CARPATHIAN JOURNAL OF FOOD SCIENCE AND TECHNOLOGY

journal homepage: **http://chimie-biologie.ubm.ro/carpathian_journal/index.html**

THE INHIBITION POTENTIAL OF THAI-COLORED RICE EXTRACT AGAINST DIABETES RELATED-ENZYMES AND MELANIN BIOSYNTHESIS-RELATED ENZYME

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https://doi.org/10.34302/crpjfst/2022.14.2.13

Article history:
Received:
27 September 2021
Accepted:
10 May 2022

Keywords:
Thai-colored rice;
α-Glucosidase inhibitory activity;
Tyrosinase inhibitory activity;
Polarity solvent.

ABSTRACT
Thailand has both colored and non-colored rice. Thai people use rice both for consumption and health treatment. This study investigates the phytochemical profile, α-glucosidase and tyrosinase inhibitory activity of water extract, ethanol extract, and methanol extract of 7 cultivars of Thai-colored rice. The results reveal that 7 cultivars of Thai-colored rice had composed of flavonoids, reducing sugar, saponins, and terpenoids. The highest potency against a-glucosidase activity was obtained from rice cultivar 6 of methanol extract with the IC_{50} value of 1.06 ± 0.13 $\mu g.ml^{-1}$, approximately 175-times more efficient than commercial drug acarbose. Moreover, methanol extract of all rice cultivars seems to have higher α-glucosidase inhibitory activity than other solvent extract and acarbose. In comparison, water extract of all rice cultivars had higher tyrosinase inhibitory activity than other solvents. The highest tyrosinase inhibitory efficiency was also obtained from rice cultivar 6 of water extract with the IC_{50} values of 10.93 ± 3.41 $\mu g.ml^{-1}$. Our results indicated that the high-polarity solvent can extract the bioactive compounds from plants with a high potency of α-glucosidase and tyrosinase inhibitory activity. The results also suggested that rice especially colored rice had contained the bio-active compounds which related with α-glucosidase and tyrosinase inhibitory activity.

1.Introduction

Alternative medicine has been used in many countries, especially in Asia (Ekor, 2014). People can use medical plants both for healthcare treatment and for ingredients in some cosmetics (Aburjai and Natsheh, 2003). Diabetes mellitus is a chronic metabolic disorder, and it can be insulin-dependent (type 1) and non-insulin-dependent (type 2), and more than 90% are diabetes mellitus type 2. Insulin is the glucose-level regulated hormone secreted from the Langerhans β cell of the pancreas (Hameed et al., 2015; Slattery et al., 2018; Zangeneh et al., 2003). The therapeutic methods for diabetes mellitus type 2 focused on inhibiting key enzymes from producing high blood sugar levels (Jeremiah et al., 2019; Singh et al., 2018; Slattery et al., 2018; Thilagam et al., 2013;). α-Glucosidase and α-amylase are carbohydrate hydrolyzing enzymes that release glucose from carbohydrates in the intestinal (Chakrabarti and Rajagopalan, 2002). Some standard inhibitors such as acarbose, miglitol, and voglibose have been used to inhibit the glucose releasing enzymes. However, these inhibitors cause many harmful side effects (Dabhi et al., 2013; Khan et al., 2014; Sugihara et al., 2014). Thus, the souse of the new inhibitor from the medicinal plant is to be importantly discovered and developed new drugs against α-glucosidase and α-amylase enzymes.

The human melanin had synthesized via L-tyrosine oxidation and related with the tyrosinase enzyme (Sari et al., 2019). The tyrosinase activity is also related to Parkinson's diseases (Asanuma et al., 2003). The commercials inhibitor is kojic acid has been used for tyrosinase inhibitory activity. However, kojic acid has been reported to cause cytotoxicity and allergy of skin (Kahn et al., 1997; Nakagawa et al., 1995). Thus the tyrosinase inhibitor with lower side effects from plant extracts is an alternative for melanin disorder and Parkinson's diseases.

Rice is a global staple food in many countries (Fairhurst and Dobermann, 2002). People use rice for consumption and treat their health, and some countries use rice as the ingredient of cosmetics (Hu et al., 2012; Marto et al., 2018). In Thailand, people like to consume brown rice, non-colored rice, and colored rice. Non-colored rice has also been reported to a related risk of cardiovascular diseases (Mohan et al., 2014). Moreover, non-colored rice has also been reported to a related risk of cardiovascular diseases (Krittanawong et al., 2017). The present study investigates the potential inhibition for a-glucosidase and tyrosinase of Thai-colored rice extracted in a different solvent, i.e., water extract, ethanol extract, and methanol extract.

2. Materials and methods

2.1. Materials

2.1.1. Plant materials and reagent

Seven cultivars of Thai colored-rice seed were obtained from Rio-Et province, Thailand. The characteristics of seven different rice cultivars were showed in Figure 1. All rice seeds were sterilized with 0.1% NaClO and washed with deionized water, then baked with hot air in an oven at 60 °C for six h. Before homogenization, the seed-coat was taken out, and the rice-seed samples were homogenized with CryoMill (Retch, Germany) by using liquid nitrogen. The homogenized samples were kept at -20 °C until extraction. The reagent comprising acabose, kojic acid, *p*-nitrophenyl-α-glucopyranoside (4-*p*NPG), L-DOPA, α-glucosidase from *Saccharomyces cerevisiae*, and tyrosinase from mushroom were obtained from Sigma-Aldrich (St. Louis, MO).

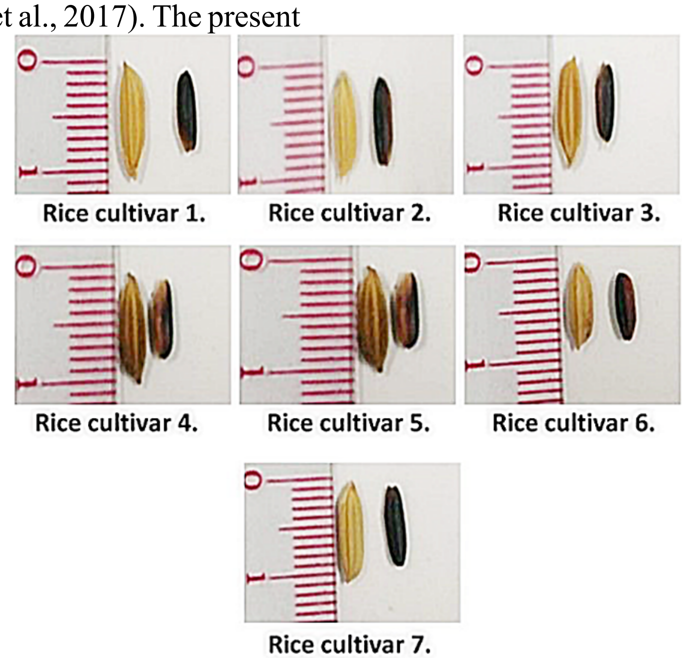

Figure 1. The 7 cultivars of Thai colored-rice harvested from Roi-Et province, Thailand. The seed-coat color of 7 cultivars is different by cultivar 3, 4, 5, and 6 are in brown, whereas cultivar 1, 2, and 7 are in yellow. The seed of 7 cultivars also shown differently by cultivar 1, 2, 3, and 7are in black, whereas cultivar 4, 5, and 6 are in red.

2.2. Methods

2.2.1. Samples extraction

The 500 g of homogenized rice samples were extracted with three solvents, i.e., water (HPLC water), ethanol (95%), and methanol (95%). The extracts were stirred for three days at room temperature. Then, the extracted rice samples were centrifuged, and the solvent was evaporated by hot air in an oven (ThermoStable ON-32, Daihan, Korea) at 60°C. The dry extraction yielding approximately 25% w/w to 40%w/w were kept at -20°C until enzyme activity occurred.

2.2.2. Phytochemical screening

The phytochemical composition of the samples was conducted by modified methods of Sansenya and Nanok, (2020). Flavonoids, reducing sugar, saponins, and terpenoids were evaluated by using the rice samples concentration of 0.10 $mg.mL^{-1}$ for each method.

For the flavonoids test, the rice samples were dissolved with ethyl acetate and then boiled for 5 min. Next, the reaction was filtered with a syringe filter 0.45 µm. Finally, the filtered solution was mixed with ammonia. The yellow color was occurred indicated that the samples were composed of flavonoids.

For the reducing sugar test, the rice samples were dissolved with HPLC water and then the solution was filtered with a syringe filter 0.45 µm for discarded the rice residues. The rice samples solution was mixed with benedict solution under base condition for determine the reducing sugar. Then, the mixture solution was boiled until brick-red precipitate appeared, which indicated that the samples was reducing sugar.

For the saponin test, the rice samples were dissolved with HPLC water and then the solution was filtered with a syringe filter 0.45 µm for discarded the rice residues. The three drops olive oil were added to the rice samples solution and shaken immediately. The mixture solution was incubated for 30 min at room temperature .The formation of emulsion and permanent bubbles indicated that the samples had saponin.

For the terpenoids test, the rice samples were mixed with 2 mL of chloroform and then shaken immediately. The rice samples solution was filtered with a syringe filter 0.45 µm for discarded the rice residues. Three milliliters of concentrated H_2SO_4 was added to the filtrate solution; a reddish-brown color indicated a positive result.

2.2.3. α-Glucosidase inhibitory activity assay

The α-glucosidase inhibitory activity of rice samples was performed in the previous study but slightly modified (Şöhretoğlu et al., 2018). In 100 mL of reaction was mixed with 5 mL of rice extracts (in 50mM sodium phosphate buffer pH 6.9) to give final concentration of 2 to 1,500 $\mu g.mL^{-1}$ and 5 mL of 5mM 4-*p*NPG and 5 mL of 0.05 $mg.ml^{-1}$ α-glucosidase. The reaction was incubated at 37°C, 10 min. Finally, 100 mL of 0.5 M Na_2CO_3 was added to stop the reaction. The absorbance was carried out at 405 nm using UV/Vis-spectrophotometer (Mapada UV-1200, Shanghai, China). Acarbose is the standard inhibitor used as the positive control. The inhibition percentage was calculated by the reaction below. The IC_{50} values of acarbose and all rice cultivars were calculated by Grafit 5.0 computer program (Erithacus Software, Horley, UK).

% Inhibition = $[(A_b - A_s)/A_b]*100$ (A_b = absorbance without sample; A_s = absorbance with sample). (1)

2.2.4. Tyrosinase inhibitory activity assay

The tyrosinase inhibitory activity assay of kojic acid and all rice samples was performed according to the method of Uchida et al. (2014) with slight modification. In brief, five mM of L-DOPA and 1 $mg.ml^{-1}$ of rice samples were prepared in 5% DMSO. The 0.1 $mg.ml^{-1}$ of tyrosinase from the mushroom was prepared in 20mM sodium phosphate buffer pH 6.8. First, 5mL of rice extracts (final concentration range of 2 $\mu g.mL^{-1}$ to 1,500 $\mu g.mL^{-1}$) was mixed with 5mL of tyrosinase (5$\mu g.mL^{-1}$ in final concentration), then the reaction mixture was incubated at 30°C for 10 min. After that, 5mLof L-DOPA (0.25mM in final concentration) was added to the reaction mixture. Then, the reaction was continuously incubated at 30°C for 15 min. The dopachrome production was analyzed by the spectrometer at 492 nm using UV/Vis-spectrophotometer (Mapada UV-1200, Shanghai, China). Kojic acid was used as the standard inhibitor, working as the positive control. The inhibition percentage was calculated by the reaction above. The IC_{50} values of kojic acid and all rice cultivars were calculated with the same a-glucosidase inhibitory activity.

2.2.5. Statistical analysis

The experiments including α-glucosidase and tyrosinase inhibitory activity of rice samples were performed in triplicate and these results showed as standard deviation of mean (SD). Statistical differences were determined by one-way analysis of variance (ANOVA), and the differences were considered significant at $P < 0.05$.

3.Results and discussions

3.1. Phytochemical compounds

The phytochemical compounds of 7 colored-rice cultivars in the different solvent extracts were evaluated and shown in Table 1. The compounds including flavonoids and reducing sugar were obtained from all rice cultivars and all solvent extract. In contrast, saponin and terpenoids were identified in some rice cultivars and some solvent extracts. However, saponin seems to have abundantly been found than terpenoids. Flavonoids from the plant have been reported for their biological activity. Flavonoids also have multiple positive health effects, primarily on metabolic disorders, such as cancer, diabetes mellitus and heart disease (Middleton et al., 2000; Al-Ishaq et al., 2019).

Table 1. Phytochemical profile of 7 colored-rice cultivars extracts

Rice cultivars	Samples	Phytochemical compounds			
		Flavonoids	Reducing sugar	Saponin	Terpenoids
1	Water extract	+	+	+	-
	Ethanol extract	+	+	+	+
	Methanol extract	+	+	+	+
2	Water extract	+	+	+	+
	Ethanol extract	+	+	+	+
	Methanol extract	+	+	+	+
3	Water extract	+	+	+	-
	Ethanol extract	+	+	+	+
	Methanol extract	+	+	+	+
4	Water extract	+	+	+	-
	Ethanol extract	+	+	-	-
	Methanol extract	+	+	+	-
5	Water extract	+	+	+	-
	Ethanol extract	+	+	-	-
	Methanol extract	+	+	+	-
6	Water extract	+	+	+	-
	Ethanol extract	+	+	+	-
	Methanol extract	+	+	+	-
7	Water extract	+	+	+	-
	Ethanol extract	+	+	+	+
	Methanol extract	+	+	+	+

+; indicated detected of the compounds. -; indicated not detected of the compounds

Saponin and terpenoids from the plant also have been reported for their biological activity. El Barky et al. (2017) reported that saponin decreased blood glucose levels in diabetes mellitus. The terpenoids have also been reported for metabolic disorders, especially for Type II diabetes (Panigrahy et al., 2021). Our results showed that the biological compounds, including flavonoids, saponin, terpenoids, had been identified from all 7 colored-rice cultivars. These rice cultivars had also demonstrated the α-glucosidase inhibitory activity. Previous reports and our results indicated that biological activity such as diabetes had related to biological plant compounds such as flavonoids, saponin, and terpenoids.

3.2. Thai colored-rice extracts against α-glucosidase activity

The results show that methanol extract of 7 colored-rice cultivars seems to have effective α-glucosidase inhibition than other solvent extraction and the positive control inhibitor acarbose Table 2.

Table 2. α-Glucosidase inhibitory activity of rice extracts.

Rice cultivars	IC$_{50}$ value (μg.ml^{-1})		
	Water extract	Ethanol extract	Methanol extract
1	229.31 ± 23.31^{b}	168.21 ± 7.72^{b}	44.04 ± 4.13^{c}
2	286.38 ± 33.17^{a}	115.61 ± 6.94^{e}	37.42 ± 3.13^{d}
3	128.63 ± 12.69^{de}	171.55 ± 7.22^{b}	38.58 ± 6.06^{d}
4	141.24 ± 5.17^{d}	186.26 ± 12.13^{a}	20.44 ± 2.85^{e}
5	179.43 ± 14.31^{c}	153.41 ± 6.84^{c}	171.44 ± 13.29^{a}
6	118.22 ± 10.07^{e}	134.57 ± 11.88^{d}	1.06 ± 0.13^{f}
7	172.01 ± 14.30^{c}	125.76 ± 5.75^{de}	135.42 ± 9.46^{b}
Acarbose	185.92 ± 15.12		

The IC$_{50}$ values were presented as mean ± standard error of the mean of triplicate measurements. The differences superscript letters in the column indicate significant differences between the inhibitory activity of rice extracts ($P < 0.05$).

The IC$_{50}$ values of methanol extract was in the range of 1.06 ± 0.13 μg.ml^{-1} to 171.44 ± 13.29 μg.ml^{-1}. The highest effective α-glucosidase inhibition of methanol extract of rice cultivar 6 (IC$_{50}$ values of 1.06 ± 0.13μg.ml^{-1}) was approximately 175 times higher than acarbose (IC$_{50}$ values of 185.92 ± 15.12 μg.ml^{-1}). While methanol extract of rice cultivar 5 (IC$_{50}$ values of 179.43 ± 14.31 μg.ml^{-1}) was less effective against α-glucosidase activity than other rice cultivars but still higher effective than acarbose. The α-glucosidase inhibitory activity of methanol extract of all colored-rice cultivar was also higher than other solvent extraction except for rice cultivar 5 and cultivar 7. More observation, the α-glucosidase inhibitory potential of ethanol extract also had higher potent than acarbose except for rice cultivar 4. The lower a-glucosidase inhibitory activity of rice extract was obtained from water extract, especially rice cultivar 2 with the IC$_{50}$ values of 286.38 ± 33.17 μg.ml^{-1}. The highest IC$_{50}$ value of rice cultivar 2 had approximately 270.17-times and 1.54-times compared with the lowest IC$_{50}$ value of rice cultivar 6 of methanol extract (highest α-glucosidase inhibitory activity) and IC$_{50}$ value of acarbose, respectively. The α-glucosidase inhibitory activity of rice bran had been reported previously by Sivamaruthi et al. (2018). The highest one against the α-glucosidase activity of rice bran was obtained from ethanol and methanol, similar to our results. The ethanol extract of black and red rice can reduce hyperglycemia, which induces diabetes in the rat by streptozotocin (Tantipaiboonwong et al., 2017). Our results and previous report indicate that the high efficiency of inhibitor against α-glucosidase activity should be extracted under methanol and ethanol conditions and the results also indicate that the inhibitor might have slight polarity.

3.3. Thai colored-rice extracts against tyrosinase activity

The tyrosinase inhibitory activity of 7 colored-rice cultivars was investigated, and their IC$_{50}$ values were shown in Table 3. Kojic acid is the commercial inhibitor that acts as the positive control. All the IC$_{50}$ values of rice extract in different cultivars and different solvent extracted were shown in higher values than kojic acid. The high tyrosinase inhibitory activity was obtained from water extract with the IC_{50} values were found to be 10.93 ± 3.41 μg.ml^{-1} to 301.39 ± 26.01 μg.ml^{-1}. Rice cultivar 6 of water extract had the highest tyrosinase inhibitory activity efficiency but still lower than kojic acid. The most increased tyrosinase inhibitory activity of rice cultivar 6 (IC_{50} values of 10.93 ± 3.41 μg.ml^{-1}) had approximately 27-times higher than the lowest one of rice cultivar 1 (IC_{50} values of 301.39 ± 26.01 μg.ml^{-1}). Still, its inhibitory activity efficacy had approximately 2.4-times lower than kojic acid (IC_{50} values of 4.64 ± 0.69 μg.ml^{-1}). Furthermore, water extract of rice cultivar 2 to rice cultivar 7 had higher tyrosinase inhibitory activity potent than ethanol and methanol extract. The IC_{50} values of ethanol extract and methanol extract were of similar potential levels. The results indicated that ethanol extract had lower tyrosinase inhibitory activity than methanol extract. The highest IC_{50} values of all extraction were obtained from ethanol extract of rice cultivar 4 and its IC_{50} values were determined to be 488.90 ± 44.92 μg.ml^{-1}. Rice cultivar 4 of ethanol extract and its IC_{50} values were approximately 105-times and 45-times higher than those of kojic acid and rice cultivar 6 (most increased tyrosinase inhibitory activity) water extract, respectively. The results suggest that tyrosinase inhibitor compounds from rice might have strong polarity. Many tyrosinase inhibitor compounds have been isolated from various plants by polarity solvent. The isolated 6 from *Quercus coccifera* (L.) has strong potent on tyrosinase inhibitory activity, and this compound was extracted with methanol. In contrast, the increase of polarity by increase of water ratio was shown in the purification step (Şöhretoğlu et al., 2014). Di Petrillo et al. (2016) also reported the extraction of *Asphodelus microcarpus* with three solvents i.e., water, ethanol, and methanol. The results showed that the high tyrosinase inhibitory activity was investigated from ethanol extract. Fu et al. (2014) also reported the high antioxidant and tyrosinase inhibition activity of *Sapium sebiferum* (L.) Roxb. extracted by water at high temperatures. The previous report may support our results, indicating that the compounds from rice with high tyrosinase inhibition activity might have strong polarity.

Table 3. Tyrosinase inhibitory activity of rice extracts.

Rice cultivars	**IC_{50} value (μg.ml^{-1})**		
	Water extract	**Ethanol extract**	**Methanol extract**
1	301.39 ± 26.01^{a}	305.90 ± 26.74^{c}	214.48 ± 21.28^{d}
2	37.44 ± 4.27^{cd}	196.10 ± 8.50^{e}	330.88 ± 29.44^{b}
3	31.83 ± 3.50^{d}	322.44 ± 30.50^{b}	180.09 ± 19.13^{e}
4	40.27 ± 4.13^{c}	488.90 ± 44.92^{a}	154.06 ± 9.90^{f}
5	40.31 ± 4.08^{c}	181.20 ± 18.95^{f}	341.61 ± 30.25^{a}
6	10.93 ± 3.41^{e}	195.94 ± 15.99^{e}	299.72 ± 21.19^{c}
7	73.15 ± 6.63^{b}	290.67 ± 20.19^{d}	210.71 ± 13.44^{d}
Kojic acid	4.64 ± 0.69		

The IC_{50} values were presented as mean ± standard error of the mean of triplicate measurements. The differences superscript letters in the column indicate significant differences between the inhibitory activity of rice extracts ($P < 0.05$).

3.4. The efficacy of α-glucosidase and tyrosinase inhibitory activity of colored rice extracts from different solvent extract

The inhibition potential on α-glucosidase and tyrosinase activity of rice extract of different solvent extractions were shown in Figure 2. The higher polarity of solvent seems to give the inhibition potential on tyrosinase activity than the lower polarity solvent. Tyrosinase inhibitory activity of water extract has high efficacy than other solvents except for rice cultivar 1. Other solvent extracts, ethanol, and methanol get high α-glucosidase inhibitory activity than tyrosinase of all rice cultivars. Three solvent-extracts, water, ethanol, and methanol are the polarity solvents, where water has the higher polarity than ethanol and methanol. The extraction has reported many inhibitors of α-glucosidase and tyrosinase with polarity solvent. Masuda et al. (2007) identifies tyrosinase inhibitor as 4-beta-D-glucopyranosyloxybenzoic acid from leaves of *Nandina domestica*, and this compound is extracted by ethanol, and it is water-soluble. Tyrosinase inhibitor has also been reported from the methanol extract. Identified from *Vitex negundo* Linn, 8 ligands have high potency on tyrosinase inhibitory activity (Malik et al., 2006). Our results agree with the report of Ohta et al. (2002) in that the methanol extract from *Pelvetia babingtonii* (Harvey) De Toni has a high effect against a-glucosidase, sucrase, and maltase activity. The new ester of fatty acid, also extracted by methanol, has potency on α-glucosidase inhibitory activity reported by Mondal et al. (2015). The other polarity solvent, such as ethyl acetate, has been used to extract the a-glucosidase inhibitor. Mauldina et al. (2017) reported that the ethyl acetate extract of *Antidesma bunius* (L.) containing triterpenoid had a-glucosidase inhibitory activity. Thus the previous reports and our results indicate that the α-glucosidase and tyrosinase inhibitor could be extracted from plants by polarity solvent. The rice extracts containing the a-glucosidase and tyrosinase inhibitor may be applied in cosmetic products such as skinning products. Moreover, these extracts may be applied to the drug for diabetes treatment.

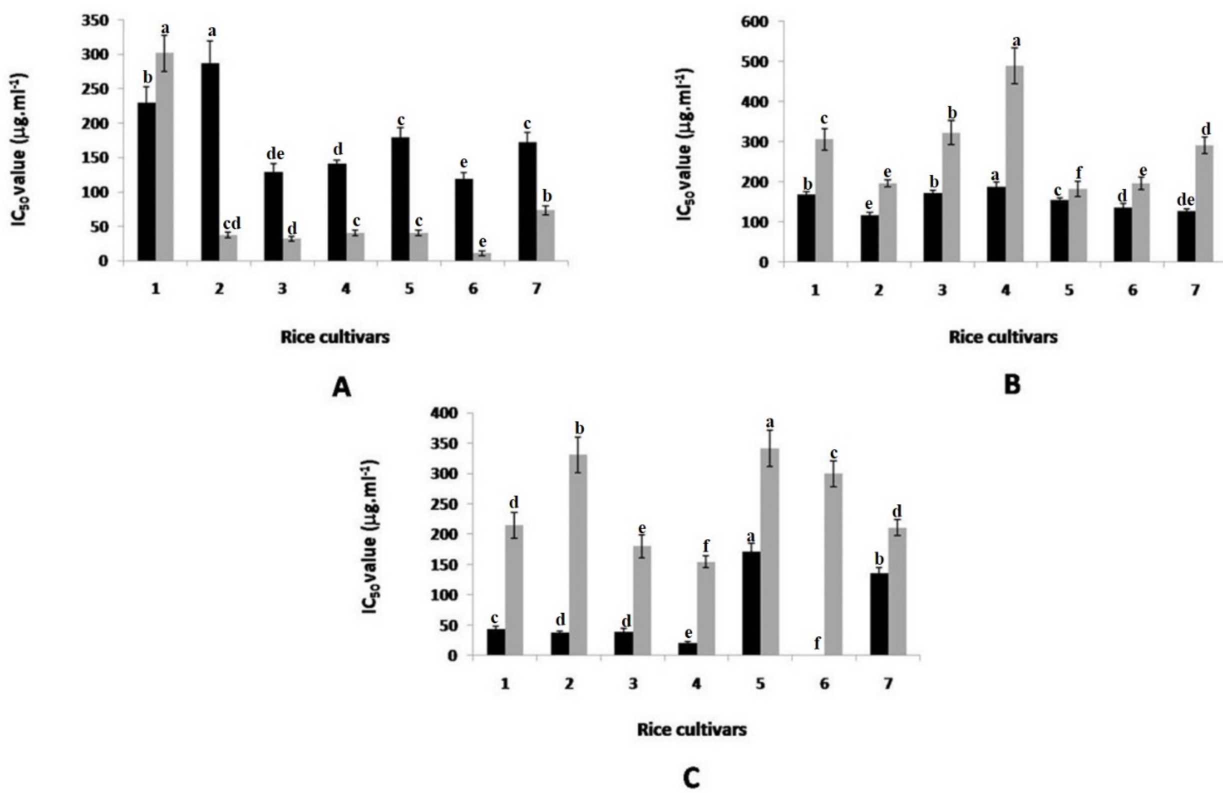

Figure 2. The comparison between α-glucosidase and tyrosinase inhibitory activity from three solvent extracts (water, ethanol, and methanol) of 7 colored-rice cultivars. A; water extract, B; ethanol extract, and C; methanol extract. The black bars represent a-glucosidase inhibitory activity, and the gray bars represent tyrosinase inhibitory activity. The error bar is also shown at the top of each bar graph. The differences letters above the error bar indicate significant differences between the inhibitory activity of rice extracts ($P < 0.05$).

4. Conclusions

We investigated the phytochemical profiled, α-glucosidase and tyrosinase inhibitory activity from water extract, ethanol extract, and methanol extract of 7 colored-rice cultivars. The flavonoids, reducing sugar, saponins, and terpenoids were identified from all colored-rice cultivars. The methanol extract had higher α-glucosidase inhibitory activity than those of other solvent extracts (water and ethanol) and acarbose. In contrast, the water extract seemed to have the lowest α-glucosidase inhibitory activity than those of ethanol extract and methanol extract. On the other hand, the water extract had higher tyrosinase inhibitory activity than other solvents but lower than kojic acid. At the same time, the ethanol extract showed the lowest tyrosinase inhibitory activity than those of methanol and water. The results indicate that rice was contained bio-active compounds that rich in α-glucosidase and tyrosinase inhibitory compounds.

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Acknowledgment

This work was supported by the National Research Council of Thailand, Thailand (Granted No. 2564A16502042 and FR64E0616) and Rajamangala University of Technology Thanyaburi (RMUTT). We are also grateful to Surasit Jitrenu for providing plant samples.