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SHORT COMMUNICATION

Anti-diabetic and anti-urease potential of *Osbeckia nutans* Wall. leaves

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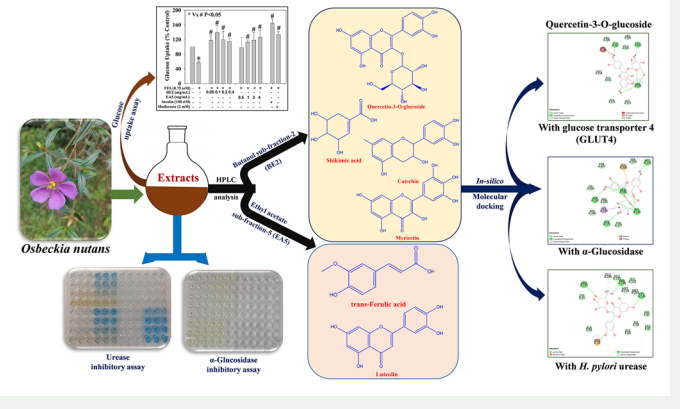
ABSTRACT

A study was conducted to investigate the anti-diabetic and anti-urease potential of *Osbeckia nutans* leaves (ONL). Six compounds, i.e. quercetin-3-O-glucoside, myricetin, shikimic acid, catechin, trans-ferulic acid and luteolin were identified from the butanol sub-fraction, BE2 and the ethyl acetate sub-fraction, EA5 of ONL. BE2 inhibited α-glucosidase and Jack bean urease with IC_{50} values of 0.036 µg/mL (437.46 µg/mL for acarbose) and 0.327 mg/mL (0.039 mg/mL for thiourea), respectively. In the glucose uptake experiment, BE2 (0.05 mg/mL) treatment resulted in a substantial increase in glucose uptake in free fatty acid (FFA)-treated cells at a concentration 10 times lower than that seen in EA5 (0.5 mg/mL) treated cells. The binding energies of quercetin-3-O-glucoside with α-glucosidase, glucose transporter GLUT4 and *H. pylori* urease were found to be −94.2585, −219.8271 and −254.391 kcal/mol, respectively. This study revealed that ONL has anti-diabetic and anti-urease abilities and further in-depth research may unveil its full potential.



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1. Introduction

Diabetes mellitus (DM), a complex metabolic disease affecting glucose, lipid and protein metabolism, is caused by inadequate insulin secretion, inefficient insulin action or both. Type 2 diabetes (T2DM) is the most frequent kind of DM caused by the body's inappropriate usage of insulin. Prolonged hyperglycaemia can cause a variety of complications including dementia, cancer, nephropathy, retinopathy and cardiovascular diseases (Din et al. 2021). Through signalling pathways, insulin and glucagon support lipids and glucose homeostasis. In order to speed up the insulin-dependent storage of glucose in muscle and fat cells, pancreatic hormones induce the translocation of the glucose transporter 4 (GLUT4) from an intracellular site to the cell surface. It is assumed that insulin resistance in T2DM may be a caused by problems with the glucose uptake mechanisms (Li et al. 2022). Understanding the pathogenesis of this illness and how phytochemicals affect insulin signalling pathways by stimulating GLUT4 translocation is essential for the treatment of this condition (Sayem et al. 2018). One of the potential therapeutic approaches presently available to manage and/or treat postprandial hyperglycaemia is the inhibition of carbohydrate hydrolysing enzymes like α-glucosidase and α-amylase (Rynjah et al. 2018). The use of synthetic α-glucosidase inhibitors such as acarbose, voglibose and miglitol, is constrained due to their expense and undesirable side effects. Therefore, the present need is for safer and more efficient α-glucosidase inhibitors to be discovered or created (Ding et al. 2018).

One of the antibiotic-resistant ureolytic bacteria, *Helicobacter pylori* infects the intestinal system and causes gastroduodenal diseases that lead to gastric cancer, posing a serious threat to human life (Ishaq and Nunn 2015; Tsay and Hsu 2018). The urease catalyses the hydrolysis of urea in the gut, which releases carbon dioxide and ammonia accordingly. One of the most efficient methods for preventing the spread of *H. pylori* is to inhibit urease. Prior research shows no proven mono-therapeutic drugs can effectively cure *H. pylori* infections. Currently, the only effective therapy involves combining antibiotics like clarithromycin, amoxicillin and metronidazole with acid-suppressing medications. But as *H. pylori*'s antibiotic tolerance rises, the use of these antibiotics is dwindling (Sharaf et al. 2022; Chelleng et al. 2023).

The North-East region of India is home to an incredible array of unexplored medicinal plants. The genus *Osbeckia* (family: Melastomataceae) contains around 50 species, *Osbeckia nutans* Wall. is one of them. It is found throughout India, Nepal, Bhutan and Myanmar. The Adi people use it extensively in all kinds of festivals, while the Chepang people of Nepal boil the root juice to treat fever (Srivastava 2009, 2010; Sharma et al. 2014; Ronald et al. 2019). The goal of this study was to identify some anti-diabetic and anti-urease compounds and confirm the anti-diabetic and anti-urease properties of *Osbeckia nutans* leaves (ONL) using *in vitro* and *in silico* experiments.

2. Results and discussion

For the first time, the anti-diabetic efficacy of ONL was investigated by using glucose uptake assay in free fatty acid (FFA) (palmitic acid) treated muscle cells. The glucose uptake was found to be markedly decreased upon exposure to FFA, suggesting the

establishment of impaired glucose metabolism due to the accumulation of palmitic acid. It has been observed that treatment with BE2 (0.05 mg/mL) caused a significant increase in glucose uptake in FFA-treated cells at a concentration 10 times lower than those seen in EA5 (0.5 mg/mL) treated cells. Treatment with the positive control (insulin and metformin) also caused an enhancement of glucose uptake compared to those seen in the FFA-treated group (Figure S1). The compounds (A) quercetin-3-O-glucoside, (B) catechin, (C) myricetin, (D) shikimic acid, (E) trans-ferulic acid and (F) luteolin were identified from ONL using HPLC analysis (Figure S2). An *in vitro* α-glucosidase inhibitory assay was conducted for extracts, fractions and sub-fractions of ONL. The sub-fraction BE2 was found to be the most active against the α-glucosidase, with an IC_{50} value of 0.036 µg/mL followed by BE1 with 0.044 µg/mL and EA5 with 0.161 µg/mL (Table S1). For the *in vitro* urease inhibitory experiment, various extracts and subfractions of ONL were examined. Butanol subfraction BE2 had an IC_{50} value of 0.327 mg/mL followed by BE3 with 0.879 mg/mL, BE4 with 1.193 mg/mL, BE1 with 1.406 mg/mL and BE0 with 2.383 mg/mL, while thiourea had an IC_{50} value of 0.039 mg/mL. The HRMS spectral analysis of the butanol sub-fraction BE2 and the ethyl acetate sub-fraction EA5 showed molecular ion peaks at *m/z* 464.33, 174.14, 318.22, 290.28, 194.13 and 286.25 for quercetin-3-O-glucoside, shikimic acid, myricetin, catechin, trans-ferulic acid and luteolin, respectively (Figures S3a and S3b). The identified compounds are shown in Figure 1.

The coordinates from the cryo-EM structure of the GLUT4 human glucose transporter coupled to cytochalasin B in detergent micelles (PDB-ID: 7WSN) were used to identify the GLUT4's active binding sites. Quercetin-3-O-glucoside formed five conventional H-bonds with the GLUT4 residues resulting in a binding energy of −219 kcal/mol. Similarly, luteolin, catechin, myricetin, shikimic acid and trans-ferulic acid exerted binding energies of −188.8727, −175.8404, −166.7123, −120.8760 and −75.9924 kcal/mol to form three, three, one, three and two conventional H-bonds with the GLUT4 residues, respectively (Table S2, Figure S4). The active binding sites of the α-glucosidase were determined using the coordinates from the crystal structure of the enzyme, where acarbose was complexed with the enzyme (PDB-ID: 7L9E). The binding energies of quercetin-3-O-glucoside, catechin, myricetin, shikimic acid, trans-ferulic acid and luteolin with α-glucosidase were −94.2585, −82.0983, −97.4712, −85.7186, −91.9946 and −76.7980 kcal/mol, respectively. Quercetin-3-O-glucoside formed nine, catechin formed six, myricetin five, shikimic acid four, trans-ferulic acid four and luteolin three conventional H-bonds with residues of α-glucosidase. Notably, myricetin proved to be the most effective molecule among the six, with its highest binding energy (Table S3, Figure S5). The PDB-ID: 4HI0 (urease accessory protein of *H. pylori*) was used for docking against ligands. The binding energy of quercetin-3-O-glucoside was found to be −254.391 kcal/mol, which formed seven conventional H-bonds with residues of *H. pylori* urease. Catechin formed three, myricetin six, shikimic acid four, trans-ferulic acid one and luteolin nine conventional H-bonds with different residues of urease. The binding energies of catechin, myricetin, shikimic acid, trans-ferulic acid and luteolin with *H. pylori* urease were −232.071, −194.344, −82.9131, −117.104 and −202.832 kcal/mol, respectively. Quercetin-3-O-glucoside had highest binding energy among the six molecules (Table S4, Figure S6).

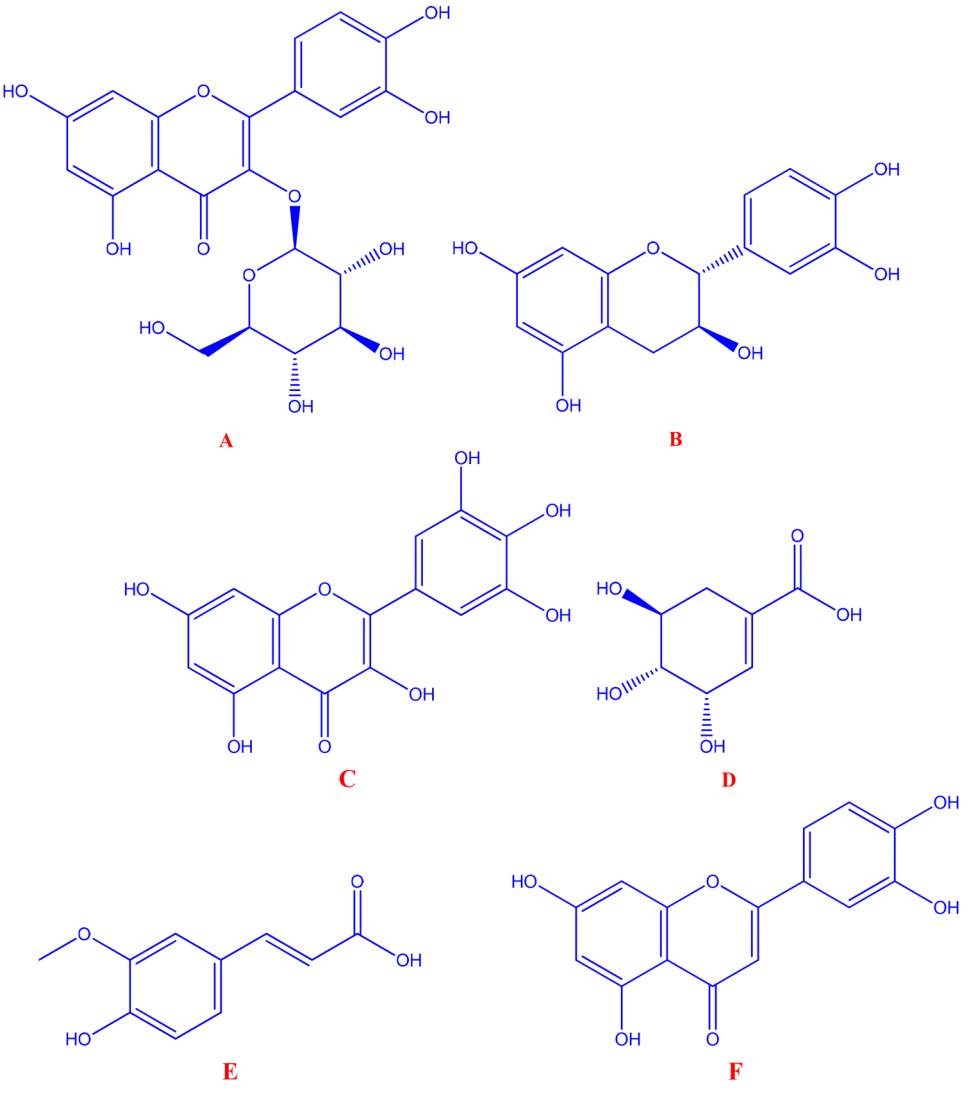

Figure 1. Identified compounds: (A) quercetin-3-O-glucoside, (B) catechin, (C) myricetin, (D) shikimic acid, (E) trans-ferulic acid and (F) luteolin of *O. nutans* leaves.

3. Conclusions

For the first time, six compounds, namely quercetin-3-O-glucoside, myricetin, shikimic acid, catechin, trans-ferulic acid and luteolin, were identified from butanol and ethyl acetate sub-fractions of *Osbeckia nutans*. The anti-diabetic efficacy of ONL was studied with a glucose uptake assay on muscle cells exposed to palmitic acid (a FFA). Sub-fractions BE2 and EA5 both increased the uptake of glucose in a concentration-dependent manner. Sub-fraction BE2 of ONL showed a very promising IC_{50} value of 0.036 µg/mL against α-glucosidase, significantly lower than that of acarbose (437.46 µg/mL), while sub-fraction BE1 and EA5 also had significant IC_{50} values of 0.044 µg/mL and 0.161 µg/mL, respectively. Sub-fraction BE2 also showed

a moderate urease inhibitory activity with an IC_{50} value of 0.327 mg/mL while standard thiourea showed an IC_{50} value of 0.039 mg/mL. To further confirm the potential role of these compounds, *in silico* molecular docking analysis was conducted. Overall, our achieved results suggest that ONL could be a promising candidate for the prevention and treatment of T2DM and *H. pylori* infections.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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