Phenolic Profile of Nipa Palm Vinegar and Evaluation of Its Antilipidemic Activities

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1.Introduction

Lipid metabolism disorders are commonly found in people who are obese. The prevalence of obesity and overweight has dramatically increased in developed and developing countries due to the increased consumption of high-fat diets and the daily intake of alcohol [1]. Obesity and overweight are associated with hyperglycemia and dyslipidemia in children and adolescents [2]. Dyslipidemia is a group of metabolic disorders and a noncommunicable disease manifested by elevation of serum cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride concentrations and a decrease in high-density lipoprotein (HDL) cholesterol concentration. It is one of the major risk factors associated with atherosclerosis which leads to the development of cardiovascular diseases and increased mortality [3]. Orlistat is a weight loss agent which inhibits gastric and pancreatic lipases in the lumen of the gastrointestinal tract delaying absorption of dietary fat that is approved by the Food and Drug Administration for the treatment of obesity. It also improves total cholesterol and low-density lipoprotein for the treatment of dyslipidemia. The major side effects, which occur at an early stage of treatment with orlistat, are mainly gastrointestinal [4]. Simvastatin is a HMG-CoA reductase inhibitor which is commonly used to decrease blood cholesterol and triglyceride levels. The major adverse effects of...
statins are myositis, myalgia [5], rhabdomyolysis [6], and hepatic disorders [7].

Recently, natural products have been reported to have the potential to be developed faster and cheaper than conventional single drug. For example, curcumin, lycopene, monacins, ankaflavin, oleanolic acid, ursolic acid, berberine, amphetamine, tanshinone IIA, hesperetin, and naringenin inhibit cholesterol absorption in enteroctyes [8]. Thus, natural products, especially phenolic compounds of these products, may inhibit pancreatic lipase, cholesterol esterase, and solubility of cholesterol micelles. Vinegar is generally used as a food condiment and as an alternative medicine for obesity [9], hyperlipidemia [10], hyperglycemia [11], and cancer [12] and as a disinfectant [13]. The nipa palm (Nypa fruticans Wurmb, voucher no. 01518) was deposited at Botanic Garden, Walailak University, Nakhon Si Thammarat, Thailand (8′12″51′′ N, 100′14″51.7′′ E). All parts of the nipa palm were authenticated and a voucher number (Nypa fruticans Wurmb, voucher no. 01518) was deposited at Botanic Garden, Walailak University, Nakhon Si Thammarat, Thailand. The nipa palm sap was collected from cut stalks. The nipa palm sap was fermented to nipa palm vinegar by the local traditional method. In brief, the collected nipa palm sap was placed in terracotta jars for 40 days at room temperature to allow the natural fermentation process to occur. The level of acidity of nipa palm vinegar reaches 4 to 5%.

2.1. Chemicals and Reagents. All chemicals and reagents of analytical grade. Folin–Ciocalteu phenol reagent, sodium carbonate, gallic acid, porcine pancreatic lipase, 4-methylumbelliferone, phosphate buffer solution, sodium chloride, orlistat, taurocholic acid, p-nitrophenylbutyrate (p-NPB), sodium phosphate buffer, sodium chloride, porcine pancreatic cholesterol esterase, simvastatin, cholesterol, oleic acid, phosphatidylcholine, methanol, and taurocholate salt were purchased from Sigma-Aldrich (St. Louis, MO).

2.2. Preparation of Nipa Palm Vinegar. Nipa palm sap was collected from Pak Phanang District, Nakhon Si Thammarat, Thailand (8′12″51′′ N, 100′14″51.7′′ E). After incubation for 30 min at room temperature, the absorbance was measured at 765 nm. A calibration curve was plotted using gallic acid solutions (31.25, 62.5, 125, 250, and 500 µg/mL). Total phenolic content was determined as µg gallic acid equivalent per ml of nipa palm vinegar (µg GAE/mL).

2.4. Determination of Phenolic Compounds by LC-MS Analysis. Nipa palm vinegar was subjected to commercial LC-MS analysis by the Central Laboratory Co., Ltd. (Bangkok, Thailand) essentially as described elsewhere [18]. Mass spectra data were recorded in ionization mode for a mass range of m/z 100–700. Phenolic standards from Sigma-Aldrich (St. Louis, MO) were gallic acid (≥99% purity), tannic acid (≥99% purity) and hydroquinone (≥99% purity), catechin (≥98% purity), rutin (≥94% purity), isoquercetin (98% purity), eriodictyol (98% purity), quercetin (95% purity), apigenin (≥95% purity), and kaempferol (≥97% purity), and their purity was determined by high-performance liquid chromatography (HPLC).

2.5. Pancreatic Lipase Inhibition Assay. Pancreatic lipase inhibition assay was undertaken as described by Adisakwattana et al. [19]. In brief, 25 µL of nipa palm vinegar diluted with distilled water, or positive control (orlistat), was mixed with 25 µL of porcine pancreatic lipase solution and 50 µL of olate ester of 0.1 mM fluorescent 4-methylumbelliferone (4-MUO) solution in phosphate buffer saline, subsequently. The mixture was incubated at 37°C for 20 min. Reaction was stopped by adding 100 µL of 0.1 M sodium citrate at pH 4.2. The fluorescence of 4-methylumbelliferone released by the lipase was measured at excitation and emission wavelengths of 320 and 450 nm, respectively. Control without sample or orlistat represented 100% pancreatic lipase (PL) activity. The tests were performed in triplicate.

2.6. Pancreatic Cholesterol Esterase Inhibition Assay. The pancreatic cholesterol esterase inhibition assay was performed according to a previously published method [20]. In brief, different concentrations of nipa palm vinegar were incubated with mixtures containing 5.16 mM taurocholic acid, 0.2 mM p-nitrophenylbutyrate (p-NPB), sodium phosphate buffer, and 100 mM NaCl at pH 7.0. Porcine pancreatic cholesterol esterase at concentration of 1 µg/mL was added into the reaction tube, and samples were incubated at 25°C for 5 min. After that, the absorbance of the solutions was measured at 450 nm. Simvastatin served as a positive control. Results were based on triplicate analysis.

2.7. Cholesterol Micellization Assay. Cholesterol micelles served as a model system for in vitro cholesterol micellization and were prepared according to a previous method [21]. In brief, the micelle solution (2 mM cholesterol, 1 mM oleic acid, and 2.4 mM phosphatidylcholine) was dissolved in methanol and then dried under nitrogen. After that, 15 mM phosphate-buffered saline (PBS) solution containing 6.6 mM taurocholate salt, pH 7.4, was added onto the dried micelles. The emulsion was sonicated twice for 30 min using
3. Results

3.1. Determination of Total Phenolic Content. The amount of total phenolics in nipa palm vinegar (NPV) was determined using the Folin–Ciocalteu method. The value was determined as µg gallic acid equivalent per ml of NPV (µg GAE/mL). The phenolic content of NPV was determined to be 167.10 ± 10.15 µg GAE/mL.

3.2. Phenolic Profile of Nipa Palm Vinegar Determined by LC-MS. LC-MS was used to identify of phenolic compounds. Gallic acid, tannic acid and hydroquinone, catechin, rutin, isoquercetin, eriodictyol, quercetin, apigenin, and kaempferol were used as standards (as shown in Table 1). The contents of gallic acid (peak 1), isoquercetin (peak 5), quercetin (peak 8), catechin (peak 2), and rutin (peak 4) were 14.14, 11.27, 10.33, 8.61, and 6.67 µg/mL in NPV, respectively (as shown in Figure 1), while hydroquinone, tannic acid, eriodictyol, apigenin, and kaempferol were not detected in NPV.

3.3. Pancreatic Lipase Inhibitory Activity of Nipa Palm Vinegar. The inhibitory activity of nipa palm vinegar against pancreatic lipase is shown in Figure 2. The nipa palm vinegar inhibited pancreatic lipase activity by 9.55, 12.51, 19.65, 28.14, 50.53, and 60.22% at concentrations of 3.13, 6.25, 12.50, 25.00, 50.00, and 100.00 µL/mL, respectively. The nipa palm vinegar had an IC₅₀ value of 69.95 µL/mL. Orlistat served as a pancreatic lipase inhibitor control, and a concentration of 2 µg/mL reduced activity by 53.67%. These results show that the NPV showed a lipase inhibiting activity.

3.4. Pancreatic Cholesterol Esterase Inhibitory Activity of Nipa Palm Vinegar. The nipa palm vinegar inhibited cholesterol esterase by 8.78, 16.33, 19.48, 23.02, 26.22, and 36.66% at concentrations of 3.13, 6.25, 12.50, 25.00, 50.00, and 100.00 µL/mL, respectively (Figure 3). Simvastatin at a concentration of 300 µg/mL was used as a positive control which inhibited cholesterol esterase by 41.66%. These findings show that the NPV has the ability to inhibit cholesterol esterase in a dose-dependent manner.

3.5. Effect of Nipa Palm Vinegar on Cholesterol Micellization. The inhibition of cholesterol micellization by NPV at various concentrations is shown in Figure 4. The NPV suppressed cholesterol micellization by 13.46, 19.23, 25.00, 38.46, and 46.15% at concentrations of 12.50, 25.00, 50.00, 100.00, and 200.00 µL/mL, respectively. Gallic acid at a concentration of 200 µg/mL was used as a positive control which inhibited cholesterol micellization by 84.62%. These results show that the NPV can inhibit the formation of cholesterol micellization in a dose-dependent manner.

3.6. Correlation Analyses of Pancreatic Lipase Inhibition, Pancreatic Cholesterol Esterase Inhibition, and Cholesterol Micellization Inhibition of Nipa Palm Vinegar. The linear regression analysis and correlation coefficients between the variables are presented in Figure 5. There were strongly positive correlations between % pancreatic lipase inhibition and % cholesterol esterase inhibition ($R^2 = 0.8801$) at concentrations of 3.13, 6.25, 12.50, 25.00, 50.00, and 100.00 µL/mL (Figure 5(a)). A strongly positive correlation was also found between the % pancreatic lipase inhibition and % cholesterol micellization inhibition ($R^2 = 0.8919$) at concentrations of 12.50, 25.00, 50.00, and 100.00 µL/mL (Figure 5(b)). Moreover, a positive correlation was also observed between % cholesterol micellization inhibition and % cholesterol (Figure 5(c)) esterase inhibition ($R^2 = 0.9943$).

4. Discussion

Dyslipidemia is a key risk factor in the development of cardiovascular diseases which leads to increased morbidity and mortality [8]. Natural products have been used as an alternative medicine for the prevention and management of cardiovascular diseases [22]. There are many risk factors for dyslipidemia including genetic factors, hormonal abnormalities, and lifestyle factors. A diet especially high in fat is believed to be one of the greatest risk factors for the development of dyslipidemia [23]. Normally, pancreatic lipase is a key enzyme that hydrolyses ester linkages of triglyceride [24]. Therefore, pancreatic lipase inhibition is a goal to reduce fat absorption to control dyslipidemia. Pancreatic cholesterol esterase is an enzyme which hydrolyses cholesterol esters, so inhibition of pancreatic cholesterol esterase can reduce cholesterol absorption and may be useful for therapeutics for controlling cholesterol [25]. Moreover, the reduction of micelle formation is a target for lowering blood cholesterol level [21]. This study evaluated nipa palm vinegar for its total phenolic content and the presence of phenolic compounds as well as determined its ability to inhibit pancreatic lipase, inhibit cholesterol esterase, and inhibit cholesterol micellization.

Natural phenolic compounds as secondary metabolites of plants consist of phenolic acids, flavonoids, tannins, stilbenes, curcuminoids, coumarins, lignans, quinones, and others [26]. Phenolic compounds have been shown to have...
several pharmacological effects including antioxidant [27], anti-hyperlipidemic activity [28], anti-hypertensive activity [29], antimutagenic activity [30], anti-inflammatory activity [31], antidiabetic effect [32], and anticancer [33].

The total phenolic content in NPV was determined by the Folin–Ciocalteu assay. In this study, the NPV contained 0.000 µL/mL. Values are expressed as mean ± SD of triplicate measurements.

Several pharmacological effects including antioxidant [27], anti-hyperlipidemic activity [28], anti-hypertensive activity [29], antimutagenic activity [30], anti-inflammatory activity [31], antidiabetic effect [32], and anticancer [33]. The total phenolic content in NPV was determined by the Folin–Ciocalteu assay. In this study, the NPV contained

Table 1: LC-MS characteristics of phenolic compounds in nipa palm vinegar.

| Peak | Compounds     | Retention time (min) | [M + H]+ (m/z) | Contents (µg/mL) |
|------|---------------|----------------------|----------------|---------------|
| 1    | Gallic acid   | 5.60 ± 0.99          | 188.0          | 14.14 ± 0.07  |
| 2    | Catechin      | 12.40 ± 0.08         | 185.0          | 8.61 ± 0.32   |
| 3    | Tannic acid   | 12.82 ± 0.04         | 503.0          | ND            |
| 4    | Rutin         | 15.05 ± 0.17         | 649.0          | 6.67 ± 0.03   |
| 5    | Isoquercetin  | 16.12 ± 0.21         | 329.0          | 11.27 ± 0.12  |
| 6    | Hydroquinone  | 24.56 ± 0.20         | 289.0          | ND            |
| 7    | Eriodictyol   | 30.71 ± 0.55         | 327.0          | ND            |
| 8    | Quercetin     | 33.02 ± 0.36         | 341.0          | 10.33 ± 0.16  |
| 9    | Apigenin      | 41.08 ± 0.40         | 271.0          | ND            |
| 10   | Kaempferol    | 42.37 ± 7.97         | 287.0          | ND            |

ND: not detected; data are expressed as mean ± standard deviation in triplicate.
167.10 ± 10.15 µg GAE/mL. According to a previous study, nipa sap vinegar produced by surface fermentation contained a phenolic content of 253.98 ± 0.14 µg GAE/mL and showed antioxidant activity against DPPH free radicals [34]. Moreover, phenolic compounds were determined by LC-MS, and the results showed that nipa palm vinegar contains gallic acid, isoquercetin, quercetin, catechin, and rutin.
Orlistat is a well-known pancreatic lipase inhibitor which is produced from Streptomyces toxytricini. It reacts with lipases at the active site serine by forming a covalent bond and thus inactivating the ability of these enzymes to hydrolyse dietary fat in the small intestine [35]. Adverse effects of orlistat are liquid stools, steatorrhea, fecal urgency, incontinence, flatulence, abdominal cramping, and fat-soluble vitamin deficiencies [36]. Recently, many researchers have been focused on the effects of natural products for the treatment of dyslipidemia [37]. Our study determined the inhibitory activity of NPV towards pancreatic lipase, and the results showed that NPV can inhibit pancreatic lipase in a concentration-dependent manner with an IC50 value of 69.95 μM/mL. In a previous study, an aqueous extract of NPV was able to significantly reduce blood glucose in streptozotocin-induced diabetic rats [15]. The aqueous extract of NPV also stimulated insulin secretion in RIN-5F cells [16]. Moreover, nipa palm sap and its syrup inhibited α-glucosidase which hydrolyses polysaccharides [38].

Pancreatic cholesterol esterase exerts important functions in controlling the bioavailability of cholesterol from dietary cholesterol esters, contributing to the incorporation of cholesterol into mixed micelles, and in helping to transport free cholesterol to enterocytes [25]. It has previously been reported that inhibition of pancreatic cholesterol esterase and the solubility of cholesterol micelles by gallic acid, catechin, and epicatechin from grape seed extract results in delaying the absorption of cholesterol [20]. The current findings revealed that NPV inhibited pancreatic cholesterol esterase and the solubility of cholesterol micelles in a concentration-dependent manner. There was a positive correlation between pancreatic lipase inhibition and pancreatic cholesterol esterase inhibition. Moreover, cholesterol micellization inhibition had a positive correlation with pancreatic lipase inhibition and pancreatic cholesterol esterase inhibition. Therefore, it could be hypothesized that the NPV can inhibit pancreatic cholesterol esterase and may protect against cholesterol micellization.

There are several reports demonstrating anti-dyslipidemia activity of natural compounds. Gallic acid has been reported to decrease levels of serum triglycerides, total cholesterol, and low-density lipoprotein in high-fat induced dyslipidemia in rats [39]. Similarly, quercetin had a strong inhibitory activity on pancreatic lipase [40], and it also reduced serum levels of triglycerides and cholesterol in a rabbit model of high-fat diet-induced atherosclerosis [41]. Moreover, isoquercetin, a glucoside derivative of quercetin, improved hepatic lipid accumulation through activating the AMPK pathway and inhibiting TGF-β signalling in a high-fat diet-induced nonalcoholic fatty liver disease rat model [42]. A previous study showed that green tea catechin suppressed cholesterol absorption in the small intestine and reduced serum cholesterol concentrations [43]. Other studies have also demonstrated the antiobesity effects of rutin by decreasing serum lipid profiles and leptin [44].

According to our in vitro finding, it can be hypothesized that phenolic compounds including gallic acid, isoquercetin, quercetin, catechin, and rutin from NPV may be the main active compounds with possible cholesterol-lowering effects through inhibition of pancreatic lipase and cholesterol esterase activities as well as the inhibition of solubility of cholesterol micelles. More in vivo studies in animal and clinical human studies are required to determine the anti-dyslipidemia activity of NPV and to confirm its mechanism for the aim of application in the prevention and treatment of dyslipidemia.

5. Conclusion

Our results indicate that nipa palm vinegar may delay the digestion of a high-fat diet and absorption through small intestine through mechanisms such as the inhibition of pancreatic lipase and cholesterol esterase activities as well as through the inhibition of solubility of cholesterol micelles. These results indicate that NPV could be used as a natural source of bioactive compounds with antilipidemic activity. Nevertheless, NPV should be extensively evaluated by animal and clinical human studies.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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