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CURRENT SCENARIO OF POLYPHENOLS IN DIABETES MELLITUS

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ABSTRACT

Polyphenols are beneficial phyto-compounds with antioxidant properties that protect from various diseases such as cardiovascular, cancer and diabetes mellitus. Among various diseases, we hereby focus on the applications of polyphenols primarily for diabetes mellitus, which is related to a dysfunction in the β-cells of the pancreas that outcome defective production and release of insulin. Here, we primarily discuss the role of curcumin and quercetin in the therapeutics of diabetes, as both polyphenols are highly potent antioxidants and their combination in a novel delivery system that would show positive effects in the management of diabetes and its complications.

Keywords: Curcumin, Quercetin, Diabetes, Polyphenols, Antioxidant

INTRODUCTION

Diabetes is a long-term continuous disorder represented by deformity in carbohydrate, fat, and protein metabolism. It is increasing drastically in the world and has become the most life-threatening and worldwide public health concern [1]. The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The overall number of diabetes sufferers is estimated to rise from 171 million in 2002 to 366 million in 2030 [2]. The long-term complications associated with diabetes like neuropathy, retinopathy, neuropathy, and the probability of atherosclerotic vascular disease are also increased with diabetes mellitus [3]. Categories: 1) central 2) nephrogenic 3) dipsogenic 4) gestational [4]. Diabetes Mellitus is a metabolic syndrome in which blood glucose level is increased due to insulin deficiency. Processes like beta cell destruction, with insulin deficiency, results in insulin resistance thus conclude the insulin action [5]. There are four categories of diabetes mellitus (DM) which are detailed in Table 1 [6]:

Table 1: Different types of Diabetes Mellitus

Type-1 Diabetes Mellitus	**Type-2 Diabetes Mellitus**	**Gestational diabetes**
Insulin-dependent	Non-insulin dependent	During pregnancy
Occurs due to insulin deficiency	Occurs due to insulin resistance or an impaired utilization of insulin	Occurs due to insulin resistance during late pregnancy
High level of ketones	High blood pressure and cholesterol	Preeclampsia, polyhydramnios
Require insulin for treatment or management	Hypoglycaemic agents	Diet, lifestyle, medications

DM is characterized by significant metabolic alterations which are associated with the development of several complications, such as cardiovascular problems, foot ulcers, sexual dysfunction, retinopathy, nephropathy and neurodegenerative diseases [7]. Diabetes is a metabolic disease that can be caused by various factors such as family history, physical stress, overweight and history of gestation diabetes. General Guidelines for managing

diabetes are dietary treatment which aims to ensure weight control, providing nutritional requirements; and cholesterol consumption should be restricted and limited to 300 mg or less daily. Glycaemic control should always be monitored There are two major groups of OHD: sulphonylureas (SUs) and biguanides (BGs). SU works by inducing the release of insulin from the beta cells and also by facilitating their action by extrapancreatic mechanisms. BG exerts its action by decreasing gluconeogenesis and by increasing the peripheral utilization of glucose. Because of the risk of lactic acidosis, it is contraindicated in: — patients with impaired renal function — elderly people above the age of 70 years — patients with heart failure, hepatic impairment, or predisposition to lactic acidosis. For the same reason, treatment with metformin should be discontinued during surgery, severe infections and intercurrent illnesses Some traditional and herbal therapies may be shown to lower blood glucose levels [8]. In the world, antidiabetic effects were seen from many plants. Various herbals like Ginseng, bitter guard, Garlic, Fenugreek are used for diabetes management.

APPLICATION OF TRADITIONAL MEDICINES FOR THE TREATMENT OF DIABETES MELLITUS (DM)

It is a well-known fact that conventional treatments and healthy lifestyle impact a lot in treating diabetes. Food and herbs are used as the primary method of primary health care. According to world health organization guidelines, herbal medicines have four divisions with distinguishing features determining safety, efficacy and quality [9].

1. Indigenous herbal medicines (used in the local region by the confined community)
2. Siddha, Unani and Herbal medicine
3. Shape, size and dosage forms modified in Herbal Medicines
4. Imported products with a herbal medicine base (should be certified)

Diabetes is known as '*Madhumeha'* which is a combination of two words- 'Madhu' and 'Meha' or means secretion of sweet urine. According to Ayurveda, three stages of Prameha are following [10]:

1. Kaphaja (early) --- *Suklameha, Udakameha, Pistameha*
2. Pittaja (acute) --- *Kaiameha, Lohitameha, Nllameha*
3. Vataja (chronic) ---*Hastimeha, MajjSmeha, VasSmeha*

Few examples of plants that show antidiabetic effects are: *Aloe vera, Acacia arabica, Achyranthes aspera, Vinca rosea, Allium cepa, Allium sativum, Anacardium occidentale L., Bidens pilosa., Curcuma Longa*, etc.

USE OF HERBAL THERAPY FOR THERAPY

Some people remain undetected with diabetes, accounting for complications at the time of diagnosis. For management purposes, patient awareness and updated knowledge about diabetes are fundamental. Currently, various antidiabetic drugs administered through oral and injectable routes are used to control diabetes [9]. Presently, antidiabetic drugs are expensive and show side effects. Herbal antidiabetics possess good antioxidative activity for effective management of the disease [11]. Garlic oil (*Allium sativum*) enhances insulin, glucose tolerance, and glycogenesis in skeletal muscle. Garlic extract stimulates the secretion of insulin from pancreatic beta cells The Cinnamomum consist of tannins, flavonoids, anthraquinones, glycosides, terpenoids and coumarins. It is considered as one of the low-risk alternatives for diabetic patients because of its inexpensive cost, high availability and safety profile [12]. Jute and Soybean are also favorable for diabetes and hypertension due to inhibitory activities on ACE [13]. *Aloe vera* extract improves hyperglycemia condition by suppressing pancreatic α-amylase activity [14]. Fenugreek seeds are beneficial for the treatment of diabetes mellitus by inhibiting catabolic processes, such as glycogenolysis, lipolysis and proteolysis. The polyherbal formulations have the potential for a reduction in low-density lipoprotein (LDL), serum cholesterol and triglycerides (TG). Since the polyherbal formulation can reduce the postprandial blood glucose levels almost as effective as metformin does. It seems to have a significant effect on high cholesterol management and fewer side effects compared to metformin alone [15].

ACTIVE ROLE OF POLYPHENOLIC DRUGS IN DIABETES TREATMENT

Polyphenols are the micronutrients, primarily plant-based food, which have beneficial effects of improving insulin resistance and thus diabetes. Few examples of plant sources containing polyphenolic compounds are stilbenes, flavonoids, coffee, cocoa, ginger, berries and cinnamon. It can be classified into many groups by the number of phenolic rings and structural elements connecting these rings. Moreover, the growing number of evidences indicates that various dietary polyphenols may prevent diabetes effectively [16]. There are over 5,000 distinct types of polyphenols, characterized by the presence of more than one phenolic group in the molecule and consist of the broad categories of flavonoids and non-flavonoids. Flavonoids consist of anthocyanins and anthoxanthins which include flavonols, flavanones, flavones and isoflavones [17]. It stimulates glucose uptake by activating the glucose transporters (GLUTs) [18], which play a crucial role in the bidirectional and energy-independent processes of glucose transport in most cells.

One of the prime reasons for the occurrence of Type 2 Diabetes is due to deterioration of glycemic control as a result of the resistance and relative deficiency of the pancreatic β-cell hormone, insulin. Numerous studies have highlighted the regenerative potential of the β-cells from pre-existing β-cells under both physiological and pathological conditions [19]. Various polyphenols are utilized for Type 2 diabetes management, which are discussed here. Cinnamon lowers the rate of stomach emptying and substantially lowers the increased blood level within two hours [20]. Capsaicin was used for neurological complications, such as neurological conditions and tropical skin allergies. Two major examples of polyphenolic compounds (i.e. Curcumin and Quercetin) are our prime interest and will be discussed in brief.

Curcumin (Figure 1 (I)) is a poorly soluble, natural bright yellowish compound, chemically known as diferuloylmethane derived from the rhizomes of Curcuma longa (Family-Zingiberaceae), shows anti-inflammatory, antioxidant and antiangiogenic activities [21]. Various research studies demonstrated that curcumin is poorly absorbed from the gut, suppresses Cytochrome P450 isoenzyme and metabolized by glucuronidation [22]. Major metabolites are glucuronides of tetra hydrocurcumin and hexahydrocurcumin, with dihydroferulic acid and ferulic acid present as minor metabolites [23]. The results of the clinical studies explained the need for a higher dose of curcumin due to its hydrophobicity. Besides lower bioavailability due to poor solubility, it is used in various diseases such as diabetes, arthritis, cancer and cardiovascular diseases. Various novel

delivery systems, such as microparticles, nanoparticles, liposomes and phospholipid complex of curcumin and its analogs (Table 2) have been developed to improve the bioavailability of curcumin [24].

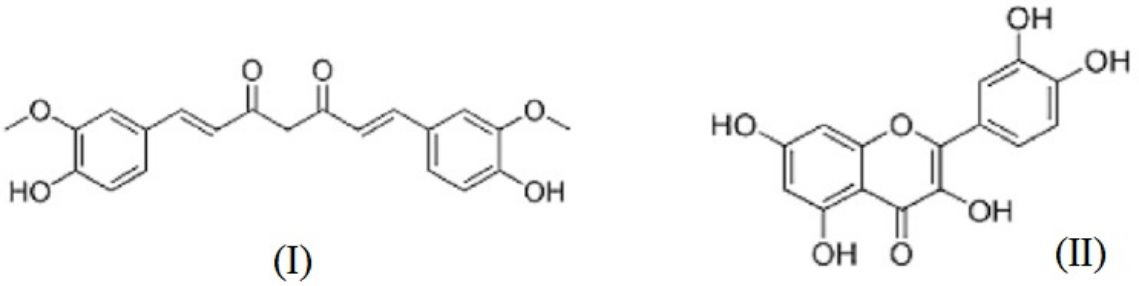

Figure 1: Chemical structure of Curcumin (I), and Quercetin (II)

Table 2: Details of various curcumin analogs

Analogs of curcumin	IUPAC Names	Chemical formula	Molecular weight
Curcumin I	1,7-bis-(4-hydroxy-3-methoxyphenyl)-hepta-1,6- diene-3,5-dione	$C_{21}H_{20}O_6$	368 g/mol
Curcumin II	1-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)-hepta-1, 6-diene-3,5, dione.	$C_{20}H_{18}O_5$	338 g/mol
Curcumin III	1,7-bis-(4-hydroxyphenyl)-hepta-1,6-diene-3,5-dione.	$C_{19}H_{16}O_4$	308 g/mol

Quercetin **(Figure 1 (II))**, also known as Meletin, Xanthaurine, Sophoretin with IUPAC name 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one, is another polyphenolic flavonoid, yellow colored powder and belongs to Biopharmaceutics Classification System (BCS) Class II drugs (Aqueous solubility < 1mg /ml) [25]. It was used in cancer, diabetes management and act as an anti-inflammatory, analgesic, antibacterial, anti-oxidant.

MECHANISM OF ACTION

Curcumin

It improves glucose tolerance by stimulating insulin secretion primarily through stimulating glucagon-like-peptide-1(GLP-1). It mainly works via G-protein coupled receptors specifically α subunit activates beta-type phospholipase C (PLC-β) which hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) to release diacylglycerol (DAG) and inositol trisphosphate (IP_3). Released IP_3 stores the calcium into the cytoplasm, while DAG activates protein kinase C (PKC) and it leaves to the membrane and releases IP_3 as a soluble molecule into the cytoplasm. These channels are specific to calcium and only allow the passage of calcium from the endoplasmic reticulum into the cytoplasm. Thus, stimulates glucagon-like peptide-1 (GLP-1) secretion which increases Insulin secretion then improves glucose tolerance [26].

Quercetin

Quercetin is active against β-cell damagebyexploiting its anti-inflammatory, antioxidant and anti-apoptotic activity. It promotes β-cell regeneration by promoting the regeneration and differentiation of ductal stem cells into pancreatic islet cells. Furthermore, glucokinase activity increases in the liver which results in higher glucose accumulation leading to lower systemic glycemia. In muscle, quercetin accelerates the work of glucose transporter 4 (GLUT 4) and insulin receptors resulting in increased glucose uptake. In the small intestine, quercetin reduces the action of maltase and glucose transporter 2(GLUT-2) results in reduced absorption of glucose in the intestinal system turning with healthy glycemia [27]. Major molecular targets for both curcumin and quercetin are shortlisted in Table 3.

Table 3: Major Molecular targets for both Polyphenols; Curcumin & Quercetin

Curcumin	Diabetes and its complications	Quercetin
TNF-α, PPAR-γ FFA, NF- κB, LPL, and Nrf2	Glycemia	↑ GLUT4, ↓ GLUT2,
Islet viability, regeneration, transplantation	Pancreatic β cell dysfunction	↓Oxidative damage, ↑ Islets ↑Insulin secretion, ↓Glycemia
Albuminuria, glomerular permeability	Diabetic Nephropathy	PC12 cells

PKC, JNK and NMDA and VEGF	Diabetic Neuropathy	PC12 cells
Cardiomyopathy, Wound healing and atherosclerosis	Vascular diseases	Cardiovascular Diseases
Lipid peroxidation, AMPK, PEPCK, G6pase, and PPAR-	Liver disorders	↑ Glucokinase and Glucose Storage and ↓ Glycemia
Musculoskeletal diseases, erectile dysfunction,	Others	Muscle: ↑ AMPK, GLUT4 and ↑ Insulin receptor which ↑ Glucose Uptake and ↓ Glycemia

ADVANTAGES OF COMBINATION OF BOTH POLYPHENOLS

A combination of curcumin and quercetin showed stronger antioxidant activity with positive effects for the control of diabetes. The antioxidant activity of combination showed a synergistic effect. The optimal dose of the combination of both polyphenols elucidated higher efficacy and safety. Various curcumin formulations based on nanotechnology include nanoparticles, self-nano emulsifying drug delivery system (SNEDDS), liposome, mixed polymeric micelles, solid lipid curcumin formulations and phytosome have already been developed successfully for the management of diabetes by improving solubility, dissolution and bioavailability (Table 4).

Table 4: List of novel formulations of curcumin for diabetes management

Formulation	**Diseases**	**Remarks**
Self nano emulsifying drug delivery system (SNEDDS)	Diabetic neuropathy	Good results against behavioral, functional and biochemical deficits in experimental diabetic neuropathy [25]
Targeted delivery	Type 2 diabetes	enable cell [28]
Polycaprolactone nanofibres	Diabetic wound dressing	Polycaprolactone nanofibre matrix proves an increased rate of wound closure [29]
Liposome	Diabetes mellitus	By intraperitoneal administration remarkable decrease malondialdehyde, and nitric oxide, [30]
Mixed Polymeric micelle	Diabetes and wound healing	Maintain the wound healing process, HDL cholesterol level and various biochemical parameters.[31]
Nanoparticles	Diabetes mellitus	Boost the activity of Phytochemicals by enhancing dissolution, solubilization, and bioavailability. [32]
Phospholipid formulation	Chronic diabetic macular edema	Improves visual acuity and reduction of macular edema in diabetic retinopathy [33]
Polyherbal formulation	Antidiabetic potential	Improved insulin release in pancreatic beta cells [34]
Hyaluronic acid-functionalized nanoparticles	Chronic diabetic wounds	Promising improvement in percutaneous permeation [35]
Garlic extract and curcumin nanoparticles	Diabetic cardiomyopathy	Decrease oxidative stress and hyperglycemia by-products accumulation in diabetic hearts [36]

Moreover, based on nanotechnology, various quercetin formulations such as core-shell corona nanoparticle, polymer-based nanoparticle, solid lipid nanoparticle, nanostructured lipid carrier, and phytosomes, have been developed for improving solubility, dissolution rate and bioavailability and thus efficacy (Table 5).

Table 5: List of novel formulations of quercetin for diabetes management

Formulation	Diseases	Remarks
Nanoparticles	Diabetes	Effective by using reduced dose [37]
Core-shell-corona nanoparticle	Diabetes	In the investigation, alginate and succinyl chitosan was used on encapsulating quercetin. [38]
Carboxypropionylated chitosan/alginate Microparticles	Diabetes	Accurately encapsulated 94% Quercetin and revealed pH sensitivity and self-sustained release [39]
Herbomineral formulation	Diabetic Nephropathy	Presence of antioxidant properties and triterpene saponins [40]
SEDDS	Cardiotoxicity, Nephrotoxicity	IncreasesOral bioavailability of Quercetin [41]
Nanohydrogel embedded with Quercetin and Oleic acid	Diabetic foot ulcer	The new topical formulation in the treatment of skin wound in diabetic patients [42]
Phytosome	Antidiabetic effect	Polyherbal phytosome preparation (Quercetin, Gallic acid and Nicotinamide) can provide a convenient and safe alternative to dosage form design and delivery [43]
Soluplus/P407 micelles	Diabetes Mellitus	Used for delivery of BCS Class II drugs [44]
pH-sensitive quercetin-succinylated chitosan-alginate core-shell-corona nanoparticles	Diabetes	Ensuring a biocompatible and biodegradable carrier for oral delivery of Quercetin for diabetes treatment [38]
Insulin and quercetin loaded liquid crystalline nanoparticle	Antidiabetic effect	Overcome drawbacks associated with diabetes [45]

FUTURE PROSPECTIVES

Although both polyphenolic drugs showed various therapeutic benefits, poor solubility of hydrophobic drugs is still a major problem to convert them into a suitable dosage form for showing optimum therapeutic effects. Different approaches such as solid dispersion, complexation with β cyclodextrin, micronization/nanonization have been adopted to improve the solubility of both drugs. However, these formulations elucidated few challenges due to environmental, poor physicochemical characteristics of drug formulation, high cost, highly skilled men-power and safety issues. The conventional techniques based on newer methods have been widely used nowadays, primarily because of their ease of use, efficiency, and wide-ranging applicability [46, 47].

As a newer technology that can be utilized to improve the solubility and bioavailability of poorly soluble polyphenolic drugs, liquisolid technology is a novel and progressive strategy and used to enhance the dissolution of the drug, bioavailability and drug release sustainability. It is the improved version of powder solution technology that converts the liquid medication into free-flowing, non-adherent, dry looking and readily compressible powders. In this technology, lipophilic drugs need to dissolve in non-volatile solvents such as PEG-400, Propylene glycol, glycerine to form liquid drug solution or suspension followed by coating with materials and disintegrating agents to convert into solid dry mass [48]. These liquisolid powder systems can be prepared to overcome barriers like high production cost, sophisticated machinery, complicated technologies, intellectual property issues and advanced preparation methods. There is always scope for the extensive research regarding different sources and grades of carrier materials and evaluation of the effect of various disintegrants such as crospovidone, sodium starch glycolate on dissolution behavior.

CONCLUSION

Based on their physicochemical properties and individual formulation approaches, a combination of both polyphenols such as curcumin and quercetin can be successfully utilized for diabetes management as both elucidated their antioxidating potential in various research findings. Moreover, conventional techniques based novel strategies can be adopted to overcome the barriers such as poor solubility, wettability and dissolution rate of lipophilic polyphenolic drugs.

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