, and *langsat* peel extracts were evaluated for antioxidant activities *in vivo*. Fruit peel extracts possessed antioxidant activities *in vivo* with rambutan peel exhibiting the highest activity, followed by mangosteen and *langsat* peels. A longer treatment period provided a better anti-oxidative effect. These fruits are potentially rich sources of natural antioxidants and can be developed into functional foods or drugs for prevention and treatment of diseases caused by oxidative stress. In the future, the specific components in these fruits with high antioxidant activates will be isolated and beneficial effects against oxidative stress will be evaluated.

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Disclosure The authors declare no conflict of interest.

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