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ANTIDIABETIC AND ANTIOBESITY POTENTIAL OF OLEANOLIC ACID DERIVATIVES

T.M.T.D. Thennakoon[1], J.M.J. Jayasundara[1] and J.M.S. Jayasinghe[2*]

[1]Postgraduate Institute of Science, University of Peradeniya, Peradeniya, Sri Lanka.
[2]Department of Chemistry, Faculty of Science, University of Peradeniya, Peradeniya, Sri Lanka.
[*]susanthij@sci.pdn.ac.lk

The pervasiveness of nontransmissible diseases like Diabetic Mellitus (DM) and obesity has risen rapidly, causing a universal significant public health problem. Undesirable side effects of the current anti-diabetic and anti-obesity drugs have amplified the demand for natural product-derived therapeutics. Oleanolic acid (3-hydroxyolean-12-en-28-oic acid) is a naturally occurring pentacyclic triterpenoid known to possess anti-diabetic and anti-obesity properties. Hence, the current study was aimed to evaluate the antidiabetic and anti-obesity properties of the semi-synthesized structural analogues of oleanolic acid, including fluorine-substituted compounds. Oleanolic acid was isolated from the methanolic crude extract of roots of *Lantana camara*, and seven derivatives were synthesized by C3-OH and C28-COOH functional group modifications. The chemical structures of oleanolic acid analogues were characterized by FT-IR, ^{1}H-NMR, ^{13}C-NMR and HRMS spectroscopic methods. *In-vitro* anti-diabetic and anti-obesity properties were assessed by alpha-glucosidase inhibition and pancreatic lipase, respectively. A significant difference in alpha-glucosidase activity was not obtained ($p > 0.05$) with oxidation of C3-OH (7.72 ± 0.02 mg L^{-1}) compared to oleanolic acid (28.60 ± 0.84 mg L^{-1}). In contrast, the highest significant decrease in alpha-glucosidase activity ($p < 0.05$) was obtained with esterification of C28-COOH (232.32 ± 5.49 mg L^{-1}), esterification of C28-COOH followed by oxidation of C3-OH (173.92 ± 14.26 mg L^{-1}), oxidation of C3-OH followed by fluorination of C28-COOH (166.63 ± 9.10 mg L^{-1}) and acetylation of C3-OH followed by fluorination of C28-COOH (83.47 ± 4.65 mg L^{-1}) compared to oleanolic acid (28.60 ± 0.84 mg L^{-1}). All seven semi-synthesized derivatives indicate a significant improvement in pancreatic lipase activity ($p < 0.05$) when compared to oleanolic acid (112.70 ± 6.85 mg L^{-1}), with the highest activity (14.04 ± 1.51 mg L^{-1}) resulted in C3 oxidation followed by fluorination of C28-COOH. The results obtained from the present anti-diabetic study indicated that the modifications at C28-COOH decrease the anti-diabetic potential. The oxidation, esterification and fluorination of C3-OH and esterification and fluorination of C28- COOH showed improved anti-obesity properties. Hence, the current study will be further extended to evaluate the *in vivo* anti-diabetic and anti-obesity properties.

Keywords: Anti-diabetic, Anti-obesity, Oleanolic acid, Structural analogues