

Phytoconstituents and Their Role as Anti-diabetic Agents

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Abstract

The universal surge in the ubiquity of diabetes mellitus (DM) calls for attention. One of the abound conditions giving rise to copious diabetic complications is hyperglycemia. Complications of diabetes are diabetic nephropathy, retinopathy, neuropathy, improper wound healing, heart failure, and diabetic ketoacidosis. Treating these complications is the plight of the attending clinician. Alongside allopathic medicines, various natural products are efficient in treating DM and related pathologist. Here, we discuss the beneficial role of different phytochemicals in treating the hyperglycemic conditions in DM. Several medicinal plants contain micronutrients, amino acids and proteins, saponins, alkaloids, flavonoids, phenolic acids, tannins, and coumarins. We discuss the effectiveness of these phytoconstituents, emphasizing the secondary metabolites which mimic the insulin mechanism and spotlight their significance as the upcoming and promising anti-diabetic agents.

Keywords: Alkaloids, diabetes mellitus, flavonoids, insulin, phytoconstituents, terpenoids

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Introduction

While listing the most ubiquitous metabolic disorders, mentioning diabetes mellitus is noteworthy. It is a chronic metabolic disorder (Kharroubi and Darwish, 2015; Teoh *et al.* 2009). It is widely known

as sugar diabetes and results from defective insulin secretion or improper insulin functioning. The anabolic hormone insulin balances the blood sugar level by signaling the liver cells and muscles to absorb glucose from the blood. The disease restricts the body's normal physiological functioning. There are three types of diabetes mellitus- Type 1, Type 2, and gestational diabetes (Deshmukh and Jain, 2015). The defective insulin secretion and insulin functioning cause blood glucose to ramp up and hampers the primary metabolic process. It is marked by incessant hyperglycemia. Diabetes Mellitus encompasses microvascular (nephropathy, retinopathy, and neuropathy) and macrovascular (about the brain- cognitive impairment, transient ischemic attack; about the heart- coronary heart diseases; formation of gangrene and lack of blood flow in legs) complications. The population explosion, increased urbanization, lack of physical activity, and desk-bound jobs have led to the fact of up-surging diabetes mellitus worldwide. Treating these complications is a challenging step. The phytoconstituents present in some medicinal plants possess anti-diabetic properties. The phytochemicals pave a revolutionary way for the invention and creation of new anti-diabetic medicines having better anti-diabetic attributes.

Type 1 DM (insulin-dependent DM) is an autoimmune disorder manifested by the destruction of pancreatic b cells; whereas type 2 DM (insulin-independent DM) patients presented with insulin resistance compensated by b cell hypersecretion of insulin (Zaccardi *et al.* 2016). The global age-standardized DM prevalence in adults has almost doubled from 5 to 7.9% and 4.3 to 9.0 from 1980 to 2014 in females and males, respectively (Collaboration 2016). This reflects a surge in the associated DM risk factors which includes obesity (WHO 2016). NCD Risk Factor Collaboration and WHO reported that DM caused 1.5 million deaths in the year 2012 (Collaboration 2016). The escalation in mortality caused by DM reduced life expectancy and increased disability-adjusted life years. All these facts had social and economic impacts (Zimmet *et al.* 2016).

The aptness of traditional medicine gained significant momentum over the gone decades. Numerous forms of traditional medicine such as traditional Chinese medicine, Ayurveda, and Unani medicine find their applications worldwide. In a few countries, traditional medicine serves as the prime source of health care attributed to its accessibility, affordability, cultural acceptability, and trust by people. Up to four billion individuals (60% of the world's population) rely on traditional

medicine for health protection purposes (Ekor 2014). Similarly, there are chronicles on the upsurging usage of natural products in DM patients (Ezuruike and Prieto 2014). This is due to the long-term application of oral hypoglycemic medicines and insulin in DM patients resulting in innumerable side effects which include hypoglycemic episodes, gastrointestinal problems (vomiting, nausea, and diarrhea), edema, and hepatorenal disturbances (Mahomoodally *et al.* 2016). It is noteworthy that every medicinal plant contains thousands of bioactive parts or phytochemicals of which only a few may be therapeutically effective. Phytochemicals mean natural plant-based components. Broadly speaking they are of six types, carbohydrate, lipids, phenolics, terpenoids and alkaloids, and other nitrogen-containing compounds present in seeds, fruits, legumes, whole grains, and vegetables (Koche *et al.* 2016). Battino *et al.* (2019) reported the effectiveness of olive oils, berries, and honey, the main food in MedDiet, for the inhibition of cancer, cardiovascular ailments, and hormonal dysfunction. The therapeutic activity of micronutrients, alkaloids, flavonoids, phenolic acids, tannins, and coumarins depends on the interaction of several classes of phytochemicals. Different plant species like *Ginkgo biloba*, *Aloe vera*, *Momordica charantia*, and ginseng were reported to exhibit effectual hypoglycemic actions (Teoh *et al.* 2010).

This review focuses on the contemporary studies that use secondary metabolites i.e. phenolic compounds, alkaloids, and terpenoids that have hypoglycemic properties.

Phytoconstituents having anti-diabetic activity

Flavonoids are the most common group of polyphenols that have a general structure of a 15-carbon skeleton consisting of two benzene rings attached via a heterocyclic pyran ring, in a C6–C3–C6 arrangement (Gonzales *et al.* 2015). Flavonoids exhibit various therapeutic responses including antioxidant, antiviral, anti-inflammatory, anticancer, and hepatoprotective properties. Flavonoids (naringenin, baicalein, kaempferol, and quercetin) isolated from *Ficus racemosa* (family Moraceae) stem bark exhibited hypoglycemic effect thereby causing a decrease in glucose level from 300 to 185 mg/dL following 2 weeks of oral flavonoids administration (90 mg/kg) in *in vivo* models. Besides, flavonoids administration enhanced the glycogen amount in the liver in comparison to the untreated diabetic experimental rats (Keshari *et al.* 2016).

Alkaloids are high molecular mass heterocyclic compounds containing nitrogen linked to at least two carbon atoms (Aniszewski 2015). Berberine ($C_{20}H_{18}NO_4^+$, molecular weight 336.37) is an isoquinoline derivative alkaloid isolated from *Rhizoma Coptidis* (the dried rhizome of *Coptis chinensis*, family Ranunculaceae, commonly known as Chinese goldthread). Berberine treatment (150 and 300 mg/kg) for 12 consecutive weeks remarkably lowered the cholesterol level, levels of HbA1c, and triglyceride, and enhanced the secretion of insulin in diabetic rats. More importantly, the results were comparable to patients treated with metformin (Dange *et al.* 2016). Berberine treatment effectively restored insulin secretion in high glucose-treated INS-IE cells and diabetic mouse islets. Berberine treatment also inhibited hepatic gluconeogenesis by down-regulating the expression of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase in diabetic rats. Also, berberine could ameliorate DM complications such as DM-induced cognitive decline, cardiac dysfunction, endothelial dysfunction, and nephropathy in diabetic rats (Chen *et al.* 2017). Other protoberberine alkaloids isolated from *Rhizoma Coptidis* showed antihyperglycemic effect and this included coptisine, palmatine, epiberberine, and jatrorrhizine, where coptisine treatment significantly promoted glucose consumption in HepG2 cells, suppressed FBG level, and ameliorated glucose tolerance in diabetic mice (Ma *et al.* 2016).

Terpenoids represent the largest and most diverse class of phytochemicals with a wide range of functions, including light-harvesting pigments, hormones, phytoalexins, semiochemicals, and others. These are derived from isopentenyl diphosphate and dimethylallyl diphosphate. Ginseng encompasses cosmopolitan plants belonging to the genus *Panax* (family Araliaceae). Worldwide usage of this genus as a therapeutic plant and functional food is noteworthy (Patel and Rauf 2016). Innumerable reports depicted that ginseng extracts exhibit hypoglycemic activities, by modifying the effects on insulin sensitization and/or insulin secretion. The fruit of *Momordica charantia* possesses anti-hyperglycemic, antioxidant, anti-inflammatory properties, and induces wound healing in diabetic rats (Teoh *et al.* 2009). Terpenoids isolated from *Prosopis juliflora* (24-methylencycloartan-3-one) demonstrated a significant hypoglycemic outcome in diabetic rabbits. More importantly, this terpenoid compound showed no toxicity effect against human red blood cells. Terpenoids isolated from *Cichorium intybus* (11b-13- dihydrolactucin, lactucin, 8-deoxylactucin, jacquinelin, 11b, 13-dihydrolactucopiricin, and lactucopiricin) showed significant inhibition against α -glucosidase (Fan *et al.* 2017).

Conclusion

The plant-derived natural products may mimic the function of insulin and act as potent antihyperglycemic agents. The action of these phytochemicals may be related to the pancreas or even extra-pancreatic. Further studies are needed on many other unexplored plant products before they can be tested in clinical trials to ascertain any potential toxic side-effects.

Future perspectives

Phytochemicals represent a good source of compounds from which new and more effective drugs could be designed for DM treatment. This is particularly important considering that metformin, the first-line drug used to control type 2 DM, has unpleasant gastrointestinal disorders including diarrhea, flatulence, and abdominal discomfort, suggesting that the formulations must be thoroughly tested before application. Several techniques, i.e. nanoparticle coatings, absorption enhancer, and self-microemulsion were employed to amplify the stability and bioavailability of phytochemicals (Wang *et al.* 2015). For instance, due to the restriction from passing through the intestinal cell membranes, orally administered berberine gets poorly absorbed, and thus its bioavailability is less. Treatment with berberine nanocrystal suspension (composed of berberine and D- α -tocopheryl polyethylene glycol 1000 succinate prepared by high-pressure homogenization technique) in the dose of 50 mg/kg/day for 6 weeks, resulted in a superior hypoglycemic effect, and lowering of the total cholesterol, in comparison to the equivalent dose of berberine- and metformin-treated diabetic mice. Several other bioactive components need to be tested for better anti-diabetic actions with lesser required dosage.

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