#### **ORIGINAL ARTICLE**



# ADNCD: a compendious database on anti-diabetic natural compounds focusing on mechanism of action

Aisha Khatoon<sup>1</sup> • Iliyas Rashid<sup>2</sup> • Sibhghatulla Shaikh<sup>1</sup> • Syed Mohd Danish Rizvi<sup>3</sup> • Shazi Shakil<sup>4,5,6</sup> • Neelam Pathak<sup>1</sup> • Snober S. Mir<sup>7</sup> • Khurshid Ahmad<sup>8</sup> • Talib Hussain<sup>3</sup> • Prachi Srivastava<sup>2</sup>

Received: 8 November 2017 / Accepted: 1 August 2018 / Published online: 6 August 2018 © Springer-Verlag GmbH Germany, part of Springer Nature 2018

#### Abstract

Diabetes is a deteriorating metabolic ailment which negatively affects different organs; however, its prime target is insulin secreting pancreatic  $\beta$ -cells. Although, different medications have been affirmed for diabetes management and numerous drugs are undergoing clinical trials, no significant breakthrough has yet been achieved. Available drugs either show some side effects or provide only short-term alleviation. The rationales behind the failure of current anti-diabetic treatment strategy are association of complex patho-physiologies and participation of various organs. Consequently, there is a critical need to search for multi-effect drugs that might impede various patho-physiological mechanisms related to diabetes. Fortunately, one natural compound could act on several diabetes linked targets. Thus, natural compounds might be regarded as a viable alternative choice to improve the progression as well as side effects of diabetes. Despite the fact that immense literatures are available on natural compounds indicating promising outcomes against diabetes, more systematic studies are still needed to establish them as effective anti-diabetic agents. Till date, we are unable to access all the information regarding modes of action, toxicity risks and physicochemical properties of anti-diabetic natural compounds on one platform. Hence, anti-diabetic natural compounds database (ADNCD) has been created to categorize each anti-diabetic natural compound on the basis of their mode of action and to provide compendious information of their physicochemical properties and toxicity risks. In short, ADNCD has imperative information for the researchers working in the field of diabetes drug development.

Keywords Diabetes · Anti-diabetic drugs · Pancreatic β-cells · Anti-diabetic natural compounds · Hyperglycaemia

Syed Mohd Danish Rizvi syedrizvi10@yahoo.com

- <sup>1</sup> Department of Biosciences, Integral University, Lucknow, India
- <sup>2</sup> Amity Institute of Biotechnology, Amity University, Lucknow, Uttar Pradesh 226028, India
- <sup>3</sup> Department of Pharmacology and Toxicology, College of Pharmacy, University of Hail, Hail, Saudi Arabia
- <sup>4</sup> Center of Innovation in Personalized Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
- <sup>5</sup> Department of Medical Laboratory Technology, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah, Saudi Arabia
- <sup>6</sup> Center of Excellence in Genomic Medicine Research, King Abdulaziz University, Jeddah, Saudi Arabia
- <sup>7</sup> Department of Bioengineering, Integral University, Lucknow, India
- <sup>8</sup> Department of Medical Biotechnology, Yeungnam University, 280 Daehak-Ro, Gyeongsan, Republic of Korea

## Introduction

Diabetes mellitus is a multifarious metabolic sickness that is associated with tenacious hyperglycemia (Malviya et al. 2010; Algahtani et al. 2013; d'Emden et al. 2015; Hameed et al. 2015; Diabetes Canada Clinical Practice Guidelines Expert Committee et al. 2018). According to IDF: International Diabetes Federation (2015) report, approximately 415 million individuals were suffering from diabetes all over the world and the figure is expected to reach 642 million by the year 2040 (International Diabetes Federation 2015). Among different types of diabetes, Type II diabetes is a major class which accounts for over 90% of diabetic cases (Olokoba et al. 2012; Maitra and Abbas 2005; Chang et al. 2013). There are various distinctive sorts of anti-diabetic medications available globally, however, the vast majority of these medications failed due to limited efficacy and undesirable side effects. It is very unfortunate that at an interval of every six seconds an individual dies due to diabetes and about 5 million people have died because



of it in the year 2015 (International Diabetes Federation 2015). Thus, the establishment of other viable strategy to tackle this deteriorating disease is essentially required. The main obstructions regarding diabetes treatment are its complex patho-physiology and association of several factors. Therefore, rather than applying single target-specific drugs, multi-target drugs appear to be a valuable and compelling approach for the management of diabetes. Interestingly, some natural compounds have demonstrated encouraging outcome against diabetes (Malviya et al. 2010; Ota and Ulrih 2017; Zeidan et al. 2017; Choudhury et al. 2017; Governa et al. 2018), while, new remedies based on natural compounds are still in great demand because of their easy availability and inexpensiveness. It is a riveting fact that a single natural compound could act on different diabetic pathophysiologies at once with minimum side effects. Consequently, natural compounds might be mulled over as the most practical choices for diabetes management or fortification of currently used treatments. An abundance of research articles on natural compounds possessing anti-diabetic potential are already available, however, research and clinical trials are currently

going on to establish these compounds as future therapeutic products for diabetes.

Some outcomes obtained from these studies were extremely encouraging, but still we are unable to find out a breakthrough medicine from these anti-diabetic natural compounds. Hence, we require an increasing number of systematic studies along with the exact classification of natural compounds based on their anti-diabetic mode of action. To the best of the author's knowledge, at present, none of the accessible databases provide data on anti-diabetic natural compounds with respect to their mode of action. Therefore, a compendious database, i.e., anti-diabetic natural compound database (ADNCD) was designed to pile up the information categorizing anti-diabetic natural compounds based on their different mechanisms of action which includes various enzymes, proteins, genes, channels, receptors, pathways and other important aspects at one platform. In addition, ADNCD would also offer an option to observe the toxicity and physicochemical properties of each and every anti-diabetic natural compound available in the database. We firmly believe that ADNCD would provide valuable information



#### Diabetes:

Diabetes is a major public health issue and its prevalence is increasing at an alarming rate globally. Diabetes is a cluster of various metabolic disorders characterized by high blood glucose level (hyperglycemia), either because insulin production is insufficient, or because the body's cells do not respond properly to insulin, or both. Diabetes caused due to the failure of insulin production by the pancreas is termed as Type I or Insulin dependent diabetes. On the other hand, diabetes initiated with insulin resistance due to improper cell response towards insulin is known as Type II or non-insulin dependent diabetes. There are a number of different types of anti-diabetic medications available all over the world, but unfortunately these medicines have some or the other side effects. Thus, researchers are looking for better medications with lesser side effects and natural compounds seem to be a better alternative option.

#### Significance behind the database:

According to International Diabetes Federation 2015, diabetes has affected at least 415 million people worldwide and the number is expected to reach 642 million by the year 2040 [http://www.diabetesatlas.org/key-messages.html]. Further, limited efficacy and undesirable side effects of currently available anti-diabetic drugs have the worsened the situation. Thus, development of an effective alternative treatment strategy against this debilitating disease is urgently required. Due to complex patho-physiology and association with other factors, drug acting on a single specific target could not be considered as an effective strategy to treat diabetes. So, instead of using target specific drugs, multi-target drugs with lesser side effects could be considered as an alternative strategy for the better treatment of diabetes. Interestingly, natural compounds provide numerous options to modify the symptoms and progress of diabetes. It has been found that a single natural compound could act on multiple diabetes associated targets with minimum side effects. Even though immense literatures on natural compounds showing promising results

Fig. 1 Home page describing the significance of the database (ADNCD screen capture http://www.adncd.com/index.php)



to the scientists, herbal drug manufacturing industries and clinicians who are struggling to find out a strong alternative against diabetes.

# Methodology

## **Database architecture and tools**

Anti-diabetic natural compounds database was arranged on apache server. However, to offer vivacity on the web interface, hypertext preprocessor program (PHP) along with JavaScript and HTML were used. Database information in tabulated form was stored in MySQL (Structured Query Language) 5.0 which is a relational database at the backend and this tool also helps in retrieving data with flexibility and speed. For the users, the database consists three main options, i.e., Home, Mode of Action and Browse information for retrieving useful scientific data on anti-diabetic natural compounds. In addition, the users have an option of direct searching for any anti-diabetic mode of action. Interestingly, under every mode of action each compound is linked to the PubChem compound database, cross references and provides information on physicochemical properties and toxicity risks. Two more options, i.e., About us and Contact us are also available for obtaining information about author's current research areas, research team and contact address.

### The database access

ADNCD database has five options along with one search option for the users. The first option is Home which provides basic information regarding diabetes and significance of ADNCD database (Fig. 1). The second option is Mode of Action that contains a table presenting a classification of different anti-diabetic mechanism of actions of natural compounds (Fig. 2). Here, the user could click on each mechanism of action and browse it directly or user could opt for the third option, i.e., Browse Information (Fig. 3). In Browse Information, the user could select the mode of action in the



Fig. 2 Mode of action page classifying different anti-diabetic mode of actions of natural compounds (ADNCD screen capture http://www.adncd .com/actionmode.php)



ADNCD	×						
$\textbf{\leftarrow}  \rightarrow  \textbf{G}  \Big[$	(i) www.adncd.com/browse.php		☆ :				
ADNCD ANTI-DIABETIC NATURAL COMPOUNDS DATABASE							
	Home	Mode of Action Browse Information	About us Contact us				
Select Mode of Action AMPK activators							
Adenosine Monophosphate-Activated Protein Kinase activators (AMPK activators)							
S.No.	Compound	Reference	Physicochemical Properties and Toxicity Risks				
1	Metformin(Known Drug)	Zhou et al. 2001. Hawley et al 2002	Properties and Risk Assessment				
2	Phenformin(Known Drug)	Yang et al., 2013	Properties and Risk Assessment				
3	3-Caffeoylquinic Acid	Zhang et al., 2013	Properties and Risk Assessment				
4	Berberine	Zheng et al., 2014 Chen et al., 2010	Properties and Risk Assessment				
5	<u>Capsaicin</u>	Kwon et al., 2013	Properties and Risk Assessment				
6	Chlorogenic Acid	<u>Ong et al., 2013</u>	Properties and Risk Assessment				
7	Dehydropipernonaline	Kim et al., 2011	Properties and Risk Assessment				
8	Epigallocatechin3-Gallate	Collins et al., 2007	Properties and Risk Assessment				
9	Galegine	Madiraju et al., 2014	Properties and Risk Assessment				
www.adncd.com/	browse.php						

Fig. 3 Browse information page with drop-down box for selecting anti-diabetic mode of action and helps in browsing information linked to natural compounds under each mode of action (ADNCD screen capture http://www.adncd.com/browse.php)

drop-down search box and retrieve information regarding each natural compound coming under the selected mode of action. At this juncture, user could get structural information about each natural compound from PubChem database, retrieve the literature from the linked cross reference and gather information regarding physicochemical properties and toxicity risks (Fig. 4) in a click.

### **Data collection**

All the sources used for gathering and compiling of data in ADNCD were authentic such as PubChem and Pubmed. For the calculation of physicochemical properties and toxicity risks of each compound, Molinspiration property calculation and Osiris property explorer online tools were used.

## Web-Link for accessing ADNCD: anti-diabetic natural compounds database

#### http://www.adncd.com/.



#### **Discussion and future prospects**

Anti-diabetic natural compounds database (ADNCD) is the first compendious database which categorizes different natural compounds based on their anti-diabetic mode of actions. In addition, it provides essential data with respect to the physicochemical properties and toxicity risks of these anti-diabetic natural compounds. Few known drugs against some anti-diabetic mode of actions are also included in the database, as a reference to compare with natural compounds.

This database would assist the researchers by limiting their endeavors to gather the information from various different resources. Here, the majority of the information would be accessible in a single click. As several researches are still going on and information is evolving day-by-day, we would bit by bit refresh the database and include new most recent informations once they become available. However, our future plan is to add information regarding structure-based anti-diabetic activity of natural compounds.

ADNCD ×				÷ - • ×				
$\leftarrow \rightarrow \mathbb{C}$ ( www.adncd.com/compoundinfo.php?4								
ADNCD ANTI-DIABETIC NATURAL COMPOUNDS D/	Search							
Home Mode o	of Action Browse	Information About us	Contact us					
Detail Information Retherine								
Physicochemical parameters of the compound Toxicity risks of the compound								
Absorption percent	94.92	Mutagenic		Low				
Topological polar surface area	40.82	Tumorigenic		Low				
Molecular weight	336.37	Reproductive effect		None				
miLogP**	0.2	Irritant		None				
Hydrogen bond donors	0							
Hydrogen bond acceptors	5	Molinspiration property calculation tool ( <u>http://www.molinspiration.com/cgi-bin/properties</u> ) was used to predict physicochemical properties of compounds. Osiris property explorer ( <u>='http://www.organic-chemistry.org/prog/peo/</u> ) was used to predict toxicity.						
Rotatable bonds	2							
Lipinski's violation	0							
	Dosign by: LTochnor	rat Solutions Dut 1 td						
ww.adncd.com/browse.php								

Fig. 4 Information about physicochemical properties and toxicity risks of each anti-diabetic natural compound. (ADNCD screen capture http://www.adncd.com/compoundinfo.php?4)

Acknowledgements Aisha Khatoon is supported by Maulana Azad National Fellowship grant from UGC, New Delhi, India (Grant number: MANF-2014-15-MUS-UTT-36526). Sibhghatulla Shaikh is supported by INSPIRE grant from the Department of Science & Technology (DST), New Delhi, India (Grant number: IF130056), which is sincerely acknowledged. We would like to thank the developers of *Mol inspiration property calculation tool* and *Osiris property explorer*.

# **Compliance with ethical standards**

**Conflict of interest** On behalf of all authors, the corresponding author states that there is no conflict of interest.

# References

- Alqahtani N, Khan WA, Alhumaidi MH, Ahmed YA (2013) Use of glycated hemoglobin in the diagnosis of diabetes mellitus and prediabetes and role of fasting plasma glucose, oral glucose tolerance test. Int J Prev Med 4:1025–1029
- Chang CL, Lin Y, Bartolome AP, Chen YC, Chiu SC, Yang WC (2013) Herbal therapies for type 2 diabetes mellitus: chemistry, biology,

and potential application of selected plants and compounds. Evid Based Complement Alternat Med 2013:378657

- Choudhury H, Pandey M, Hua CK, Mun CS, Jing JK, Kong L, Ern LY, Ashraf NA, Kit SW, Yee TS, Pichika MR, Gorain B, Kesharwani P (2017) An update on natural compounds in the remedy of diabetes mellitus: a systematic review. J Tradit Complement Med 8:361–376
- d'Emden MC, Shaw JE, Jones GR, Cheung NW (2015) Guidance concerning the use of glycated haemoglobin (HbA1c) for the diagnosis of diabetes mellitus. Med J Aust 203:89–90
- Diabetes Canada Clinical Practice Guidelines Expert Committee, Punthakee Z, Goldenberg R, Katz P (2018) Definition, classification and diagnosis of diabetes, prediabetes and metabolic syndrome. Can J Diab 42:S10–S15
- Governa P, Baini G, Borgonetti V, Cettolin G, Giachetti D, Magnano AR, Miraldi E, Biagi M (2018) Phytotherapy in the management of diabetes: a review. Molecules 23:E105
- Hameed I, Masoodi SR, Mir SA, Nabi M, Ghazanfar K, Ganai BA (2015) Type 2 diabetes mellitus: from a metabolic disorder to an inflammatory condition. World J Diab 6:598–612
- International Diabetes Federation (2015) http://www.diabetesatlas.org/ key-messages.html. Accessed 21 Jan 2017



- Maitra A, Abbas AK (2005) Endocrine system. In: Kumar V, Fausto N, Abbas AK (eds) Robbins and cotran pathologic basis of disease, 7th edn. Saunders, Philadelphia, pp 1156–1226
- Malviya N, Jain S, Malviya S (2010) Antidiabetic potential of medicinal plants. Acta Pol Pharm 67:113–118
- Olokoba AB, Obateru OA, Olokoba LB (2012) Type 2 diabetes mellitus: a review of current trends. Oman Med J 27:269–273
- Ota A, Ulrih NP (2017) An overview of herbal products and secondary metabolites used for management of type two diabetes. Front Pharmacol 8:436
- Zeidan M, Rayan M, Zeidan N, Falah M, Rayan A (2017) Indexing natural products for their potential anti-diabetic activity: filtering and mapping discriminative physicochemical properties. Molecules 22:E1563

