

Documents

Mahmudul Hasan, Md.^{a f}, Ahmed, Q.U.^{a b}, Latip, J.^c, So ad, S.Z.M.^b, Taher, M.^d, Sabere, A.S.M.^b, Zakaria, Z.A.^e

An in vitro adipogenic potential and glucose uptake stimulatory effect of betulinic acid and stigmasterol isolated from tetracera indica in 3t3-L1 cell line [Potensi Adipogenik in vitro dan Kesan Rangsangan Pengambilan Glukosa Asid Betulinik dan Stigmasterol Dipencilkan daripada Tetracera indica dalam Titisan Sel 3T3-L1]

(2023) *Sains Malaysiana*, 52 (2), pp. 501-512.

DOI: 10.17576/jsm-2023-5202-14

^a Drug Discovery and Synthetic Chemistry Research Group, Department of Pharmaceutical Chemistry, Kulliyah of Pharmacy, International Islamic University Malaysia, 25200 Kuantan, Pahang Darul Makmur, Malaysia

^b Pharmacognosy Research Group, Department of Pharmaceutical Chemistry, Kulliyah of Pharmacy, International Islamic University Malaysia, 25200 Kuantan, Pahang Darul Makmur, Malaysia

^c Department of Chemical Sciences, Faculty of Science and Technology, Universiti Kebangsaan Malaysia, 43600 UKM Bangi, Selangor Darul Ehsan, Malaysia

^d Department of Pharmaceutical Technology, Kulliyah of Pharmacy, International Islamic University Malaysia, 25200 Kuantan, Pahang Darul Makmur, Malaysia

^e Borneo Research for Algesia, Inflammation and Neurodegeneration (BRAIN) Group, Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah, 88400 Kota Kinabalu, Sabah, Malaysia

^f School of Biosciences, Faculty of Health and Medical Sciences, Taylor s University, 47500 Subang Jaya, Selangor Darul Ehsan, Malaysia

Abstract

Aerial parts of *Tetracera indica* Merr. (Dilleniaceae) are rich in betulinic acid and stigmasterol and traditionally used to treat diabetes. This study was aimed to evaluate an in vitro antidiabetic potential of betulinic acid and stigmasterol to ascertain whether they may contribute antidiabetic effect to *T. indica*. Initially, betulinic acid and stigmasterol were isolated from the most effective subfraction (ethyl acetate) and subjected to an in vitro antidiabetic investigation through adipogenesis and fluorescence glucose (2-NBDG) uptake assays using 3T3-L1 fibroblast. MTT viability assay was performed at 0.78 to 100 µg/mL for 48 h to determine the safe concentration. Both compounds were subjected to 2-NBDG uptake test on the differentiated adipocytes. The cells were treated in safe concentrations (25-100 µg/mL) as well as in different adipogenic cocktails, which were modified by the addition of compounds to be investigated and in the presence or absence of insulin (10 µM). Rosiglitazone (10 µM) was used as standard. Stems ethanol extract and its fractions (hexane and ethyl acetate), betulinic acid and stigmasterol were found safe at their highest concentration (100 µg/mL) by inhibiting cells well below their IC50 values viz. 18.60, 35.27, 21.40, 28.86 and 33.06%, respectively. Both betulinic acid and stigmasterol at the highest safe concentration (100 µg/mL) significantly ($p < 0.05$) induced adipogenesis like insulin, enhanced adipogenesis like rosiglitazone and exhibited glucose uptake activity. The present study demonstrates that both betulinic acid and stigmasterol possess an in vitro antidiabetic potential. However, in vivo antiglycemic study on these compounds and their chemical analogs are still warranted to ensure their therapeutic potential as safe antidiabetic agents. © 2023 Penerbit Universiti Kebangsaan Malaysia. All rights reserved.

Author Keywords

2-NBDG uptake activity; 3T3-L1 preadipocyte cells; Adipogenesis; Betulinic acid; Insulin like activity; Insulin sensitizing activity; Stigmasterol

Index Keywords

acid, angiosperm, cell, diabetes, disease treatment, fluorescence

References

- Ahmed, Q.U., Ali, A.H.M., Mukhtar, S., Meshari, A.A., Parveen, H., Sabere, A.S.M., Nawi, M.S.M., Alhassan, A.M.
Medicinal potential of isoflavonoids: Polyphenols that may cure diabetes
(2020) *Molecules*, 25 (23), p. 5491.
- Ahmed, Q.U., Umar, A., Taher, M., Susanti, D., Amiroudine, M.Z.A.M., Latip, J.
Phytochemical investigation of the leaves of *Tetracera scandens* Linn. and in vitro antidiabetic activity of hypoletin
(2014) *Proceedings of the International Conference on Science, Technology and Social Sciences (ICSTSS) 2012*, pp. 591-608.

- Ahmed, Q.U., Dogarai, B.B.S., Amiroudine, M.Z.A.M., Taher, M., Latip, J., Umar, A., Muhammad, B.Y.
Antidiabetic activity of the leaves of *Tetracera indica* Merr. (Dilleniaceae) in vivo and in vitro
(2012) *Journal of Medicinal Plants Research*, 6, pp. 5912-5922.
- Alhassan, A.M., Ahmed, Q.U., Latip, J., Shah, S.A.A.
A new sulphated flavone and other phytoconstituents from the leaves of *Tetracera indica* Merr. and their alpha-glucosidase inhibitory activity
(2019) *Natural Product Research*, 33 (1), pp. 1-8.
- Choi, J.H., Banks, A.S., Kamenecka, T.M., Busby, S.A., Chalmers, M.J., Kumar, N., Kuruvilla, D.S., Marciano, D.P.
Anti-diabetic actions of a non-Agonist PPAR γ ligand blocking Cdk5-mediated phosphorylation
(2011) *Nature*, 477, pp. 477-481.
- Choi, J.Y., Na, M., Hyun, H.I., Ho, L.S., Young, B.E., Yeon, K.B., Seog, A.J.
Isolation of betulinic acid, its methyl ester and guaiane sesquiterpenoids with protein tyrosine phosphatase 1B inhibitory activity from the roots of *Saussurea lappa* C.B. Clarke
(2009) *Molecules*, 14 (1), pp. 266-272.
- de Melo, C.L., Queiroz, M.G., Arruda, F.A.C., Rodrigues, A.M., de Sousa, D.F., Almeida, J.G., Pessoa, O.D., Rao, V.S.
Betulinic acid, a natural pentacyclic triterpenoid, prevents abdominal fat accumulation in mice fed a highfat diet
(2009) *Journal of Agricultural and Food Chemistry*, 57, pp. 8776-8781.
- Drzewoski, J., Hanefeld, M.
The current and potential therapeutic use of metformin-The good old drug
(2021) *Pharmaceuticals*, 14 (2), p. 122.
- Fazakerley, D.J., Koumanov, F., Holman, G.D.
GLUT4 on the move
(2022) *Biochemical Journal*, 479 (3), pp. 445-462.
- Hasan, M.M., Ahmed, Q.U., Soad, S.Z.M., Latip, J., Taher, M., Syafiq, T.M.F., Sarian, M.N., Zakaria, Z.A.
Flavonoids from *Tetracera indica* Merr. induce adipogenesis and exert glucose uptake activities in 3T3-L1 adipocyte cells
(2017) *BMC Complementary Medicine & Therapies*, 17 (1), pp. 431-444.
- Jin, T., Yu, H., Huang, X.F.
Selective binding modes and allosteric inhibitory effects of lupane triterpenes on protein tyrosine phosphatase 1B
(2016) *Scientific Reports*, 6, p. 20766.
- Kooti, W.
The role of medicinal plants in the treatment of diabetes: A systematic review
(2016) *Electron Physician*, 8 (1), pp. 1832-1842.
- Li, S., Eguchi, N., Lau, H., Ichii, H.
The role of the Nrf2 signaling in obesity and insulin resistance
(2020) *International Journal of Molecular Sciences*, 21 (18), p. 6973.
- Ma, J.Z., Yang, X.W., Zhang, J.J., Liu, X., Deng, L.L., Shen, X.L., Xu, G.
Sterols and terpenoids from *Viburnum odoratissimum*
(2014) *Natural Products and Bioprospecting*, 4, pp. 175-180.

- Moseti, D., Regassa, A., Kim, W.K.
Molecular regulation of adipogenesis and potential anti-Adipogenic bioactive molecules
(2016) *International Journal of Molecular Sciences*, 17 (1), p. 124.
- Nazaruk, J., Borzym-Kluczyk, M.
The role of triterpenes in the management of diabetes mellitus and its complications
(2015) *Phytochemistry Reviews*, 14, pp. 675-690.
- Ogurtsova, K.
IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040
(2017) *Diabetes Research and Clinical Practice*, 128 (1), pp. 40-50.
- Panda, S., Jafri, M., Kar, A., Meheta, B.K.
Thyroid inhibitory, antiperoxidative and hypoglycemic effects of stigmasterol isolated from *Butea monosperma*
(2009) *Fitoterapia*, 80, pp. 123-126.
- Park, J.H., Kim, R.Y., Park, E.
Antidiabetic activity of fruits and vegetables commonly consumed in Korea: Inhibitory potential against α -glucosidase and insulinlike action in vitro
(2012) *Food Science and Biotechnology*, 21, pp. 1187-1193.
- Roheem, F.O., Ahmed, Q.U., Mat So ad, S.Z., Shah, S.A.A., Latip, J., Alhassan, A.M., Syed Mohammad, S.N.A.
Assessment of free radical scavenging and digestive enzyme inhibitory activities of extract, fractions and isolated compounds from *Tetracera macrophylla* leaves
(2020) *Journal of Herbal Medicine*, 22, p. 100351.
- Ruiz-Ojeda, F.J., Rupérez, A.I., Gomez-Llorente, C., Gil, A., Aguilera, C.M.
Cell models and their application for studying adipogenic differentiation in relation to obesity: A review
(2016) *International Journal of Molecular Sciences*, 17 (7), p. 1040.
- Singab, A.N., El-Beshbishy, H.A., Yonekawa, M., Nomura, T., Fukai, T.
Hypoglycemic effect of Egyptian *Morus alba* root bark extract: Effect on diabetes and lipid peroxidation of streptozotocin-induced diabetic rats
(2005) *Journal of Ethnopharmacology*, 100, pp. 333-338.
- Wang, J., Huang, M., Yang, J., Ma, X., Zheng, S., Deng, S., Huang, Y., Zhao, P.
Anti-diabetic activity of stigmasterol from soybean oil by targeting the GLUT4 glucose transporter
(2017) *Food & Nutrition Research*, 61 (1), p. 1364117.
- Wang, T., Wang, J., Hu, X., Huang, X.J., Chen, G.X.
Current understanding of glucose transporter 4 expression and functional mechanisms
(2020) *World Journal of Biological Chemistry*, 11 (3), pp. 76-98.
- (2020) *Expert panel endorses protocol for COVID-19 herbal medicine clinical trials*, Accessed on April 14, 2021
- Zimmet, P.Z.
Diabetes and its drivers: The largest epidemic in human history?
(2017) *Clinical Diabetes and Endocrinology*, 3 (1), p. 1.

Correspondence Address

Mahmudul Hasan Md.; Drug Discovery and Synthetic Chemistry Research Group, 25200 Kuantan, Malaysia; email: quahmed@iium.edu.my

Publisher: Penerbit Universiti Kebangsaan Malaysia

ISSN: 01266039
Language of Original Document: English
Abbreviated Source Title: Sains Malays.
2-s2.0-85151394724
Document Type: Article
Publication Stage: Final
Source: Scopus

ELSEVIER

Copyright © 2023 Elsevier B.V. All rights reserved. Scopus® is a registered trademark of Elsevier B.V.

 **RELX** Group™