ORIGINAL ARTICLE

Prediction of Alpha-Glucosidase Inhibition Activity for the Management of Type 2 Diabetes Using the Prediction of Activity Spectra of Substances Software

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Abstract

Background: Alpha-glucosidase inhibition was found to be an effective strategy in the management of type 2 diabetes mellitus, a disorder of multiple factors mainly defined by abnormality in either or both insulin secretion or its required function in the body. **Objective:** The core purpose of the study was to predict the active moieties from a pool of pharmacologically important phytoconstituents for alpha-glucosidase inhibition property using the prediction of activity spectra of substances (PASS) software. **Methods:** PASS is valuable software which is used in this study for the prediction of alpha-glucosidase inhibition activity of different selected constituents. Canonical Simplified Molecular-Input Line-Entry System is used in the prediction of the activity which is obtained from the PubChem website. The predicted activity was compared with the marketed standard drug, acarbose. **Results:** It was found that among the screened compounds, rutin, isoquercitrin, and hyperoside are having highest probable activity (Pa) value of 0.858, 0.842, and 0.842, respectively. These phytoconstituents showed less predicted activity against alpha-glucosidase inhibition, as compared to acarbose with Pa of 0.958. **Conclusion:** Rutin, isoquercitrin, and hyperoside showed good Pa against alpha-glucosidase inhibition, and these phytoconstituents can be further investigated for the same activity using *in vitro* and *in vivo* techniques and hence might become future drugs as alpha-glucosidase inhibitors.

Key words: Type 2 diabetes, alpha-glucosidase, hyperglycemia, acarbose, insulin

INTRODUCTION

Diabetes mellitus has been considered to be the world main public health problem[1] which results either due to defects in β-cell that regulates insulin secretion or due to in ability of cells to get sensitized by the insulin (resistance), followed by β-cell inability to compensate the excess glucose in blood,[2,3] characterized by persistent high level of blood glucose, weight loss, polyuria, ketonemia, polydipsia, inflammation, and hyperlipidemia[4,5] and associated with complications such as retinopathy, nephropathy, neuropathy, cardiovascular complications, protein glycation, and impaired cellular immunity.[6] Obesity, lack of exercise, high-fat diet, aging, genetic defects, and other environmental factors are the major contributing factors in the pathophysiology of diabetes.[7] It is classified based on the etiology into type 1 (defined by β-cell destruction and managed by administration of insulin), type 2 (defined by insulin resistance and treated by administration of oral hypoglycemic agents),[8] gestational diabetes (occur in case of pregnancy), and others such as drug-/chemical-induced diabetes, and diabetes due to abnormality in genes related to insulin release or its secretion.[5]

The oral hypoglycemic agents are the drugs used in the management of type 2; the drugs enhance insulin secretion or enhance insulin action by increasing its sensitivity to the

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tissues and some interfere with carbohydrate metabolism [Figure 1]. However, almost all the oral hypoglycemic agents are associated with adverse effects such as hypoglycemia, weight gain, and others.[1,9] Alpha-glucosidase inhibitors do not cause hypoglycemia or weight gain which makes them safer as compared to other classes though they are reported to be causing diarrhea in 3% of cases.[10] Acarbose, voglibose, and miglitol are the approved marketed drugs currently in clinical use as α-glucosidase enzyme inhibitors [Figure 2], and they inhibit these enzymes competitively which are in charge of the carbohydrate catabolism into smaller units (mostly glucose), hence slow down the digestion process, reduce glucose formation and absorption, and ultimately prevent postprandial hyperglycemia.[11] One of the limitations of these drugs is reversible inhibition and they only inhibit digestion at the upper part of the small intestine, but digestion occurs at the ileum [Figure 3].[12]

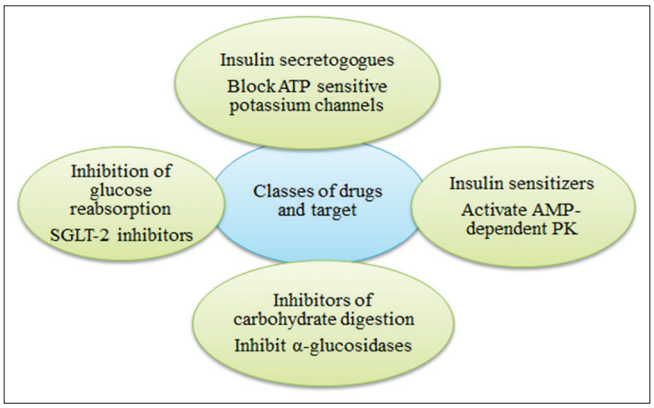


Figure 1: Classes of oral hypoglycemic drugs and their target

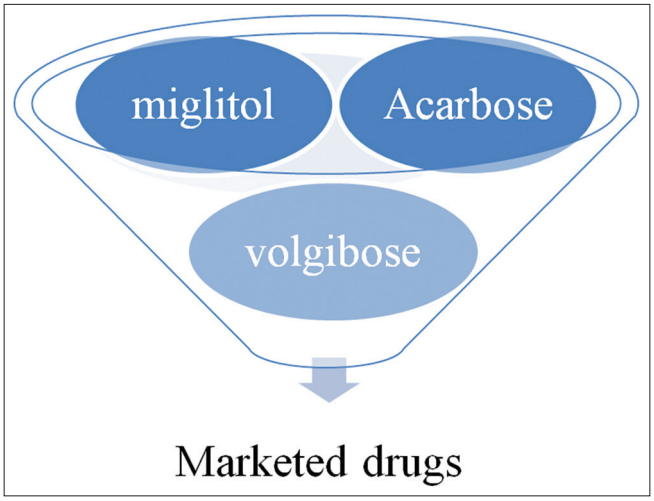


Figure 2: Marketed approved drugs

The main sources of drugs and medicines are mostly from the natural source (plants) either traditional or allopathic systems of medicine; extract of various plants were reported by so many researchers to be having alpha-glucosidase inhibition activity and useful in control of type 2 diabetes, but the limitation and drawback of evaluating extract from plant or its part are uncertainty about the active moiety in the extract. The purpose of this work is to determine the potential possible important phytoconstituents with alpha-glucosidase inhibition property using the prediction of activity spectra of substances (PASS) software as per Kumar *et al.*[13]

METHODS

The method followed is as per Kumar *et al.*, 2018. Chemical constituents of plants which their extracts were reported to be efficacious in blocking the activity of α-glucosidase enzyme but none of the constituents from the extract are reported for the same activity were selected for the study. The structure and canonical Simplified Molecular-Input Line-Entry System (SMILES) of each moiety was obtained from the PubChem website, and then, the canonical SMILES of individual moiety was pasted into the PASS software for the prediction of α-glucosidase inhibition activity. The probable activity (Pa) and probable inactivity (Pi) values of each compound were recorded and compared with the standard acarbose drug [Figure 4].

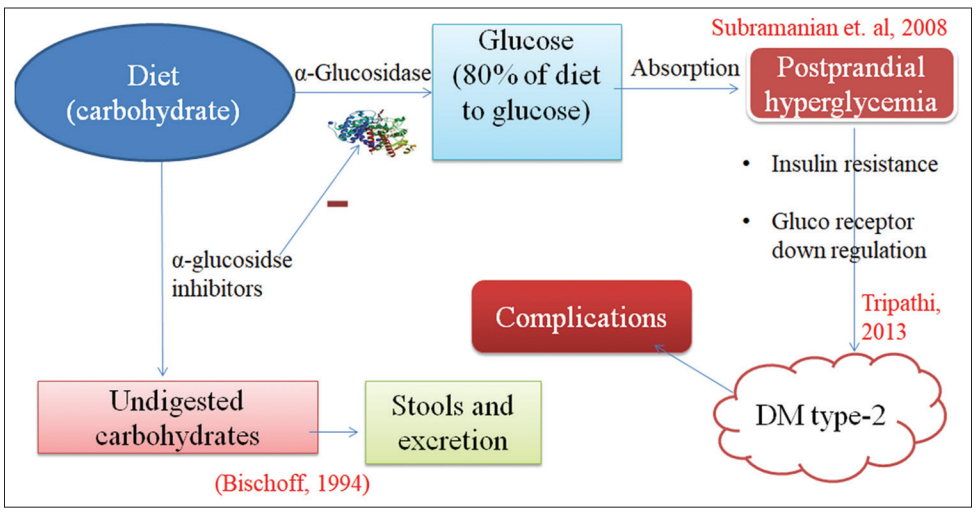


Figure 3: Alpha-glucosidase as target for the management of type 2 and mechanism of action of alpha-glucosidase inhibitors

RESULTS

The results are expressed in the form of bar chart; Tables 1 and 2 and Figure 5 represent the results. It was found that among the screened compounds, rutin, isoquercitrin, and hyperoside are having highest Pa value of 0.858, 0.842, and 0.842, respectively. These phytoconstituents showed less predicted activity against alpha-glucosidase inhibition, as compared to acarbose with Pa of 0.958.

DISCUSSION

Statistics have shown that diabetes is becoming the major health issue globally and estimated that 366 million people will be diabetic by 2030;[21] diabetes is associated with abnormalities in the metabolism and glucose utilization with multiple etiological factors such as genetic defects, obesity, age, and diet; and it is defined by either insulin resistance or inability of the β-cells to secrete the required amount of insulin for homeostasis of glucose in blood.[2,7] Oral hypoglycemic agents are used for the management of type 2 although insulin can also be used in some extreme conditions; however, most of the classes produce side effects such as hypoglycemia and weight gain,[1,10] but alpha-glucosidase inhibitors are not hypoglycemic agents and do not cause hypoglycemia or weight gain[12] which makes them a special target for the management of type 2 although they are mostly used in combination with other classes of oral hypoglycemic drugs.[22] Various plants' extracts have been reported to be more potent either *in vitro* or *in vivo* in alpha-glucosidase inhibition activity as compared to the standard drugs, but the individual constituents when evaluated for the same activity mostly do not show significant activity as seen in the results of this work. The extract is more potent may be due to synergistic effect of the various constituents present in the plant extract. Considering the structural similarity of rutin, hyperoside, and isoquercetrin and being flavonoids, their pharmacophore might be considered responsible for this activity and new molecules can be developed for α-glucosidase inhibition activity based on this rationale.

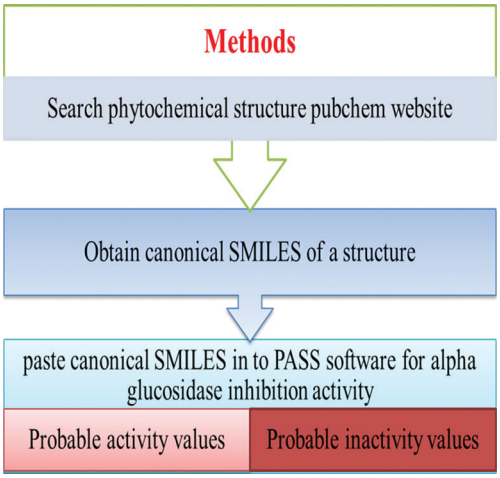


Figure 4: Step-wise procedure of the methodology

PASS software is freely available online, and it predicts the biological activities of a compound base on structural activity relationship of a compound with >95% accuracy. Pa and Pi values vary between 0 and 1; pharmacological activity of a compound is likely only when Pa > Pi values and compounds with >0.5 Pa value have a high probability of showing promising results in further pharmacological experiments.[23] However, the limitations of using this software is that without the structure of the molecule, one can`t predict any biological

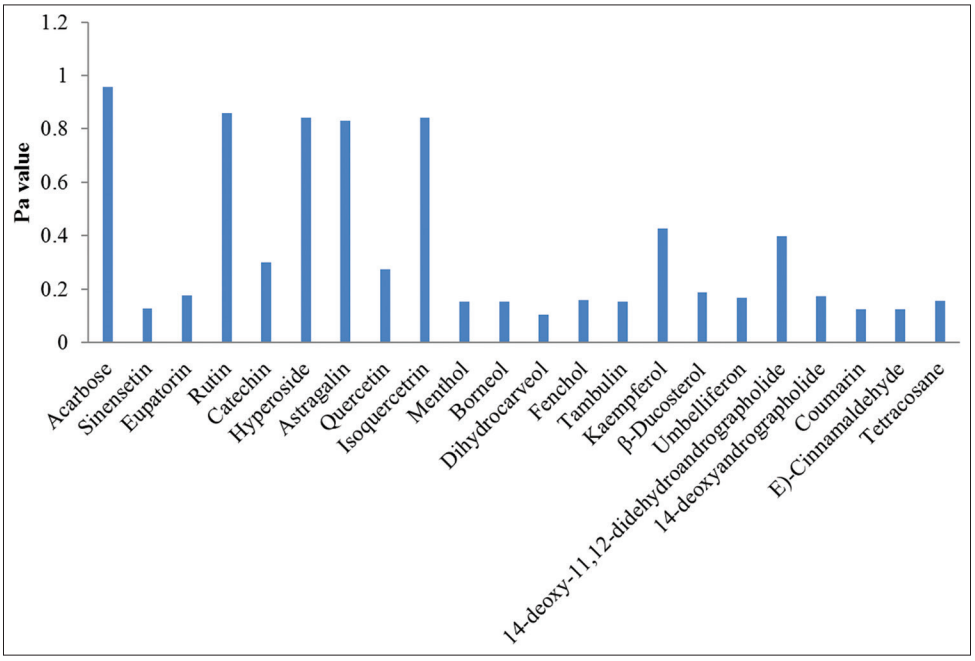


Figure 5: Pa values of screened compounds in comparison with the acarbose as standard drug

Table 1: Phytochemicals with their biological source, canonical Simplified Molecular-Input Line-Entry System, and chemical structure

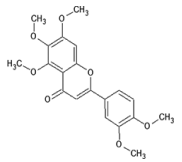
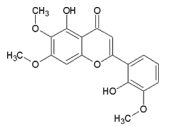
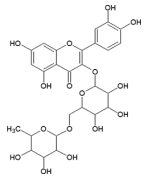
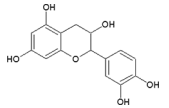
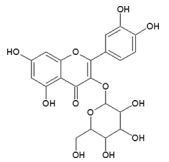
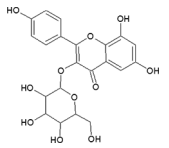
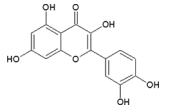
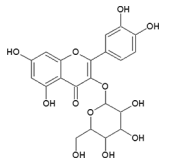
Name of compound	Biological source	Canonical SMILES	Chemical structure	References
Sinensetin	*O. stamineus*	COC1=C (C=C (C=C1) C2=CC(=O) C3=C (C(=C (C=C3O2) OC) OC) OC) OC		[14]
Eupatorin	*O. stamineus*	COC1=C (C=C (C=C1) C2=CC(=O) C3=C (C(=C (C=C3O2) OC) OC) O) O		[14]
Rutin	*N. nucifera*	CC1C (C (C (C (O1) OCC2C (C (C (C (O2) OC3=C (OC4=CC(=CC(=C4C3=O) O) O) C5=CC(=C (C=C5) O) O) O) O) O) O) O) O		[15]
Catechin	*N. nucifera*	C1C (C (OC2=CC(=CC(=C21) O) O) C3=CC(=C (C=C3) O) O) O		[15]
Hyperoside	*N. nucifera*	C1=CC(=C (C=C1C2=C (C(=O) C3=C (C=C (C=C3O2) O) O) OC4C (C (C (C (O4) CO) O) O) O) O) O		[15]
Astragalin	*N. nucifera*	C1=CC(=CC=C1C2=C (C(=O) C3=C (C=C (C=C3O2) O) O) OC4C (C (C (C (O4) CO) O) O) O) O		[15]
Quercetin	*N. nucifera*	C1=CC(=C (C=C1C2=C (C(=O) C3=C (C=C (C=C3O2) O) O) O) O) O		[15]
Isoquercitrin	*N. nucifera*	C1=CC(=C (C=C1C2=C (C(=O) C3=C (C=C (C=C3O2) O) O) OC4C (C (C (C (O4) CO) O) O) O) O) O		[15]

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Table 1: (*Continued*)

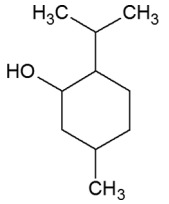
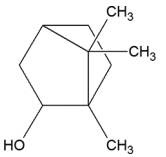
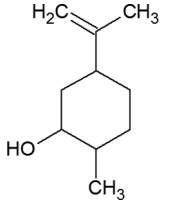
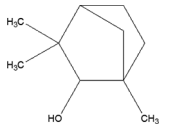
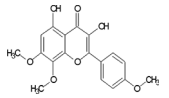
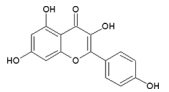
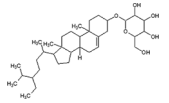
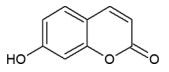
Name of compound	Biological source	Canonical SMILES	Chemical structure	References
Menthol	*Mentha* species	CC1CCC (C (C1) O) C (C) C		[16]
Borneol	*Mentha* species	CC1(C2CCC1(C (C2) O) C) C		[16]
Dihydrocarveol	*Mentha* species	CC1CCC (CC1O) C(=C) C		[16]
Fenchol	*Z. armatum*	CC1(C2CCC (C2)(C1O) C) C		[17]
Tambulin	*Z. armatum*	COC1=CC=C (C=C1) C2=C (C(=O) C3=C (O2) C(=C (C=C3O) OC) OC) O		[17]
Kaempferol	*Z. armatum*	C1=CC(=CC=C1C2=C (C(=O) C3=C (C=C (C=C3O2) O) O) O) O		[17]
β-Ducosterol	*Z. armatum*	CCC (CCC (C) C1CCC2C1(CCC3C2CC=C4C3(CCC (C4) OC5C (C (C (C (O5) CO) O) O) O) C) C) C (C) C		[17]
Umbelliferone	*Z. armatum*	C1=CC(=CC2=C1C=CC(=O) O2) O		[17]

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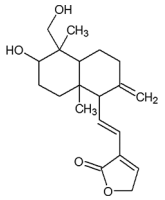
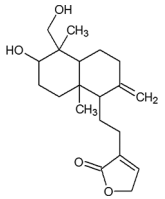
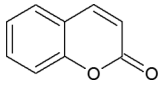
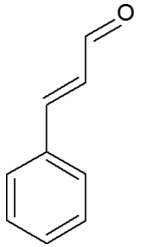
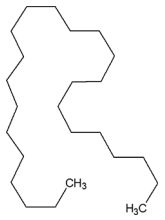
Table 1: (*Continued*)

Name of compound	Biological source	Canonical SMILES	Chemical structure	References
14-deoxy -11,12-didehydroandrographolide	*A. paniculata*	CC12CCC (C (C1CCC(=C) C2C=CC3=CCOC3=O)(C) CO) O		[18,19]
14-deoxyandrographolide	*A. paniculata*	CC12CCC (C (C1CCC(=C) C2CCC3=CCOC3=O)(C) CO) O		[18,19]
Coumarin	*C. zeylanicum*	C1=CC=C2C(=C1) C=CC(=O) O2		[20]
(E)-Cinnamaldehyde	*C. zeylanicum*	C1=CC=C (C=C1) C=CC=O		[20]
Tetracosane	*C. zeylanicum*	CCCCCCCCCCCCCCCCCCCCCCCC		[20]

SMILES: Simplified Molecular-Input Line-Entry System, *O. stamineus*: *Orthosiphon stamineus*, *N. nucifera*: *Nelumbo nucifera*, *Z. armatum*: *Zanthoxylum armatum*, *A. paniculata*: *Andrographis paniculata*, *C. zeylanicum*: *Cinnamomum zeylanicum*

Table 2: Probable activity and probable inactivity values of alpha-glucosidase inhibition predicted by the prediction of activity spectra of substances software

Name of compound	Pa value	Pi value
Acarbose	0.958	0.000
Sinensetin	0.126	0.016
Eupatorin	0.176	0.007
Rutin	0.858	0.001
Catechin	0.300	0.003
Hyperoside	0.842	0.001
Astragalin	0.829	0.001
Quercetin	0.273	0.004
Isoquercitrin	0.842	0.001
Menthol	0.152	0.010
Borneol	0.154	0.009
Dihydrocarveol	0.103	0.028
Fenchol	0.159	0.009
Tambulin	0.153	0.009
Kaempferol	0.428	0.004
β-Ducosterol	0.187	0.006
Umbelliferone	0.168	0.007
14-deoxy-11, 12-didehydroandrographolide	0.398	0.002
14-deoxyandrographolide	0.172	0.007
Coumarin	0.125	0.017
(E)-Cinnamaldehyde	0.124	0.017
Tetracosane	0.156	0.009

Pa: Probable activity, Pi: Probable inactivity

activity. This software does not take into consideration the structure of target receptor unlike other *in silico* methods like docking in which with the knowledge of target is considered. With this, structure of a new molecule can be designed specifically for the target receptor, but still the PASS software can be useful as an additional *in silico* method.

CONCLUSION

Rutin, isoquercitrin, and astragalin showed good Pa against alpha-glucosidase inhibition, and these phytoconstituents can be further investigated for the same activity application of *in vitro* and *in vivo* techniques, and these may become future drugs as alpha-glucosidase inhibitors.

REFERENCES

1. Wu Y, Ding Y, Tanaka Y, Zhang W. Risk factors contributing to Type 2 diabetes and recent advances in the treatment and prevention. Int J Med Sci 2014;11:1185-200.
2. Srinivasan K, Viswanad B, Asrat L, Kaul CL, Ramarao P. Combination of high-fat diet-fed and low-dose streptozotocin-treated rat: A model for type 2 diabetes and pharmacological screening. Pharmacol Res 2005;52:313-20.
3. Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC. Beta-cell deficit and increased beta-cell apoptosis in humans with Type 2 diabetes. Diabetes 2003;52:102-10.
4. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014;37 Suppl 1:S81-90.
5. Cameron F. Teenagers with diabetes management challenges. Aust Fam Physician 2006;35:386-90.
6. Rossetti L. Glucose toxicity: The implications of hyperglycemia in the pathophysiology of diabetes mellitus. Clin Invest Med 1995;18:255-60.
7. Ling C, Groop L. Epigenetics: A molecular link between environmental factors and Type 2 diabetes. Diabetes 2009;58:2718-25.
8. Ortiz MR. Hypoglycemia in diabetes. Nurs Clin North Am 2017;52:565-74.
9. Cramer JA. A systematic review of adherence with medications for diabetes. Diabetes Care 2004;27:1218-24.
10. Paquot N, Philips JC, Radermecker R, Lefèbvre P. Recent advances in the management of diabetes mellitus. Rev Med Liege 2007;62:317-23.
11. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, *et al.* Management of hyperglycaemia in Type 2 diabetes: A patient-centered approach. Position statement of the american diabetes association (ADA) and the european association for the study of diabetes (EASD). Diabetologia 2012;55:1577-96.
12. Bischoff H. Pharmacology of alpha-glucosidase inhibition. Eur J Clin Invest 1994;24 Suppl 3:3-10.
13. Kumar R, Kumar R, Anand A, Sharma N, Khurana N. Prediction of anti-parkinson potential of phytoconstituents using prediction of activity spectra of substances software. Asian J Pharm Clin Res 2018;11:48-56.
14. Mohamed EA, Ahmad M, Ang LF, Asmawi MZ, Yam MF. Evaluation of α-glucosidase inhibitory effect of 50% ethanolic standardized extract of orthosiphon stamineus benth in normal and streptozotocin-induced diabetic rats. Evid Based Complement Alternat Med 2015;2015:754931.
15. Ohkoshi E, Miyazaki H, Shindo K, Watanabe H, Yoshida A, Yajima H. Constituents from the leaves of *Nelumbo Nucifera* stimulate lipolysis in the white adipose tissue of mice. Planta Med 2007;73:1255-9.
16. Hussain AI, Anwar F, Nigam PS, Ashraf M, Gilani AH. Seasonal variation in content, chemical composition and antimicrobial and cytotoxic activities of essential oils from four mentha species. J Sci Food Agric 2010;90:1827-36.
17. Singh TP, Singh OM. Phytochemical and pharmacological

profile of *Zanthoxylum armatum* DC. An overview. Indian J Nat Prod Resour 2011;2:275-85.
18. Subramanian R, Asmawi MZ, Sadikun A. *In vitro* alpha-glucosidase and alpha-amylase enzyme inhibitory effects of *Andrographis paniculata* extract and andrographolide. Acta Biochim Pol 2008;55:391-8.
19. Kapil A, Koul IB, Banerjee SK, Gupta BD. Antihepatotoxic effects of major diterpenoid constituents of *Andrographis paniculata*. Biochem Pharmacol 1993;46:182-5.
20. Singh G, Maurya S, DeLampasona MP, Catalan CA. A comparison of chemical, antioxidant and antimicrobial studies of cinnamon leaf and bark volatile oils, oleoresins and their constituents. Food Chem Toxicol 2007;45:1650-61.
21. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047-53.
22. Yang W, Liu J, Shan Z, Tian H, Zhou Z, Ji Q, *et al.* Acarbose compared with metformin as initial therapy in patients with newly diagnosed Type 2 diabetes: An open-label, non-inferiority randomised trial. Lancet Diabetes Endocrinol 2014;2:46-55.
23. Kumar R, Kumar R, Anand A, Mahajan R, Khatik GL, Duggal N, *et al*. Potential of prediction of activity spectra of substances software to justify 3Rs ethics for in vivo anti-alzheimer's studies of phytochemicals. Int J Green Pharm 2018;12:66-72.

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