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REVIEW

Oral Nano Drug Delivery Systems for the Treatment of Type 2 Diabetes Mellitus: An Available Administration Strategy for Antidiabetic Phytocompounds

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Abstract: In view of the worldwide serious health threat of type 2 diabetes mellitus (T2DM), natural sources of chemotherapies have been corroborated as the promising alternatives, with the excellent antidiabetic activities, bio-safety, and more cost-effective properties. However, their clinical application is somewhat limited, because of the poor solubility, instability in the gastrointestinal tract (GIT), low bioavailability, and so on. Nowadays, to develop nanoscaled systems has become a prominent strategy to improve the drug delivery of phytochemicals. In this review, we primarily summarized the intervention mechanisms of phytocompounds against T2DM and presented the recent advances in various nanosystems of antidiabetic phytocompounds. Selected nanosystems were grouped depending on their classification and structures, including polymeric NPs, lipid-based nanosystems, vesicular systems, inorganic nanocarriers, and so on. Based on this review, the state-of-the-art nanosystems for phytocompounds in T2DM treatment have been presented, suggesting the preponderance and potential of nanotechnologies.

Keywords: type 2 diabetes mellitus (T2DM), phytocompounds, drug delivery systems, nanoparticles (NPs), antidiabetic effects

Introduction

Diabetes mellitus, a chronic lifelong metabolic disorder, is a major global health issue that has reached alarming levels.[1] According to the latest data from the International Diabetes Federation, approximately 463 million adults worldwide are currently suffering from diabetes. Without sufficient action to control the pandemic, 578 million people will live with diabetes by 2030. By 2045, the number will jump to an astonishing 700 million.[2] T2DM is the most common type of diabetes. It has been estimated that nearly 95% of diabetic patients in the world have T2DM.[3,4] The major pathogenesis of T2DM is insufficient insulin secretion from β cells under the background of insulin resistance. After insulin being produced by the pancreas, it cannot be efficiently utilized by the cells, which is named "insulin resistance".[5] T2DM is characterized by high levels of blood glucose called hyperglycemia. Long-term hyperglycemia results in the glycation of proteins that in turn leads to secondary complications,[6] including retinopathy, cardiovascular disease, diabetic foot, neuropathy, and nephropathy. As a consequence, the quality

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of life decreases and the risk of disability or even mortality increases.[7,8] Frustratingly, there is no cure for T2DM.[9] At present, the therapeutic strategies for T2DM mainly include regular physical exercise, proper low-carbohydrate diets, and adherence to long-term medication therapy, like the oral administration of chemical hypoglycemic drugs and the injection of insulin.[4] However, most diabetes medications promote weight gain, gastrointestinal disturbances,[10] diarrhea, renal failure, hypersensitivity,[11] and there is a proportionate risk of hypoglycemia using them to achieve tight glycemic control.[12,13] Drug resistance is another serious obstacle. For example, sulfonylureas lose their effectiveness after treatment for 6 years in approximately 44% of diabetics.[14] Therefore, it is momentous to discover new antidiabetic candidates with greater safety but fewer side effects.

Plants have always been an exemplary source of ethnic medicines or natural drugs. Phytocompounds are natural components isolated from plants, which have been paid increased attention with progressively in-depth research of modern medicine in the field of alternative medicine.[15] Nowadays, approximately 50% of the drugs approved by the Food and Drug Administration (FDA) are plant-derived compounds or their derivatives.[16] For instance, metformin, a biguanidine-type antidiabetic drug, is developed from galegine which is isolated from *Galega officinalis* L. (Fabaceae)[17] and is currently used as the first-line oral medication for T2DM treatment.[18,19] Compared with conventional therapies, natural plant-derived agents are more affordable and accessible, with fewer side-effects, so pharmaceutical research is increasingly inclined to discover new antidiabetic drugs from plants.[20,21] About 1200 plants have been claimed to contain antidiabetic compounds, and more than 400 plants and their bioactive compounds have been scientifically evaluated for T2DM treatment.[21,22] Phytocompound-based therapies are able to be developed as new approaches to treat T2DM or as adjuvants to support the existing monotherapies.

Generally, oral administration is recognized as the easiest and most convenient way. It is preferred by the patients with chronic diseases who require repeated dosing,[23] like T2DM patients, since the oral administration of therapeutic drugs shows good patient compliance without any pain and risk of needlestick injuries. However, the shortcomings of orally delivered phytocompounds, such as poor solubility, instability in the GIT, extremely low bioavailability, short half-life, and so on, restrain the translation of biological activities from in vitro evaluations to in vivo applications,[24,25] so it is of paramount importance to design innovative oral delivery systems for diabetic patients. Nanomedicine has been proven to be able to effectively improve the oral delivery efficacy of compounds through circumventing various delivery restrictions.[26] It has been reported that the uptake of nanostructures is 15~250 times greater than that of microparticles.[27] Besides, nanostructures are always employed to sustain the release of encapsulated compounds in order to reduce dose and dosing frequency, thereby increasing patient compliance and minimizing side effects.[28] At present, a comprehensive review covering various oral nano delivery systems of phytocompounds for T2DM treatment in the preclinical stage is not available. In this review, we aimed to systematically summarize and critically analyze phytocompound-based oral nano delivery systems for T2DM treatment in recent years, and identify their therapeutic effects supported by experimental evidence in vitro or/and in vivo. On this basis, researchers could apply excellent delivery systems to undeveloped antidiabetic phytocompounds to explore more therapeutic possibilities in the future.

Main Antidiabetic Mechanisms of Phytocompounds

It is common for people to use natural plant medicine to prevent and/or treat diabetes in Central America, Asia, and West Africa.[29] According to an estimate published by the World Health Organization in 2008, about 80% of diabetic patients currently rely on medicinal plants for their successive treatments.[29,30] A wide variety of phytocompounds derived from medicinal plants, including flavonoids, polyphenols, terpenoids, alkaloids, saponins, quinones, polysaccharides, etc., have been intensively investigated for their antidiabetic effects.[14,29,31–34] The main mechanisms of phytocompounds for T2DM therapy might be based on four aspects involving certain key targets (Figure 1).[35]

Reduction of Carbohydrate Decomposition and Glucose Absorption

Polyphenols, terpenoids, and tannins display inhibitory effects on α-glucosidase and α-amylase, the major carbohydrate hydrolyzing digestive enzymes.[36] α-Amylase hydrolyzes macromolecules like starch into oligoglucans. At the brush border of the small intestine, these substances are further degraded by α-glucosidase into absorbable glucose and then permeate into blood circulation.[37]

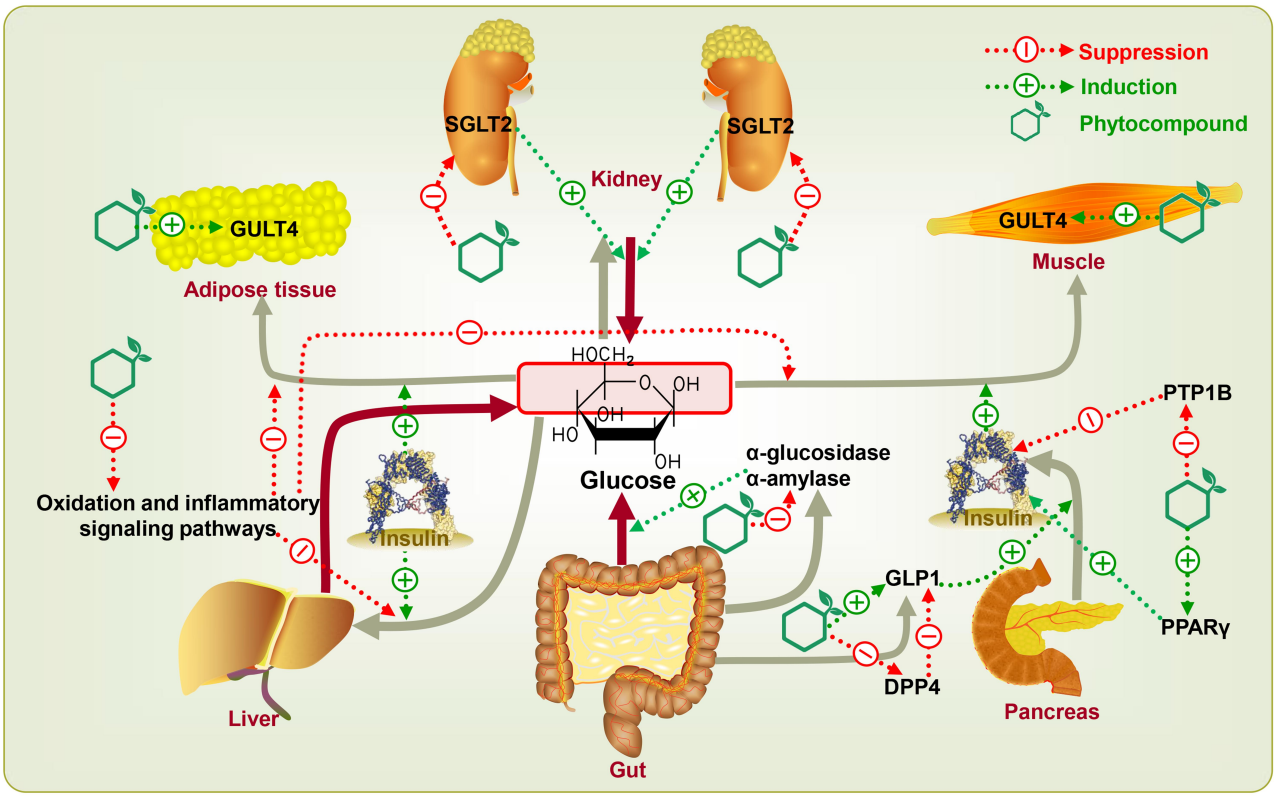

Figure 1 Multiple therapeutic targets of phytocompounds for T2DM treatment.

Under these conditions, phytocompounds can significantly reduce postprandial blood glucose levels by inhibiting α-glucosidase and α-amylase.[36] Hyperglycemia may make the kidney reabsorb glucose above the normal level.[38] Sodium-glucose co-transporter 2 (SGLT2) is the principal co-transporter of glucose reabsorption in the proximal convoluted tubule of the kidney. Phlorizin, chlorogenic acid, quercetin, kaempferol, kurarinone, and sophoraflavanone, with SGLT2 inhibitory activity, can promote the excretion of glucose in urine and suppress the reabsorption of glucose in the kidney. The excretion of glucose leads to a decrease of glucose in plasma levels, thus ameliorating all glycemic parameters. Typically, some synthetic compounds derived from phlorizin, including dapagliflozin, canagliflozin, ertugliflozin, and empagliflozin, have been approved by the FDA for T2DM treatment.[39,40]

Promotion of Glucose Uptake and Metabolism

Flavonoids and polyphenolic compounds can potentiate glucose transporter isoform 4 (GLUT4) expression as well as glucose uptake.[41,42] GLUT4 is located at adipose tissue and skeletal muscle, which is mainly controlled by insulin secretion. Insulin stimulates the translocation of GLUT4 from an intracellular location to the cell surface, which can transport glucose into the inner and in turn decrease blood glucose levels. Pathologically, diabetic patients have lower expression of GLUT4.[43] The abnormality of GLUT4 expression causes a malfunction in the glucose uptake system and eventually results in insulin resistance in T2DM. Sayem et -al[44] reviewed the action of phytocompounds on the modulation of GLUT4 translocation through insulin signaling pathways. For instance, berberine and vanillic acid improved the translocation of GLUT4 via adenosine 5‘-monophosphate-activated protein kinase (AMPK)-dependent pathway whereas resveratrol via phosphatidylinositol 3-kinase (PI3K)-protein kinase B (Akt) pathway.

Improvement of Insulin Action and Sensitivity

Glucagon-like peptide 1 (GLP1), an incretin hormone, can stimulate postprandial insulin secretion. Dipeptidyl peptidase 4 (DPP4) is a GLP1-degrading enzyme.[45,46] The evidence suggests that polyphenols such as chlorogenic acid, epicatechin, and syringic acid can stimulate the secretion of GLP1 from intestinal L-cells, increase the

half-life of GLP1 by inhibiting DPP4, stimulate the secretion of insulin from β-cells, irritate the peripheral response to insulin, and ultimately result in improving the overall effects of the GLP1-insulin axis.[45] Phytocompounds can also regulate insulin sensitivity via the blockage of protein tyrosine phosphatase 1B (PTP1B) and the stimulation of peroxisome proliferator-activated receptor γ (PPARγ). PTP1B is an enzyme responsible for reversing the autophosphorylation of the insulin receptor. The inhibition of PTP1B results in a prolonged insulin signaling cascade, thereby increasing insulin sensitivity.[47] Researches have reported approximately 500 PTP1B inhibitors (248 phenolics, 159 terpenoids, 40 alkaloids, 24 fatty acids, and 17 steroids) isolated from 100 species of natural sources. These phytocompounds could be developed as antidiabetic drugs or at least as promising drug candidates in the near future.[48] PPARγ is the predominant molecular target of the thiazolidinedione class of insulin-sensitizing drugs like pioglitazone, troglitazone, and rosiglitazone.[49] Many in vivo studies have implied that some natural product activators of PPARγ like honokiol, amorphastilbol, amorfrutin 1, and amorfrutin B have similar effects on stimulating glucose uptake as full thiazolidinedione agonists, but with reduced side effects.[50,51]

Antioxidant and Antiinflammatory Actions

The oxidation and inflammatory responses can establish a causal relationship in the occurrence of T2DM, which further leads to insulin resistance, or oxidation and inflammatory responses may be augmented by the hyperglycemic state, which results in T2DM-related complications.[52–58] Recently, Ahangarpour et al[58] and Gothai et al[57] reviewed the research progress of phytocompounds, including chlorogenic acid, ellagic acid, curcumin, resveratrol, apigenin, quercetin, naringenin, catechin, etc., ameliorating insulin resistance and diabetic complications by suppressing oxidation or/and inflammatory signaling pathways. Phytocompounds can not only treat diabetes but also reduce the risk of T2DM-associated complications, which is a very attractive feature.

The Necessity of Developing Antidiabetic Phytocompounds-Loaded Nano Drug Delivery Systems

Despite the promising pharmacological activities of various phytocompounds, there are still some difficulties in translating their beneficial effects via oral route in clinical practice.[59] A review of clinical trials showed that the dose of phytocompounds for diabetes treatment was a crucial variable affecting clinical response.[60] In most studies, higher doses of phytocompounds exhibited better curative activity which may be due to the low bioavailability. Improving oral bioavailability plays a key role in further clinical applications. The way to overcome the low bioavailability of phytocompounds through higher doses showed better efficacy but simultaneously caused toxicity in several organs.[60] This is because the apparent volume of distribution of phytocompounds is quite large, which results in a large accumulation of drugs in normal organs, thus increasing undesired side effects.[61] There is another problem with antidiabetic phytocompounds. Because of the low stability of phytocompounds in the process of absorption, they have a lower potential antidiabetic effect in vivo.[62] Great attempts have been made to develop delivery systems in order to overcome these critical shortcomings.

Conventional drug delivery systems like microspheres,[63,64] microemulsions,[65] amorphous solid dispersion,[66,67] β-Cyclodextrin,[68] pH-sensitive hydrogels[69] have been used to deliver antidiabetic phytocompounds for T2DM treatment. However, conventional drug delivery systems always have some restrictions, such as lack of curative effect because of ineffective or improper dose, diminished potency or altered effects because of drug metabolism, and lack of precise target specificity. More and more researches are focused on nano delivery systems.[70] In the past two decades, several nanotherapeutics have been approved by the FDA for the treatment of diabetes, high cholesterol, cancer, hepatitis, neurological diseases, autoimmune diseases, cardiovascular diseases, Parkinson's disease, and certain infectious diseases.[71] Oral nano delivery systems can not only protect antidiabetic phytocompounds from enzymatic and/or chemical degradation in GIT but also provide other benefits, such as avoidance of first-pass metabolism, improvement of pharmacokinetic and pharmacodynamic profile, fast onset of action, targeted drug delivery, sustained drug release, lower dose and dosing frequency, and fewer side effects.[2]

Oral Nano Drug Delivery Systems of Antidiabetic Phytocompounds

This section will focus on different types of oral nano delivery systems of antidiabetic phytocompounds

(Table 1) (Figure 2), their impact on pharmacokinetic parameters, and their therapeutic effects.

Polymeric NPs

NPs are colloidal drug delivery systems that cover particles ranging from 10 nm to 1000 nm in diameter. They can be a reservoir system in which drugs are enclosed in a cavity surrounded by polymeric membranes called nanocapsules or as a matrix system in which drugs are dispersed throughout particles called nanospheres (Figure 2).[2] Polymers have attracted much attention in therapeutic applications because of the design flexibility based on functionalization, polymer diversity, and macromolecular synthesis methods.[117] According to the different materials used to construct them, polymer-based delivery systems can be divided into synthetic polymer NPs and inartificial polymer NPs.[2]

NPs Based Upon Inartificial Polymers

Inartificial polymers have the characteristics of low cost in processing and high abundance in nature.[118] Non-toxicity and biocompatibility are the primary advantages of inartificial polymers as compared to synthetic polymers.[119] Sodium alginate, chitosan, gum arabica, gum rosin, and dextran are the inartificially occurring polymers that have been developed for the delivery of antidiabetic phytocompounds.

Chitosan-Based NPs

Chitosan, a kind of polycationic polysaccharide, is produced by alkaline deacetylation of chitin[120] which is derived from the cell walls of fungi, the cuticle of insects, and the exoskeleton of crustaceans.[121,122] By far, chitosan is the most extensively used for the delivery of antidiabetic phytocompounds due to its easy surface modification, property to blend with multitudinous polymers, non-immunogenicity as well as non-toxicity, and significant compatibility with cells and tissues.[123] A bottom-up ionic gelation method was applied to prepare chitosan NPs encapsulating ferulic acid[72] or curcumin.[124] Chauhan et al[124] reported, in L6 rat skeletal muscle cells in vitro, curcumin chitosan NPs exhibited a superior effect on the translocation of GLUT4 to the cell surface as compared to free curcumin. In another study of Panwar et al,[72] ferulic acid chitosan NPs showed fourfold enhanced oral bioavailability in vivo compared with free ferulic acid and displayed better antidiabetic potential in streptozotocin (STZ)-induced diabetic rats than ferulic acid. This might be attributed to the unique ability of chitosan to temporarily open the tight junctions between epithelial cells.[125] Moreover, the high positive charge of chitosan makes it well suitable for oral drug delivery because it enhances the adhesion to negatively charged mucosal surfaces, thereby increasing the uptake of cells.[126] Besides, the $-OH$ and $-NH_2$ active groups on the chitosan molecule are prone to chemical reactions.[127] Zhu et al investigated the grafting of catechin onto chitosan using hydrogen peroxide (H_2O_2) and ascorbic acid (Vc) as redox initiator in acetic acid solution.[128] In vitro antidiabetic activity revealed that the inhibitory effect of α-glucosidase decreased in the order of catechin-g-chitosan > catechin > acarbose > chitosan, and the inhibitory effect of α-amylase decreased in the order of acarbose > catechin-g-chitosan > catechin > chitosan. Although chitosan possesses favorable biological properties, it is rarely used alone for oral drug administration because chitosan as a carrier is subject to leak out the entrapped drugs as it dissolves easily in acidic conditions.[125,129]

Alginate/Chitosan-Based NPs

Another inartificial polymer sought with chitosan is alginate. Alginate is a hydrophilic anionic copolymer broadly distributed in the cell walls of brown algae. The wide pharmaceutical applicability of alginate is owing to its unique ability to form gels in aqueous medium or at low pH under the presence of divalent cations like calcium ions.[130] Alginate and chitosan are able to form polyelectrolyte complexes through electrostatic interactions between oppositely charged groups.[125] The poor solubility of alginate network at low pH decreases the high solubility of chitosan at low pH, while chitosan which is less soluble at high pH stabilizes alginate which is more soluble at high pH.[118] The alginate/chitosan complex protects the encapsulated phytocompounds and effectively slows down the release than either chitosan or alginate alone. For instance, in vitro assays, the chitosan-alginate polyelectrolyte complex prolonged the average release time of curcumin by 40 min in simulated gastric fluid and concurrently reduced the loss of curcumin by 20%. Besides, the curcumin nanoformulation prepared by chitosan-alginate complex had a 30% higher glucose-lowering effect in vivo than that prepared by chitosan only.[73] Maity et al[74] prepared a novel alginate coated chitosan core-shell nanocarrier system which was effectively used in the oral delivery of naringenin to STZ-induced diabetic rats. The innovation spot lied in its structural chemistry because the core-shell construction was designed to

Table 1 Oral Nano Delivery Systems Of Antidiabetic Phytocompounds For T2DM Treatment Investigated in vivo (↑) Increase, (↓) Decrease

Drug Delivery System	Phytocompound	Dose (mg/kg b.w)	Size (nm)	Outcomes in vivo	Reference
Chitosan NPs	Ferulic acid	10	119.5 ± 3.9	Bioavailability↑; Glucose lowering effects↑; Antihyperlipidemic effects↑	[72]
Chitosan-alginate NPs	Curcumin	50	<50	Hepatic glycogen↑; Glucose lowering effects↑; Deposition of curcumin in the liver↑	[73]
Chitosan-alginate NPs	Naringenin	50	216.44 ± 0.6	Glucose lowering effects↑; Normalization of pancreatic and hepatic abnormalities↑; Prevention of glycation-induced iron-mediated oxidative stress↑; No toxicity	[74]
Chitosan-alginate NPs	Quercetin	100	91.58 ± 1.14	Glucose lowering effects↑; Antihyperlipidemic effects↑; No toxicity	[75]
Gum rosin nanocapsules	Thymoquinone	20 and 40 and 80	70.21	Glucose lowering effects↑; Antihyperlipidemic effects↑; HbA1c level↓	[76]
Chitosan-gum arabica NPs	Glycyrrhizin	20 and 40	181.4	Glucose lowering effects↑; Antihyperlipidemic effects↑	[77]
PLGA NPs	Quercetin	150	179.9±11.2	Bioavailability↑; Sustained release; Glucose lowering effects↑; Antioxidant effects↑	[78]
PLGA NPs	γ-oryzanol	320	214.8 ± 4.3	Glucose lowering effects↑; Antihyperlipidemic effects↑; Antiinflammation effects↑; Regulation of hypothalamus and pancreatic islets dysfunction	[79]
PLA NPs	Lutein	25 and 50	152.38	Glucose lowering effects↑; Antihyperlipidemic effects↑; Antioxidant effects↑	[80]
PLA–PEG NPs	Curcumin	20	117	Glucose lowering effects↑; Plasma insulin lever↑; Antiinflammation effects↑;	[81]
NEs	Bitter gourd seed oil	-	93.9 ± 2.6	Glucose lowering effects↑; Antioxidant effects↑	[82]
NEs	Berberine	25 and 50 and 100	30.56 ± 0.35	Bioavailability↑; Glucose lowering effects↑; Regulation of liver function	[83]
NEs	Sage Essential Oil	100	143.2	Glucose lowering effects↑; Regeneration of pancreatic tissue	[84]
NEs	α-tocopherol	30	85 ± 0.8	Bioavailability↑; Limited glucose lowering effects; Antioxidant effects↑	[85]
SNEDDS	Polypeptide-k	400 and 800	31.89	Glucose lowering effects↑; Antioxidant effects↑; Antihyperlipidemic effects↑; Regeneration of pancreatic tissue	[86]
SNEDDS	Polypeptide-k and Curcumin	Polypeptide-k:400 and Curcumin:40 Polypeptide-k:200 and Curcumin:20	75.4	Glucose lowering effects↑; Antihyperlipidemic effects↑; Antioxidant effects↑; Regeneration of pancreatic tissue	[87]
SNEDDS	Resveratrol	10 and 20	336 ± 11.6	Glucose lowering effects↑; Antihyperlipidemic effects↑	[88]

(*Continued*)

Table 1 (Continued).

Drug Delivery System	Phytocompound	Dose (mg/kg b.w)	Size (nm)	Outcomes in vivo	Reference
SNEDDS	Trans-cinnamic acid	80	28	Bioavailability↑; Glucose lowering effects↑; Antihyperlipidemic effects↑; Activities of ALT and AST↑	[89]
SLNs	Myricitrin	1 and 3 and 10	50–150	Antioxidant effects↑; Glucose lowering effects↑; β-cell's function index↑; Skeletal muscle glycogen content↑; GLUT4 gene expression↑; Insulin resistance↓; Pancreas apoptosis↓	[90]
SLNs	Resveratrol	10	248	Antioxidant effects↑; Glucose lowering effects↑; Insulin resistance↓; Expression of Snap23, Stx4, and Vamp2↑	[91]
SLNs	Berberine	50 and 100	76.8	Bioavailability↑; Glucose lowering effects↑; Glucose tolerance↑; Insulin sensitivity↑; Islet function↑;	[92]
SLNs	Berberine	50 and 100	76.8	Predominant accumulation of curcumin in the liver; Hepatosteatosis↓	[93]
NLCs	Silymarin	38.13	SLM-NLCs-CP: 265.9 ± 13.4 SLM-NLCs-SA: 213.6 ± 16.0	Glucose lowering effects↑; TG levels↓; No toxicity; Antihyperalgesic effects	[94, 95]
NLCs	Baicalin	200	92 ± 3.1	Glucose lowering effects↑; TC, TG, and HbAlc levels↓	[96]
Liposomes	Betanin	20	40.06 ± 6.21	Antioxidant effects↑; Glucose lowering effects↑; Serum insulin levels↑; Antihyperlipidemic effects↑; Prevention of damage in kidney, liver and pancreas	[97]
Niosomes	Lycopene	100 and 200	202 ± 41	Glucose lowering effects↑; Antihyperlipidemic effects↑;	[98]
Niosomes	Embelin	-	500–734	Glucose lowering effects↑; Antioxidant effects↑	[99]
Niosomes	Gymnemic acid	100 and 200	138.8	Glucose lowering effects↑; Antihyperlipidemic effects↑; Antioxidant effects↑; Antiinflammation effects↑; Antiglycation (AGEs) effect↑	[100]
Phytosomes	Berberine	100	165.2 ± 5.1	Bioavailability↑; Glucose lowering effects↑; Antihyperlipidemic effects↑	[101]
Micelles	Amentoflavone	200	58.44 ± 2.21	Bioavailability↑; Glucose lowering effects↑; Insulin sensitivity↑; Antihyperlipidemic effects↑; Antiinflammation effects↑; Protein and mRNA expressions of PPARγ, and GLUT4↑	[102]
Micelles	Quercetin	50	85–108	Bioavailability↑; Glucose lowering effects↑; Antioxidant effects↑	[103]
Micelles	Silymarin	50	247 ± 11	Glucose lowering effects↑; Insulin level↑; Antihyperlipidemic effects↑; Antioxidant effects↑; Gene expression of Pdx1 and Nkx6.1↑; β-cell regeneration↑; Prevention of damage in liver	[104]
Micelles	Curcumin	100	333 ± 6	Glucose lowering effects↑; Antihyperlipidemic effects↑; Antioxidant effects↑; Gene expression of insulin, Pdx1 and Nkx6.1↑; Prevention of damage in liver	[105]

(*Continued*)

Table 1 (Continued).

Drug Delivery System	Phytocompound	Dose (mg/kg b.w)	Size (nm)	Outcomes in vivo	Reference
Micelles	Curcumin	100 μg	-	Bioavailability↑; Glucose lowering effects↑; Antihyperlipidemic effects↑; Prevention of damage in kidney, liver and pancreas; No toxicity; β-cell regeneration↑; Wound healing effects↑	[106]
Zinc oxide NPs	Docosahexaenoic acid	10	90	Glucose lowering effects↑; Insulin lever↑; Insulin resistance↓; Antioxidant effects↑; Improvement of erythrocyte membrane fatty acids; PI3K level↓; Antihyperlipidemic effects↑	[107]
Selenium NPs	*Catathelasma ventricosum* polysaccharides	0.5 and 2 and 4	49.73	Glucose lowering effects↑; Antioxidant effects↑; Antihyperlipidemic effects↑	[108]
Selenium-coated NLCs	Berberine	50	161.2	Bioavailability↑; Glucose lowering effects↑	[109]
Mesoporous silica NPs	16-Hydroxycleroda-3,13-Dine-16,15-Olid	10 and 30	258 ± 5.7	Glucose lowering effects↑; TG, GOT, and CHOL levels	[110]
Nanocrystals	Curcumin	15	32	Glucose lowering effects↑; Gene expression and activities of insulin and insulin receptor↑	[111]
Nanocrystals	Curcumin	6 and 12	40 − 50	Glucose lowering effects↑; Insulin level↑; Antioxidant effects↑	[112]
Nanosuspensions	Ursolic acid	25 and 50	246.4	Glucose lowering effects↑; Antioxidant effects↑; Antihyperlipidemic effects↑	[113]
Nanosuspensions	Berberine	50	73.1 ± 3.7	Glucose lowering effects↑; Antihyperlipidemic effects↑	[114]
Nanosuspensions	Gymnemic Acids	400	-	Glucose lowering effects↑; Insulin level↑; Antihyperlipidemic effects↑; tHb level↑; HbA1c level↓	[115]
Nanosuspensions	Betulin	20	110	Bioavailability↑; Glucose lowering effects↑	[116]

Abbreviations: NPs, nanoparticles; HbA1c, glycosylated hemoglobin; PLGA, poly (lactic-co-glycolic acid); PLA, poly (lactic acid); PEG, poly (ethylene glycol); NEs, nanoemulsions; SNEDDS, self-nanoemulsifying drug delivery systems; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SLNs, solid lipid NPs; GLUT4, glucose transporter isoform 4; Snap23, synaptosomal-associated protein 23; Stx4, syntaxin4; Vamp2, vesicle-associated membrane protein 2; NLCs, nanostructured lipid carriers; SLM-NLCs-CP, silymarin-loaded nanostructured lipid carriers produced with cetyl palmitate as solid lipid; SLM-NLCs-SA, silymarin-loaded nanostructured lipid carriers produced with stearic acid as solid lipid; TG, triglyceride; TC, total cholesterol; AGEs, advanced glycation end products; mRNA, messenger ribonucleic acid; PPARγ, peroxisome proliferator-activated receptor γ; Pdx1, pancreatic and duodenal homeobox 1; Nkx6.1, NK6 homeobox 1; PI3K, phosphatidylinositol 3-kinase; GOT, glutamate oxaloacetate transaminase; CHOL, cholesterol; tHb, total hemoglobin.

decrease the particle size and assure efficient prevention of embedded naringenin from fast-pass metabolism through sheltering it within the core of NPs. Similarly, in another study of Mukhopadhyay et al,[75] a pH-sensitive polymeric NPs with core-shell-corona morphology for encapsulating quercetin were prepared by the use of succinyl chitosan and alginate. Succinyl chitosan and alginate show excellent pH sensitivity due to the presence of carboxyl groups (-COOH) on their structure. The spherical nanoformulation could perform a pH-sensitive controlled release of quercetin and follow an anomalous (non-Fickian) trend, no matter in vitro or in vivo studies. Compared with native phytocompounds, both core-shell NPs exerted pronounced hypoglycemic effects and effective maintenance of glucose homeostasis in STZ-induced diabetic rats. Besides, both NPs displayed no toxicity in vivo.

Gum-Based NPs and Gum/Chitosan-Based NPs

Natural gums, like guar gum, gellan gum, karaya gum, gum acacia, locust bean gum, konjac gel, or xanthan gums

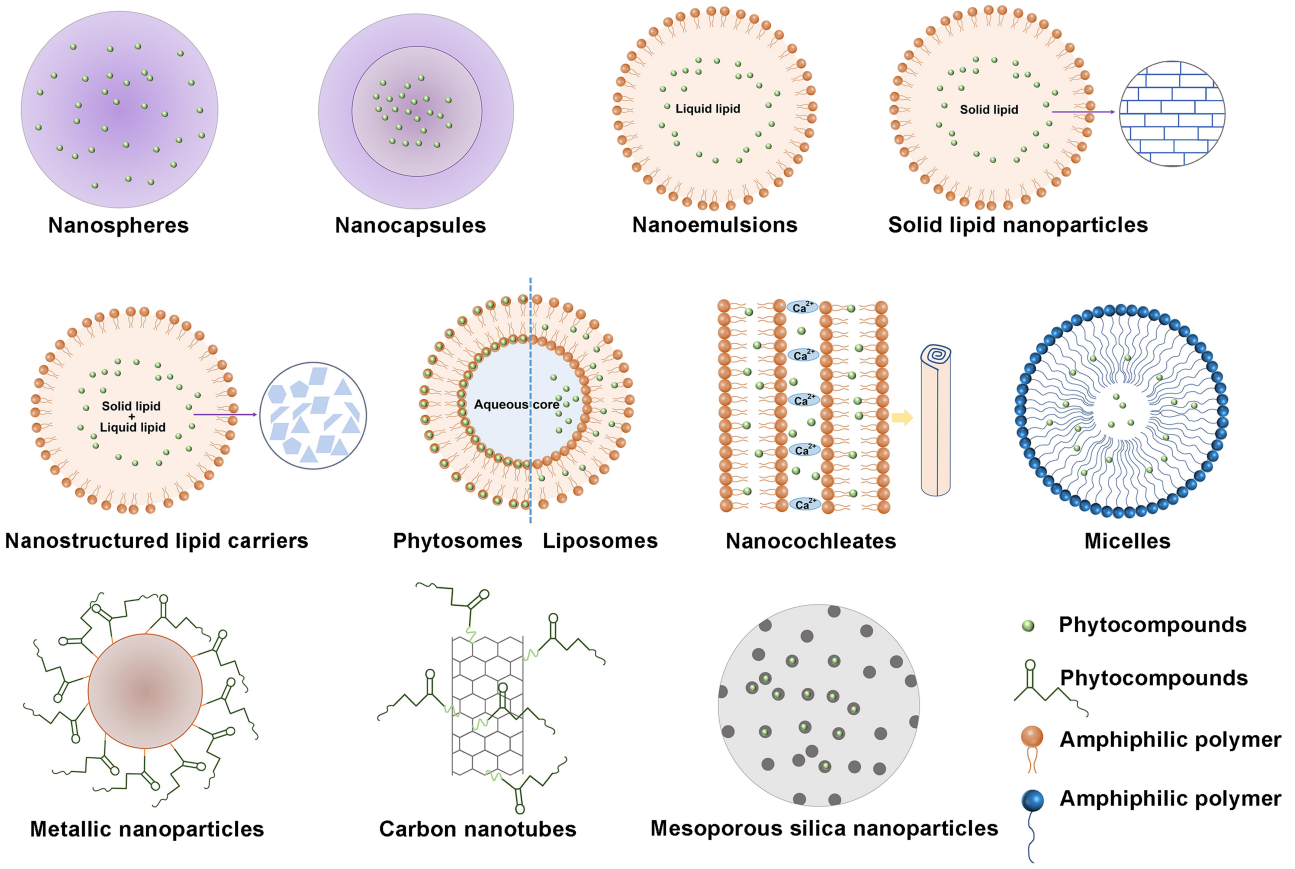

Figure 2 Different types of oral nano delivery systems of antidiabetic phytocompounds for T2DM treatment.

have been extensively employed to develop friendly drug delivery systems. They have the capacity to form hydrogels when exposed to water and show high stability in a broad pH range.[131] Gum rosin is an inartificial anionic polymer derived from pine trees.[132] Rani et al[76] developed thymoquinone-loaded gum rosin nanocapsules using the nanoprecipitation method, also called the solvent displacement method. Thymoquinone nanoformulations contained only half the amount administrated as native thymoquinone but performed a better antihyperglycemic activity in type 2 diabetic rats. Rani et al[77] chose gum arabica and chitosan as basic polymers for the preparation of the glycyrrhizin-loaded NPs which were synthesized by the electrostatic interaction of negatively charged carboxylic groups (−COO) of gum arabica with positively charged amine group (−NH2) of chitosan. Glycyrrhizin-loaded NPs exerted striking antihyperglycemic and antihyperlipidemic effects in type 2 diabetic rats, which were comparable to the standard antidiabetic drug, metformin. In another study of Rani et al,[133] two kinds of nanoformulations discussed above were mixed to explore their combined effects. Compared with the single nanoformulation, even at a decreased drug load, combined nanoformulations exhibited significant improvement on antidiabetic activity in vivo as proven by encouraging responses in all eight tested parameters.

Dextran-Based NPs

Dextran is a highly water-soluble polysaccharide with negatively charged. It predominantly contains linear α-1,6-linked glucopyranose units and some degree of 1.3-branching.[134] Dextran mainly comes from the sucrose-rich environment of *Lactobacillus, Streptococcus*, and *Leuconostoc*.[135] Because of the low affinity between hydrophilic polymeric matrix and lipophilic drugs, drug encapsulation is difficult. Kapoor et al[136] modified dextran by connecting hexadecyl chains with ether bonds to make it amphiphilic. This synthesized O-hexadecyl-dextran could self-assemble in aqueous media, enclosing berberine into the hydrophobic pockets, fabricating NPs. In vitro study on primary hepatocytes, berberine-loaded O-hexadecyl-dextran NPs, even at a 20-fold reduced concentration, were as efficient as berberine in preventing high

glucose-induced oxidative stress, mitochondrial depolarization as well as downstream events of apoptotic cell death.

Despite their highly biodegradable, the limitation of inartificial polymers is their batch-to-batch variability because they are usually extracted from different species, regions, and under various climatic conditions, which makes them less attractive than synthetic polymers that are more versatile and reproducible.[137]

NPs Based Upon Synthetic Polymers

Unlike the inartificial polymers, synthetic polymers are available in a large variety compositions with desirable properties, the ease of control over the synthetic processes, and batch-to-batch reproducibility.[2,135,138] Synthetic polymer NPs usually consist of poly (vinyl alcohol) (PVA), poly (ε-caprolactone) (PCL), poly (lactic acid) (PLA), poly (lactic-co-glycolic acid) (PLGA), and poly (methyl methacrylate) (PMMA), which are approved by the FDA due to their biodegradability and biocompatibility.[1,139] Polyesters are applied in amphiphilic diblock copolymers where the versatility provided by changing the compositions and adjusting the block lengths can make changes in drug loading capacity, carrier size, and drug release.[140]

PLGA-Based NPs

At first, PLGA acted as clinical suture materials because they could be thoroughly absorbed by the body. PLGA-based particles have been utilized as carriers for more than 15 small molecular drugs approved by the FDA.[137] PLGA polymers, with the capability to encapsulate a wide range of hydrophilic or hydrophobic drugs, are usually made by the ring-opening co-polymerization of glycolide and lactide. One of the most notable characteristics of PLGA polymers as drug delivery systems is the possibility of adjusting the physicochemical properties like lactide/glycolide ratio in order to obtain the desired release profile.[141] By following the solvent displacement technique, pelargonidin was encapsulated in PLGA to form nano pelargonidin which was found to protect alloxan-induced hyperglycemic L6 cells against mitochondrial dysfunction, oxidative stress, DNA damage, imbalance in glucose homeostasis in vitro and exhibited better protective effect than native pelargonidin with a ~10-fold reduced dose or showed a ~10-fold greater protective effect with an equivalent dose.[141,142] Chitkara et al adopted the emulsion diffusion evaporation method to produce quercetin-loaded PLGA NPs for diabetes care with the aim to reduce dose and dosing frequency. In a pharmacokinetic study, the relative oral bioavailability of nano quercetin was increased by 523% as compared with quercetin suspension. The therapeutic effect on STZ-induced diabetic rats implied that the same dose of quercetin nanoformulation every 5 days was enough to produce a similar effect to the daily dose of quercetin suspension.[78] Using the same preparation method as quercetin, Kozuka et al[79] successfully fabricated γ-oryzanol-loaded PLGA NPs. Compared with regular γ-oryzanol, nano γ-oryzanol markedly ameliorated lipid and blood glucose metabolism in obese diabetic ob/ob mice with an unexpected amount (about 1000-fold lower dose). Even under the condition of treatment once every 2 weeks, such a prominent impact was also accomplishable. Marked efficacy differences between antidiabetic phytocompounds and their PLGA-based nanoformulations can be ascribed to the specialized uptake of NPs through payer's patches via M-Cells into lymphatic system and then directly into systemic circulation and thus avoiding first-pass metabolism.[143] Furthermore, the PLGA matrix provided a barrier for phytocompounds to prevent them from enzymatic degradation in the GIT.[144]

PLA-Based NPs, PCL-Based NPs, and PVA-Based NPs

PLA is often used with PGA to form PLGA. It is formed by the condensation polymerization of lactic acid, which is produced by the fermentation of sugars from carbohydrate sources like sugarcane, corn, or tapioca.[145] PLA is a hydrophobic polymer because of the presence of $–CH_3$ side groups.[146] The stevioside was encapsulated into Pluronic-F-68-PLA through the nanoprecipitation method.[147] The use of Pluronic F-68 surfactants in NPs synthesis can usually improve drug loading capacity, stability as well as cell–nanoparticle interaction.[148,149] In this research, Pluronic-F-68 copolymer increased the encapsulation and bioavailability of stevioside and provided a longer sustained-release activity. The half release and complete release were respectively observed at 25 ± 4 h and 200 ± 10 h in vitro.[147] Another compound, rebaudioside A, with one more extra glucose molecule in its chemical structure than stevioside, also possesses strong antidiabetic activity. To assess the effect of nano rebaudioside A and compare it with nano stevioside, the entirely same methodology as stevioside was applied to fabricate rebaudioside A PLA NPs. The antidiabetic effect of rebaudioside A NPs was claimed to be superior than that of stevioside NPs on account of achieved higher drug loading ability and similar in vitro release properties.[150]

PCL is a hydrophobic, semi-crystalline polymer.[151] It is achiral and has the ability to resist chemical hydrolysis,

which improves the structural stability of polymeric chains in the nanoencapsulation.[148] Kamaraj et al[152] made 14-deoxy, 11, 12-didehydroandrographolide-loaded PCL NPs using the solvent evaporation technique. The results obtained from the study demonstrated that after nanoencapsulation, the glucose uptake effect in L6 myotubes in vitro was found to be improved because of its prolonged and sustained drug delivery. A biphasic pattern of drug release in vitro exerted an initial burst release at 24 h followed by a sustained release for up to 11 days.

PVA is a polymer with -OH hydrophilicity. It is produced by the radical polymerization of vinyl acetate and then followed with partial hydrolysis. Because of its unique properties like water solubility and multiple -OH groups for further chemical modification, it has been broadly used in drug delivery applications.[153] Mishra et al[80] completed the preparation of lutein PVA NPs by the precipitation method. The results showed that lutein PVA NPs at much lower doses caused a significant blood glucose-lowering effect along with prominent antihyperlipidemic and antioxidant effects compared with native lutein in non-insulin-dependent diabetic rats.

Poly (Ethylene Glycol) (PEG) Surface Modification

However, there are certain limitations of synthetic polymers such as opsonization by plasma proteins and subsequent recognition and clearance by mononuclear phagocyte system because of high surface hydrophobicity.[154] These drawbacks can be overcome by PEGylation approach. PEG is a hydrophilic, nontoxic, blood-compatible polymer that is the most widely used material for the surface modification of NPs.[155] PEG is applied to endow nanocarriers with a hydrophilic camouflage surface, which can provide several advantages in vivo applications, such as improving the hydrophilicity of synthetic polymer, minimizing immunogenicity and phagocytosis as related to rapid reticuloendothelial system, reducing intermolecular aggregation, and increasing aqueous solubility and stability in blood, eventually contributing to the prolonged circulation of NPs.[156]

El-Naggar et al[81] successfully developed curcumin-loaded PLA–PEG NPs using the emulsion-diffusion evaporation technique. In this amphiphilic system, PLA represented the hydrophobic segment of the copolymer and PEG, the hydrophilic one.[59] Hydrophobic curcumin was encapsulated into hydrophobic polymer's portion and stabilized by cationic surfactant (cetyltrimethylammonium bromide). The results validated the superiority of curcumin encapsulated into PLA–PEG NPs over both polymer NPs itself and free curcumin in elevating the level of plasma insulin, decreasing the level of plasma glucose, protecting the liver from inflammation, and ameliorating hepatic functioning in STZ-induced diabetic rats.[81] Used PLGA-PEG-COOH and PCL conjugate as carriers, novel polymeric NPs, which efficiently encapsulated fisetin, were fabricated by the nanoprecipitation technique. In the drug delivery system, PCL exhibited extraordinary capability to form blends with other polymers, which made it possible to design degradation kinetics and mechanical properties.[157] During the preparation of NPs, the PCL block could interact with PLGA to build a hydrophobic core, while the hydrophilic PEG-COOH chains could protrude from the particle surface to stabilize the core.[158] In vitro release assays demonstrated that NPs could preserve and protect the release of fisetin under gastric-simulated conditions, along with controlling release in the intestinal medium. What's more, fisetin nanoformulation obtained an approximately 20-fold higher α-glucosidase inhibitory effect than commercial acarbose.[157] Recent reports implied that PEG could cause an immunogenic response in mammals. However, the extent of this response elicited by the binding of anti-PEG antibodies is not clear. PEG remains the FDA approved polymer and is still the most extensively utilized polymeric coating of nanomedicines, either in industrial use or academic research.[159]

Despite synthetic polymers-based NPs with numerous benefits, there are still a couple of concerns about potential toxicity. Polymer toxicity can be a result of residual monomer in the prepared polymer product and/or physical interactions with biological homeostatic mechanisms, that is, gill oxygen transport.[160] Besides, NPs also have certain other weaknesses including high manufacturing costs, unpredictable stability, and short shelf life.[2,161]

Lipid-Based Nano Systems

Lipid-based nano delivery systems are comprised of biocompatible/biodegradable lipid ingredients generally recognized as safe (GRAS), which have attracted considerable research attention over the last 15 years after the discovery that the oral bioavailability of poorly water-soluble drugs could be improved when they are co-administered with a diet rich in fat.[162] Lipids are absorption enhancers because they can increase oral bioavailability of poorly water-soluble drugs in multitudinous ways like promoting dissolution as a micellar solution, acting as inhibitors of efflux transporters, and increasing

the lymphatic uptake.[162–164] Besides, the structural and chemical richness of lipids provides multiple possibilities to form delivery systems with different characteristics and contain various active compounds.[165]

Nanoemulsions (NEs) and Self-Nanoemulsifying Drug Delivery Systems (SNEDDS)

NEs

NEs are colloidal dispersions consisting of an oily phase, surfactant, and a water phase.[166] It remains controversial in defined size values of NEs, with the upper limit fixed at 100 nm, 200 nm,or 500 nm.[167] Generally, as oil droplets' size decreases, the energy density required to break down oil droplets increases, which signifies that high energy input is necessary to form NEs. Mechanical devices are often used, like ultrasonification, microfluidizers, and high-pressure homogenizers.[168] NEs are drug delivery systems with the ability to entrap hydrophobic and hydrophilic molecules.[166] It markedly enhanced the absorption of antidiabetic phytocompounds entrapped in NEs, which can be realized by the small particle size and high surface-to-volume ratio of NEs, the surfactant-induced membrane fluidity then permeability improvement, the stimulation of various lipid sensing mechanisms in GIT, and the initiation of intestinal lymphatic transport pathway.[168–170]

Bitter gourd seed oil was emulsified by the two-stage homogenization process for NEs preparation with a low surfactant to oil ratio (0.65). Bitter gourd seed oil NEs significantly ameliorated hyperglycemia and oxidative stressed state in alloxan-induced type 2 diabetic rats. Interestingly, compared with equivalent doses of bitter gourd seed oil conventional emulsion and 1% (w/v) bitter gourd seed oil NEs, 0.5% (w/v) bitter gourd seed oil NEs displayed maximum therapeutic efficiency possibly due to increased bioavailability.[82] Further studies on pharmacokinetics are needed to conduct. Xu et al[83] reported that NEs decreased the P-gp efflux of berberine by 2-fold and increased its permeability by 5.5-fold in vitro Caco-2 cells transport and in situ single-pass intestinal perfusion investigations. Compared with berberine control, NEs enhanced the oral bioavailability of berberine in vivo by 212.02% and reduced the blood glucose level of diabetic mice by 3-fold. Moreover, the therapeutic effect of berberine NEs on diabetes was better than that of metformin. Cyclodextrin-based nanosponges, an innovative delivery system, are made up of hyper-cross-linked cyclodextrins connected in a three-dimensional network.[171] They can surpass the limitations of native cyclodextrins.[172] Superior properties are ascribed to their nanoporous, sponge-like structure, beneficial for encapsulation of complex lipophilic and hydrophilic phytocompounds.[173] Nait Bachir et al synthesized two engineered NEs in order to enhance the bioactivity and stability of sage essential oil.[84] The first one was stabilized by native β-cyclodextrin employing physical method and the second one was stabilized by β-cyclodextrin nanosponges using naphthalene dicarboxylic acid as a cross-linking agent and employing polycondensation method. The experiment results revealed the stability of the latter was higher than that of the former. The antidiabetic activity in vivo of NEs stabilized by β-cyclodextrin nanosponges performed better curative efficacy than that of NEs stabilized by natural β-cyclodextrin and free sage essential oil.[84] Hatanaka et al prepared three NEs of α-tocopherol at different loading amounts (10%, 30%, and 50%) via the mechanochemical method using a homomixer and microfluidizer. By comparison with the control mixture of oil and α-tocopherol, 10% α-tocopherol -loaded NEs exhibited a 2.6-fold increased bioavailability in vivo and a more significant antioxidative effect on several organs, especially the liver, in STZ-induced diabetic rats. However, when the content of α-tocopherol of NEs was 30% or higher, severe droplet aggregation occurred during long-time storage.[85] The main restriction that reduces the wide application of NEs is stability.[174] NEs are thermodynamically unstable and kinetically stable systems.[175] In other words, if NEs are given sufficient time, phase separation eventually occurs. Ostwald ripening is the main destabilization mechanism of NEs.[176] It was reported that during storage and applications, the stability of NEs could be maintained against environmental factors including pH and temperature by controlling size, surfactant, and oil concentrations.[177]

SNEDDS

In contrast to NEs, SNEDDS do not incorporate any water, so they are much more chemically as well as physically stable, and therefore can be easily stored for a longer time.[178] Besides, free energy required to produce SNEDDS is very low, and the formulation is thermodynamically spontaneous.[179] SNEDDS (pre-emulsion concentrates) are anhydrous isotropic mixtures of oil, drug, surfactant, and/or co-surfactant. Such systems are diluted by aqueous phase (gastrointestinal fluids) in vivo, and then under gentle agitation provided by the digestive motility of the intestine and stomach, they can form fine oil-in-water NEs, providing a large interfacial surface area for

improving drug absorption. So, one of the most crucial features of SNEDDS is the change that occurs when the system is diluted by body fluids after administration.[162,180,181] Hence, it is crucial to identify efficient self-emulsification regions and decide on the most suitable concentrations of surfactant, cosurfactant, and oil for the formulation of SNEDDS with good stability. Garg et al[87] prepared SNEDDS of polypeptide-k and curcumin for better antidiabetic efficacy in STZ-induced diabetic rats. A pseudo-ternary phase diagram was constructed through oil (labrafil M 1944 CS), surfactant (tween-80), cosurfactant (transcutol P) to select the efficient self-emulsification region. Box–Behnken design was utilized to optimize the liquid formulation based on the results of zeta potential, percentage drug loading, polydispersity index, and mean droplet size. Under the condition of variation in pH, dilution, and temperature, the absence of phase separation and drug precipitation suggested that the optimized formulation was stable. The rate of emulsification is a crucial index for the evaluation of the efficiency of emulsification. The self-emulsification time of optimal formula resveratrol SNEDDS (propylene glycol, tween 80, and olive oil in the ratio 533.3:266.7:200) was only 27 ± 0.8 s without precipitation in vitro. Ten milligram/kilogram resveratrol nanoformulation displayed significant hypolipidemic and hypoglycemic effects on STZ and glucose induced-diabetic rats, similar to the high dose (20 mg/kg) of free resveratrol.[88] In another study, the relative oral bioavailability in vivo of trans-cinnamic acid SNEDDS (10% PEG 400, 30% isopropyl myristate, and 60% Kolliphor EL) was approximately 246% as compared with trans-cinnamic acid suspension, indicating that SNEDDS have a remarkable capability to improve bioavailability.[89] These phenomena can be attributed to multi-concerted mechanisms like reduced intra-enterocyte metabolism through cytochrome P450 enzymes, decreased P-gp efflux activity, and bypassed hepatic first-pass metabolism through lymphatic absorption.[182] SNEDDS of trans-cinnamic acid enhanced the antidiabetic efficacy of trans-cinnamic acid in alloxan-induced diabetic rats, which could be comparable to that of metformin.[89] SNEDDS are related with many merits, but they still have some defects. Characterization- and formulation-associated issues include the correlation of in vitro model with in vivo studies, the usage of a high amount of surfactant, the precipitation of drug in vivo, the oxidation potential of lipid components, the difficulty of low encapsulation, etc.[183] Nowadays, research is moving towards some novel applications of SNEDDS to make up for their shortcomings, such as self-double emulsions (w/o/w), solid SNEDDS, controlled release SNEDDS, supersaturated SNEDDS, targeted SNEDDS.[175,184,185] For example, solid SNEDDS are more stable and amenable to compress into tablets as compared to their liquid counterparts.[186] Garg et al[86] solidified liquid SNEDDS of polypeptide-k using Aerosil 200 as hydrophobic carrier through the spray drying technique. The biochemical, hematological, and histopathological results of STZ-induced diabetic rats revealed better antidiabetic potential of polypeptide-k loaded in SNEDDS than that of naive form.

Solid Lipid NPs (SLNs) and Nanostructured Lipid Carriers (NLCs)

Lipid-based NPs possess an inner solid lipid phase. According to their internal structure, lipid-based NPs are divided into solid lipid NPs (SLNs) and nanostructured lipid carriers (NLCs).[187] As the first generation of lipid-based NPs, SLNs are only composed of solid lipids, whereas NLCs, as the upgrade of SLNs, are composed of a mixture of liquid and solid lipids, but the solid lipid is in a relatively high amount to fabricate nanoparticles. This solid matrix realizes the controlled release of enclosed either lipophilic or hydrophilic molecules, protects them from degradation, and increases the long-time stability of the system.[188] Numerous methods have been reported for the preparation of lipid NPs like hot and cold high-pressure homogenization, microemulsion-based technique, solvent emulsification/evaporation, solvent diffusion method, etc.[163] Probably the most vital reasons for lipid NPs as a suitable alternative to previous polymeric NPs, are low toxicity potential and the ease of large-scale production.[189]

SLNs

Because myricitrin is susceptible to high temperature, the cold homogenization method has been employed to prepare myricitrin SLNs. SLNs of myricitrin exhibited antioxidant, antidiabetic, and antiapoptotic activities in STZ-nicotinamide-induced diabetes in mice and hyperglycemic myotubes.[90] In another study, a solvent injection method was utilized to develop the resveratrol SLNs. Compared with pure resveratrol, oral administration of resveratrol SLNs to rats with T2DM showed better hypoglycemic effects and more significantly reduced the expression of SNARE proteins associated with insulin resistance in

muscle and adipose tissue.[91] Xue et al[92] prepared berberine SLNs using their patented method, the solvent diffusion method (No 201210495674.4, People's Republic of China patent). Oral pharmacokinetic studies in vivo showed $AUC_{0\sim t}$, C_{max}, $t_{1/2}$, and $VRT_{0\sim t}$ of berberine SLNs were 113.57 ± 72.93 μg·h/L, 44.65 ± 4.77 μg/L, 11.50 ± 10.78 h, and 42.58 ± 21.82 h, respectively, in contrast to 56.48 ± 29.61 μg·h/L, 11.06 ± 6.24 μg/L, 9.228 ± 5.13 h, and 23.40 ± 13.92 h of pure berberine. The above results indicated that nanoformulations could promote absorption, possess a slow-release character, and reduce fluctuations in drug concentrations. Consequently, berberine SLNs exerted more powerful effectiveness than an equivalent dose of berberine in db/db mice, especially for the effect on improving insulin sensitivity and glucose tolerance. After further research, Xue et al[93] found that the drug concentration of berberine SLNs group in the liver was approximately 2-fold higher than that of berberine group. The maximum drug concentration in the liver was 20-fold higher than that in the blood after oral administration of berberine SLNs, suggesting a predominant accumulation of berberine SLNs in the liver. However, the capability of SLNs to transform crystalline phases-low-energetic form results in an increased degree of order which decreases the imperfections in the crystal lattice followed by drug expulsion phenomena and low encapsulation efficiency (Figure 2).[71,190] For example, the encapsulation efficiency of the discussed SLNs of myricitrin,[90] resveratrol,[91] berberine[92,93] is 56.2%, 79.9%, 58%, respectively.

NLCs

NLCs are designed to triumph over SLNs shortcomings. NLCs are also maintained in solid state at room and body temperature.[165] However, instead of only a solid lipid, a liquid lipid or a mixture of liquid lipids are used to replace the part of a solid lipid, leading to a less ordered lipid matrix-imperfect crystal lattice (Figure 2) which contributes to increased loading efficiencies, enhanced stability along with the prevention of drug expulsion during storage,[190,191] as illustrated by the following studies.

Two lipid-based nanocarriers for oral delivery of silymarin were prepared through the method of emulsion/evaporation/solidifying.[94,95] The first one was produced with lauroglycol 90 as liquid lipid, cetyl palmitate as solid lipid, and Brij S20 as surfactant,[94] the second one with capryol 90 as liquid lipid, stearic acid as solid lipid, and Brij S20 as surfactant.[95] Both encapsulation efficiency was more than 92% with excellent chemical and physical stability. In vitro release studies showed that NLCs may improve the passive permeation of silymarin via the Caco-2 cell layer. In vivo, both silymarin-loaded NLCs exhibited a more significant down-regulation of triglyceride and blood glucose levels compared with native silymarin. Besides, both nanoformulations performed a remarkable antihyperalgesic activity on STZ-induced neuropathy. However, the second nanoformulation showed more pronounced and longer lasting therapeutic effects.[94,95] Similarly, in another study, baicalin NLCs were formed by the hot melting high-pressure homogenization method using miglyol as liquid lipid and precirol as solid lipid. The results suggested that baicalin NLCs had a better capability to retain drugs and possessed relatively good physical stability. To be specific, during 1 month of storage at 4°C, aggregation and gelation were not found by visual observation and no significant change of zeta potential, particle size, and polydispersity index was discovered by data analysis, indicating relative good physical stability of baicalin NLCs; the average encapsulation efficiency of freshly prepared baicalin NLCs was 85.29 ± 3.42%, indicating their better ability to retain drugs. Compared with pure baicalin, baicalin NLCs had better hypoglycemic and hypolipidemic effects in vivo.[96] In the past few years, at the academic level, the potential of NLCs as drug delivery systems has been broadly researched. However, to the best of our knowledge, no NLCs for therapeutical use have obtained the regulatory approval or even have reached the clinical study stage until now.[191]

Vesicular Systems

Vesicles are colloidal systems with a size of less than a micrometer.[192] Vesicular delivery systems are composed of an aqueous core generally surrounded by one or more lipidic bilayers.[193] The hydrophilic agents are enclosed in the inner aqueous core, while lipophilic drugs in the lipid bilayer.[194] The agents encapsulated in lipid vesicles can easily cross the cell membrane, which alters the rate and extent of the absorption of agents and their disposition.[195] Vesicular delivery systems of antidiabetic phytocompounds that have been studied so far are discussed below.

Liposomes

Phospholipids are the major component of all biological membranes.[196] Liposomes are phospholipid bilayer vesicles. It has been over 50 years that liposomes explored in pharmaceutical research as drug delivery systems.[197] Due to

the use of phospholipids, liposomes possess a biofilm similar structure and exhibit excellent biocompatibility.[198,199] More than 40 liposomes loaded with drugs are under different clinical research stages or have been successfully marketed.[199]

Amjadi et al used the ultrasonic-mechanical method for the fabrication of betanin liposomes. In vitro release studies, betanin-loaded liposomes exhibited a relatively favorable sustained release profile in simulated intestinal and gastric fluids. Liposomal encapsulation improved the physicochemical stability of betanin during in vitro digestion and more effectively regulated hyperlipidemia, hyperglycemia, and oxidative stress than free betanin in STZ-induced rats.[97] Yucel et al prepared nanoliposomal formulations containing resveratrol using the dry film hydration method. It was concluded that nanoformulation significantly decreased high glucose levels along with increasing insulin levels in glucose and STZ-induced diabetic β-TC3 cells, and exerted prolonged antioxidant activity for 24 h as compared with resveratrol solution.[200] However, the therapeutical use of liposomes exists some restrictions, predominantly their high formulation cost and poor stability under harsh conditions, typically exposed to the GIT. Some studies have been reported on the use of cochleates as an alternative platform to liposomes in order to surpass these limitations.[201]

Nanocochleates

Nanocochleates are stable phospholipid precipitates derived from the physical interaction of divalent cation with anionic lipid vesicles,[202] generally phosphatidylserine and calcium.[203] Nanocochleates have cylindrical (cigar-like) microstructures made up of solid, lipid bilayer sheet which was rolled up in a spiral or in stacked sheets to minimize their interaction with water, consequently, nanocochleates with no or little internal aqueous space.[203,204] This unique structure provides protection for the encapsulated drugs from biodegradation, even if they are exposed to hazardous environmental conditions in the GIT.[205] Yucel et al[206] developed resveratrol-loaded nanocochleates by the trapping method and assessed their therapeutic efficiency in diabetic pancreatic β TC cell line in vitro. Compared with native resveratrol, the lower dose of nanocochleates loaded with resveratrol better improved the decreased insulin levels rendered with glucose and STZ, markedly reduced the increased glucose levels, and also exhibited prolonged antioxidant activity for 24 h. However, self-aggregation, which usually happens during production and storage, is currently the major obstacle hindering the development of efficient cochleate-based drug delivery systems.[207]

Niosomes

Niosomes are such hydrated vesicular systems mainly consisting of cholesterol along with nonionic surfactants. Niosomes can keep stable over a longer period of time in different conditions and require less cost of production, so break through major restrictions of liposomes.[208] Sharma et al[209] prepared lycopene-loaded niosomes by developing a novel method called adsorption-hydration technique. The release mechanism of lycopene was Fickian type and followed zero-order release kinetics in the first 10 h, after that the regression equation best matched Korsmeyer-Peppas model. Thus, the lycopene release from niosomes in vitro was sustained and prolonged profile, which was beneficial to reduce dosing frequency. Antidiabetic studies in vivo showed lycopene-loaded niosomes had an activity similar to a standard antidiabetic drug, glibenclamide.[98] Similarly, embelin-loaded niosomes, produced by the thin-film hydration process, displayed a hypoglycemic effect in vivo which was comparable to another standard antidiabetic agent, repaglinide. Moreover, lipid peroxidation decreased and glutathione (GSH), catalase (CAT), and superoxide dismutase (SOD) increased significantly, which verified the antioxidant efficacy of the nanoformulation.[99] In another study of Singhal et al,[100] researchers used the thin-film hydration technique to prepare gymnemic acid-loaded niosomes which revealed antioxidant, antihyperglycemic, antihyperlipidemic, and antiglycation (AGEs) effects and eventually, exerted a protective action in STZ-nicotinamide-induced diabetic nephropathy in Wistar rats.

Phytosomes

Phytosomes, also known as phytophospholipid complexes, are prepared by interactions between active phytocompounds and the polar part of phospholipids.[210,211] The biggest difference between liposomes and phytosomes is that, in liposomes, the active phytocompound is distributed in lipid layers of the membrane or in the medium containing a cavity,[211] whereas, in phytosomes, it is an integral part of the membrane, which gives the greater stability and better bioavailability because of the chemical links between active phytocompounds and phospholipid molecules (Figure 2).[213,214] Yu et al[101] prepared phytosomes loaded with berberine phospholipid complex using the

rapid solvent evaporation method followed by self-assembly technique. In vivo studies, this nanoformulation could produce a 3-fold enhanced oral bioavailability of berberine. More importantly, the antidiabetic efficacy was improved remarkably in db/db mice by ameliorating hyperlipidemia and lowering fasting glucose levels. Besides, the types of phospholipid matrix applied in the preparation of phytosomes influenced their performance. For instance, compared with pure chrysin and chrysin prepared with soya phosphatidylcholine, chrysin prepared with egg phospholipid exhibited a greater glucose uptake promoting effect in C2C12 muscle cells through upregulating gene expression of PPARγ and GLUT4.[214]

Micelles

Micelles have been extensively studied as nanocarriers for hydrophobic drugs with core/shell design. They commonly have a particle size within 5–50 nm range.[215] Micelles are made by the self-assembly of amphiphilic molecules in aqueous media above the critical micelle concentration (CMC).[216] The hydrophobic portion of amphiphilic molecules constitutes the core of the micelle, which serves as a reservoir and protects the agent, while the hydrophilic portion constitutes the micelles' shell, which confers steric stability and aqueous solubility to the micellar structure.[217,218]

The transplantation of islet β-cells is an efficient therapy for type 1 and 2 diabetes. However, the isolated islets are under hypoxic conditions and then undergo the apoptotic process. Therefore, it is necessary to protect islets against hypoxia for enhancing the efficacy of islet transplantation. A peptide micelle-mediated curcumin delivery system was demonstrated to be effective for islet β-cells protection in the process of transplantation in vitro. This delivery system was developed by Han et al through an oil-in-water (O/W) emulsion/solvent evaporation method. In addition, the peptides consisted of a 3-arginine hydrophilic stretch and a 6-valine hydrophobic stretch.[219] Zhang et al used the dialysis method to fabricate an amentoflavone-loaded micelle system composed of amphiphilic copolymer (N-vinyl pyrrolidone and maleic acid guerbet alcohol monoester). Owing to the micelle formation, the oral bioavailability of amentoflavone was increased by nearly 3.2 times in vivo. The antidiabetic effect of amentoflavone nanoformulation is comparable to that of metformin in insulin-resistant diabetic KKAy mice.[102] Soluplus® is one such commercially triblock copolymer composed of PCL-Polyvinyl acetate (PVAc)-PEG units with the capability to enhance the solubility and bioavailability of poorly water-soluble drugs.[220] Singh et al[103] prepared quercetin-loaded soluplus®/poloxamer 407 micelles by the cosolvent evaporation method. In this system, poloxamer 407 was used as a surfactant in order to enhance the solubilization of quercetin and increase the stability of nanomicelles. In vivo pharmacokinetic studies, the relative oral bioavailability of quercetin nanoformulation was 1676% as compared to pure drug suspension. Moreover, quercetin nanoformulation showed significantly lower glucose levels, higher catalase and SOD levels in STZ-induced diabetic rats. Pluronics is another type of triblock copolymers with a central hydrophobic poly (propylene oxide) (PPO) chain and two hydrophilic poly (ethylene oxide) (PEO) on each side, arranged in PEO-PPO-PEO structure.[221] Pluronic micelles are capable to increase the stability and solubility of incorporated drugs and improve their pharmacokinetics and biodistribution.[222] El-Far et al developed silymarin-loaded pluronic nanomicelles[104] and curcumin-loaded pluronic nanomicelles[105] using the nanoprecipitation technique. Nanoformulations were found to significantly improve the antihyperlipidemic, antioxidant, and antihyperglycemic properties in STZ-induced diabetic rats when compared with their native candidates. As we discussed, both synthetic and inartificial polymers have their own merits and defects. Combinations of these polymers could make the best use of the advantages and bypass the disadvantages. Using alginate, chitosan, maltodextrin, pluronic P123, pluronic F127, and tween 80, Akbar et al[106] developed curcumin-loaded mixed polymeric micelles by the thin-film hydration method. The achieved results showed that the antidiabetic activity of curcumin-loaded mixed polymeric micelles was comparable to that of metformin in bisphenol A-induced diabetics rats. Besides, curcumin-loaded mixed polymeric micelles administered topically on the surface of wound performed superior wound healing potential (fast wound closure) with the reduction of scar formation in vivo. However, the primary challenge faced by micelles is that micelles tend to disintegrate and cannot keep entrapped drugs stabilized when they are diluted below the CMC. This phenomenon typically occurs when the drug/micelle formulation is infused into body and will lead to severely decrease drugs' bioavailability and deteriorate therapeutic performance.[223]

Inorganic Nanocarriers

Inorganic materials have been employed to explore nanocarriers with controlled morphology and size.[224] Recent breakthroughs on the surface functionalization and

structural control of inorganic nanocarriers have brought more possibilities for drug delivery.[225]

Metallic NPs

Metallic NPs such as selenium,[226,227] gold,[228] silver,[229,230] and zinc oxide NPs[107,231] appear very promising for the treatment of T2DM.[232] However, metallic NPs are synthesized by physical and chemical methods with many shortcomings, including high energy consumption, the use of toxic solvents, and the generation of hazardous by-products.[233] The biosynthesis of metallic NPs through medicinal plants has obtained widespread attention as a proper alternative to hazardous chemical synthetic technique.[234] Antidiabetic phytocompounds act as reducing and stabilizing agents during the synthesis of metallic NPs. Currently, there have been many papers reporting the use of antidiabetic phytocompounds as stabilizing and reducing agents to synthesize metallic NPs, such as gymnemic acid gold NPs,[235] vicenin gold NPs,[236] escin gold NPs,[237] docosahexaenoic acid zinc oxide NPs,[107] and guavanoic acid gold NPs.[238] In these studies, all of them showed good antidiabetic effects in vitro or/and in vivo. Besides, phytocompounds with antidiabetic effects can enhance the diabetic efficacy of metal NPs. For instance, *Catathelasma ventricosum* polysaccharides SeNPs exhibited significantly higher antidiabetic effects than other selenium preparations like SeNPs, selenocysteine, sodium selenite.[108] On the base of berberine-loaded NLCs, Yin et al[109] used an in-situ reduction technique to fabricate berberine-loaded SeNLCs, as Se^{4+} was reduced to Se which precipitated on the surface of NPs. In vivo studies reported berberine SeNLCs yielded the highest C_{max} and AUC_{0-t}, up to 172.88 ng/mL and 1,107.80 ng·h/mL, when compared with berberine solution (C_{max}=45.06 ng/mL, AUC_{0-t}=173.74 ng·h/mL) and berberine NLCs (C_{max} =148.21 ng/mL, AUC_{0-t}=689.54 ng·h/mL). Accordingly, the hypoglycemic activity of berberine SeNLCs was also significantly superior to that of berberine solution and berberine NLCs. It turned out that Se coating, plus the synergy of selenium, was basically responsible for increased oral bioavailability and enhanced hypoglycemic activity in vivo.

Carbon Nanotubes

Carbon nanotubes are tiny tubes approximately 10,000 times thinner than a human hair. They consist of rolled-up sheets of carbon hexagons.[239] Either by noncovalent interactions or covalent attachment, drugs can be loaded within the interior core or onto the surface of carbon nanotubes.[240] In comparison with spherical NPs, carbon nanotubes' needlelike shape gives them superior flow dynamics and enhanced capacity to penetrate cellular membranes.[241] Ilie et al[242] firstly prepared nanotubes with oxidation properties using 1:3 (v/v) concentrated nitric acid and sulfuric acid, which gave them stability and hydrophilicity in aqueous systems because of the formation of -OH and -COOH groups on the lateral sides of or at the end of the tubes. And then, Ilie et al[242] covalently conjugated nicotinamide onto the surfaces of oxidized multiwalled carbon nanotubes. In vitro study, 1.4E7 cells administrated with nicotinamide-functionalized multiwalled carbon nanotubes better regulated insulin secretion and increased insulin production as compared with nicotinamide or multiwalled carbon nanotubes.

Mesoporous Silica NPs (MSNs)

Based on unique intrinsic properties of MSNs such as large pore volume, high surface area, facile functionalization of surface, uniform and tunable pore size, and stable framework, they have been utilized extensively as drug carriers.[225,243] It is widely agreed in published literature that endocytosis is a common mechanism for the translocation of MSNs.[243] Huang et al[110] designed the surface functionalization of MSNs with amine groups to act as reservoirs for efficient immobilization of phytocompounds into pores for antidiabetic therapies. The results revealed that 16-Hydroxycleroda-3,13-Dine-16,15-Olid incorporated into MSNs caused a reduction of DPP4 activity in a dose- and time-dependent fashion in vitro and simultaneously possessed less adverse effects and reliable efficacy in down-regulation of hyperglycemia in diet-induced diabetic mice.

Although inorganic NPs can be metabolized by the kidney after their degradation into small-sized fragments,[244] most inorganic nanomaterials still have high bioaccumulation risks.[245] Moreover, the generated ions, especially heavy metals, may lead to toxicity or damage to the related organs during the excretion.[244] Therefore, it is essential to systematically study the toxicity of these nanomaterials to different organs in the process of metabolism.[246]

Nanosuspensions

Drug nanocrystals are nanosized drug particles often formed as nanosuspensions, namely submicron dispersions in liquid media where surfactants and/or polymers act as

stabilizers. Although, without any carriers, nanosuspensions are an excellent delivery platform for poorly water-soluble drugs.[247] Reducing the drug size to nanoscale usually causes a significant increase in solubility and dissolution rate along with a distinct improvement in oral bioavailability.[248] Up to now, several studies have been reported that nanosuspensions enhanced the therapeutic effects of antidiabetic phytocompounds on diabetes, such as ursolic acid,[113] berberine,[114] curcumin,[111] gymnemic acids.[115] Chen et al[249] prepared *Fructus Mori* polysaccharides with spherical particles by the antisolvent precipitation method. According to the research results, the smaller the particle, the higher the bioavailability. We can deduce that the smaller size after spheroidization is able to be beneficial for the improved bioavailability. In comparison with the corresponding native polysaccharide, the spheroidization improved the hypoglycemic activity and antioxidant ability in vitro. Zhao et al[116] developed betulin nanocrystallization by the antisolvent precipitation technique. The results exhibited that nano betulin possessed the same chemical structure as raw betulin, but have smaller crystal size and lower crystallinity. The solubility and dissolution rate of nano betulin were, respectively, 1.54 and 3.12 times of raw drug. Compared with raw betulin, betulin nanosuspensions showed a 1.21-fold increased bioavailability in vivo and an excellent hypoglycemic effect in STZ-induced diabetic rats. However, instability is the most disadvantage of nanosuspensions and restricts their application to pharmaceutical industry.[250] Stabilizers are crucial to prevent the aggregation of high energy nanosuspensions. Nonetheless, a suitable stabilizer is often selected by a trial and error method.[251] Meanwhile, the potential raised toxicity concerns if the stabilizers are used in large quantities for a long term.[252]

Conclusion

As antidiabetic agents, phytocompounds are potential candidates with abundant sources, significant curative effects, and low side-effects. Generally, there are four hypoglycemic mechanisms of phytocompounds, including reduction of carbohydrate decomposition and glucose absorption, promotion of glucose uptake and metabolism, improvement of insulin action and sensitivity, and antioxidant and antiinflammatory actions. However, conventional oral administration of antidiabetic phytocompounds has some inherent defects. Oral nano drug delivery systems for phytocompounds to treat T2DM not only maintain the advantages of oral administration but also overcome the shortcomings of conventional oral drug delivery.

In this review, we discussed phytocompounds-based oral nano delivery systems for T2DM treatment, including polymeric NPs, lipid-based nanosystems, vesicular systems, micelles, inorganic nanocarriers, and nanosuspensions. As observed in studies, oral nano drug delivery systems for T2DM treatment have the following advantages: 1) phytocompounds encapsulated into nano delivery systems can improve the stability of the former and protect them from enzymatic and/or chemical degradation in GIT. 2) nano delivery systems act at the molecular level to increase the cellular drug uptake or block drug efflux mechanisms like P-glycoprotein (P-gp) pump, which further improves the pharmacokinetic and pharmacodynamic profile of antidiabetic molecules.[2] 3) oral drug bioavailability can be significantly limited by first-pass hepatic metabolism. Intestinal lymphatic drug transport is regarded as the best for improving oral drug delivery through bypassing first-pass metabolism. Nano delivery systems can be transferred into the lymph, arrive at lymphatic system through M cells, and increase the subsequent release of drugs in systemic circulation.[253] 4) tailored engineering of nanocarriers fulfills controlling drug release, preventing opsonization, and targeting drug delivery.[2] Due to the above advantages, phytocompounds have clearly shown better antidiabetic efficacy in oral nano drug delivery systems with increased bioavailability, decreased toxicity, targeted specific site, and reduced dose and dosing frequency.

However, there are still some deficiencies in the existing research. On the one hand, it is worth noting that a control group administered with non-loaded carrier is not conducted in the vast majority of works so that the drug-independent effect of the carrier cannot be ignored. Rho et al[254] reported that empty self-assembled hyaluronic acid NPs without any drug could be used as a therapeutic agent for T2DM treatment. On the other hand, most of those materials used for the preparation of nano delivery systems are usually obtained from inorganic matter or synthetic polymers through a rather complex and tedious synthesis process, which may inevitably result in potential toxicity. Even if materials from natural sources are employed as nanocarriers, organic chemicals may be introduced into the process due to the requirement for the preparation. Security is a prime concern. However, the majority of published data come from cellular and animal models but not a clinical study.

Since toxicological research in animals has limitations, clinical trials are ultimately required. There are few clinical trials on potential antidiabetic nano phytocompounds, only curcumin nanomicelle,[255] curcumin nanocapsules.[256] Despite few severe adverse effects were reported during the treatment, long-term human toxicology research is still lacking. The FDA recently issued guidance to help promote the safe development of nanotechnology-based products for clinical use.[257] More clinical research is worth conducting.

Above all, oral nano drug delivery systems for T2DM treatment are an available administration strategy for antidiabetic phytocompounds. This review could provide researchers with promising antidiabetic phytocompounds and excellent oral delivery systems to explore more therapeutic possibilities. With the extensive development of the pharmacological activity research of antidiabetic phytocompounds and the continuous progress of material science and technology, more and more excellent oral nano phytocompounds will be employed in clinical pharmaceutical intervention for T2DM treatment.

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