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Discovery of potent α-glucosidase inhibitor flavonols: Insights into mechanism of action through inhibition kinetics and docking simulations

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ABSTRACT

Beside other pharmaceutical benefits, flavonoids are known for their potent α-glucosidase inhibition. In the present study, we investigated α-glucosidase inhibitory effects of structurally related 11 flavonols, among which quercetin-3-*O*-(3″-*O*-galloyl)-*β*-galactopyranoside (**8**) and quercetin 3-*O*-(6″-*O*-galloyl)-*β*-glucopyranoside (**9**) showed significant inhibition compared to the positive control, acarbose, with IC_{50} values of 0.97 ± 0.02 and 1.35 ± 0.06 μM, respectively. It was found that while sugar substitution to C3-OH of C ring reduced the α-glucosidase inhibitory effect, galloyl substitution to these sugar units increased it. An enzyme kinetics analysis revealed that **7** was competitive, whereas **1**, **2**, **8,** and **9** were uncompetitive inhibitors. In the light of these findings, we performed molecular docking studies to predict their inhibition mechanisms at atomic level.

1. Introduction

Flavonoids are polyphenolic color pigments widely distributed in many plants. They are benzo-4*H*-pyrone derivatives consisting of two aromatic rings (A and B) linked via a 4*H*-pyran ring (C) and classified according to the oxygenation state and unsaturation of the C3 unit. The main flavonoid subclasses are flavones, flavonols, flavanones, flavan-3-ols (flavanols), and isoflavones. Most naturally occurring flavonols are present as glycosides, and their sugar moieties can have further substituents attached to them (e.g. galloylation). They are among the components of plants used in human diets, including vegetables, fruits, and beverages like tea, cocoa, and wine [1,2].

Diabetes mellitus (DM) is a chronic disease characterized by hyperglycemia due to inadequate production of insulin and/or inability of the body to fully respond to insulin. DM causes life threatening health complications, such as cardiovascular diseases, nephropathy, and retinopathy, which can be delayed or prevented by management of high glucose levels [3,4]. Approximately 8.8% of world adult population (20–79 years of age) has DM, which is among the top 10 causes of death globally, and 4.0 million adults were estimated to die from diabetes in 2017. The healthcare expenditure on diabetes also in tremendous increase, growing from USD 232 billion worldwide in 2007 to USD 727 billion [5]. The major classes of oral antidiabetic drugs are biguanides, sulfonylureas, meglitinides, thiazolidinediones, dipeptidyl peptidase 4 inhibitors, sodium-glucose cotransporter inhibitors, and α-glucosidase inhibitors. α-glucosidase inhibitors prevent breakdown of disaccharide and oligosaccharide substrates into absorbable monosaccharides, which, in turn leads to a delayed intestinal carbohydrate digestion/absorption and reduced postprandial hyperglycaemia [6]. However, currently marketed α-glucosidase inhibitors exhibit some adverse hepatic events and increase hepatic enzyme levels [7]. Therefore, it is important to search for new potent α-glucosidase inhibitors with lower side effects.

Flavonoids are important because they are essential components of diet and exhibit therapeutic potential. According to epidemiological studies, there is a positive correlation between regular dietary flavonoid intake and lower occurrence of a variety of diseases such as, cardiovascular diseases, neurodegenerative diseases, cancer, and DM [8–12]. Furthermore, flavonoid intake not only decreases DM incidence, it also reduces cardiovascular risk factors DM type 2 populations [13]. In our previous studies, we investigated *Potentilla spec*. used for treatment of diabetes in folk medicine and conducted bio-guided isolation, by which we obtained a set of isoflavones and flavonols with high α-glucosidase inhibitory effect [14,15]. Here we tested α-glucosidase inhibitory effect

Abbreviations: ALBS, allosteric ligand-binding sites; DM, diabetes mellitus; SCM, *Saccharomyces cerevisiae*; OLBS, orthosteric ligand-binding site

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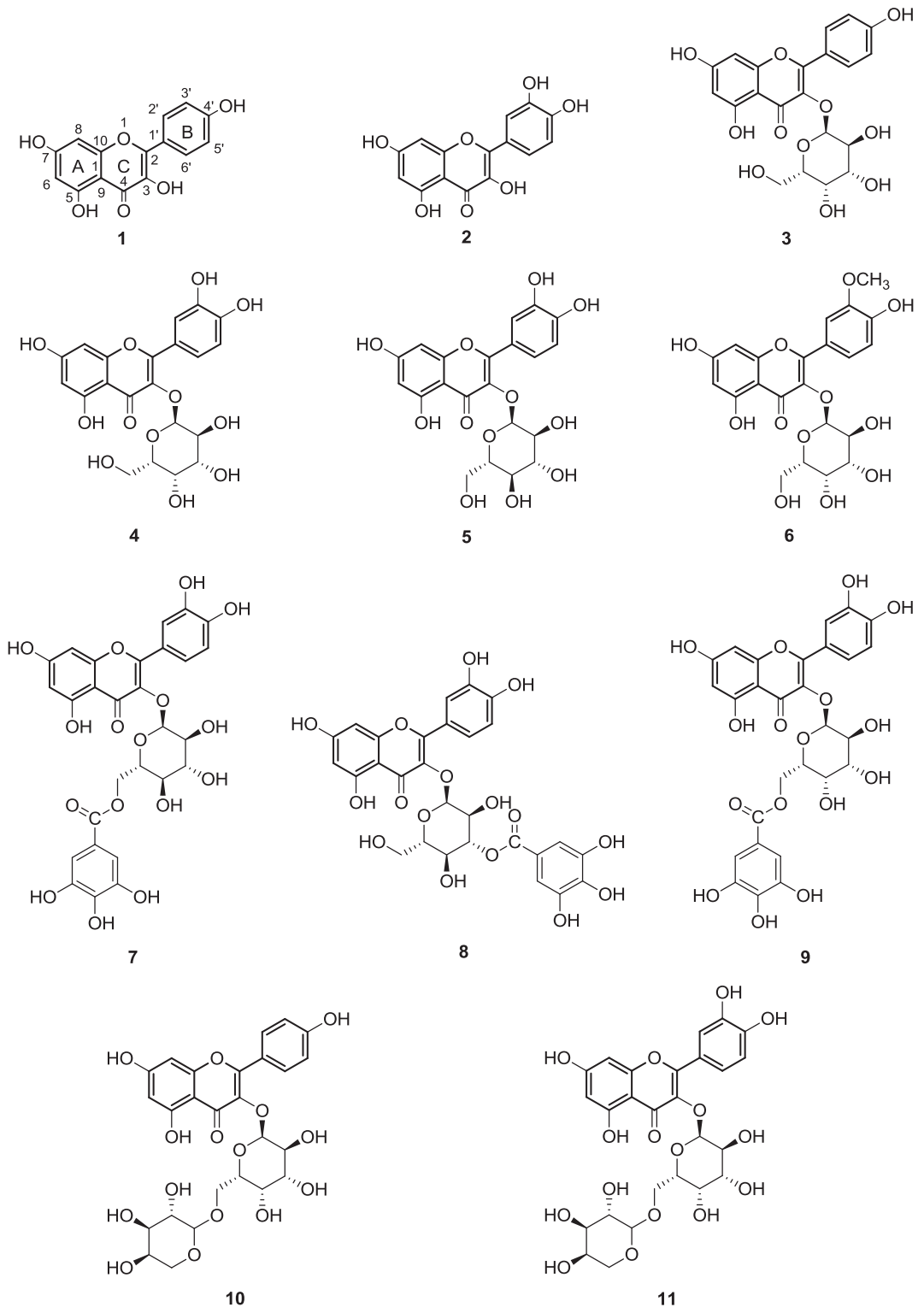

Fig. 1. Molecular structures of the isolated compounds: kaempferol (**1**), quercetin (**2**), kaempferol 3-*O*-*β*-glucopyranoside (**3**), quercetin 3-*O*-*β*-glucopyranoside (**4**), quercetin 3-*O*-*β*-galactopyranoside (**5**), isorhamnetin 3-*O*-*β*-glucopyranoside (**6**), quercetin 3-*O*-(6″-*O*-galloyl)-*β*-galactopyranoside (**7**), quercetin 3-*O*-(3″-*O*-galloyl)-*β*-galactopyranoside (**8**), quercetin 3-*O*-(6″-*O*-galloyl)-*β*-glucopyranoside (**9**), kaempferol 3-*O*-vicianoside (**10**), quercetin 3-*O*-vicianoside (**11**). The nomenclature of flavonoids is shown on **1** as an example [16].

of some structurally related flavonols we had isolated from different plants in our previous studies to find new hits and figure out a structure-activity pattern (Fig. 1). We also evaluated their enzyme kinetics *in vitro* and using molecular docking approach we tried to provide insights into their binding properties to possible ligand binding sites of the enzyme.

2. Results and discussion

2.1. α-Glucosidase inhibition assay

α-Glucosidase inhibitory potencies of **1–11** were evaluated by determination of their IC_{50} values in comparison to the positive control,