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Original article

Biological activity of rice extract and the inhibition potential of rice extract, rice volatile compounds and their combination against α-glucosidase, α-amylase and tyrosinase

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Summary

Rice is produced for consumption and traditional medicine. Rice is also used as an ingredient in cosmetic products. In this study, the author investigated the biological activity and inhibition potential against α-glucosidase, α-amylase and tyrosinase activity of rice extract (black rice [BR], red rice [RR] and white rice [WR]), rice volatile compounds, rice extract combined with volatile compounds, rice extract combined with standard inhibitors and volatile compounds combined with standard inhibitors. The results revealed that the free-radical scavenging capacity of rice extract is related to the phenolic content and flavonoids. BR showed the highest potential to inhibit α-glucosidase and α-amylase activity, whereas WR showed the highest potential to inhibit tyrosinase activity. Among rice volatile compounds, vanillin and vanillyl alcohol had the highest inhibition potential against α-glucosidase and α-amylase, respectively, whereas guaiacol had the highest inhibitory activity against tyrosinase. Molecular docking supported by the high binding efficiency was also obtained from vanillin and guaiacol when located at the active site of these enzymes. The combination of RR with acarbose (AB) had the highest inhibition potential and showed a synergic effect on both α-glucosidase and α-amylase. Interestingly, the combination of rice extract (BR, RR and WR) and vanillin and vanillyl alcohol had a synergic effect on α-amylase. Moreover, the combination of WR and vanillyl alcohol had the highest inhibition potential and showed a synergic effect on tyrosinase, whereas rice volatile compounds had a synergic effect on tyrosinase obtained from 2-pentylfuran/kojic acid (KA), vanillin/KA and vanillyl alcohol/KA.

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Data availability statement

Author elects to not share data.

Supporting Information

Filename	Description
ijfs14816-sup-0001-FigS1.tif TIFF image, 163 KB	**Figure S1**. The characteristics of coloured and non-coloured rice. A: non-coloured rice (WR); B and C: BR and RR, respectively.
ijfs14816-sup-0002-FigS2.tif TIFF image, 460.3 KB	**Figure S2.** GC-MS chromatogram showing the volatile compound patterns of standard compounds (A), BR (B), WR (C), and RR (D).
ijfs14816-sup-0003-FigS3.tif TIFF image, 186.4 KB	**Figure S3.** The chemical structure of 4 volatile compounds. A: 2-pentylfuran; B: guaiacol; C: vanillin; and D: vanillyl alcohol.
ijfs14816-sup-0004-TableS1.docx Word document, 12.5 KB	**Table S1.** The binding affinity values of α-glucosidase (3A4A), α-amylase (7TAA), and tyrosinase (3NQ1) with 2-pentylfuran, guaiacol, vanillin, and vanillyl alcohol, respectively
ijfs14816-sup-0005-TableS2.docx Word document, 12.6 KB	**Table S2.** The concentration of rice volatile compounds (2-pentylfuran, guaiacol, vanillin, and vanillyl alcohol) in coloured rice extract (BR and RR) and non-coloured rice extract (WR)
ijfs14816-sup-0006-MethodS1.docx Word document, 14.6 KB	**Method S1.** Supplementary methods.

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Original article

Biological activity of rice extract and the inhibition potential of rice extract, rice volatile compounds and their combination against α-glucosidase, α-amylase and tyrosinase

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Summary Rice is produced for consumption and traditional medicine. Rice is also used as an ingredient in cosmetic products. In this study, the author investigated the biological activity and inhibition potential against α-glucosidase, α-amylase and tyrosinase activity of rice extract (black rice [BR], red rice [RR] and white rice [WR]), rice volatile compounds, rice extract combined with volatile compounds, rice extract combined with standard inhibitors and volatile compounds combined with standard inhibitors. The results revealed that the free-radical scavenging capacity of rice extract is related to the phenolic content and flavonoids. BR showed the highest potential to inhibit α-glucosidase and α-amylase activity, whereas WR showed the highest potential to inhibit tyrosinase activity. Among rice volatile compounds, vanillin and vanillyl alcohol had the highest inhibition potential against α-glucosidase and α-amylase, respectively, whereas guaiacol had the highest inhibitory activity against tyrosinase. Molecular docking supported by the high binding efficiency was also obtained from vanillin and guaiacol when located at the active site of these enzymes. The combination of RR with acarbose (AB) had the highest inhibition potential and showed a synergic effect on both α-glucosidase and α-amylase. Interestingly, the combination of rice extract (BR, RR and WR) and vanillin and vanillyl alcohol had a synergic effect on α-amylase. Moreover, the combination of WR and vanillyl alcohol had the highest inhibition potential and showed a synergic effect on tyrosinase, whereas rice volatile compounds had a synergic effect on tyrosinase obtained from 2-pentylfuran/kojic acid (KA), vanillin/KA and vanillyl alcohol/KA.

Keywords Rice extract, synergic effect, tyrosinase inhibitory activity, α-glucosidase and α-amylase inhibitory activity.

Introduction

Rice is a staple food around the world, and people produce rice for both consumption and use in traditional medicine. Rice has also been used as an ingredient in cosmetics. Thailand has a variety of rice cultivars, and Thai people consume both coloured and non-coloured rice. However, coloured rice seems to be more suitable for human health than non-coloured rice based on its nutritional values (Pramai *et al*., 2018). Furthermore, people's rice consumption depends on its aromatic intensity. The aromatic intensity of rice comes from a mix of more than 100 volatile compounds. Some of these volatile compounds have been reported to have pharmaceutical properties. Hexanal, 2-methoxy-4-vinylphenol and octanal are the major compounds that contribute to the aromatic intensity of rice and have shown antioxidant, anti-inflammatory, antimicrobial and anti-diabetes properties (Jeong *et al*., 2011; Liu *et al*., 2012). Moreover, some volatile compounds identified from coloured rice, such as vanillin, vanillyl alcohol, guaiacol and 2-pentylfuran, have also been reported to show antioxidant, anti-

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inflammatory, and antifungal activity (Jung *et al.*, 2008; Azadfar *et al.*, 2015; Romero-Cortes *et al.*, 2019). Furthermore, some of these volatile compounds have shown cosmeceutical potential (anti-tyrosinase activity) (Razak *et al.*, 2017). Evidence indicates that both rice extract, especially from coloured rice, and rice volatile compounds have the potential for further application as pharmaceutical treatment, such as anti-diabetes treatment, and as a cosmetics ingredient based on the study of anti-tyrosinase activity.

Diabetes mellitus is a chronic disease and can be classified into insulin-dependent and noninsulin-dependent types (Slattery *et al.*, 2018). One diabetes treatment is focused on decreasing blood glucose levels. The key enzymes α-glucosidase and α-amylase release glucose from starch in the intestine (Chakrabarti & Rajagopalan, 2002). Thus, inhibition of these enzymes can decrease blood glucose levels and might be applied for diabetes treatment. Currently, acarbose is the most common commercial drug for diabetes therapy; however, it has shown many side effects (Sugihara *et al.*, 2014). Thus, an inhibitor candidate from plant extract with fewer side effects might be important to investigate for application in diabetes treatment.

Skin colour disorder is caused by various factors, such as exposure to sunlight. The sunlight factor is related to the tyrosinase enzyme, which is the key enzyme for human melanin biosynthesis (Saeedi *et al.*, 2019). The commercial tyrosinase inhibitor is kojic acid; however, it has many side effects, such as cytotoxicity and skin allergies (Nakagawa *et al.*, 1995). Thus, a natural inhibitor from plant extract with fewer side effects might be important to investigate for use as an ingredient in skin cream products.

The aim of this study was to investigate the biological activity of different coloured rice cultivar extracts (white rice [WR], red rice [RR] and black rice [BR] cultivars). Moreover, the inhibition potential of rice extract; rice volatile compounds including vanillin, vanillyl alcohol, guaiacol, and 2-pentylfuran; and the combination of rice extract and volatile compounds, rice extract and standard inhibitors, and volatile compounds and standard inhibitors against α-glucosidase, α-amylase, and tyrosinase was also investigated for further application in diabetes treatment and in cosmetic products.

Material and methods

Rice material

The seeds of coloured (BR and RR) and non-coloured rice (WR) were obtained from Pathum Thani rice research centre (Fig. S1). The rice seeds were ground thoroughly to produce rice powder. The sample powder was kept at − 20 °C until extraction.

Chemical reagent

The following were obtained from Sigma-Aldrich (St. Louis, MO, USA): rice volatile compounds including vanillin, vanillyl alcohol, guaiacol, and 2-pentylfuran; the chemical reagent for free-radical scavenging assay including 2,2-diphenyl-1-picrylhydrazyl (DPPH•) and 2,2'-azino-bis (3-ethylbenzthiazoline-6-sulphonic acid) (ABTS•+); and the chemical reagent for enzymatic assay including AB, KA, *p*-nitrophenyl-α-glucopyranoside (4-*p*NPG), amylose from potatoes, 3,4-dihydroxy-l-phenylalanine (L-DOPA), α-glucosidase from *Saccharomyces cerevisiae*, α-amylase from *Aspergillus oryzae* and tyrosinase from mushrooms.

Rice compound extraction

One hundred grams of rice compounds (BR, RR and WR) were extracted using 300 mL of 95% methanol over 3 days. Next, the extraction solution was centrifuged at 6000 rpm for 15 min, and then, the supernatant was filtered with a 0.45 µm syringe filter. The methanol was removed from the filtrate by a hot air oven at 60°C to produce crude extract.

Free-radical scavenging capacity of rice extract

The free-radical scavenging capacity of 3 rice extracts (BR, RR and WR) was determined by DPPH• and ABTS•+ assay with the modified methods of Pourmorad *et al.* (2006). The absorbance of the final product was determined using a UV/Vis spectrophotometer at 517 nm for DPPH• assay and at 734 nm for ABTS•+ assay. The per cent of inhibition was calculated by $[(A_b - A_s)/A_b]*100$ (A_b = absorbance without sample; A_s = absorbance with sample). To determine IC_{50} values, the final concentrations of BR and RR were 10 µg mL^{-1} to 1000 µg mL^{-1} for DPPH• and 10 µg mL^{-1} to 1500 µg mL^{-1} for ABTS•+, whereas the final concentration of WR was 100 µg mL^{-1} to 4000 µg mL^{-1} for DPPH• and 50 µg mL^{-1} to 4000 µg mL^{-1} for ABTS•+. IC_{50} values of BR, RR and WR were calculated using Grafit 5.0 computer software (Erithacus Software).

Total phenolic content and total flavonoid content of rice extract

Total phenolic and flavonoid content was determined using the modified methods of Pourmorad *et al.* (2006). For phenolic content determination, 1 mL of sample solutions (1 mg mL^{-1}) was mixed with 200 µL of 10% (v/v) Folin–Ciocalteu reagent and shaken for 3 min. Then, the reaction solution was mixed with 800 µL of 20% (w/v) sodium carbonate, followed by incubation for 60 min in the dark, and absorbance was measured at 715 nm. The total phenolic rice extract was calculated by the calibration curve of gallic acid (y = 0.0215x + 0.1596; R^2 = 0.9998) and expressed as milligrams of gallic acid equivalent (GAE) per gram of dry weight (dw).

To determine flavonoid content, briefly, the reaction mixture included 300 μL of the sample solution (1 mg mL^{-1} in methanol), 200 μL deionised water and 30 μL of 5% $NaNO_2$ and was shaken for 5 min. Then, the reaction mixture was added with 30 μL of 10% $AlCl_3$ and shaken for 5 min, followed by adding 200 mL of 1M NaOH. Finally, the final volume of the reaction was adjusted to 1 mL by deionised water and incubated at room temperature for 15 min. The final product was measured at 415 nm. The total flavonoid content was expressed as milligrams of quercetin equivalent (QE) per gram of dw and was calculated by the calibration curve of quercetin (y = 0.0036x + 0.2833; R^2 = 0.9989).

Inhibition potential of rice extract and volatile compounds against α-glucosidase, α-amylase and tyrosinase

The inhibition potential of rice extract against α-glucosidase, α-amylase, and tyrosinase was determined by the modified method of Sansenya & Nanok (2020). AB and KA were used as the standard inhibitors for α-glucosidase and α-amylase activity and tyrosinase activity, respectively. 4-*p*NPG was used as the substrate for α-glucosidase and α-amylase activity, whereas L-DOPA was used as the substrate for tyrosinase activity. The final sample concentration in the enzymatic reaction was 0.10 mg mL^{-1}.

For α-glucosidase inhibitory assay, 100 μL of reaction mixture was mixed with 0.25 mM 4-*p*NPG, 0.0025 mg mL^{-1} α-glucosidase and 0.10 mg mL^{-1} of sample solution. Next, the reaction mixture was incubated at 37°C for 20 min. The enzyme activity was stopped by adding 0.50 M Na_2CO_3. The release of the final product was measured at 405 nm using a UV/Vis spectrophotometer.

For α-amylase inhibitory assay, the reaction (100 μL) was mixed with 0.005 mg mL^{-1} amylose, 0.005 mg mL^{-1} α-amylase and 0.10 mg mL^{-1} of sample solution. The reaction experiment was incubated at 37°C for 30 min. The enzyme activity was stopped by heating in boiling water for 5 min. The glucose released was determined by peroxidase-glucose oxidase assay at 475 nm using a UV/Vis spectrophotometer.

For tyrosinase inhibitory assay, the enzymatic reaction (100 μL) was mixed with 0.025 mg mL^{-1} tyrosinase and 0.10 mg mL^{-1} of sample solution. Then, the reaction experiment was incubated at 37°C for 15 min. Next, the reaction was mixed with 0.25 mM L-DOPA (in 5% DMSO) and continuously incubated at 37°C for 20 min. The release of the final dopachrome product was measured at 492 nm using a UV/Vis spectrophotometer.

The per cent of rice extract (BR, RR and WR) inhibition against α-glucosidase, α-amylase, and tyrosinase was calculated by $[(A_b - A_s)/A_b]*100$ (A_b = absorbance without sample; A_s = absorbance with sample).

The effect of rice extract combined with volatile compounds and with standard inhibitors (AB and KA) against α-glucosidase, α-amylase and tyrosinase

The inhibitory activity assay of combinations (rice extract with volatile compounds and rice extract with a standard inhibitor [AB and KA]) against 3 enzymes was maintained at the same concentration as in the respective reactions above. In the combination reaction, the final concentration of samples was 0.10 mg mL^{-1} and the final concentration of volatile compounds and standard inhibitors was 0.10 mg mL^{-1}. The percentage of the combinations' inhibitory activity was determined similarly to the assay above.

The effect of rice extract and volatile compound concentration on inhibition potential of AB and KA against α-glucosidase, α-amylase and tyrosinase

The volatile compounds that have the highest α-glucosidase, α-amylase and tyrosinase inhibitory activity were selected to study the effect of concentration on the inhibition potential of standard inhibitors against the 3 enzymes. The enzyme and substrate concentrations in the enzymatic reaction were kept the same as in the respective reactions above. The final concentrations of volatile compounds and rice extract in the combinations varied from 0.05 to 1.50 mg mL^{-1}, whereas the concentration of standard inhibitors (AB and KA) was fixed at 0.10 mg mL^{-1}. The percentage of combinations' inhibitory activity was determined similarly to the assay above.

Molecular docking study

The initial structures of ligands such as vanillin, 2-pentylfuran, vanillyl alcohol and guaiacol were generated and optimised at the B3LYP/6-311++G(d,p) level of theory using the Gaussian 03W program (Frisch et al., 2004).

The X-ray crystal structures of α-glucosidase, α-amylase and tyrosinase were collected from the Protein Data Bank with the data bank codes 3A4A, 7TAA and 3NQ1, respectively. The crystal structures were analysed and prepared by removing all water molecules and inhibitors, as well as adding polar hydrogen atoms using AutoDockTools (Morris *et al.*, 2009).

All molecular docking calculations were performed using AutoDock Vina (Trott & Olson, 2010). The grid box was set at 30 Å × 30 Å × 30 Å with space points of 1 Å. The visualisations of molecular docking results were created by the VMD program (Humphrey *et al.*, 1996).

Statistical analysis

All the results were determined in triplicate. The determinations are reported as mean ± SD. Statistical differences were determined by one-way analysis of variance (ANOVA), and the differences were considered significant at P values less than 0.05.

Results

Free-radical scavenging capacity of rice extract

The free-radical scavenging capacity of different coloured rice cultivars was determined using ABTS•+ and DPPH• assay, and the results are shown in Table 1. The free-radical scavenging capacity of RR was significantly ($P < 0.05$) higher than BR, and the scavenging efficiency of coloured rice, both BR and RR, was significantly ($P < 0.05$) higher than that of WR. Moreover, RR had the highest free-radical scavenging capacity, 9.50-fold higher than that of WR.

Total phenolic content and total flavonoid content of rice extract

The significantly ($P < 0.05$) highest total phenolic content and total flavonoid content values of rice extract were observed from RR (5.64 ± 0.01 mgGAE/dw) and BR (23.09 ± 0.01 mgQE/dw), respectively (Table 1). However, the total phenolic content and total flavonoid content of WR showed the lowest values when compared with the coloured rice.

Inhibition potential of rice extract, rice volatile compounds and rice extract combined with volatile compounds and with standard inhibitors against α-glucosidase, α-amylase and tyrosinase

The inhibition potential of rice extract (BR, RR, and WR) against α-glucosidase, α-amylase, and tyrosinase is shown in Table 2. The results indicate that coloured rice showed higher inhibition potential against α-glucosidase and α-amylase than non-coloured rice did, whereas the inhibition potential of WR against tyrosinase was higher than that of coloured rice. Regarding α-glucosidase and α-amylase's inhibitory activity, BR showed the highest potential, with an inhibition percentage of 81.83 ± 0.47 for α-glucosidase and 48.96 ± 0.34 for α-amylase. Moreover, the results show that the inhibitory activity of BR against α-glucosidase was significantly ($P < 0.05$) higher than that of the standard inhibitor AB.

The inhibitory activity of volatile compounds (2-pentylfuran, guaiacol, vanillin and vanillyl alcohol) against α-glucosidase, α-amylase and tyrosinase is shown in Table 2. Volatile compounds showed the highest potential to inhibit tyrosinase compared to their potential to inhibit the other enzymes (α-glucosidase and α-amylase). However, the inhibition percentage values of volatile compounds were lower than standard inhibitors AB and KA were. The highest inhibition potential of volatile compounds against α-glucosidase, α-amylase, and tyrosinase was obtained from vanillin (inhibition percentage of 52.97 ± 0.85), vanillyl alcohol (inhibition percentage of 39.11 ± 0.75) and guaiacol (inhibition percentage of 70.04 ± 0.50), respectively.

The inhibition potential of rice extract (BR, RR and WR) combined with volatile compounds and with AB is shown in Table 2. Coloured rice extract (BR and RR) combined with volatile compounds had higher inhibitory potential against α-glucosidase than WR combined with volatile compounds did. The combinations of BR/vanillin, BR/2-pentylfuran, RR/2-pentylfuran and RR/guaiacol had significantly higher

Table 1 The antioxidant potential, total phenolic content and total flavonoid content of rice extract

Sample	IC_{50} (μg mL^{-1}) DPPH•	ABTS•+	Total phenolic content (mgGAE/dw)	Total flavonoid content (mgQE/dw)
BR	82.00 ± 8.5^{b}	93.67 ± 7.02^{b}	3.80 ± 0.01^{b}	23.09 ± 0.01^{a}
RR	34.33 ± 8.5^{c}	78.67 ± 5.86^{c}	5.64 ± 0.01^{a}	16.41 ± 0.02^{b}
WR	323.33 ± 28.7^{a}	383.33 ± 35.11^{a}	1.14 ± 0.01^{c}	10.65 ± 0.03^{c}

The superscript letters (a to c) indicate significant differences within the column between coloured rice extract (BR and RR) and non-coloured rice extract (WR) ($P < 0.05$).

Table 2 The inhibition potential of rice extract, volatile compounds and rice extract combined with volatile compounds and standard inhibitors

Sample	%Inhibition at 0.10 mg mL^{-1}		
	α-Glucosidase	α-Amylase	Tyrosinase
AB	65.08 ± 0.86^{ef}	54.14 ± 0.35^{h}	NM
KA	NM	NM	71.77 ± 0.05^{b}
BR	81.83 ± 0.47^{b}	48.96 ± 0.34^{j}	13.89 ± 0.52^{p}
RR	59.80 ± 0.80^{h}	38.41 ± 0.39^{m}	15.87 ± 0.21^{q}
WR	42.64 ± 0.79^{l}	17.40 ± 0.48^{p}	21.47 ± 0.47^{n}
2-Pentylfuran	51.20 ± 1.22^{j}	31.59 ± 0.44^{n}	60.00 ± 0.41^{g}
Guaiacol	37.24 ± 0.81^{m}	25.22 ± 1.02^{o}	70.04 ± 0.50^{c}
Vanillin	52.97 ± 0.85^{i}	32.47 ± 0.63^{n}	62.25 ± 0.41^{f}
Vanillyl alcohol	38.72 ± 1.15^{n}	39.11 ± 0.75l^{m}	63.54 ± 0.16^{e}
BR/AB	64.60 ± 0.57^{f}	86.48 ± 0.71^{d}	NM
BR/KA	NM	NM	68.76 ± 0.57^{d}
BR/2-pentylfuran	69.22 ± 0.24^{c}	50.67 ± 1.15^{i}	68.38 ± 0.12^{d}
BR/guaiacol	63.01 ± 0.15^{g}	44.17 ± 1.14^{k}	52.64 ± 0.26^{j}
BR/vanillin	69.87 ± 0.36^{c}	99.32 ± 1.18^{a}	56.11 ± 0.71^{i}
BR/vanillyl alcohol	65.94 ± 0.15^{e}	96.55 ± 0.12^{b}	57.25 ± 0.37^{h}
RR/AB	87.31 ± 0.70^{a}	89.73 ± 0.89^{c}	NM
RR/KA	NM	NM	68.84 ± 0.64^{d}
RR/2-pentylfuran	67.22 ± 0.21^{d}	39.97 ± 1.62^{l}	42.52 ± 0.93^{l}
RR/guaiacol	67.98 ± 0.13^{d}	25.62 ± 0.53^{o}	55.55 ± 0.13^{i}
RR/vanillin	62.09 ± 0.25^{g}	84.90 ± 0.86^{e}	34.15 ± 1.35^{m}
RR/vanillyl alcohol	62.87 ± 0.19^{g}	96.05 ± 0.09^{b}	52.64 ± 1.88^{j}
WR/AB	53.97 ± 0.42^{i}	80.25 ± 1.13^{g}	NM
WR/KA	NM	NM	67.88 ± 0.13^{d}
WR/2-pentylfuran	45.00 ± 0.85^{k}	49.28 ± 1.26^{j}	45.94 ± 0.20^{k}
WR/guaiacol	39.80 ± 0.89^{m}	11.77 ± 0.35^{q}	62.00 ± 0.59^{f}
WR/vanillin	31.33 ± 0.81^{o}	82.59 ± 0.76^{f}	60.08 ± 0.22^{g}
WR/vanillyl alcohol	24.39 ± 1.23^{q}	96.59 ± 0.07^{b}	75.78 ± 1.16^{a}

The superscript letters (a to q) indicate significant differences within the column between standard inhibitors (AB and KA), rice extract, volatile compounds, rice extract combined with a standard inhibitor and rice extract combined with volatile compounds ($P < 0.05$). NM: not measured.

inhibition potential than AB did. However, the combination of BR with volatile compounds had lower inhibition potential when compared with BR alone. On the other hand, the combinations of RR/2-pentylfuran and RR/guaiacol had significantly higher inhibition potential than RR alone did. The combination of RR/AB showed the highest α-glucosidase inhibitory potential, with a per cent inhibition of 87.31 ± 0.70, and this combination also had higher potential than RR and AB alone did. The trend of α-amylase inhibitory potential of combinations (rice extract with volatile compounds) was similar to that of α-glucosidase inhibitory potential. The combination of coloured rice extract and volatile compounds had higher inhibitory potential than non-coloured rice extract combinations did. The highest α-amylase inhibitory potential was obtained from BR/vanillin, with an inhibition percentage of 99.32 ± 1.18, and this combination had higher potential than AB and BR alone did. Other combinations that had higher inhibitory potential than that of rice extract and AB alone included BR/vanillyl alcohol, RR/vanillin, RR/vanillyl alcohol, WR/vanillin and WR/vanillyl alcohol. Moreover, the combination of rice extract with AB (BR/AB, RR/AB and WR/AB) also had higher inhibition potential than rice extract and AB alone did. The highest potential was obtained from RR/AB, with an inhibition percentage of 89.73 ± 0.89. The potential of all the combinations of rice extract with volatile compounds to inhibit tyrosinase was significantly higher than that of rice extract alone (BR, RR and WR). However, these combinations had lower inhibitory potential than KA alone did, except for the combination of WR/vanillyl alcohol, which had a higher potential than that of KA, with an inhibition percentage of 75.78 ± 1.16. The combination of rice extract with KA (BR/KA, RR/KA and WR/KA) had similar values (not significant) for tyrosinase inhibitory activity, and all these potentials were higher than that of rice extract alone but lower than that of KA alone.

The inhibition potential of volatile compounds combined with standard inhibitors (AB and KA) against α-glucosidase, α-amylase and tyrosinase

The inhibitory activity of volatile compounds combined with AB against α-glucosidase and α-amylase and of volatile compounds combined with KA against tyrosinase is shown in Table 3. The results indicate that all combinations of volatile compounds with KA had higher inhibition of tyrosinase activity than all combinations of volatile compounds with AB had on

Table 3 The percentage of inhibition of volatile compounds combined with the standard inhibitor AB against glucosidase and amylase and KA against tyrosinase

Samples	%Inhibition at 0.10 mg mL^{-1}		
	α-Glucosidase	α-Amylase	Tyrosinase
AB	65.08 ± 0.86^{a}	54.14 ± 0.35^{a}	NM
KA	NM	NM	71.77 ± 0.05^{c}
2-Pentylfuran/AB or KA	43.08 ± 1.03^{cd}	40.13 ± 1.74^{b}	80.94 ± 0.17^{b}
Guaiacol/AB or KA	44.05 ± 078^{c}	34.00 ± 0.98^{d}	70.17 ± 0.67^{d}
Vanillin/AB or KA	42.47 ± 0.11^{d}	36.27 ± 0.44^{c}	84.17 ± 0.66^{a}
Vanillyl alcohol/AB or KA	45.99 ± 0.73^{b}	33.25 ± 1.79^{d}	81.45 ± 0.61^{b}

AB, acarbose for α-glucosidase and α-amylase inhibitory activity; KA, kojic acid for tyrosinase inhibitory activity; NM, not measured.
The superscript letters (a to d) indicate significance differences within the column between standard inhibitors (AB and KA) and a combination of standard inhibitors with volatile compounds ($P < 0.05$).

α-glucosidase and α-amylase activity. Moreover, all combinations of volatile compounds with KA had significantly higher inhibition potential against tyrosinase than KA alone did, except for guaiacol/KA. The highest inhibition values against tyrosinase activity were obtained from vanillin/KA, with an inhibition percentage of 84.17 ± 0.66. For the α-glucosidase and α-amylase inhibitory activity, all combinations showed lower inhibition potential than AB alone did.

Enhancing the inhibition potential of AB against α-glucosidase and α-amylase activity by increasing rice extract concentration

Table 2 shows that the combination of RR/AB had higher inhibition potential than standard AB did against both α-glucosidase and α-amylase activity, whereas only for α-amylase activity did BR/AB and WR/AB have higher inhibition potential than standard AB. Thus, we studied the effect of RR concentration to enhance the inhibition potential of RR/AB against α-glucosidase and α-amylase activity, whereas BR and WR were selected only for study of α-amylase inhibitory activity. The results indicate that when RR concentration was increased from 0.05 mg mL^{-1} to 0.15 mg mL^{-1} in the combination of 0.10 mg mL^{-1} of AB, the inhibition potential of the combination against α-glucosidase increased from 63.92 ± 1.68 (%) to 97.42 ± 1.23 (%) (Table 4). The trend of the inhibition potential of RR/AB against α-amylase also increased when RR concentration was increased from 0.05 mg mL^{-1} to 0.15 mg mL^{-1} (inhibition percentage of 77.96 ± 0.63 to 99.05 ± 1.49; Table 4). The inhibition potential of BR/AB and WR/AB showed a trend similar to that of RR/AB against α-amylase. When BR and WR concentration was increased from 0.05 mg mL^{-1} to 0.15 mg mL^{-1}, the inhibition potential increased from 72.71 ± 1.73 (%) to 90.017 ± 0.15 (%) for BR/AB and from 63.09 ± 1.54 (%) to 98.60 ± 1.22 (%) for WR/AB. However, the inhibition potential of RR/AB against α-amylase was higher than that of BR/AB and WR/AB for each rice extract concentration.

Table 4 The effect of rice extract concentration in the combination of rice extract with AB on the α-glucosidase and α-amylase inhibitory activity

Standard inhibitor	Sample	Sample concentration (mg/mL)	%Inhibition α-glucosidase	%Inhibition α-amylase
AB (0.10 mg mL^{-1})	BR	0.05	NM	72.71 ± 1.73
		0.10	NM	86.48 ± 0.67
		0.15	NM	90.017 ± 0.15
	RR	0.05	63.92 ± 1.68	77.96 ± 0.63
		0.10	87.31 ± 0.70	89.73 ± 0.89
		0.15	97.42 ± 1.23	99.05 ± 1.49
	WR	0.05	NM	63.09 ± 1.54
		0.10	NM	80.25 ± 1.13
		0.15	NM	98.60 ± 1.22

NM, not measured.

Enhancing the inhibition potential of KA against tyrosinase activity by increasing vanillin concentration

Table 3 shows that vanillin/KA had the highest potential to inhibit tyrosinase among all volatile compound combinations. Thus, vanillin was selected to study the effect of concentration on the potential of vanillin/KA to inhibit tyrosinase activity. The results showed that when vanillin concentration was increased from 0.05 mg mL^{-1} to 0.15 mg mL^{-1}, the inhibition against tyrosinase also increased, from 71.51 ± 1.73 (%) to 91.33 ± 0.61 (%). Moreover, at concentrations of 0.10 mg mL^{-1} and 0.15 mg mL^{-1}, vanillin/KA had higher tyrosinase inhibitory activity than KA alone did (Table 5).

Table 5 The effect of vanillin concentration in the combination of vanillin/KA against tyrosinase activity

Standard inhibitor	Sample	Sample concentration (mg/mL)	%Inhibition tyrosinase
KA (0.1 mg mL^{-1})	Vanillin	0.05	71.51 ± 1.73
		0.10	84.17 ± 0.66
		0.15	91.33 ± 0.61

Discussion

The correlation between free-radical scavenging capacity, phenolic content and flavonoid content of rice extract

The free-radical scavenging capacity of plant extract and rice extract has commonly been analysed using DPPH• and ABTS•+ assays (Chaiyasut *et al*., 2017; Bari *et al*., 2019; Zafar *et al*., 2019; Sansenya & Nanok, 2020). The free-radical scavenging capacity of plant extract is closely related to the phenolic content and flavonoid content (Amri & Hossain, 2018). Almost all of these compounds represent the most important group of natural antioxidants (Gonçalves *et al*., 2017). In rice extract, the relationship between the free-radical scavenging capacity and the phenolic content and flavonoid content has also been shown. Peanparkdee *et al*. (2019) reported that the highest phenolic content and flavonoid content values of rice extract were obtained from 65% (v/v) ethanol, and this solvent condition had the highest free-radical scavenging capacity using DPPH• assay. In addition, the phenolic content, flavonoid content and free-radical scavenging capacity of rice have been reported to be higher in coloured rice than in non-coloured rice (Peanparkdee *et al.*, 2019). Our results also support the previously reported evidence that the total phenolic content and total flavonoid content of coloured rice extract (BR and RR) were higher than those of non-coloured rice (WR). Moreover, the free-radical scavenging capacity of coloured rice extract using ABTS•+ and DPPH• assays was closely related to the phenolic content and flavonoid content and was higher than that of non-coloured rice.

Comparison of the potential of BR, RR and WR to inhibit α-glucosidase, α-amylase and tyrosinase activity

The researcher reported that coloured rice seems to have more nutritional benefits related to human health than non-coloured rice has. Pramai *et al.* (2018) reported that germinated coloured rice seems to have more nutritional value and biological activity than germinated non-coloured rice has. Non-coloured rice seems to have more negative health effects than coloured rice has, such as related to cardiovascular diseases (Krittanawong *et al.*, 2017). Moreover, Prasad *et al.* (2019) showed that methanol RR extract had stronger inhibitory activity against α-amylase and α-glucosidase than the standard inhibitor AB did. We also obtained the highest α-glucosidase and α-amylase inhibitory activity from BR, followed by RR, and the lowest was obtained from WR. However, only BR has higher α-glucosidase and α-amylase inhibitory activity than that of standard AB. On the other hand, our results showed that the highest tyrosinase inhibition potential was obtained from WR, followed by RR and BR; however, the inhibition potential of all rice extracts was lower than that of the standard inhibitor KA. In contrast with our results, Miyazawa *et al.* (2003) reported on a study of BR bran compounds 1 to 8, which showed high tyrosinase inhibitory activity. However, Soradech *et al.* (2016) showed that the different coloured rice extract cultivars also showed significant differences in tyrosinase inhibitory activity, with the highest and lowest potentials obtained for Rice Berry and Sri-Nin (both rice cultivars are the coloured rice), respectively. Previous reports and our results indicate that coloured rice extract might be more suitable than non-coloured rice extract for application in diabetes mellitus treatment, whereas the tyrosinase inhibitory activity of rice extract varied depending on the rice cultivar.

The potential of rice volatile compounds to inhibit α-glucosidase, α-amylase and tyrosinase activity

Four rice volatile compounds (i.e. 2-pentylfuran, guaiacol, vanillin and vanillyl alcohol) comprise the group of aroma compounds of rice. Moreover, guaiacol, vanillyl alcohol and vanillin belong to the phenolic group, whereas 2-pentylfuran is a heterocyclic aromatic compound. These compounds have been identified from both coloured rice and non-coloured rice (Jung *et al.*, 2008; Azadfar *et al.*, 2015; Sansenya *et al.*, 2018; Romero-Cortes *et al.*, 2019). The results indicated that 2-pentylfuran, guaiacol, and vanillin were identified from both BR and WR, whereas 2-pentylfuran and guaiacol were only found in RR (Table S2 and Fig. S2). In addition, vanillyl alcohol was not detected by our technique in both coloured rice extracts (BR and RR) and non-coloured rice extract (WR). However, based on the similar structure to the guaiacol and vanillin of this rice volatile compound, its enzymatic properties were also tested (Fig. S3). The results show that the 4 volatile compounds had higher inhibition potential against tyrosinase than against α-glucosidase and α-amylase, respectively (Table 2). The binding efficacy of the 4 volatiles compounds with the amino acid in the active site of 3 enzymes was also investigated by docking study. The results revealed that the 4 rice volatile compounds with an amino acid in the active site of tyrosinase had better inhibition efficiency than the other two enzymes, with the binding free energy of about $-$ 5.0 to 5.7 kcal mol^{-1} (Table S1 and Fig. S1). Regarding the tyrosinase inhibitory activity of the 4 rice volatile compounds, the highest percentage of inhibition was obtained from guaiacol, followed by vanillyl alcohol and vanillin, whereas 2-pentylfuran had the lowest inhibition percentage. Guaiacol, vanillin and vanillyl alcohol are the group of monophenols with the same ortho-substituted but different para-substituted; two of these positions might affect the binding of the inhibitor with amino acid in the active site of the enzyme. Garcia-Molina *et al.* (2012) also reported that ortho-substituted and para-substituted phenols affected tyrosinase inhibitory activity. However, 2-pentylfuran showed the lowest tyrosinase inhibitory activity, which the docking results with the binding affinity (-4.6 kcal mol^{-1}) also supported, and also lacked a hydrogen bond between the inhibitor and amino acid in the active site of tyrosinase when compared to other volatile compounds (Table S1 and Fig. 1i to l).

The potential of rice extract combined with volatile compounds and rice extract combined with standard inhibitors to inhibit α-glucosidase, α-amylase and tyrosinase activity

Rice volatile compounds including 2-pentylfuran, guaiacol and vanillin were identified from rice extract (BR, RR and WR) but in different concentrations, whereby 2-pentylfuran, vanillin and guaiacol had the highest concentrations identified from RR, BR and

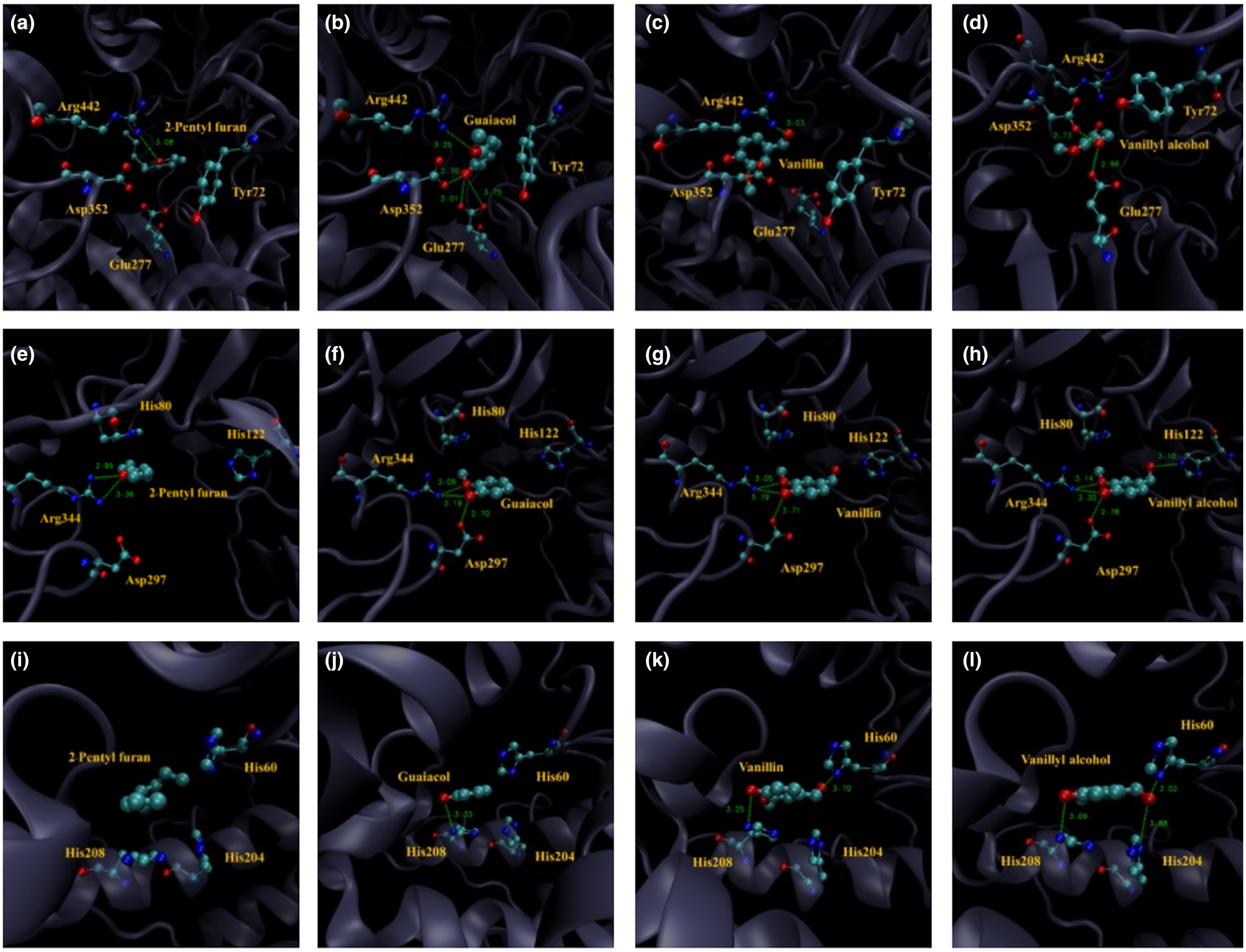

Figure 1 The docked structure of inhibitor (2-pentylfuran, guaiacol, vanillin and vanillyl alcohol, respectively) and amino acid in the active site of α-glucosidase (a to d), α-amylase (e to h) and tyrosinase (i to l).

WR, respectively (Table S2). Our results showed that 4 rice volatile compounds had inhibitory activity against α-glucosidase, α-amylase and tyrosinase enzymes (Table 2). Thus, the addition of these compounds to the rice extract might be enhanced and confirm the enzyme inhibitory activity of these compounds composed in the rice extract. Regarding the inhibitory activity of rice extract combined with rice volatile compounds against 3 enzymes, RR/2-pentylfuran showed higher inhibitory activity against α-glucosidase, α-amylase and tyrosinase than RR and 2-pentylfuran alone. BR/vanillin also showed higher inhibitory activity against α-glucosidase and tyrosinase than vanillin alone; the combination had higher potential than BR and vanillin alone, especially against α-amylase, whereas WR/guaiacol had only higher inhibitory activity on α-glucosidase than guaiacol alone. The results indicated that the addition of rice volatile compounds might affect the inhibitory potential of volatile compounds composed in the rice extract by enhancing its inhibitory potential. Furthermore, a synergic effect was only observed on α-amylase by BR/vanillin, BR/vanillyl alcohol, RR/vanillin, RR/vanillyl alcohol, WR/vanillin and WR/vanillyl alcohol. Interestingly, the combination of rice extract (BR, RR and WR) and vanillyl alcohol showed similar inhibition potential. The docking study revealed that the binding affinities of $-$ 5.7 kcal mol^{-1} for vanillin and $-$ 5.5 kcal mol^{-1} for vanillyl alcohol on α-amylase were higher when compared to those of other volatile compounds (Table S1). Thus, the synergic effect on α-amylase of these combinations might be affected by the binding of vanillin and vanillyl alcohol with amino acid in the active site of this enzyme.

The results indicated that RR/AB had the highest α-amylase inhibitory activity, followed by BR/AB and WR/AB. These combinations also showed higher inhibition potential than rice extract and AB alone. Regarding α-glucosidase inhibitory activity, only RR/AB showed higher inhibition potential than rice extract and AB alone. However, the combination of coloured rice extract with AB seemed to have higher inhibition potential against both enzymes than non-coloured rice combined with AB did. We also know that coloured rice has more beneficial nutrients than non-coloured rice has. More bioactive compounds (e.g. flavonoid and phenolic compounds) have also been found in coloured than in non-coloured rice. Tantipaiboonwonga *et al.* (2017) reported that BR and RR extract showed antihyperglycaemic and antihyperlipidaemic properties in a rat model. Previous results and our report suggest that the bioactive compounds in coloured rice might increase the inhibition potential against α-glucosidase and α-amylase of coloured rice extract combined with AB.

The results also showed that RR combined with the standard inhibitor KA showed higher tyrosinase inhibitory activity than BR and WR combined with KA did. Table 1 shows that RR has higher total phenolic content than BR and WR extract have. Prasad *et al.* (2019) also showed that RR extract has a variety of phenolic compounds, such as quercetin, ferulic acid, vanillic acid and catechin. Yu *et al.* (2019) reported that the combination of phenolic compounds quercetin, cinnamic acid and ferulic acid showed higher inhibition potential against tyrosinase than the compounds alone because the combination has shown a K_i value lower than compound alone. Our results and previous reports suggest that the variety of phenolic compounds in rice extract might affect tyrosinase inhibitory activity.

The potential of volatile compounds combined with standard inhibitors to inhibit α-glucosidase, α-amylase and tyrosinase activity

The results indicated that only volatile compounds combined with KA showed a synergic effect on tyrosinase. Volatile compounds combined with AB showed an antagonist effect on α-glucosidase and α-amylase. The binding affinity of vanillin (-5.5 kcal mol^{-1}) and vanillyl alcohol (-5.7 kcal mol^{-1}) on tyrosinase was higher than that of other volatile compounds (Table S1). The combinations of vanillin/KA and vanillyl alcohol/KA showed the highest potential to inhibit tyrosinase. Sendovski *et al.* (2011) reported that KA bound strongly, through interactions with residues in the active site entrance, with amino acids including Phe197, Pro201, Asn205, and Arg209. The docking study revealed that 4 rice volatile compounds located at the active site interact with His60, His204 and His208. The inhibition potential of KA is competitive for the monophenolase activity and mixed for the diphenolase activity of mushroom tyrosinase (Chang, 2009). Rice volatile compounds were located at the active site with a similar position to the KA, but not the same. Moreover, the inhibitor KA and volatile compounds might compete at the active site of the enzyme, and the volatile compounds might not interfere with the KA. These reasons can explain why the combination of volatile compounds with KA showed a synergic effect. On the other hand, the combination of volatile compounds with AB showed an antagonist effect on α-glucosidase and α-amylase. The binding affinity values of vanillin and vanillyl alcohol on α-glucosidase and α-amylase were similar to that of tyrosinase; however, the combinations (vanillin/AB and vanillyl alcohol/AB) showed an antagonist effect on two these enzymes. Brzozowski & Davies (1997) reported that AB interacts with amino acid in the active site of α-amylase at -3 subsite to $+3$ subsite. However, all rice volatile compounds were located at the -2 subsite of this enzyme (Fig. 1). Thus, the binding between volatile compounds and amino acid at the -2 subsite might interfere with the binding efficiency of AB with α-amylase and finally cause an antagonist effect for volatile compounds combined with AB.

Enhancing the inhibition potential of standard inhibitors by varied rice extract concentrations and vanillin concentrations

AB is the commercial drug for diabetes mellitus treatment. However, the common side effects of this drug are flatulence, abdominal bloating and discomfort, and diarrhoea (Sugihara *et al.*, 2014). Reducing AB side effects might be important during diabetes mellitus treatment. A decrease in AB concentration through combination with bioactive compounds is one way to reduce side effects. Combining AB with *Oroxylum indicum* seed extract can reduce the dose of AB by 80% (Sun *et al.*, 2017). In a kinetic study, the combination of black tea with AB functioned as a mixed-type inhibitor, and this combination showed a synergistic inhibitory effect on plasma glucose levels in vivo (Satoh *et al.*, 2015). Moreover, the combination of *Coccinia indica* leaf extract with a low dose of AB produced a significant decrease in the blood glucose level of rats after 7 weeks (Kohli & Kumar, 2014). Our results also indicate that increasing the RR extract concentration can increase the percentage of α-glucosidase and α-amylase inhibition at 0.10 mg mL^{-1} AB. Increasing BR and WR extract concentrations leads to an increase in the percentage of α-amylase inhibition at 0.10 mg mL^{-1} AB. Our results and previous reports suggest that the plant extract combined with AB can reduce AB concentration for application in diabetes mellitus treatment.

KA is a common commercial reagent for whitening cream products. However, a common side effect is contact dermatitis (Nakagawa *et al.*, 1995). The combination of KA with other bioactive compounds to reduce the KA concentration has been reported by previous researchers. The combination of KA with hydroquinone is a superior depigmenting agent (Deo *et al.*, 2013). Our results also showed that increasing the vanillin concentration increased the percentage of tyrosinase inhibition at 0.1 mg mL^{-1} KA. Our results and previous reports suggest that the study of KA in combination with bioactive compounds is important to reduce the concentration and the side effects of KA and to find new combinations for cosmetic products.

Conclusion

The free-radical scavenging capacity of rice extract (BR, RR and WR) is closely related with the phenolic content and flavonoid content, and the highest free-radical scavenging capacity, phenolic content and flavonoid content were obtained from RR and BR. The highest α-glucosidase and α-amylase inhibitory activity was from BR, whereas WR had the highest tyrosinase inhibitory activity. Among rice volatile compounds, vanillin, vanillyl alcohol and guaiacol had the highest potential to inhibit α-glucosidase, α-amylase and tyrosinase, respectively. The docking study also showed the high binding efficiency of these compounds with these enzymes. The combination of rice extract with AB had a synergic effect on α-glucosidase and α-amylase, whereas rice extract with KA had an antagonist effect on tyrosinase. The combination of rice extract with volatile compounds had a synergic effect on α-amylase (BR, RR, and WR), whereas WR/vanillyl alcohol had an antagonist effect on tyrosinase. The addition of rice volatile compounds to the rice extract affected the inhibition potential of the combination. The combination of rice volatile compounds with AB had an antagonist effect on α-glucosidase and α-amylase, whereas 2-pentylfuran/KA, vanillin/KA and vanillyl alcohol/KA had a synergic effect on tyrosinase. Increasing RR concentration in the RR/AB combination resulted in an increase of the percentage of inhibition against α-glucosidase and α-amylase. Increasing the BR and WR concentrations also increased the percentage of inhibition on α-glucosidase, similar to that of RR. Increasing the vanillin concentration in the vanillin/KA combination increased the percentage of inhibition against tyrosinase.

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Conflicts of interest

The author confirms that there are no conflicts of interest.

Author contribution

Sompong Sansenya: Conceptualization (lead); Data curation (lead); Formal analysis (lead); Investigation (lead); Methodology (lead); Project administration (lead); Writing-original draft (lead); Writing-review & editing (lead). **Apirak Payaka:** Data curation (equal); Formal analysis (equal). **Wachirawit Wannasut:** Data curation (equal); Formal analysis (equal); Methodology (equal). **Yanling Hua:** Formal analysis (supporting); Methodology (supporting). **Saowapa Chumanee:** Data curation (equal); Formal analysis (equal).

Ethical approval

Ethics approval was not required for this research.

Peer Review

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Data availability statement

Author elects to not share data.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. The characteristics of coloured and non-coloured rice. A: non-coloured rice (WR); B and C: BR and RR, respectively.

Figure S2. GC-MS chromatogram showing the volatile compound patterns of standard compounds (A), BR (B), WR (C), and RR (D).

Figure S3. The chemical structure of 4 volatile compounds. A: 2-pentylfuran; B: guaiacol; C: vanillin; and D: vanillyl alcohol.

Table S1. The binding affinity values of α-glucosidase (3A4A), α-amylase (7TAA), and tyrosinase (3NQ1) with 2-pentylfuran, guaiacol, vanillin, and vanillyl alcohol, respectively

Table S2. The concentration of rice volatile compounds (2-pentylfuran, guaiacol, vanillin, and vanillyl alcohol) in coloured rice extract (BR and RR) and non-coloured rice extract (WR)

Method S1. Supplementary methods.