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Review Article

Combating Diabetes and its Emerging Complications Utilizing Natural Phytochemicals

Karim Raafat*

ABSTRACT

Introduction: Natural phytochemicals are considered a primary health care measure for many chronic diseases and for assurance of urban health and wellbeing. Diabetes and its related complications are major chronic diseases increasingly threatening human health and wellbeing. Till date, these diseases are not fully managed by the current therapies. Thus, there is an increasing need to find more safe and efficient therapies for diabetes and its related complications. **Methods:** An evidence-based review of the novel phytotherapies to diabetes and its related complications and discussing their main mechanisms of actions are the main aims of the current study. Data collection were done for the phytotherapies that were extracted, chromatographically standardized, fractionated and the main effective compounds were isolated and evaluated for their potentials against diabetes and its related complications. Special emphasis was given for the extracts and their isolated phytochemicals that had significant hypoglycemic and antinociceptive effects towards diabetes and its related complications, particularly diabetic-neuropathy. **Results:** The phytochemicals main mechanisms of action were found to be mainly due to their insulin secretagogue, beta-cells regeneration, anti-oxidant potentials. **Conclusion:** Therefore, clinicians should consider natural phytochemicals when treating chronic diseases and when reassuring better urban health and wellbeing.

Key words: Combating Diabetes, Emerging Complication, Natural Phytochemicals Mechanism of action, Complementary medicine.

INTRODUCTION

Natural phytochemicals are considered a primary health care measure for many chronic diseases and for assurance of urban health and wellbeing.[1] Diabetes (DM) and its related complications are major chronic diseases increasingly threatening human health and wellbeing.[2]

Type 1 DM is ameliorated with insulin, exercise and dietary changes. On the other hand, type 2 DM might be ameliorated with oral hypoglycemics, reduction of weight or changes in diet.[3] Till date, these diseases are not fully managed by the current therapies.[3] Thus, there is an increasing need to find more safe and efficient therapies for diabetes and its related complications.

Diabetes mellitus is associated with vascular-disorders. Current reports have accompanied hyperglycemia and oxidative stress and its relation to diabetic complications. Natural phytochemicals are famous for their free radical scavenging potentials which might be involved in amelioration of diabetes and its complication.[4]

Therefore, an evidence-based review of the novel phytotherapies to diabetes and its related complications and discussing their main mechanisms of actions are the main aims of the current study.

MATERIALS AND METHODS

Search strategy

The investigation in the primary-literature was done between August and September 2018. A web-based search was done in SCOPUS and PUBMED. Databases were searched using a search-strategy done by combining the following keywords: diabetes or diabetic neuropathy or diabetes diagnosis or diabetes current-therapies or diabetes mechanisms or diabetes extract or diabetes phytotherapies or diabetes therapy-recommendations. The related research article references were searched for the relevant tertiary and secondary literature.

Inclusion and Exclusion criteria

The subsequent inclusion and exclusion criteria were used; paper type: 1ry, 2ry or 3ry literature, printed in English, in well-reputed published books or peer-reviewed journals. The study design included pre-clinical or clinical models. The selection of natural phytochemicals was established on their potentials in amelioration of diabetes in clinical or pre-clinical models.

Karim Raafat*

Department of Pharmaceutical Sciences, Faculty of Pharmacy, Beirut Arab University, Beirut 115020, LEBANON.

Correspondence

Dr. Karim Raafat

Department of Pharmaceutical Sciences, Faculty of Pharmacy, Beirut Arab University (BAU), Beirut, LEBANON.

Phone no : +961 1300110

E-mail: k.raafat@bau.edu.lb

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Quality-assessment

The included researches quality was evaluated by a standardized-tool. This tool consisted of 8 factors: (A) The sample was representative to the population, (B) the design of studies, (C) external-factors control (D) blinding (E) data-collection consistency, (F) the criteria for exclusion and inclusion, (G) reliability of the method and (H) analyses of the method. The researches were included in this study in the condition of all criteria were fulfilled.[5]

Data-synthesis

With the purpose of combing the retrieved results, a narrative synthesis technique was used. The 1ry research characteristics were evaluated using a pre-set procedure and the subsequent data has been extracted: natural phytochemicals' family and name, the part used, scope of the study, most bioactive ingredients, uppermost dose used, analyses-methods, administration method, clinical model or pre-clinical, existence of positive-control and its administration route, the results-section, diabetes limitations and indications.

RESULTS AND DISCUSSION

Current-therapies

As from a pharmacological-perspective, conventional-drugs ameliorating diabetes are summarized in Table 1.[6,7] Despite the lack of full information from meta-analyses, various conventional-drugs showed clinically-sounding effects on diabetes and its related symptoms and complications (Table 1).

Natural Phytochemicals

Currently, natural phytochemicals were used as a complementary therapy for the amelioration of DM.[8-10] Many researchers presented proof underlying the beneficial potentials of natural phytochemicals towards DM (Table 2).

The *R. ribes* showed to be among the most effective natural phytochemicals. Bio-guided separation techniques have shown evidence that rutin significantly decreased hyperglycemia (Table 2) and this effect suggested to be due to the increase of natural-antioxidant effect, serum catalase.[11] However, more full clinical interventions are needed to strengthen its

Table 1: DM current therapies.

Group	Individuals	Mechanism
Sulfonylurea	Glibenclamide Gliclazide Glipizide	Insulin secretagogue (Type 2 DM)
Meglitinide analogues	Gliemepiride Repaglinide Nateglinide	Insulin secretagogue (Type 2 DM)
Biguanides	Metformin	↓hepatic glucose production ↓ intestinal-absorption of glucose and ↑insulin sensitivity (Type 1 and 2 DM)
Thiazolidinediones	Rosigliltazone Pioglitazone	↑Adipogenesis and fatty-acid uptake (Type 2 DM)
Alpha-glycosidase inhibitors	Acarbose	Alpha-glycosidase inhibitors (Type 1 and 2 DM)
Insulin	Insulin	Control the metabolism of carbohydrates, fats and protein (Type 1 DM)

Table 2: Natural Phytochemicals and their potentials in amelioration of DM.

Natural Phytochemical	Family	Used plant part(s)	Most active constituent	Highest dose-Administration route	Preclinical/ Clinical Model	Positive control-Administration route	Indication/ DM Type	Reference(s)
- *Rheum ribes*	Polygonaceae	Roots	Rutin	50 mg/kg-IP	Alloxan-induced DM in mice	Glibenclamide 5 mg/kg-IP	Type 1 and 2 DM	(K. Raafat, Aboul-Ela, & El-Lakany, 2014; Vincent, Edwards, Sadidi, & Feldman, 2008)
- *Cannabis sativa*	Cannabaceae	Flowers	Cannabinoids	32 mg THC per session-Inhaled	Double blind randomized clinical trials	—	Type 2 DM	(Andreae *et al.*, 2015)
- *Ferula hermonis*	Apiaceae	Roots	Ferutinin	50 mg/kg-IP	Alloxan-induced DM in mice	Glibenclamide 5mg/kg-IP	Type 1 DM	(K. Raafat & El-Lakany, 2015)
- *Sambucus nigra*	Adoxaceae	Inflorescence	Kaempferol	200 mg/kg-IP	Alloxan-induced DM in mice	Glibenclamide 5mg/kg-IP	Type 1 DM	(K. Raafat & El-Lakany, 2015)
- *Curcuma longa*	Zingiberaceae	Roots	Curcumol	*Curcuma longa* 100 mg/kg and curcumol 40 mg/kg-IP	Alloxan-induced DM in mice	Glibenclamide 5mg/kg-IP	Type 1 DM	(K. M. Raafat & Omar, 2015; Rahimi, Nikfar, Larijani, & Abdollahi, 2005).

- *Punica granatum*	Punicaceae	Fruit rind	Gallic acid	100 mg/kg-IP	Alloxan-induced DM in mice	Glibenclamide 5mg/kg-IP	Type 1 DM	(Bakirel, Bakirel, Keles, Ulgen, & Yardibi, 2008; K. Raafat, Boukhary, Aboul-Ela, & El-Lakany, 2013).
- *Salvia libanotica fruticosa*	Lamiaceae	Roots	Flavonoids	50 mg/kg-IP	Alloxan-induced DM in mice	Glibenclamide 5mg/kg-IP	Type 1and 2 DM	(K. Raafat, *et al.*, 2013)
- *Centaurea horrida*	Asteraceae	Herb and root	Flavonoids	100 mg/kg-IP	Alloxan-induced DM in mice	Glibenclamide 5mg/kg-IP	Type 1 DM	(K. Raafat, *et al.*, 2013)
- *Hordeum spontaneum*	Poaceae	Grains	Gluten	50 mg/kg-IP	Alloxan-induced DM in mice	Glibenclamide 5mg/kg-IP	Type 1 and 2 DM	(Volis, Mendlinger, Turuspekov, & Esnazarov, 2002) and (K. Raafat, *et al.*, 2013)
- *Hypericum perforatum*	Hypericaceae	Seeds	Hyperforin and hypericin	60 mg/Kg-PO	STZ-induced diabetes in rats	—	Type 1 and 2 DM	(Galeotti, Maidecchi, Mattoli, Burico, & Ghelardini, 2014)
- Rhodiola rosea	Crassulaceae	Roots	Glycosides	100 mg/kg-IP	STZ-induced diabetes in rats	Insulin-IP	Type 2 DM	(Deciga-Campos *et al.*, 2016)
- *Ficus racemosa*	Moraceae	Stem bark	Phytosterols	Aqueous extract 500 mg/kg and ethanolic extract 400 mg/kg	STZ-induced diabetes in rats	—	Type 1 and 2 DM	(Solanki & Bhavsar, 2015)
- *Gymnema sylvestre*	Apocynaceae	Leaves	Gymnemic acids	100 mg/kg/day-PO	STZ-induced diabetes in rats	—	Type 1 and 2 DM	(Fatani *et al.*, 2015)
- *Citrullus colocynthis* (Topical)	Cucurbitaceae	Fruit	Polyphenolics	Topical formulation	Double blind randomized clinical trials	—	Type 1 and 2 DM	(Heydari, Homayouni, Hashempur, & Shams, 2015)
- *Dioscorea japonica*	Dioscoreaceae	Rhizome	Saponins	100 mg/kg, daily-PO	Type-2 Diabetic db/db Mice	Glibenclamide-OP	Type 1 and 2 DM	(Moon *et al.*, 2014)
- Cleome viscosa	Capparaceae	Herb	Polyphenolics	400 mg/kg-PO	STZ-induced diabetes in rats	—	Type 1 and 2 DM	(Rao *et al.*, 2014)
- *Camellia sinensis*	Theaceae	Leaves	Polyphenolic catechins: epigallocatechin-3-gallate (EGCG), epigallocatechin, gallocatechin and epicatechin	300 mg/kg-PO	Oxaliplatin-induced DM in rats	—	Type 1 and 2 DM	(Lee *et al.*, 2012)

utilization. The *C. sativa* showed potent hypoglycemic effects (Table 2). Randomized double-blind clinical trials showed that THC administered by inhalation significantly decreased Blood Glucose Level (BGL) and ameliorated diabetic neuropathy by inhibition of peripheral and central sensitization.[12,13]

Moreover, *F. hermonis* has shown potent hypoglycemic activity (Table 2). Ferutinin has shown to be *F. hermonis* most active constituent responsible for the amelioration of DM. The potential antioxidant effect of ferutinin might be the underlying cause of management of DM.[14] *The S. nigra* showed potent antihyperglycemic activity (Table 2). Even though there is no detailed clinical-trial till date was reported, Kaempferol has shown to be its most bioactive substance and Kaempferol anti-oxidative stress potentials might be responsible for this effect.[14] The study performed on *C. longa* indicated its potentials against DM and curcumol might be its key constituent responsible for the alleviation of DM4 (Table 2). More deep clinical-trials are needed to completely-understand *C. longa* hypoglycemic mechanism.

The investigation on *P. granatum* (Table 2) showed its promising hypoglycemic activities on Type 1 and 2 DM. The antioxidative stress activity of gallic acid might be responsible for this activity.[15] Other studies including *S. fruticosa, C. horrida* and *H. spontaneum* has shown hypoglycemic activity, but also lacks the clinical evidence.16 *H. perforatum*, *R. rosea, F. racemosaand G. sylvestre* (Table 2) have showed significant anti-hyperglycemic potentials. These findings reflect positive outcomes for further investigation.[17-19] Inside the inclusion-criterion of the current study, *C. colocynthis, D. japonica, C. viscosa* and green tea have been appropriately researched for the amelioration of DM. More studies are needed to ascertain their potentials on the overall quality of life.[20-23]

Generally, natural phyto-chemicals showed to be effective and well-tolerated by their *in vivo*-models of DM. Serious side-effects of these phyto-chemicals did not show as an arising problem. Nevertheless, natural phyto-chemicals require additional clinical-trials to show possible side-effects and to support natural phyto-chemicals clinical use.

CONCLUSION

The phytochemicals main mechanisms of action were found to be mainly due to their insulin secretagogue, beta-cells regeneration, anti-oxidant potentials. Therefore, clinicians should consider natural phytochemicals when treating chronic diseases and when reassuring better urban health and wellbeing.

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CONFLICT OF INTEREST

The author declares no conflicts of interest.

ABBREVIATIONS

BGL: Blood glucose level; **DM:** Diabetes mellitus; **DN:** Diabetic neuropathy; **HbA1c:** Glycated hemoglobin; ***R. ribes*:** *Rheum ribes*; **T1DM:** Type 1 diabetes mellitus; **T2DM:** Type 2 diabetes mellitus.

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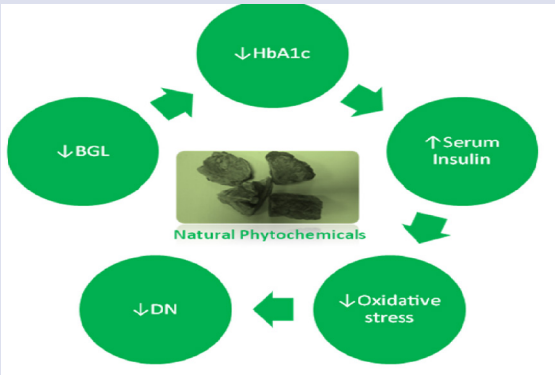
GRAPHICAL ABSTRACT



SUMMARY

- The phytochemicals main mechanisms of action were found to be mainly due to their insulin secretagogue, beta-cells regeneration, anti-oxidant potentials. Therefore, clinicians should consider natural phytochemicals when treating chronic diseases and when reassuring better urban health and wellbeing.

ABOUT AUTHORS

Dr. Karim M. Raafat is an Associate Professor of Phytochemistry and Pharmacognosy at Faculty of Pharmacy, Beirut Arab University. He has completed his PhD from German University in Cairo, New Cairo, Egypt, under the channel system and joint supervision scheme between The German University in Cairo (GUC) and Johann Wolfgang Goethe-University Frankfurt, Germany and post-doctoral studies from Beirut Arab University (BAU) and German University in Cairo. He is a visiting Scientist of Johann Wolfgang Goethe-University, Frankfurt, Germany. He is the Head of Phytochemistry Research Team and Junior Research Team, BAU, Lebanon. He has published more than seventy books, book chapters, patent and peer reviewed journal articles and presentations in scientific conferences. He has been honored with several national and international awards in the scientific field and public service.