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Prediction of Toxicological Mechanisms of Selected Phytochemicals in Leaf of *Moringa* sp. and Antidiabetic Medicines

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Abstract: ***Moringa sp. is an important medicinal plant, and the leaf of this plant contains several phytochemicals, which are used for anti-diabetic agents as per traditional knowledge. The present study predicted toxicity and toxicological mechanism of selected phytochemicals of Moringa sp. and antidiabetic medicines by using ProTox-II webserver. Among 26 phytochemicals, 6 phytochemicals and 2 synthetic medicines related to Tox-21 nuclear signaling pathway and stress response pathway were predicted to know toxicological mechanisms. The results indicate that selected phytochemicals and synthetic medicines were found inactive on the different parameters, but Anthraquinone was predicted to be active for ER parameter for Tox-21 nuclear receptor pathway while Tox-21 stress response pathway revealed that all the compounds were found inactive on the different parameters, but Anthraquinone was predicted active for MMP parameter. It is concluded that these phytocompounds were found to have similar activity as Glibenclamide and Metformin like medicines. In future study, it is suggested to conduct in vivo bioassay to validate this in silico study.***

Keywords: *Moringa* sp., *In silico* study, Phytochemicals, Toxicological mechanism prediction, Synthetic medicines

1. Introduction

The disease diabetes mellitus (DM) is well-known metabolic syndrome, alter the life-style pattern, chronic effect, etc., which leads to increase glycaemia and various co-morbidities. [1]

Many investigators find that individuals with insulin resistance, the expression of the insulin receptor (IR) observed either reduced or absent.[2-4] Moreover, the regulation of insulin- mediated glucose metabolism in peripheral tissues via insulin receptor substrate/ phosphoinositide 3 kinase/protein kinase B (IRS/PI3K/Akt) signalling pathway plays a key role in the prevalence of the disease.[4]

In recent days, phytomedicines concern to prevent the DM without any side effects. Among several plant species, *Moringa oleifera* Lam. commonly called as "Sajne in Bengali" and "Drumstick in English" and found in most places of India. As per traditional knowledge, the extract of leaves of this plant has the ability to prevent DM in animal studies. [5-9]

The leaves extract contains many phytochemicals in which few of these may pose allelopathic effect and ultimately toxicity to animals or humans. [10,11] Few studies have been conducted to know the potential phytocompound(s) to prevent DM as per predictive toxicity of the leaves of *M. oleifera* compared to established synthetic drugs viz. Metformin and Glibenclamide, [12-15] but toxicological mechanisms as Tox-21 nuclear signalling and stress response pathways predictions are unexplored.

The present study was attempted an *in silico* approach to screen toxicological mechanisms of established phytochemicals of leaf from *Moringa* sp. and antidiabetic drugs.

2. Materials and Methods

All established phytochemicals of leaves of Moringa sp. (Lam.) and synthetic medicine viz. Glibenclamide and Metformin were taken from available literature.[12-16] Banerjee et al.[17] developed the ProTox-II platform in which toxicological pathways such as nuclear receptor signalling pathway is classified seven target- pathway based models viz. aryl hydrogen receptor (AhR), androgen receptor (AR), androgen receptor ligand binding domain (AR- LBD), aromatase, estrogen receptor alpha (ER), estrogen receptor ligand binding domain (ER-LBD), and peroxisome proliferator activated receptor gamma (PPARGamma) as well as stress response pathway is classified five target-pathway based models such as nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (ARE), heat shock factor response element (HSE), mitochondrial membrane potential (MMP), phosphoprotein tumor suppressor (p53), and ATPase family AAA domain-containing protein 5 (ATAD5).

3. Results

Table 1 predicts the results of selected phytochemicals and synthetic medicines on the activity or inactivity of Tox-21 nuclear signalling pathway. All the compounds were found inactive on the different parameters, but Anthraquinone was predicted to be active for ER parameter.

Table 1: Prediction of Tox-21 nuclear signaling pathway of different compounds

S. No.	Phytochemicals	AhR	P (%)	AR	P (%)	AR- LBD	P (%)	Ar	P (%)
1.	Anthraquinone	I	65	I	78	I	99	I	97
2.	Laurifoline	I	72	I	91	I	98	I	89
3.	Flavylium	I	56	I	92	I	92	I	70
4.	Serpentine	I	62	I	95	I	93	I	87
5.	Niazirin	I	73	I	94	I	95	I	92
6.	Niazirinin	I	75	I	97	I	95	I	91
7.	Glibenclamide	I	97	I	97	I	97	I	98
8.	Metformin	I	99	I	100	I	99	I	99
S. No.	Phytochemicals	ER	P (%)	ER- LBD	P (%)	PPAR- ϒ	P (%)		
1.	Anthraquinone	A	93	I	99	I	99		
2.	Laurifoline	I	92	I	99	I	98		
3.	Flavylium	I	59	I	97	I	88		
4.	Serpentine	I	89	I	95	I	97		
5.	Niazirin	I	81	I	86	I	93		
6.	Niazirinin	I	84	I	91	I	94		
7.	Glibenclamide	I	97	I	99	I	92		
8.	Metformin	I	98	I	99	I	99		

AhR = Aryl hydrocarbon Receptor; AR = Androgen Receptor; AR-LBD = Androgen Receptor Ligand Binding Domain; Ar = Aromatase; ER = Estrogen Receptor Alpha; ER-LBD = Estrogen Receptor Ligand Binding Domain; PPAR-ϒ = Peroxisome Proliferator Activated Receptor Gamma; I = Inactive; A = Active and P = Probability

Table 2 predicts the results of selected phytochemicals and synthetic medicines on the activity or inactivity of Tox-21 stress response pathway. All the compounds were found inactive on the different parameters, but Anthraquinone was predicted to be active for MMP parameter.

Table 2: Prediction of Tox-21 stress response pathway of different compounds

S. No.	Phytochemicals	ARE	P (%)	HSE	P (%)	MMP	P (%)	P53	P (%)	ATAD5	P (%)
1.	Anthraquinone	I	99	I	99	A	100	I	95	I	73
2.	Laurifoline	I	92	I	92	I	78	I	93	I	98
3.	Flavylium	I	93	I	93	I	70	I	80	I	60
4.	Serpentine	I	90	I	90	I	76	I	88	I	93
5.	Niazirin	I	91	I	91	I	76	I	88	I	92
6.	Niazirinin	I	92	I	92	I	75	I	88	I	96
7.	Glibenclamide	I	99	I	99	I	81	I	97	I	99
8.	Metformin	I	99	I	99	I	98	I	98	I	97

ARE = Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element; HSE = Heat shock factor response element; MMP = Mitochondrial Membrane Potential; P53 = Phosphoprotein (Tumor Supressor); ATAD5 = ATPase family AAA domain-containing protein 5; I = Inactive; A = Active and P = Probability

4. Discussion

In an earlier study, the prediction of toxicity indicated that all 6 phytocompounds of *Moringa* sp. and synthetic antidiabetic medicines were observed toxic class of V except the phytocompound Serpentine as class III while others two compounds viz. Laurifoline and Metformin as class IV predicted and Laurifoline and Serpentine were predicted immunotoxic while Anthraquinone and Flavylium were predicted mutagenic and Flavylium were predicted carcinogenic through the online webserver (ProTox-II).[15]

The findings indicated that selected phytochemicals and synthetic medicines were found inactive on the different parameters, but Anthraquinone was predicted to be active for ER parameter for Tox-21 nuclear receptor pathway while Tox-21 stress response pathway revealed that all the compounds were found inactive on the different parameters, but Anthraquinone was predicted active for MMP parameter. According to Awodele et al.,[18] the aqueous extract of leaves was found safe after oral intake by the rats. Moreover, Heymans Institute of Pharmacology[19] (1989) determined LD50 value of Serpentine was 42 mg/Kg in 31 rats and overdoses may cause toxicity but in the present predictive data of the LD50 value was 250 mg/Kg.

Interestingly, phytocompounds viz. Niazirin and Niazirinin predicted non-toxic phytocompounds as like antidiabetic drug Glibenclamide. According to the investigator, these compounds from *M. oleifera* inhibit oxidative stress in DM as an antioxidative effect.[20] Therefore, the reduction of oxidative stress in DM may reduce hyperglycemia. Mishra and Talapatra [15] obtained Niazirin, a lead compound as per receptor-ligand binding energy and affinity through molecular docking.

5. Conclusion

In conclusion, among these phytocompounds, Niazirin and Niazirinin were found similar activity as Glibenclamide and Metformin like drugs. In future study, it is suggested to conduct *in vivo* bioassay to validate these predictive results.

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Conflict of interest

No conflict of interest during study and manuscript preparation.

References

[1] De Vegt F, Dekker JM, Stehouwer CDA, Nijpels G, Bouter LM, Heine RJ. The 1997 American Diabetes Association criteria versus the 1985 World Health Organization criteria for the diagnosis of abnormal glucose tolerance - Poor agreement in the Hoorn study. Diabetes Care. 1998;21:1686-1690.

[2] Taylor SI, Accili D, Imai Y. Insulin resistance or insulin deficiency. Which is the primary cause of NIDDM? Diabetes. 1994;43(6):735-740.

[3] Foti D, Chiefari E, Fedele M, Iuliano R, Brunetti L, Paonessa F, Manfioletti G, Barbetti F, Brunetti A, Croce CM, Fusco A, Brunetti A. Lack of the architectural factor HMGA1 causes insulin resistance and diabetes in humans and mice. Nat Med. 2005;11(7):765-773.

[4] Escribano O, Beneit N, Rubio-Longás C, López-Pastor AR, Gómez-Hernández A. The Role of Insulin Receptor Isoforms in Diabetes and Its Metabolic and Vascular Complications. J Diabetes Res. 2017;2017:1403206.

[5] Ndong M, Uehara M, Katsumata S, Suzuki K. Effects of Oral Administration of Moringa oleifera Lam on Glucose Tolerance in Goto-Kakizaki and Wistar Rats. J Clin Biochem Nutr. 2007;40(3):229-233.

[6] Jaiswal D, Kumar Rai P, Kumar A, Mehta S, Watal G. Effect of Moringa oleifera Lam. leaves aqueous extract therapy on hyperglycemic rats. J Ethnopharmacol. 2009;123(3):392- 396.

[7] Manohar VS, Jayasree T, Kiran Kishore K, Mohana Rupa L, Dixit R, Chandrasekhar N. Evaluation of hypoglycemic and antihyperglycemic effect of freshly prepared aqueousextract of *Moringa oleifera* leaves in normal and diabetic rabbits. Journal of Chemical and Pharmaceutical Research. 2012;4(1):249-253.

[8] Soliman GZA. Anti-diabetic activity of dried Moringa oleifera leaves in normal and streptozotocin (STZ)-induced diabetic male rats. Indian J Appl Res. 2013;3(23):18-23.

[9] Omodanisi EI, Aboua GY, Oguntibeju OO. Therapeutic potentials and pharmacological properties of Moringa oleifera Lam in the treatment of diabetes mellitus and related complications. Tropical Journal of Pharmaceutical Research. 2017;16(7):1737-1746.

[10] Mali AA, Kanade MB. Allelopathic effect of two common weeds on seed germination, root-shoot length, biomass and protein content of jowar. Annals of Biological Research. 2014; 5(3):89-92.

[11] Mondal M, Asaduzzaman M, Asao T. Adverse effects of allelopathy from legumecrops and its possible avoidance. American Journal of Plant Sciences. 2015;6: 804-810.

[12] Bösenberg LH, van Zyl DG. The mechanism of action of oral antidiabetic drugs:A review of recent literature. Journal of Endocrinology, Metabolism and Diabetes of South Africa. 2008; 13(3):80-88.

[13] Pandarekandy ST, Sreejesh PG, Harikumaran Thampi BS, Sreekumaran E. Hypoglycaemic effect of glibenclamide: A critical study on the basis of creatinine and lipid peroxidation status of streptozotocin-induced diabetic rat. Indian J Pharm Sci. 2017;79(5):768-777.

[14] Zainab B, Ayaz Z, Alwahibi MS, Khan S, Rizwana H, Soliman DW, Alawaad A, Mehmood Abbasi A. In-silico elucidation of Moringa oleifera phytochemicals against diabetes mellitus. Saudi J Biol Sci. 2020;27(9):2299-2307.

[15] Mishra K, Talapatra SN. Prediction of toxicity, pharmacokinetics of selected phytochemicals of leaf of drumstick (*Moringa sp.)* and molecular docking on two receptors as insulin tyrosine kinase for antidiabetic potential. Journal of Advanced Scientific Research. 2022;13(02):67-75.

[16] Yang M, Tao L, Kang X-R, Li L-F, Zhao C-C, Wang Z-L, Sheng J, Tian Y. Recent developments in Moringa oleifera Lam. polysaccharides: A review of the relationship between extraction methods, structural characteristics and functional activities. Food Chemistry: X. 2022;14:100322.

[17] Banerjee P, Eckert AO, Schrey AK, Preissner R. ProTox-II: a webserver for the prediction of toxicity of chemicals. Nucleic Acids Research. 2018;46:W257-W263.

[18] Awodele O, Oreagba IA, Odoma S, da Silva JA, Osunkalu VO. Toxicological evaluation of the aqueous leaf extract of *Moringa oleifera* Lam. (Moringaceae). J Ethnopharmacol, 2012; 139(2):330-336.

[19] Heymans Institute of Pharmacology. Archives Internationales De Pharmacodynamie Et De Therapie, 1989;123(168).

[20] Wang F, Bao Y, Shen X, Zengin G, Lyu Y, Xiao J, Weng Z. Niazirin from Moringa oleifera Lam. attenuates high glucose-induced oxidative stress through PKCζ/Nox4 pathway. Phytomedicine: International Journal of Phytotherapy and Phytopharmacology. 2021;86: 153066.