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Original Article

Evaluation for Antidiabetic Activities of Flavonoids

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Abstract:
This study aims to evaluate the effects on antidiabetic activities of petroleum ether extract (SMPE), ethyl acetate extract (SMAE), and flavonoids isolated from Syzygium malaccense. The results discovered compounds 2, 5, 7, and 9 exhibited weak inhibitory activity against α-glucosidase with percent inhibition rate of 2.74±0.26 ~ 10.20±0.33 at 1.00×10-6 mol/L and 9 showed weak promotion on glucose consumption in HepG2 cells with consumption rate of 4.03±2.70 % at 1.00×10-6 mol/L. All compounds were firstly tested their HepG2 cells glucose consumption activities, and 6 and 8 ~ 10 were the first report on their α-glucosidase inhibitory effect. This research provided new evidences for antihyperglycemic activity of S. malaccense.

Keywords: Syzygium malaccense, flavonoids, α-glucosidase, HepG2 cell, glucose consumption

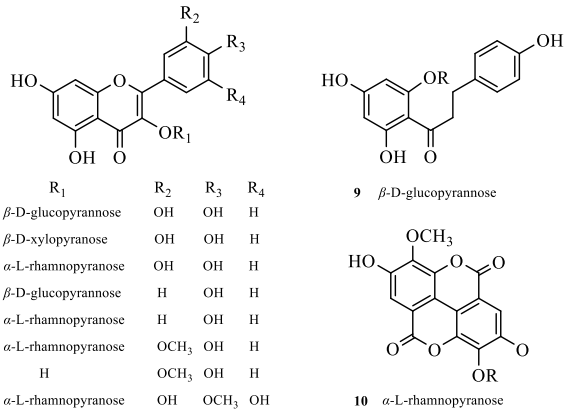
Introduction

TYPE 2 DIABETES MELLITUS (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from either insufficient insulin secretion or impaired insulin action, and it has emerged as a major public health concern worldwide[1,2]. Prolonged hyperglycemia contributes to the development of severe complications, including nephropathy, neuropathy, cardiovascular disease, and retinopathy[3,4]. Previous studies have demonstrated that inhibition of *α*-glucosidase activity can delay carbohydrate digestion and absorption, thereby representing a

primary therapeutic strategy for the management of postprandial hyperglycemia[5].

HepG2 cells, a human-derived hepatocellular carcinoma cell line, exhibit phenotypic characteristics closely resembling those of normal hepatocytes. Following exposure to high concentrations of insulin, the number of insulin receptors on the surface of HepG2 cells is downregulated, and the extent of this reduction correlates positively with both insulin concentration and stimulation duration. Consequently, HepG2 cells are widely considered an ideal in vitro model for elucidating the pathogenesis of insulin resistance and investigating the mechanisms underlying the action of glucose-lowering agents[6].

As a ubiquitous class of polyphenolic compounds in medicinal plants, flavonoids have attracted substantial interest for their potential to manage type 2 diabetes mellitus (T2DM) through diverse mechanisms, such as improving insulin sensitivity, preserving *β*-cell function, and regulating the activity of carbohydrate-metabolizing enzymes[7,8]. The objective of this study was to discover SMPE, SMAE, and flavonoids (Figure 1) from *S. malaccense*[9] with the *α*-glucosidase inhibitory activity and HepG2.



	R_1	R_2	R_3	R_4
1	*β*-D-glucopyrannose	OH	OH	H
2	*β*-D-xylopyranose	OH	OH	H
3	*α*-L-rhamnopyranose	OH	OH	H
4	*β*-D-glucopyrannose	H	OH	H
5	*α*-L-rhamnopyranose	H	OH	H
6	*α*-L-rhamnopyranose	OCH_3	OH	H
7	H	OCH_3	OH	H
8	*α*-L-rhamnopyranose	OH	OCH_3	OH

9 *β*-D-glucopyrannose

10 *α*-L-rhamnopyranose

Figure 1. The structures of compounds **1** - **10**

Cell glucose consumption activity to support the development of novel therapeutic agents.

The assay was performed as the reported method[10]. A mixture of 20 μL of five different concentrations of the test samples, *α*-glucosidase solution (0.025 U/mL), 10 μL of 0.1 M buffer (pH 6.9) and 20 μL of 1 mM *p*-nitrophenyl-*α*-D-glucopyranoside solution was incubated in 96-well plates at 37 ℃ for 50 min. After incubation, optical density (OD) was recorded at 405 nm by a microplate reader (SpectraMax M2, Molecular Devices Corp., operated by SoftmaxProv.4.6 software, Sunnyvale, CA, USA) and compared with that of the positive control (acarbose), which had 20 μL buffer solutions. The *α*-glucosidase inhibitory activity was indicated as percent inhibition and was calculated as follows.

$$\% \text{ inhibition} = (1 - OD_{sample}/OD_{control}) \times 100$$

Human hepatocellular carcinoma HepG2 cells were cultured in high-glucose Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS) under standard conditions (37°C, 5% CO_2). For the assay, cells were seeded in 96-well plates. After attachment, they were rinsed and incubated in serum-free, low-glucose (5.5 mM) DMEM containing the test compounds and positive control (1 μM **metformin**) for 24 hours[11].

Glucose consumption and viability assessment

Following incubation, culture supernatants were collected. Glucose concentration was measured using a glucose oxidase (GOD) assay kit, and consumption was calculated relative to the initial medium and normalized to total cellular protein content determined by a BCA assay. To confirm that metabolic effects were not due to cytotoxicity, cell viability was assessed in parallel under identical treatment conditions using the Cell Counting Kit-8 (CCK-8) assay. This method was adapted from established protocols with modifications[12]. Data are presented as mean ± SD of glucose consumed per mg protein from at least three independent experiments. The glucose consumption rate (GC) and **sample-promoted cellular glucose consumption rate** (SCGC) was calculated as follows:

GC = [(glucose content in the medium − glucose content in the experimental group)/glucose content in the medium] × 100%

SCGC = [(glucose content in the control group − glucose content in the sample-treated group)/glucose content in the control group] × 100%

The SMPE, SMAE, and all isolates were evaluated on their inhibitory effects against *α*-glucosidase with acarbose as a positive control, and tested for their HepG2 cell glucose consumption activity with metformin as a positive control. As shown in Table 1, compounds **2**, **5**, **7** and **9** exhibited weak inhibitory effects with

exhibition rate from 2.74 ± 0.26 to 10.20 ± 2.54% at 1.00×10^{-6} mol/L, the SMPE and SMEA demonstrated weak exhibition effect with exhibition rate of 8.84±1.78% and 12.17±7.24% at 0.2 μg/mL, respectively, and the positive control (acarbose) showed exhibition rate of 85.44±3.82 % at 10^{-8} mol/L by comparison. Only compound **9** exhibited weak activity for HepG2 cell glucose consumption with **consumption rate of** 4.03±2.70 % at 1.00×10^{-6} mol/L. The results revealed that dihydrochalcone possess both α-glucosidase inhibitory activity and HepG2 cell glucose consumption activity. Unexpectedly, some pure compounds from *S. malaccense* showed weaker inhibitory activity than its extracts, indicating the multiple constituents in the extract interact with each other to jointly exert the effect. These findings suggest that *S. malaccense*, and their flavonoids may be promising candidates for managing type 2 diabetes, deserving further research.

Table 1 Antidiabetic activities of the test samples and positive controls (%)

	1[a]	**2**[a]	3[a]	***4***[a]	***5***[a]	**6**[a]	**7**[a]
% inhibition (α-glucosidase)	0	10.20±0.33	0		2.74±0.26	0	4.72±5.14
GC %	39.58±2.38	36.73±0.14	40.03±1.00	29.96±12.40	40.70±1.69	31.15±6.14	36.88±0.69
SCGC %	0	0	0	0	0	0	0
	8[a]	9[a]	***10***[a]	**SMPE**[b]	**SMAE**[b]	***control***[c]	
% inhibition (α-glucosidase)	0	5.36±0.51	0	8.84±1.78	12.17±7.24	85.44±3.82	
GC %	31.42±11.26	42.15±0.66	34.68±10.82	33.62±10.71	34.94±10.73	48.46±2.43	
SCGC %	0	4.03±2.70	0	0	0	14.56±0.66	

[a]Compounds were tested at 1.00×10^{-6} mol/L, [b]extracts were tested at 0.2 μg/mL, [c]acrabose and **metformin** were tested at 1.00×10^{-8} and 1.00×10^{-6} mol/L, respectively.

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Conflict of Interest Statement:The authors declare no conflict of interest.

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