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PHYTOCHEMICAL ANALYSIS OF *ELATERIOSPERMUM TAPOS* AND ITS INHIBITORY EFFECTS ON ALPHA-AMYLASE, ALPHA-GLUCOSIDASE AND PANCREATIC LIPASE

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Elateriospermum tapos contains high unsaturated fat and phytochemicals with many health benefits. This paper focuses on activities and inhibitory effects of *E. tapos* on digestive enzymes. Cold water, hot water and 70% ethanol extracts of the seed and shell of the fruit of *E. tapos* were used in this study. The extracts were screened for antioxidant activity, total phenolic content, total flavonoid content, and inhibitory effects on α-amylase, α-glucosidase and pancreatic lipase. Hot water extraction of shell of the *E. tapos* fruit had the highest total phenolic content (1298.60 ± 4. 24 µg GAE 100 g^{-1}), total flavonoid content (16685.58 ± 487.77 µg CE 100 g^{-1}) and antioxidant activity by 2, 2-diphenyl-2-picrylhydrazyl and β-carotene methods (84.16 and 122.17% respectively). The seed cold extract showed maximum α-amylase inhibition with IC_{50} (half maximal inhibitory concentration) of 0.03 mg mL^{-1}. The lowest IC_{50} (0.02 mg mL^{-1}) for α-glucosidase inhibition was from seed ethanol extracts while shell cold extract had the lowest IC_{50} for pancreatic lipase inhibition (37.80 mg mL^{-1}). Results confirmed *E. tapos* as potential antioxidant and inhibitor of digestive enzymes for lipid (pancreatic lipase) and carbohydrate (α-amylase and α-glucosidase) which are beneficial to combat obesity and diabetes.

Keywords: Antioxidant, total phenolic content, flavonoid, digestive enzymes, obesity, diabetes

INTRODUCTION

The digestion of carbohydrates is primarily carried out by digestive enzymes including amylase and glucosidase (Rossi et al. 2006) while pancreatic lipase is responsible for fat hydrolysis (Zhang et al. 2015). Orlistat, the drug treatment for obesity has been reported to be a potent inhibitor of carboxylester lipase, gastric lipase and pancreatic lipase (Sahib et al. 2012). However, this drug poses undesirable side effects such as gastrointestinal disorders (bloating, flatulence and diarrhoea) (Johansson et al. 2009, Florez et al. 2010). Since dietary triglyceride and carbohydrate are the main sources of ingested lipid and glucose respectively, controlling the absorption of these nutrients is the most effective approach to prevent excess calorie and sugar intake.

Phenolic compounds possess a broad array of biochemical agents including antioxidant, anti-mutagenic, anti-cancer agents (Nakamura et al. 2003) and show valuable therapeutic potential for diabetes and other obesity-related complications such as hyperlipidemia (Alam et al. 2016). Polyphenols can act as a hypolipidemic agent by reducing cholesterol level in obese rats (Son et al. 2010). Studies also reported protective links between flavonoids and cardiovascular diseases and cancer (Kris-Etherton et al. 2004). Unfortunately, there are very limited studies to prove the potential of natural products as anti-obesity agents. Phenols and flavonoids facilitate weight loss through regulation of different pathways, including triglycerides absorption, energy consumption and spending and lipid hydrolysis (Mohamed et al. 2014, Torres-Fuentes et al. 2015).

Elateriospermum tapos (Euphorbiaceae), locally known as *perah*, is abundant in Peninsular

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Malaysia, particularly in Pahang (Osada et al. 2003, Ooi & Salimon 2006). *Elateriospermum tapos* seed is eaten once cooked or fermented (Lim 2012). Various parts of *E. tapos* have been used by aboriginals to treat injuries. The bark, leaves and fruit stalks produce white and sticky latex which is used to treat cracked soles of the feet (Chai et al. 1989, Lim 2012). In Sumatra, Indonesia the latex is used to heal wounds. The oil from *E. tapos* seed has significant concentrations of α-linolenic acid, oleic acid, linoleic acid, gamma-linolenic acid and palmitoleic acid which are essential to human well-being (Hamidah et al. 2011, Husin et al. 2013). This study was aimed at determining the total phenolic and total flavonoid contents of three different extracts from the shell and seed of *E. tapos*, and to evaluate their inhibitory activities on digestive enzymes.

MATERIALS AND METHODS

Plant sample preparation

Fresh fruits of *E. tapos* were collected from the Forest Research Institute Malaysia substation in Maran, Pahang. The specimen was deposited at the Institute of Bioscience, Universiti Putra Malaysia with voucher number SK3154/17. After being oven dried (60 °C) overnight, the seeds were separated from the shell and ground and then sieved.

Hot, cold aqueous and ethanol extraction

Samples were extracted using three extraction methods (hot, cold and ethanol). For hot extract, powdered samples in distilled water (1:10 w/v) were soaked at 70 °C for 24 hours (Cheurfa & Allem 2015). For cold extraction, samples in 500 mL distilled water were left at 28 °C for 2 days (Rahimzadeh et al. 2014). The aqueous extracts were filtered then freeze dried. For ethanol extraction, 50 g of samples were extracted in 70% ethanol at a ratio 1:9 for 3 days (Cheurfa & Allem 2015). The mixture was agitated, filtered and evaporated at 40 °C before storage.

Preparation of test concentration

Aqueous (hot and cold) and ethanol extracts of samples were dissolved in 2% dimethyl-sulfoxide (DMSO) and 70% ethanol respectively to give a stock solution of 50 mg mL^{-1}. Subsequently, 1 mL aliquot of each stock solution was used to give a final concentration of 0.1 mg mL^{-1}.

Total phenolic content analysis

Folin-Ciocalteu assay was used to analyse the total phenolic content (TPC) (Kong et al. 2001). Folin-Ciocalteu (0.2 N, 0.15 mL) was diluted in 15 mL distilled water. An amount of 0.6 g sodium bicarbonate (Na_2CO_3) was added in 10 mL distilled water. Sample concentrations from 250 µg mL^{-1} were prepared at two fold dilution. Following that, 20 µL of sample or standard, 100 µL Folin-Ciocalteu reagent and 80 µL Na_2CO_3 were added into wells of a 96-well plate and agitated for 20 min after which the absorbance was read at 725 nm using microplate reader. Gallic acid solution was used as standard (250, 125, 62.5, 31.25, 15.63, 7.8, 3.9, 1.95 and 0 µg mL^{-1}) and was prepared using the similar procedure. The assay was conducted in triplicate and results were expressed as mg gallic acid equivalents (GAE) g^{-1} of sample.

Total flavonoid content analysis

Aluminium chloride colorimetric assay was used to analyse total flavonoid content in the samples (Baba & Malik 2015). Samples (2500 µg mL^{-1}) and standard solutions of catechin (2500, 1250, 625, 312.5, 156.25, 78.125, 39, 19.5, 9.8, 4.88 and 0 µg mL^{-1}) were prepared by serial dilution. Next, 20 µL of sample was mixed with 6 µL of 5% $NaNO_2$ solution and 48 µL distilled water and 6 µL of 10% $AlCl_3$ solution was added after 5 min of incubation. The mixture was allowed to stand for 6 min before 40 µL of 1 mol mL^{-1} NaOH solution was added and the final volume was brought to 80 µL with double-distilled water. The mixture was allowed to stand for 15 min and the absorbance was read at 510 nm using microplate reader. The assay was conducted in triplicate and results were expressed as mg catechin equivalents (CE) g^{-1} of the sample.

DPPH for radical scavenging method

The 2, 2-diphenyl-2-picrylhydrazyl (DPPH) assay was used (Brand-Williams et al. 1995) to measure the radical scavenging activity of *E. tapos* extracts The extracts were diluted from the stock solution described above. Several different concentrations of the extracts (1000, 500, 250, 125, 62.5, 31.25,

and 15.6 μg mL^{-1}) were prepared by serial dilution from 1 mL of stock solution. The similar procedure was repeated using standard butylated hydroxytoluene (BHT). Methanolic DPPH was prepared by adding 2.8 mg of DPPH in 35 mL methanol. Following this, 100 μL of the DPPH and 100 μL of sample or standard were added into the wells of a 96-well plate. The samples were read at 517 nm after incubation at 37 °C in the dark for 20 min. The assay was conducted in triplicate.

Beta-carotene bleaching assay

This method was adapted from Velioglu et al. (1998). BHT was used as standard. An amount of 2.0 mg of β-carotene was dissolved in 10 mL chloroform, 0.02 mL linoleic acid and 0.2 mL Tween 40. Chloroform was evaporated using rotary evaporator and 50 mL of distilled water were added to the mixture. Sample extract or standard was mixed in the 96-well plate then incubated for 2 hours at 50 °C before reading at different times (0, 20, 40, 60, 80, 100 and 120 min) using microplate reader. The samples were read at 470 nm after incubation for 2 hours at 50 °C. The assay was conducted in triplicate.

Alpha-amylase inhibitory assay

The method for α-amylase inhibitory assay was based on Rahimzadeh et al. (2014). Alpha-amylase (0.5 mg) was dissolved in 1 mL of 20 mM phosphate buffer (pH 6.9 with 6.7 mM NaCl). Next, 50 μL α-amylase was added into 50 μL of sample extract and the mixture was then incubated at room temperature for 30 min. Starch solution (1% w/v, 50 μL) in 20 mM sodium phosphate buffer was added to each tube within 5 s and the mixture was incubated again for 3 min. Dinitrosalicylic acid colour reagent (100 μL) was added to stop the reaction. The mixture was then incubated in a water bath at 85 °C for 15 min and cooled to room temperature before being diluted with 900 μL distilled water. An amount of 200 μL of the solution was aliquoted into the 96-well plate. The assay was conducted in triplicate. Absorbance (A) was read at 540 nm and the inhibition (%) was calculated as below:

$$\text{Percentage of inhibition (\%)} = [1 - (\Delta A_{sample} / \Delta A_{control})] \times 100$$

Alpha-glucosidase inhibitory assay

Alpha-glucosidase inhibitory assay was conducted following the method adapted from Bhutkar and Bhise (2012). The α-glucosidase was dissolved in phosphate buffer (0.1 M, pH 6.9) to a concentration of 1 unit mL^{-1}. Sample extract (50 μL) were added to wells containing 25 μL of α-glucosidase (0.15 unit mL^{-1}) and 25 μL of glutathione (3 mM). The mixture was incubated at 37 °C for 5 min and the absorbance was read at 450 nm. An amount of 50 μL of p-nitrophenyl-α-D-glucopyranoside substrate solution (5 mM) in 0.1 M phosphate buffer (pH 6.9) were added at 5 s intervals and the mixture was incubated at 37 °C for 30 min. The reaction was stopped by adding 100 μL of sodium carbonate solution (0.1 M). The assay was conducted in triplicate. Absorbance was measured at 405 nm and the inhibition (%) was calculated as the above.

Pancreatic lipase inhibitory assay

The assay was conducted based on the method by Chater et al. (2016). Crude porcine pancreatic lipase (PPL) (1 mg mL^{-1}) was prepared by suspending in a Tris-HCl buffer (2.5 mM, pH 7 with 2.5 mM NaCl) and centrifuging at 1500 rpm for 10 min. The p-nitrophenyl butyrate substrate was dissolved in acenonitrile to give a concentration of 0.1 mM. PPL solution (50 μL) was then added into 100 μL sample extract and then diluted to 1 mL using Tris-HCl buffer. The mixture was then incubated at 37 °C for 15 min after which 100 μL of the mixture was aliquoted into wells and the absorbance was measured at 405 nm. The assay was conducted in triplicate. Change in absorbance (A) from the initial time ($T_{initial}$) was calculated as below and percentage of inhibition, as the above.

$$\Delta A_{405} = (A_{405})_{initial} - (A_{405})_{final}$$

Statistical analysis

Data were analysed using IBM SPSS v23 software and expressed as means ± standard deviations. One-way analysis of variance (ANOVA) followed by least significant difference post hoc test was used in the data analysis and p-value < 0.05 was considered as significant.

RESULTS

Total phenolic content

In comparison with seed extract, shell extract had higher TPC (Table 1). Significant differences were observed across samples. Shell hot water extract had the highest TPC (1298.60 ± 4.24 μg GAE 100 g^{-1}) followed by shell cold water extract (537.19 ± 4.58 μg GAE 100 g^{-1}), seed cold water extract (34.01 ± 0.80 μg GAE 100 g^{-1}), seed hot water extract (15.81 ± 0.29 μg GAE 100 g^{-1}), shell ethanol extract (3.60 ± 0.07 μg GAE 100 g^{-1}) and the lowest, seed ethanol extract (0.46 ± 0.06 μg GAE 100 g^{-1}).

Total flavonoid content

Significant differences were observed between all sample extracts (Table 2). As in TPC, total flavonoid content was highest in shell hot water extract (16,685.58 ± 487.77 μg CE 100 g^{-1}). This was followed by shell cold water extract (4462.26 ± 241.57 μg CE 100 g^{-1}), seed hot water extract (27.56 ± 2.93 μg CE 100 g^{-1}) and seed cold water extract (24.79 ± 0.00 μg CE 100 g^{-1}). Ethanol extracts had low total flavonoid content and that from from the seed was the lowest (0.17 ± 0.09 μg CE 100 g^{-1}).

DPPH antioxidant activity

Significant differences in DPPH antioxidant activity were observed between samples. Shell extraction exhibited much higher antioxidant activity than seed extraction (Table 3). Shell hot water extract had the highest antioxidant activity (84.16%), followed by shell cold water (79%), shell ethanol (77.26%), seed cold water (11.51%), seed hot water (4.51%) and finally, seed hot water extract (3.12%).

Beta-carotene anti-oxidant activity assay

All sample extracts were significantly different from each other (Table 4). Shell hot water had the highest antioxidant activity (122.17%). This was followed by seed ethanol extract (47.29%),

Table 1 Total phenolic content (μg GAE 100 g^{-1})

Sample	Types of extract		
	70% ethanol	Hot water	Cold water
Shell	3.60 ± 0.07^{a}	1298.60 ± 4.24^{b}	537.19 ± 4.58^{c}
Seed	0.46 ± 0.06^{d}	15.81 ± 0.29^{e}	34.01 ± 0.80^{f}

Results are expressed as means ± standard deviations; values with different letters differ significantly at $p < 0.05$

Table 2 Total flavonoid content (μg GAE 100 g^{-1})

Sample	Types of extract		
	70% ethanol	Hot water	Cold water
Shell	12.92 ± 0.62^{a}	16685.58 ± 487.77^{b}	4462.26 ± 241.57^{c}
Seed	0.17 ± 0.09^{d}	27.56 ± 2.93^{e}	24.79 ± 0.00^{de}

Results are expressed as means ± standard deviations; values with different letters differ significantly at $p < 0.05$

Table 3 DPPH antioxidant scavenging activity (%)

Sample	Types of extract		
	70% ethanol	Hot water	Cold water
Shell	77.26 ± 0.24^{a}	84.16 ± 0.00^{b}	79.00 ± 0.18^{c}
Seed	3.12 ± 0.12^{d}	4.51 ± 0.72^{e}	11.51 ± 0.54^{f}

Results are expressed as means ± standard deviations; values with different letters differ significantly at $p < 0.05$

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Table 4 Antioxidant activity by β-carotene bleaching assay (%)

Sample	Types of extract		
	70% ethanol	Hot water	Cold water
Shell	18.22 ± 5.91[a]	122.16 ± 0.00[b]	35.57 ± 0.00[c]
Seed	47.29 ± 0.85[d]	ND	ND

Results are expressed as means ± standard deviations; values with different letters differ significantly at $p < 0.05$; ND = not determined

cold water extraction (35.57%) and lastly, shell ethanol extract (18.23%). However, the values for seed hot water and seed cold water extracts could not be determined.

Alpha-amylase inhibition assay

Alpha-amylase inhibition assay showed that the highest IC_{50} (half maximal inhibitory concentration) was observed in shell ethanol extract (0.07 ± 0.01 mg mL^{-1}) followed by seed ethanol extract (0.06 ± 0.00 mg mL^{-1}), shell cold water extract (0.06 ± 0.01 mg mL^{-1}), seed hot water extract (0.05 ± 0.01 mg mL^{-1}) then closely followed by shell hot extract and seed cold extract (0.03 ± 0.00 and 0.03 ± 0.00 mg mL^{-1} respectively) (Table 5).

Alpha-glucosidase inhibition assay

In the α-glucosidase inhibition assay, shell cold extract showed the highest IC_{50} value (0.09 mg mL^{-1}) closely followed by seed cold extract (0.08 ± 0.01 mg mL^{-1}), seed hot extract (0.05 ± 0.00 mg mL^{-1}), shell hot extract (0.04 ± 0.00 mg mL^{-1}), then shell (0.03 ± 0.01 mg mL^{-1}) and finally seed ethanol extracts (0.02 ± 0.00 mg mL^{-1}) (Table 5).

Pancreatic lipase inhibition assay

Pancreatic lipase inhibition of shell ethanol extract had the highest IC_{50} value (250.2 ± 0.01 mg mL^{-1}), followed by seed ethanol extract (95.8 ± 0.01 mg mL^{-1}), then seed hot water extract (71.8 ± 0.02 mg mL^{-1}), seed cold water extract (46.9 ± 0.00 mg mL^{-1}), shell hot water extract (46.8 ± 0.01 mg mL^{-1} and, finally, shell cold water extract had the lowest IC_{50} (37.9 ± 0.00 mg mL^{-1}) (Table 5).

DISCUSSION

Vernarelli and Lambert (2017) succeeded in showing that flavonoids consumption was inversely associated with obesity in both women and men. The study demonstrated significant lower body mass index and waist circumference in samples in the high quartile flavonoid intake compared with those in the low quartile. This indicated that flavonoid plays a key role in weight loss management. Meanwhile, the digestive enzymes inhibition is a common assay used to determine the potential effect of medicinal plants against obesity (Bustanji et al. 2011). Inhibition of digestive enzymes including α-amylase, α-glucosidase and pancreatic lipase limits the absorption of lipid and carbohydrates leading to weight loss.

In this study, shell extracts had higher TPC compared with seed extract. This study had similar findings with Villarreal-Lozoya et al. (2007) and Fu et al. (2014) who worked on *Jatropha curcas* which is in the same family as *E. tapos*. The study reported that shell contained high TPC, which may be interrelated with the function of the shell for protection of the seed. A study by Tan et al. (2014) using seed of *E. tapos* found that ethanol extraction gave the lowest TPC compared with other extraction methods similar to this study. Hot aqueous extraction was reported to have higher TPC compared with ethanol extraction (Gan et al. 2013). Heat causes disintegration of the covalent bonds of phenolic compounds causing maximum increase in TPC (Ghimeray et al. 2013). It may also be due to the fact that phenolic compounds and flavonoids, both polar compounds, display high solubility in aqueous solvents than in organic solvents (Nyirenda et al. 2012).

Total flavonoid content depends on the phenolic compound in the samples (Kopjar et al. 2009, Stanković 2011). The colour of the *E. tapos* shell is reddish brown, indicating the presence phenols and polyphenols for protection of the seed. The existence of phenols and polyphenols in the external part of the seed provide structural support to plants (Loginov et al. 2013). Thus, shell as waste plant material

Table 5 IC_{50} (half maximal inhibitory concentration) of all the inhibitory assays on digestive enzymes of different parts and extraction of *E. tapos*

Extract		IC_{50} (mg mL^{-1})		
		α-amylase	α-glucosidase	Pancreatic lipase
Hot extraction	Seed	0.05 ± 0.01 *	0.05 ± 0.00**	71.8 ± 0.02*
	Shell	0.03 ± 0.00**	0.04 ± 0.00*	46.8 ± 0.01**
Cold extraction	Seed	0.03 ± 0.00**	0.08 ± 0.01*	46.9 ± 0.00*
	Shell	0.06 ± 0.01**	0.09 ± 0.00**	37.9 ± 0.00**
70% ethanol extraction	Seed	0.06 ± 0.00*	0.02 ± 0.00*	95.8 ± 0.01*
	Shell	0.07 ± 0.01*	0.03 ± 0.01*	250.2 ± 0.01*
Orlistat		0.01 ± 0.00**	0.06 ± 0.01**	17.2 ± 0.00*
Acarbose		14.91 ± 0.01*	0.04 ± 0.00*	0.153 ± 0.00*

* and ** = values are significantly different at $p < 0.05$ and $p < 0.01$ respectively

could instead represent an important new source of natural antioxidant. Fruit peel has higher antioxidant activity than its edible pulp (Lim et al. 2013, Okonogi et al. 2007). This may due to the high content of phenolic compounds such as procyanidins, anthocyanins, flavonoids and total polyphenols in waste part of the fruits compared to the edible part (Duda-Chodak & Tarko 2007). Meanwhile, water extracts of both shell and seed demonstrated higher DPPH activity as compared ethanol extract. A similar trend was observed in DPPH radical scavenging study of *Centaurea* species whereby water extraction had higher scavenging activity than methanol extraction (Aktumsek et al. 2013).

In β-carotene assay, hot shell extracts demonstrated the highest antioxidant activity. Similarly, a study of seaweed by Ismail and Tan (2012) revealed that water extraction produced extracts containing higher antioxidant activity compared with ethanol extraction. In contrast, for the seed part, the highest antioxidant activity was for the 70% ethanol extract. As mentioned by Husin et al (2013), fermented seed has higher unsaturated fat content as compared with the fresh seed. Lipid substrates are highly prone to be oxidised due to their composition of oxygen-derived free radicals. High content of antioxidant can affect the activities of unsaturated fat in human body by lowering lipid peroxidation which leads to the inhibitory effects of digestive enzymes. Thus, high concentrations of polyunsaturated fatty acids increases oxygen usage and elevates redox metal ions which will cause reduction in antioxidant activity in the sample (Kotegagilu et al. 2015).

Overall, water extraction had better results in α-amylase inhibition. The results provided a hint that the plant may contain potential α-amylase and α-glucosidase inhibitors which are lipophilic and more soluble in organic solvents (Ye et al. 2010). Alcohol forms strong hydrogen bonds with water molecules, making it hydrophilic. As the size of the alkyl group increases, the van der Waals interactions increase to a point where they can dominate the hydrogen bond, and thus transforming the character of the alcohol to be lipophilic (Ye et al. 2010).

The greater effect of α-amylase and α-glucosidase inhibition in *E. tapos* seed extract may be due to the high contents of fatty acids in the seed (Podsedek et al. 2014). These fatty acids were previously identified to possess inhibitory effects against α-amylase and α-glucosidase (Rosak & Mertes 2012). The better inhibitory effect may be attributed to the high-flavonoid and phenolic contents, as well as antioxidant and free radical scavenging activities found in the shell of *E. tapos* (Kazemipoor et al. 2015). The potential of *E. tapos* to inhibit pancreatic lipase activity may also be attributed by fatty acids including palmitic, oleic and linoleic acids in its seed as well as phytochemical compounds such as tannins, flavonoids, alkaloids and phenolic compounds present in the seed and shell (Hamidah et al. 2011). A study of pancreatic lipase inhibition activity of *Ginkgo biloba* also found that the pancreatic lipase inhibition was associated with the presence of fatty acid in the extract (Bustanji et al. 2011). Presently available synthetic drugs such as acarbose have strong α-amylase inhibitory effect, leading to gastrointestinal adverse effects

such as flatulence and abdominal discomfort due to unusual fermentation of undissolved carbohydrates by bacteria in the colon (Tiwari et al. 2011, Boeing et al. 2014). Therefore, a combination of potent α-glucosidase inhibition with moderate α-amylase inhibitory activity may offer a better approach with lesser side effects to control the amount of glucose available for absorption.

CONCLUSIONS

Shell hot extract exhibited greater TPC, total flavonoid content and anti-oxidant activity and thus, appeared to be a promising anti-obesity agent. The inhibitory activities of *E. tapos* seed and shell extracts against pancreatic lipase, α-amylase, α-glucosidase observed in this study strongly highlighted their potential as health supplements.

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