Research Article
Pancreatic Lipase Inhibitory Effects of Mangosteen Pericarps

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Abstract: Pancreatic lipase plays a key role in the digestion and absorption of lipids, inhibition of Pancreatic Lipase (PL) is considered as a new approach to obesity treatment. The objective of the present study was to find PL inhibitors from natural food sources. Eighteen natural food products sampled from local supermarkets in Zhuhai were tested for PL inhibitory activity using a copper-soap photometric method. Among the samples tested, the crude extracts from mangosteen pericarp, lemon pulp, celery, cucumber and dry longan were found to be able to suppress the PL activity to different extents, while dry red chili, fresh green chili and dry clove exhibited a promotion effect on the PL. Shiitake mushroom, green bell pepper, lemon peel and spices (ginger, oregano leaf, bay leaf, cinnamon and dry tangerine) showed no significant influence either on the inhibition or promotion. The crude extract of mangosteen pericarp was further fractioned to trace active fractions. It was found that the *n*-butanol fraction was the major contributor to the PL-inhibitory effect of mangosteen pericarp and the inhibition rate was 43.9% at the concentration of 1 mg/mL, the IC_{50} value was 0.918 mg/mL. Mangosteen pericarp is worthy of utilization as functional food constituents for the prevention and treatment of obesity.

Keywords: Mangosteen pericarp, natural food products, obesity, pancreatic lipase

INTRODUCTION

Obesity results from an imbalance involving excessive calorie consumption and/or inadequate physical activity. It is a complex health issue involving a variety of factors including metabolism, behavior, environment, genetics, etc. The prevalence of obesity is growing at a dreadful rate. The population of worldwide obesity in 2011 has more than doubled as compared to the population in 1980, WHO (World Health Organization) (2011). Obesity used to be considered as health and social problems of developed nations, now begins to threaten the health of low-and middle-income countries, including China. According to statistics from WHO (2011), the prevalence of obesity (BMI≥30) was 4% in China, while it was only 2.9% in 1997 (Wang *et al*., 2001; Ministry of Health *et al*., 2002). These data indicate that obesity has turned to a serious public health crisis in China. Obesity is considered to be a major risk factor contributing too many chronic diseases, such as type-2 diabetes, cardiovascular diseases and certain cancers. Thus, effective ways of preventing and treating obesity are required. As the fundamental reason of obesity is energy imbalance, many biomedical researches aim to establish an appropriate regulation of energy homeostasis.

Pancreatic lipase plays an important role in the digestion of dietary fat. It hydrolyzes and converts dietary triglycerols into monoglycerides and free fatty acids. Orlistat, a hydrogenated derivative of lipstatin derived from *Streptomyces toxitricini*, is a potent inhibitor of gastric, pancreatic and carboxyl ester lipase and has proved to be effective for the treatment of human obesity (Ballinger and Peikin, 2002). Although Orlistat has been clinically approved as an over-the-counter drug for obesity treatment, it has some side-effects involving gastrointestinal tract, including oily spotting, liquid stools, fecal urgency, etc., (Chaput *et al*., 2007). As consumption of Orlistat may have these adverse effects, its usage should be taken with caution. Therefore, there is an elevated demand for development of non-toxic and readily accessible products from natural foods.

As decreasing lipid absorption is one of the major mechanisms of anti-obesity effects, pancreatic lipase-inhibitory effect is one of the most important factors for determining potential efficacy of anti-obesity agents (Birari and Bhutani, 2007). There are a few reports on pancreatic lipase-inhibitory activities of natural food products in the literatures (Xu *et al*., 2005; McDougall *et al*., 2009; Gondoin *et al*., 2010; Zheng *et al*., 2010), while some common natural food products with anti-obesity properties have not been studied yet.

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In China, the record of anti-obesity has existed for thousands of years. Many natural foods are utilized in treatment of obesity according to the book Huangdi Neijing. For example, bitter melon has been used as an herb for hundreds of years in China and it is well known for an active component which is considered as "plant insulin" (Khanna *et al.*, 1981). Many food products are considered to be able to prevent or treat obesity in civil practices in China, such as lemon, pitaya and cucumber. However, the mechanisms of some natural food products on weight loss are not fully understood, their applications are lack of scientific evidence of efficacy and mechanism of action. Therefore, the aim of this study was to explore the potential of several natural food products in inhibiting pancreatic lipase *in vitro*.

MATERIALS AND METHODS

Reagents and chemicals: Porcine pancreas lipase, lecithin from soybean, sodium taurocholate, *n*-tris (hydroxymethyl) methyl-2-aminoethanesulfonic acid (TES) and 2, 9-dimethyl-4, 7-diphenyl-1, 10-phenanthroline (bathocuprione) were purchased from Shanghai Yuanye Bio-technological Co., Ltd. De-ionized water was utilized. The other reagents were of analytical grade.

Food materials: Eighteen food materials:

- Lemon peel
- Lemon pulp
- Pitaya peel
- Mangosteen pericarp
- Celery stem and leaf
- Cucumber
- Dry longan
- Cinnamon
- Fennel seed
- Dry red chili
- Dry clove
- Green chili
- Green bell pepper
- Oregano leaf
- Ginger
- Sweet bay leaf
- Dry shiitake mushroom
- Dry tangerine

were sampled. All of them were purchased from the local supermarkets in Zhuhai, Guangdong Province, China.

Preparation of crude extracts from food samples: A method of Xu *et al.* (2007) was applied to obtain crude extracts from food samples with slight modification. Briefly, fresh samples were ground in a mortar. A portion of 20 g of the ground sample was extracted in a capped centrifuge with 20 mL of solvent consisting of acetone/water/acetic acid (70: 29.5: 0.5, v/v/v). The mixture was shaken at 300 rpm at ambient temperature on an orbital shaker for 3 h and then was left in dark overnight for additional 12 h. The extracts were centrifuged by a centrifuge (TG16-WS, Xiangying Centrifuge Co., Ltd., Changsha, Hunan, China) at 3000 rpm for 10 min and the supernatants were removed into another tube. The residue was extracted by adding another 20 mL of respective solvents for the second time. The two extracts were combined. The crude extract was condensed at 45°C using a rotary evaporator (RE-52AA, Yarong Instrument Co., Ltd., Shanghai, China) and then was further dried at 45°C in a vacuum drying oven (Shanghai Bluepard Experimental Instruments Co., Ltd., China). The residue of dried acetone extract was weighted and dissolved by 0.1 M *n*-tris (hydroxymethyl) methyl-2-aminoethanesulfonic acid (TES) buffer (pH 7.0) containing 0.1 M NaCl. The sample solutions were stored at -20°C in the dark until further analysis.

Solvent fractionation of crude extracts from food samples: The dried extract was suspended in 15 mL of distilled water. The resulting aqueous suspension was extracted by petroleum ether, ethyl acetate and *n*-butanol successively, with a ratio of 1:1 at room temperature. Petroleum ether, ethyl acetate, *n*-butanol and water fractions were obtained. The extracts obtained from petroleum ether and ethyl acetate fractions were condensed and dried at 45°C under vacuum using the rotary evaporator. The other two extracts from *n*-butanol and water fractions were firstly condensed at 55°C under vacuum in the rotary evaporator and then dried in a freeze drier (Labconco, FreezeZone, Kansas City, MO, U.S.A.) under vacuum to a complete dryness. The dried petroleum ether, ethyl acetate, *n*-butanol and water fractions were weighted. Sample solutions were prepared by dissolving the dried extracts with 0.1 M TES buffer containing 0.1 M NaCl and stored at -20°C in the dark until further analysis.

Measurement of pancreatic lipase activity *in vitro*: A slightly modified method from Xu *et al.* (2005) was utilized to measure the pancreatic lipase activity. By measuring the rate of release of oleic acid from triolein, lipase activity was determined. A suspension of triolein (80 mg), lecithin (10 mg) and sodium taurocholate (5 mg) in 9 mL of 0.1 M TES buffer (pH 7.0) containing 0.1 M NaCl was sonicated for 5 min. (0.1 mL) of this sonicated substrate suspension was incubated with 0.05 mL (10 units) of pancreatic lipase and 0.1 mL of sample solution in various concentrations (0.25, 0.5 0.75 and 1 mg/mL, respectively) for 30 min at 37°C in a final volume of 0.25 mL. Instead of the sample solutions, 0.1 mL of TES buffer containing 0.1 M NaCl

was added into the substrate suspension to serve as a control group. The amount of oleic acid produced was measured by the method of Zapf *et al*. (1981) with a slight modification (Tsujita and Okuda, 1983). An aliquot (3 mL) of a 1:1 (v/v) mixture of chloroform and heptane containing 2% (v/v) methanol was added to the incubation mixture in the tubes and an extraction of oleic acid was conducted by shaking the tubes horizontally for 10 min on an orbital shaker. The mixture was centrifuged at 2000×g for 10 min and the upper aqueous phase was removed by suction. Copper reagent (1 mL) was then added to the lower organic phase. The copper reagent was prepared by mixing 10 mL of a 1 M solution of triethanolamine containing 1.21 g of Cu $(NO_3)_2$ with 6 mL of 1 M NaOH and the volume of mixture was adjusted to 100 mL with distilled water and 33 g of NaCl was then added. The tube was shaken for 10 min and then the mixture was centrifuged at 2000×g for 10 min. The upper organic phase (1 mL), which contained copper salts of the extracted free fatty acids, was treated with 1 mL of 1 g/L bathocuproine in chloroform containing 0.5 g/L 2-(3) -tert-butyl-4-hydroxyanisole. The color changes of solutions were visible after treating with bathocuproine. The absorbance was then measured by a TU-1901 UV-Visible spectrophotometer (Beijing Purkinje General Instrument Co., Ltd., Beijing, China) at 480 nm against distilled water as blank. Pancreatic lipase activity was calculated by the following equation and was expressed as % control:

Pancreatic lipase activity = ((Absorbance of sample - treated solutions) /Absorbance of control) ×100%

Statistical analysis: Experiments were performed in triplicates. Means, standard deviations were done using Microsoft Excel 2003. Figures were plotted with software Sigma Plot (version 7.0). Correlation analyses were statistically analyzed by SPSS 17.0. A p-value <0.05 was accepted as statistically significant.

RESULTS AND DISCUSSION

Preliminary screening of lipase-inhibitory effect of 18 food samples: The screening results were summarized in Table 1. The crude extracts of several natural food products inhibited the pancreatic lipase activity *in vitro*, while the extracts from other food samples showed no inhibitory effect or promoting effect on pancreatic lipase activity. The correlation between the sample concentration and the effects on pancreatic lipase activity was significant (p<0.05) for the following samples: mangosteen pericarp (Fig. 1B), cucumber (Fig. 1D), longan (Fig. 1E), red chili and dry clove (Fig. 1F), which indicated a dose-dependent manner of their effects on lipase activity. Among those samples, the crude extract of mangosteen pericarp

(Fig. 1B) had the most significant inhibitory effect on pancreatic lipase activity *in vitro* in a dose-dependent manner. The red chili and dry clove (Fig. 1F) presented pancreatic lipase promotion effect in a dose-dependent manner.

The present study was to explore *in vitro* pancreatic lipase-inhibitory properties of natural food products and to further trace the active fractions from samples with significant effect. It was found that many natural food products had the lipase-inhibitory property, especially mangosteen pericarp. The crude extract of mangosteen pericarp was found highly effective in inhibiting lipase activity *in vitro* at a relatively low concentration. At a concentration of 0.75 mg/mL, it inhibited almost 50% of lipase activity and its inhibitory effect did not develop significantly as its concentration increased to 1 mg/mL. It was shown that its effect on lipase activity was in a dose-dependent manner. Although there has no researcher claimed that the extract of mangosteen pericarp is able to suppress the lipase activity, Zhao and Li (2007) discovered that the extract of mangosteen pericarp had preventive and therapeutical effect in experimental hyperlipidemia rabbits. As a human study found that the application of Orlistat, the lipase suppressor, in therapy of obesity with hyperlipidemia could improve patients' serum lipid parameter (Mićić *et al*., 1999), it is possible that the lipase-inhibitory effect contributes to the lowering of serum lipid concentration.

Despite of mangosteen pericarp, extracts from other natural food products demonstrated a mild or slightly inhibitory effect on pancreatic lipase activity *in vitro*, such as lemon pulp (Fig. 1A), celery (Fig. 1C), cucumber, fennel seed, dry longan and dry sweet bay, current study further verified our latest report (Liu *et al*., 2012) on pancreatic lipase inhibitory effects of lemon, celery, cucumber, longan and mangosteen. Most of them had the largest inhibition rate lower than 50% in the tested range of concentration. Some food samples (lemon pulp, pitaya pericarp, celery, fennel seed and bay leaf) did not act in a dose-dependent manner. For pitaya pericarp, the pancreatic lipase-inhibition rate reached nearly 45% when the sample concentration was 0.25 mg/mL and the inhibition rate kept in a relatively stable status at the higher concentrations. Thus, the inhibition caused by pitaya pericarp extracts in the range of concentrations between 0 and 0.25 mg/mL is needed to be tested in further studies. For the other samples, the largest inhibition occurred at a concentration between 0 and 1 mg/mL and the inhibitory effect became weak with the increasing concentration. A possible reason for this situation is that the low concentration was the optimum concentration for these food samples to inhibit pancreatic lipase activity.

Table 1: Effects of natural food samples on pancreatic lipase activity *in vitro*

Common name	Scientific name	Part used	Effects	Dose-dependency
Lemon	*Citrus limon* (L.) Burm.	Pericarp	No effect	-
Lemon	*Citrus limon* (L.) Burm.	Pulp	Inhibitory	-
Pitaya	*Hylocereus undatus*	Pericarp	Inhibitory	-
Mangosteen	*Garcinia mangostana* L.	Pericarp	Inhibitory	+
Celery	*Apium graveolens*	Stem and leaf	Inhibitory	-
Cucumber	*Cucumis sativus*	Fresh fruit	Inhibitory	+
Longan	*Dimocarpus longan*	Dried fruit	Inhibitory	+
Cinnamon	*Cinnamomum scassia.*	Dried bark	No effect	-
Fennel	*Foeniculum vulgate.*	Seed	No effect	-
Red chili	*Capsicum annuum* L.	Dried fruit	Promotion	+
Clove	*Syzygium aromaticum*	Dried flower	Promotion	+
Green chili	*Capsicum annuum* L.	Fresh fruit	Promotion	-
Green bell pepper	*Capsicum annuum* L.	Fresh fruit	No effect	-
Oregano	*Origanum vulgare* L.	Leaf	No effect	-
Ginger	*Zingiber officinale*	Rhizome	No effect	-
Sweet bay	*Laurus nobilis* L.	Leaf	No effect	-
Shiitake mushroom	*Lentinus edodes*	Fruit body	No effect	-
Tangerine	*Citrus reticulata* Blanco	Dried tangerine	No effect	-

+: Dose-dependent inhibitory/promotion effect; -: Non-dose-dependent effect
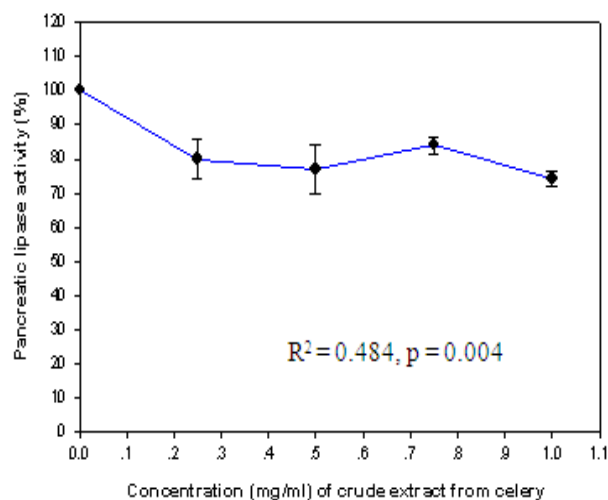

(A)

(B)

(C)

(D)

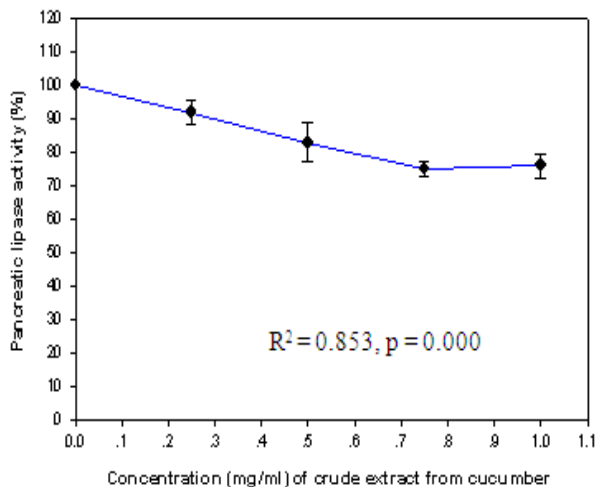(E)   (F)
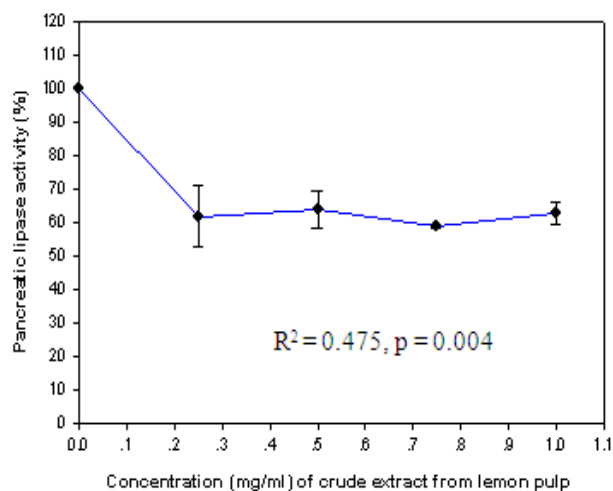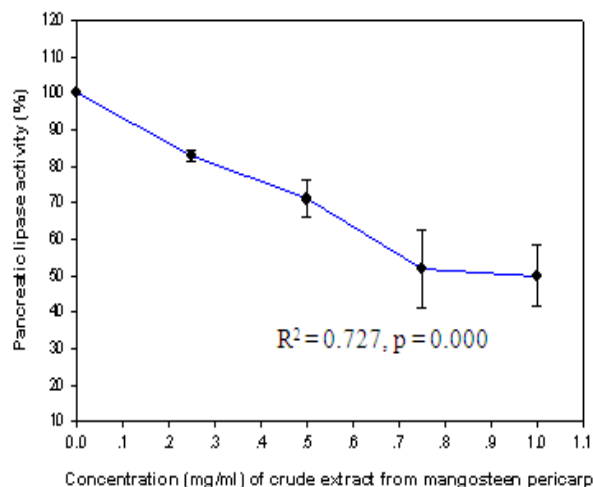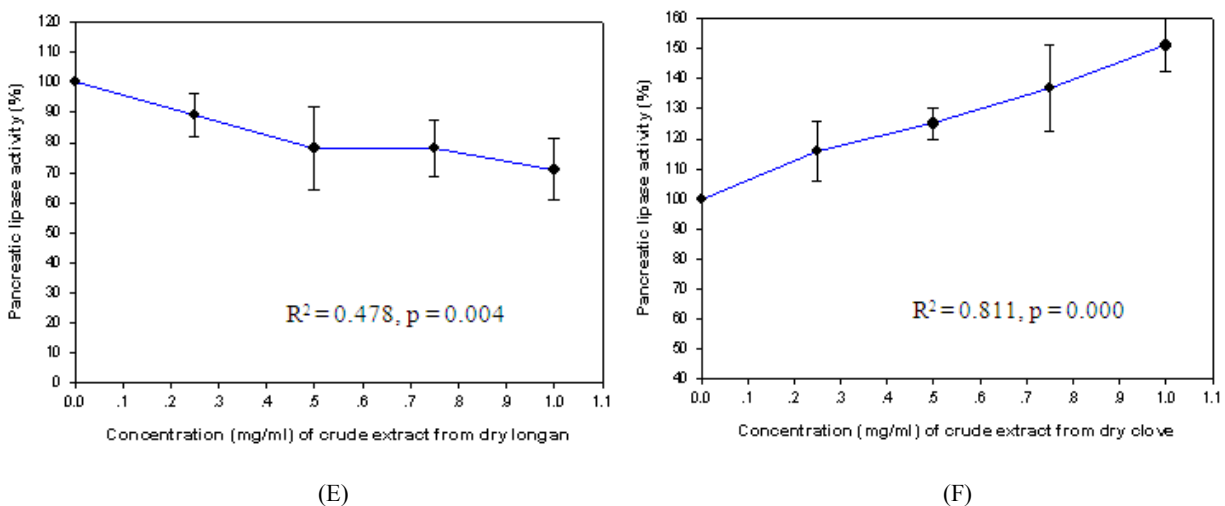
Fig. 1: Pancreatic lipase-inhibitory activity of natural food samples *in vitro*, (A) lemon pulp, (B) mangosteen pericarp (C) celery, (D) cucumber, (E) dry longan, (F) dry clove. Results are expressed as means±S.D., n = 3

Some of these samples have been tested for the lipase-inhibitory property in plenty of researches. For celery, Mansi *et al*. (2009) reported that the serum triglyceride concentration was reduced in the celery-treated rats and hepatic triacylglycerol lipase activity was found to be significantly lower than that in the control group. Combining with the results in the present study, the results might give a considerable agreement to the traditional use of celery in the treatment of hyperlipidemia. For cucumber, according to Taniguchi *et al*. (1985), the extract of cucumber with peel could inhibit 37.9% of pancreatic lipase activity *in vitro*. The results of fennel seed in this study were not identical with that of a study conducted by Platel and Srinivasan (2003). They claimed that a 70% increase in intestinal lipase activity was observed in animals given single oral dose of fennel; in contrast, a continued intake led to a decreased lipase activity in the animals. As they directly fed spices to animals, the composition of the fennel they used and the crude extract obtained in this study might be different. It is the first time that the pancreatic lipase-inhibitory properties of food samples including lemon pulp, pitaya peel, dried longan and dried sweet bay were found.

There were three samples, dried red chili, green chili and dried clove, acting as activators of pancreatic lipase *in vitro*. The findings about dried red chili and green chili agree with another study conducted by Platel and Srinivasan (2000), who reported that capsaicin, a major component from red and green chili, activated the pancreatic lipase activity in rats. However, there was a discrepancy between the finding about dried clove in current study and the report by Khan (2003), who indicated that the clove extract had a strong inhibitory effect on serum lipase. The whole clove was utilized in Khan's study and was extracted by *n*-hexane, while in the present study the dried clove was extracted

by acidic acetone; the components in the extracts might not be same due to different polarity. Probably the lipase inhibitors in clove had a very low polarity that they cannot be extracted by acetone. Another possibility was that during the drying process, the active components were alternated under the presence of oxygen, light and heat, as clove has a strong antioxidant capacity (Atawodi *et al*., 2011).

Green bell pepper, oregano leaf, ginger, shiitake mushroom, the peel of lemon, cinnamon and dried tangerine did not exhibit either inhibitory or promotion effect on the pancreatic lipase activity *in vitro*. Although bell pepper is also a cultivar group of *Capsicum annuum* L., it does not contain capsaicin, which contributes to the pungency of peppers. As capsaicin is a major component promoting the pancreatic lipase activity, lacking of capsaicin might make green bell pepper lose the lipase-inhibitory property. Ramakrishna *et al*. (2003) reported that ginger was an effective activator of pancreatic lipase. However, ginger was found non-effective in inhibiting lipase activity *in vitro* in this study, even though the lipase activity was mostly higher than 100% at the concentration between 0.25 and 0.5 mg/mL, respectively. In the study of Taniguchi *et al*. (1985), shiitake mushroom did not exhibit any effect on pancreatic lipase activity *in vitro*, which was consistent with the results in the present study. There has no report about the effects of oregano leaf and dried tangerine on pancreatic lipase activity yet.

Many researchers have reported some other natural food extracts with the property of inhibiting pancreatic lipase activity *in vitro*. Xu *et al*. (2005) found that the total saponin fraction from Radix Platycodi had a potential of inhibiting the hydrolysis of triolein emulsified with phosphatidycholine by pancreatic lipase *in vitro*. At the concentration of 0.5 mg/mL,
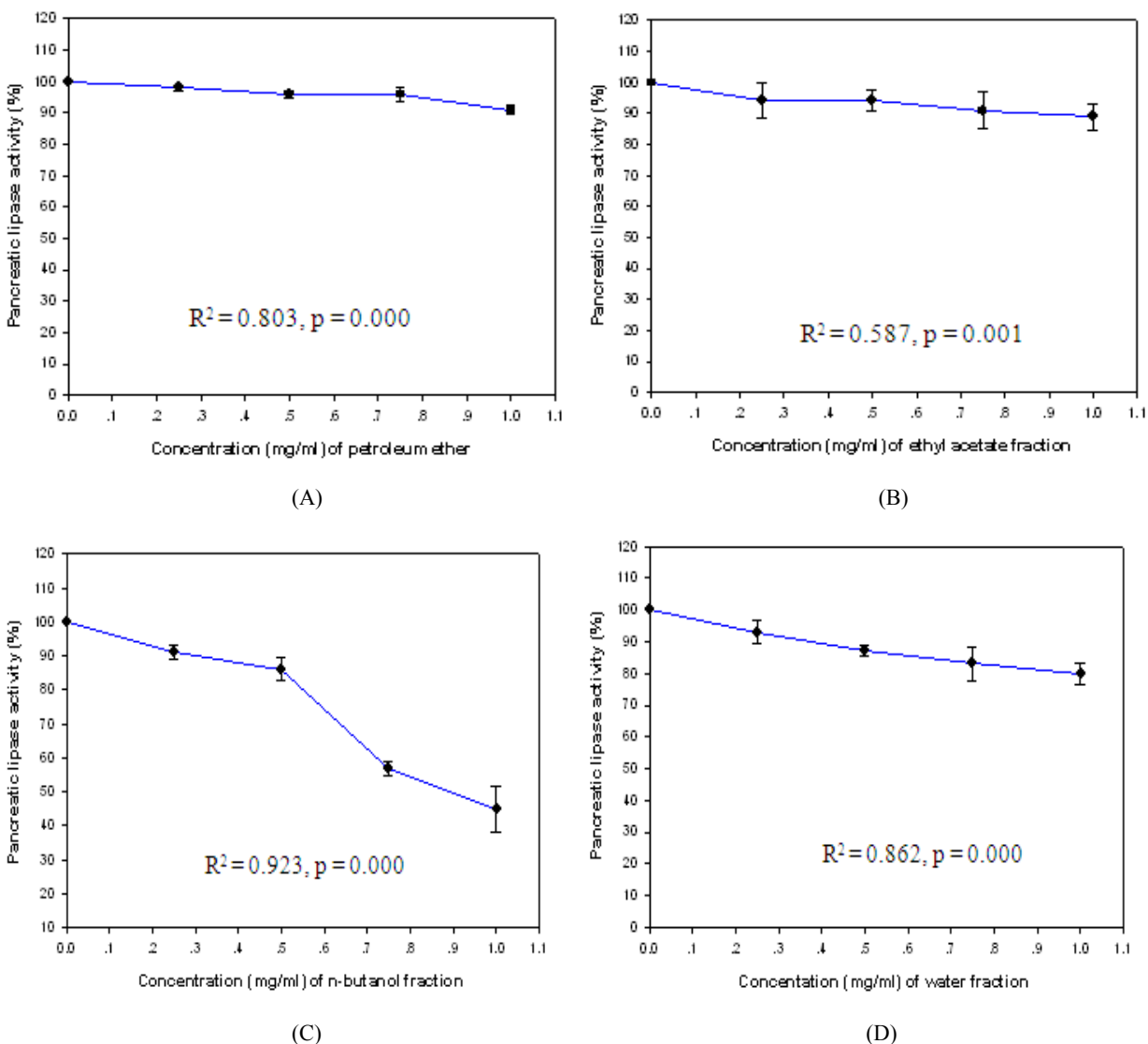
Fig. 2: Pancreatic lipase inhibitory effects of fractions from mangosteen pericarp, (A) petroleum ether fraction, (B) ethyl acetate fraction, (C) *n*-butanol fraction, (D) water fraction, [a]: Results are expressed as mean±S.D., n = 3

platycodin A, one of the purified triterpenoidal saponins, exhibited the most significantly inhibitory activity with only 3.3% pancreatic lipase activity versus control. Berries, considered as a source of rich polyphenols, also illustrate their ability to inhibit pancreatic lipase activity *in vitro* and an inhibition which saturation effect is an apparent EC_{50} of around 5 µg phenols/mL was performed by the cloudy berry extract (McDougall *et al*., 2009). According to Zheng *et al*. (2010), extracts of two traditional Chinese herbal medicines, *Prunella vulgaris* L. (Labiatae) and *Rheum palmatum* L. (Polygonaceae), revealed notable anti-lipase properties at a concentration of 200 µg/mL. Tea is also a target food product potentially inhibiting lipase, while various kind of tea may have different effects. The report from Gondoin *et al*. (2010) claimed that the EC_{50} values for inhibition of pancreatic lipase

in vitro were 22 µg/mL for white tea extract and 35 µg/mL for green tea extract but very large for black tea extract. As original black tea has the lowest content of polyphenols and samples enriched in polyphenols gave high EC_{50} values of inhibition, they strongly suggested that the inhibition was caused the phenolic components. Compared to these foods, the inhibitory effect on pancreatic lipase activity *in vitro* of food samples in this study was still a bit weaker. Further purification may improve the efficacy of inhibition.

Pancreatic lipase inhibitory effects of fractions from mangosteen pericarp: Dried extracts of four fractions from mangosteen pericarp were weighed. The yield of petroleum ether, ethyl acetate, n-butanol and water extracts was 0.05, 0.23, 1.23 and 2.92%, respectively. The results of lipase activity assay using solvent-

fractioned extracts of mangosteen pericarp were shown in the Fig. 2. The *n*-butanol fraction of mangosteen pericarp had stronger inhibitory activity than the other three fractions.

The correlation analyses showed that all of these four fractions possessed an inhibitory effect on lipase activity in a dose-dependent manner (p<0.05). However, the petroleum ether and ethyl acetate fractions exhibited very slight inhibitory effects. At a concentration of 1 mg/mL, both of petroleum ether fraction (Fig. 2A) and ethyl acetate fraction (Fig. 2B) led to an inhibition less than 15%. The *n*-butanol fraction (Fig. 2C) presented the most significant inhibitory effect on lipase activity in a dose-dependent manner ($R^2 = 0.923$, p<0.05), the IC_{50} value was 0.918 mg/mL. The water fraction (Fig. 2D) had a mild effect that the highest inhibition rate was nearly 20% when the concentration increased to 1 mg/mL.

The further investigation on the different fractions from mangosteen pericarp indicated that the *n*-butanol fraction was the most efficient on the suppression of lipase activity. At a concentration of 1 mg/mL, it demonstrated a nearly 60% inhibition (Fig. 2C). It might exhibit a more powerful suppression on the lipase activity as the concentration further increases. There has no research focusing the lipase-inhibitory effect of the *n*-butanol fraction of mangosteen pericarp. A limited amount of papers investigated the major components in *n*-butanol fraction. Yu *et al*. (2007) obtained three phenolic components from the *n*-butanol extract of the 70% methanol extract from mangosteen pericarp, including 1, 3, 6, 7-tetrahydroxy-2, 8- (3-methyl-2-butenyl) xanthone, 1, 3, 6-trihydroxy-7-methoxy-2, 8- (3-methyl-2-butenyl) xanthone and epicatechin. As the major components are xanthones and epicatechin, the *n*-butanol extract of mangosteen pericarp may have a considerable antioxidant activity. A research conducted by Zhang *et al*. (2009) found that the *n*-butanol extract obtained from the 95% ethanol extract of mangosteen pericarp demonstrated stronger antioxidant activities and higher content of flavonoids and polyphenols than other extracts. For the other three fractions, Zhou *et al*. (2011) investigated the antioxidant activities of petroleum ether, ethyl acetate and water extracts and the results indicated that the ethyl acetate extract had the highest antioxidant activity and total phenolic content and followed by the water extract, while those of petroleum ether extract were very low.

As the pericarp of mangosteen fruit owns plenty of antioxidants and a significantly inhibitory effect on lipase, it may provide health benefits including anti-obesity by lowering the intake of energy from dietary fat. Commonly mangosteen pericarp is discarded as it is inedible; however, that would be a huge waste of active components especially antioxidants in it.

CONCLUSION

Using a copper-soap photometric method, the effects of eighteen natural food products on the pancreatic lipase activity were determined *in vitro*. Mangosteen pericarp, lemon pulp, celery, cucumber and dry longan were found to be effective in suppressing the lipase activity and dried red chili, green chili and dry clove had the opposite effect, while shiitake mushroom, ginger, oregano leaf, green bell pepper, lemon peel, cinnamon and dry tangerine had no significantly inhibitory or promoting effect. Among them, the lipase-inhibitory effect of mangosteen pericarp was the most significant and was in a dose-dependent manner and the fractioning of mangosteen pericarp crude extract demonstrated that the *n*-butanol fraction contributed to the most of lipase-inhibitory effect of mangosteen pericarp. Based on the significant anti-lipase property, mangosteen pericarp is worthy of utilization as functional food constituents for the prevention and treatment of obesity.

ACKNOWLEDGMENT

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