REVIEW

Phytobioactive compound-based nanodelivery systems for the treatment of type 2 diabetes mellitus – current status

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Abstract: Type 2 diabetes mellitus (T2DM) is a major chronic disease that is prevalent worldwide, and it is characterized by an increase in blood glucose, disturbances in the metabolism, and alteration in insulin secretion. Nowadays, food-based therapy has become an important treatment mode for type 2 diabetes, and phytobioactive compounds have gained an increasing amount of attention to this end because they have an effect on multiple biological functions, including the sustained secretion of insulin and regeneration of pancreatic islets cells. However, the poor solubility and lower permeability of these phyto products results in a loss of bioactivity during processing and oral delivery, leading to a significant reduction in the bioavailability of phytobioactive compounds to treat T2DM. Recently, nanotechnological systems have been developed for use as various types of carrier systems to improve the delivery of bioactive compounds and thus obtain a greater bioavailability. Furthermore, carrier systems in most nanodelivery systems are highly biocompatible, with nonimmunologic behavior, a high degree of biodegradability, and greater mucoadhesive strength. Therefore, this review focuses on the various types of nanodelivery systems that can be used for phytobioactive compounds in treating T2DM with greater antidiabetic effects. There is also additional focus on improving the effects of various phytobioactive compounds through nanotechnological delivery to ensure a highly efficient treatment of type 2 diabetes.

Keywords: type 2 diabetes, nanodelivery system, phytobioactive compounds, oral delivery

Introduction

Type 2 diabetes mellitus (T2DM) is a major chronic disease with an increasing prevalence worldwide, and it is a major burden in many developing and developed countries due to the numerous complications associated with the diseases.[1,2] The disease associated with numerous factors, including genetics, age, lack of physical activity, food habits, high stress, inflammation, and obesity. Many factors related to this disease can be controlled through a change in lifestyle and activities.[3,4] Inflammation for this disease, and the associated complications, can be effectively reduced by taking certain drugs, and recently, the consumption of phytobioactive compounds – such as polyphenols, flavanones, curcumin, terpenoids, and quercetin rich foods – has shown potential antidiabetic effects without any other complications.[5,6] Many researchers have orally administered phytobioactive compounds to show its beneficial effect on T2DM and its complications.[7–15] However, many food grade bioactive compounds taken through oral means undergo a substantial loss in bioactivity, and thereby, the antidiabetic activity of the phytobioactive compounds is diminished.

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Various nanodelivery systems have been developed to improve the oral bioavailability of phyto-based antidiabetic compounds and to ensure sustained antidiabetic activities.[16] Baicalin successfully formulated nanostructured lipid carrier (NLC) delivery systems with particle sizes of 92 nm, and these showed a higher antidiabetic activity with a sustained release of these compounds through oral delivery.[17] Stevioside is another phyto compound that has shown improved antidiabetic activity via controlled release of the compounds through polyethylene glycol-polylactic acid nanoparticle delivery systems with a particle size of 150 nm.[18] In addition to the potential delivery of phytobioactive compounds for systematic circulation, many researchers are searching for effective delivery materials with highly nontoxic and nonmutagenic behavior as well as good water solubility. Although different nanodelivery systems plays a critical role in the delivery of active compounds to many diseases.[19,20] Only a few novel nanodelivery systems, such as solid lipid nanoparticles, nano-phytosome, and nanoemulsion, have shown good efficacy in the delivery of phytobioactive compounds. Very recently controlled delivery of drugs was studied using nanowire systems,[21–23] and their efficacy in delivery of drugs to the diabetic model is still limited. The current review presents the potential use of various nanoscale drug delivery systems for phyto-based bioactive compounds to treat T2DM and its associated complications.

The role of phytobioactive compounds in T2DM through oral delivery

Traditional medicines have extensively used phytobioactive compounds to treat T2DM.[24–31] These bioactive compounds, including but not limited to flavonoids, curcumin, polyphenol, and glucosides, have shown showed higher antidiabetic activity in various animal models. Due to the higher availability and multiple efficacies of these food-based medicines, they are currently in great demand in the market. The possible molecular mechanisms through which phyto compounds treat T2DM are shown in Figure 1. T2DM is associated with many complications, and few phytoactive compounds that are regularly consumed in food have shown multiple antidiabetic effects, thereby reducing drug loads during treatment. Curcumin from turmeric and bitter melon has shown multiple antidiabetic activities in various animal models.[32–37] Although various food grade phytobioactive compounds are currently used in the treatment of T2DM, they lose efficacy during oral delivery, and therefore the development of novel delivery systems is crucial in improving their effects.
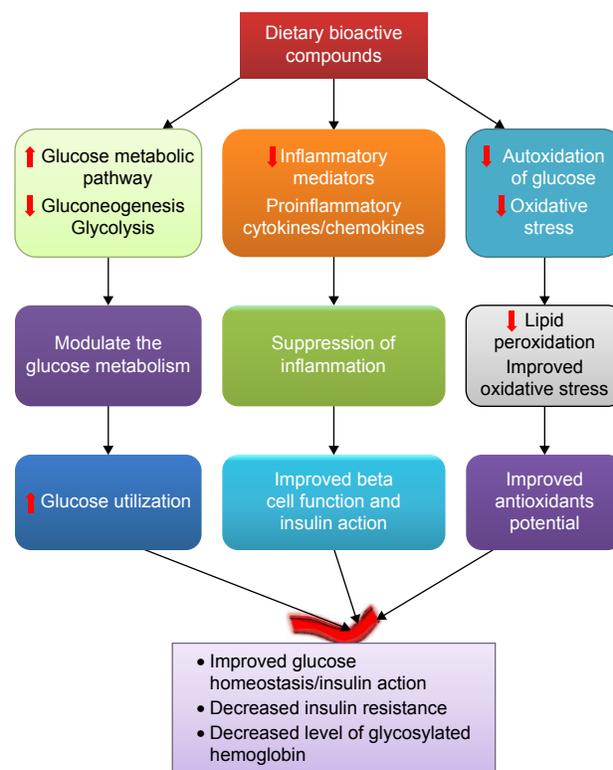

Figure 1 Possible molecular mechanism for phytobioactive compounds in treating type 2 diabetes.

Phytobioactive compounds are rich in antidiabetic foods or extracts, and their efficacy through oral delivery is relatively low due to the multiple challenges faced by the compounds, such as gastrointestinal fluid solubilization, cell uptake, and changes in the structure of the bioactive compounds.[38–40] The bioavailability of antidiabetic phyto-based bioactive compounds curcumin has been improved by coingesting them with certain lipids.[41] In addition, curcumin delivery was greatly enhanced through the mixed lipid and protein-based digestible colloidal nanoparticles.[40,42] Recently, alternative approaches have been proposed to improve the efficacy and sustained bioavailability through oral development of excipient foods rich in antidiabetic activities using various delivery technologies from macro to nanoscale, thereby limiting the digestion of these compounds through oral delivery.[39,40,43–45]

Nanodelivery systems used to treat T2DM

Currently, nanodelivery systems are an area of intense focus for the delivery of bioactive compounds through oral means to ensure effective treatment of various chronic diseases, including T2DM, hypertension, and cancer. Antidiabetic compounds, including curcumin and berberine, among other phyto compounds, have been effectively formulated
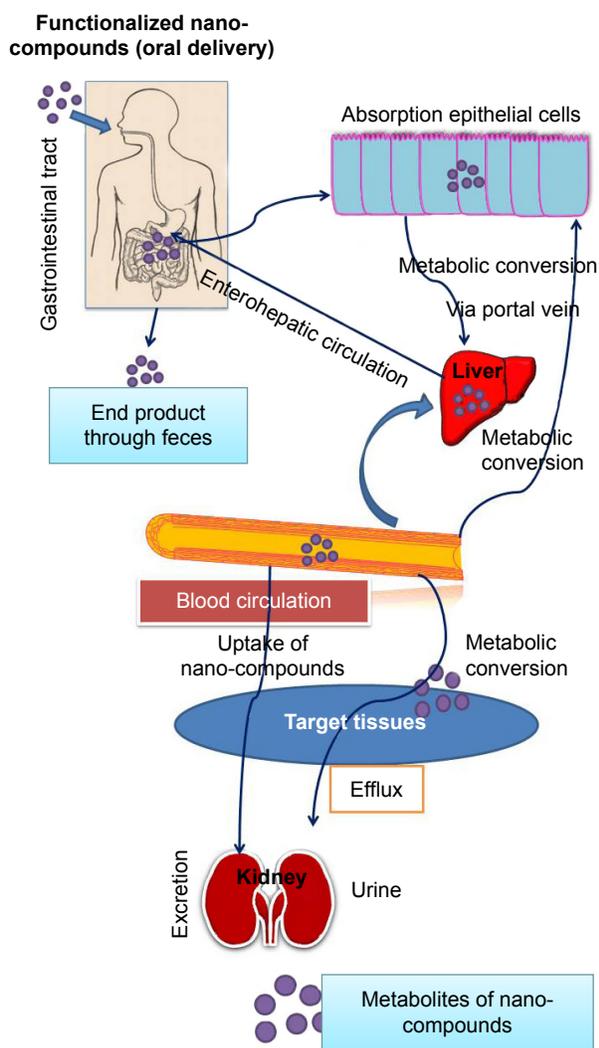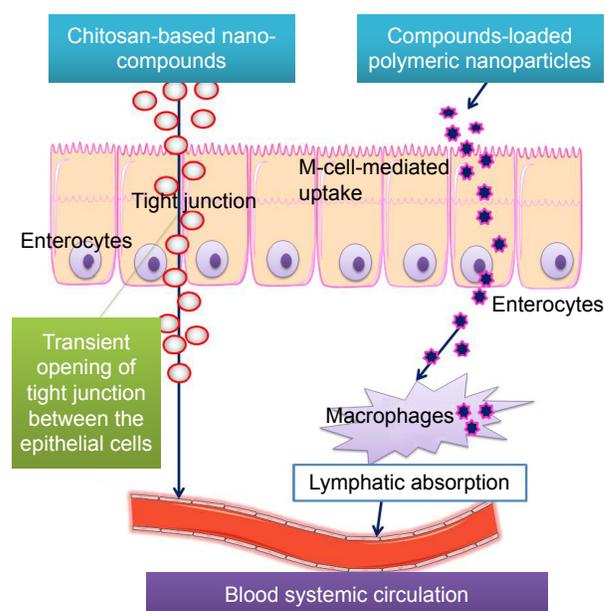
Figure 2 Possible nano phytobioactive compound bioavailability through oral delivery systems in humans.

Figure 3 Possible delivery mechanism for phytobioactive compound-based nanodelivery systems.

using various nanodelivery technologies, resulting in higher antidiabetic potential in T2DM animal models. The effective oral delivery of nano phytobioactive compounds is shown in Figure 2. To ensure effective delivery of the bioactive compounds in the nanosystems, it is important to carefully design these delivery systems. Effective delivery and functional food development can be achieved through several approaches using nanoemulsions with improved delivery of lipid-soluble bioactive compounds. The delivery pathways for phytobioactive compound-based nanodelivery systems are shown in Figure 3. Several nanodelivery systems and their efficacy in treating T2DM are discussed further.

Solid lipid nanoparticles

Solid lipid nanoparticle delivery systems are used for the oral delivery of various antidiabetic compounds due to certain

advantages over conventional oral delivery systems, such as a higher bioavailability, lower toxicity, sustained delivery, higher cellular uptake, and macrophage distribution.[46–50] Various animal models have shown a higher efficacy of these nanodelivery systems for oral delivery of various phyto-based bioactive compounds. Recently, berberine-loaded solid lipid nanoparticle delivery systems were developed with an average particle size of ~76 nm and a uniform size, and treated rats showed a higher antidiabetic activity by suppressing gains in body weight, lowering fasting blood glucose levels, and promoting islet cell functions. The same research group also studied the effect of berberine-loaded solid lipid nanoparticles on the diabetic fatty liver and found that the drug's presence was 20× higher in the liver, thereby effectively preventing lipogenesis and enhancing lipolysis in the liver of diabetic mice models.[51,52] In another study, berberine-loaded solid lipid nanoparticles were developed with a particle size of ~154 nm, showing an improved hypoglycemic effect in the C57BL/6 mice model of T2DM.[53] Similarly, bioactive compounds from mistletoe have shown an enhanced antidiabetic effect in the T2DM animal model with a lowered hyperglycemic effect.[46] However, other potentially active antidiabetic compounds, such as quercetin, curcumin, and catechin, have also been studied for formulation using solid lipid nanoparticles, but their potentiality in the diabetic animal model is still limited. Various studies have confirmed that solid lipid nanoparticles can be effectively used to deliver phyto-based bioactive compounds through oral administration in order to treat T2DM.

Nanostructured lipid carriers

NLC are another type of lipid-based nanodelivery systems with certain advantages over solid lipid delivery systems, such as a lower particle size and improved loading capacity in order to obtain effective delivery of the phyto ingredients in the treatment of T2DM.[54] Recently, baicallin was studied to develop NLC delivery systems, and the results indicated that a particle size of ~92 nm showed an enhanced antidiabetic effect in the rat model with sustained release.[17] As most antidiabetic phytobioactive compounds, such as quercetin, thymoquinone, and resveratrol, face significant challenges in delivery. NLC delivery systems enhanced those bioactive compounds delivery with sustained release.[55–58] Baicalin-loaded NLC have shown a sustained release through oral delivery with a particle size of ~244 nm.[59] A higher bioavailability with sustained release of quercetin was observed in quercetin-loaded NLC developed using a phase inversion method with a particle size of ~32 nm.[60] In another study, quercetin-loaded NLC systems were developed with a particle size of 47 nm, resulting in a higher bioaccessibility of ~60%.[61] Recently, cationic-modified NLC delivery systems were developed with quercetin with a particle size of ~126 nm, showing a higher bioavailability in lung, kidney, and liver tissues.[62] Although various phyto-derived antidiabetic compounds have shown a sustained release in oral studies, their bioavailability in the diabetic animal model is still limited. Thus, NLC systems can be considered as novel oral delivery systems with sustained release of the antidiabetic phyto compounds.

Nanoemulsions

Nanoemulsions greatly improve the delivery of various lipophilic bioactive compounds with high antidiabetic properties by providing a high stability of the compounds along with an increased bioavailability.[63–66] Recently, bitter gourd seed oil nanoemulsions containing 50% α-eleostearic acid were studied in the diabetic rat model. The results indicated that bitter gourd seed oil nanoemulsions with a particle size of <100 nm were highly stable and could deliver enhanced antidiabetic properties through oral administration.[67] The same research group also studied the effect of gourd seed oil nanoemulsion with a higher cellular uptake and prolonged antioxidant activities.[68] In another study, alpha-tocopherol-loaded nanoemulsions with various particle sizes showed improved protective behavior in various organs, especially in streptozotocin-induced diabetic rat model.[16] Similarly, many other phyto-derived

bioactive compounds, including curcumin or quercetin, have shown an enhanced bioavailability through nanoemulsion delivery systems. A curcumin-encapsulated nanoemulsion was prepared with a particle size of ~130 nm, and it showed improved oral bioavailability in addition to liver protection.[69] The quercetin-loaded nanoemulsion was also studied to provide efficient oral delivery of these compounds, quercetin was found to be highly protected through these delivery systems, with improved antioxidant activity along with no toxicity of the carrier system.[70,71] Many recent studies have confirmed that naturally derived bioactive compounds can be efficiently delivered through oral means using nanoemulsion. However, many studies are still needed, in particular to determine the role of the individual compounds in the diabetic model when this delivery system is used.

Nanoliposomes

Nanoliposomes are effective in delivering bioactive compounds that are both hydrophilic and hydrophobic with enhanced stability, efficacy, and bioavailability along with a lower particle size.[72–76] The delivery of phytobioactive compounds with antidiabetic properties was greatly enhanced through the nanoliposome systems.[72,75–77] Recently, *Orthosiphon stamineus*, an antidiabetic medicinal herbal extract, was studied with a nanoliposome system in terms of its efficacy. The study showed that this extract can be effectively loaded into nanoliposome systems with a particle size of 152 nm to improve the antioxidant properties.[78] Similarly, resveratrol, another antidiabetic compound, was studied for its oral bioavailability in an animal model when administered using nanoliposome systems. The results indicated that the animal group treated with resveratrol-loaded nanoliposome showed a 2 times increase in the bioavailability of resveratrol than the control group.[79] Recently, catechin was successfully encapsulated using a nanoliposome system and was studied to develop functional food. Researchers found that catechin-loaded nanoliposomes can efficiently protect catechins from various factors, and these could be used as a possible functional food to deliver catechins.[80] Folic acid-functionalized insulin-loaded liposomes were studied, and these showed enhanced bioavailability of insulin in the animal model through oral administration.[81] Although many antidiabetic phytobioactive compounds have been successfully studied for their oral bioavailability and their efficacy in reaching circulation systems, nanoliposomes loaded with phytobioactive compounds in antidiabetic animal models still have limited use.

Nanosuspensions

Nanosuspensions are delivery techniques for oral administration of active ingredients in the liquid phase with a particle size of <1 μm, and these are prepared using various techniques, including wet or dry milling.[82–85] Many phyto ingredients have been effectively prepared using nanosuspension techniques and have shown more effective antidiabetic effects than regular systems.[86,87] Recently antidiabetic compounds, namely gymnemic acids, were prepared using a nanosuspension method with enhanced bioavailability.[86] The same research group also studied the effect of those gymnemic acid nanosuspensions in humans and found that an enhanced antidiabetic effect with a greater glucose-lowering effect in humans.[88] Similarly, berberine nanosuspensions, another antidiabetic compound, showed an improved antidiabetic effect in T2DM animal models at a low dosage level. Similarly, other active phyto compounds, such as quercetin, have shown antidiabetic effects, and were studied in terms of their efficacy in oral delivery through nanosuspensions in order to prevent their loss of bioactivity. Quercetin nanosuspension with a uniform size have shown a higher bioavailability through oral delivery, with a 70× increase relative to control quercetin.[89] In another study, curcumin-loaded nanosuspensions were prepared with a particle size of 210 nm, and these showed an enhanced absorption of curcumin through various digestive system parts with a higher change in confirmation and a fluidity change of the intestinal mucosal membrane.[90] These studies open mechanisms to develop nanosuspension-based phytoconstituents for antidiabetic activity in various animal models.

PLGA NPs

Polylactic-co-glycolic acid nanoparticles (PLGA NPs act as an effective carrier in oral delivery systems for various phytobioactive compounds due to the effective bioavailability and stability of those compounds.[91] Antidiabetic phyto compounds, such as quercetin and curcumin, are effectively entrapped or absorbed in PLGA nanoparticles with a size <100 nm using various methods, such as solvent evaporation or nanoprecipitation, and these novel delivery systems have shown improved antidiabetic effects.[92,93] Recently, quercetin-loaded PLGA NPs were studied for their efficacy in the diabetic model. Quercetin-loaded PLGA NPs were prepared with a particle size of ~179 nm, with a uniform particle size and smooth appearance. An animal study showed that the effect of the PLGA NPs every 5 days through oral delivery is equivalent to an everyday dosage of control quercetin. This study confirmed that PLGA NPs are very effective

in delivering quercetin, thereby limiting the need for everyday dosage and reducing the frequency of taking the drug.[94] PLGA NPs loaded with fenugreek seed extract showed a higher antidiabetic efficacy in the alloxan-induced diabetic model[95] with a higher antioxidant and antilipid peroxidation activity. Thymoquinone from black seeds has potent antidiabetic efficacy and was studied to develop thymoquinone-loaded PLGA NPs, which showed an enhanced antioxidative effect along with sustained release in simulated gastrointestinal systems.[96] Costus speciosus extract-loaded PLGA NPs were also studied for their efficacy in the antidiabetic model, and the study confirmed that costus speciosus extract-loaded PLGA NPs can effectively control glucose.[97]

Nano phytobioactive compounds used in the treatment of T2DM

Nanoscale phyto-derived bioactive compounds or phyto extracts showed improved bioavailability in many chronic diseases, including T2DM. Nanoscale processing improves the efficaciy of these compounds through higher exposure of the active sites, thereby improving the bioactivity.[98] Furthermore nanodelivery systems can overcome many barriers in gastrointestinal systems, thereby improving the bioavailability to various target sites and preventing oxidative stress-related disease along with chronic disease, including T2DM. A few nano-phytobioactive compounds with improved bioactivity are discussed in this section.

Nano-silibinin

Silibinin is a major bioactive compounds in milk thistle, and it has shown higher antidiabetic activities in various cell and animal models.[99–103] Many animal models have shown that a higher consumption of those compounds results in improved antidiabetic activities along with the neuropathy and nephropathy. Although these compounds have shown antidiabetic activities with higher potential, their systematic bioavailability and absorption in the stomach and intestine are relatively low.[104–106] Recently, various nanodelivery approaches have been studied to improve their bioavailability in diabetic animal models, and this could be a novel approach to silibinin-based nano treatment of T2DM. PLGA-loaded silibinin NPs were studied for their antidiabetic activities in streptozotocin-induced diabetes rat models. The silibinin-loaded NPs with a size of ~230 nm showed an improved bioavailability of such compounds in the systematic circulation along with a higher restoration of the pancreatic cells. The study also confirmed that higher

antidiabetic activities of silibinin-loaded NPs were most likely due to a higher passive transport and restoration of the antioxidative status.[107] Similarly, silibinin-loaded nano-liposomes showed improved bioavailability in other chronic disease models. In another study, silibinin-coloaded with another glycyrrhizic acid-loaded nanoliposome showed improved stability and bioactivity in cell models.[108] These studies have shown that nanodelivery systems can improve the availability and therapeutic nature of bioactive compounds to manage diabetes.

Nano-quercetin

Quercetin is another phytobioactive compound, and it has shown potential bioactivity against various oxidative stress-related diseases, including T2DM.[109–113] Although quercetin shows beneficial activities in various cell and animal antidiabetes study models, its efficacy through oral delivery systems is very low due to the postabsorptive metabolism and gastrointestinal conditions.[114–117] Several approaches have been carried out to improve the bioavailability of quercetin in order to improve its bioactivity. The nanodelivery approach is quite promising in the delivery of the quercetin through oral intake, thereby enhancing its antidiabetic activities. Recently, PLGA-loaded quercetin NPs were developed with a particle size of ~179 nm, showing improved bioavailability in a streptozotocin-induced diabetic rat model. This study confirmed that in spite of reduced dosage and dosing times, the antidiabetic potential of the quercetin can be improved by using PLGA delivery systems.[94] Few other nanodelivery approaches have also been developed to improve the bioavailability of quercetin for other chronic diseases, including brain bioavailability. Quercetin nanorods were recently developed and characterized, showing improved antidiabetic activity along with certain organ functions restored.[116] This has further confirmed that nanodelivery systems can improve the bioavailability of such compounds in various organs.

A few studies have compared various delivery methods in terms of the efficacy of quercetin delivery, such as solid lipid NPs, NLC, and nanoemulsions, systems for quercetin indicate that NLC has improved the bioaccessibility of quercetin in an in vitro model. Furthermore, this opens up many research avenues to conduct quercetin-based nanocarrier development to improve oral delivery of these compounds with a lower dose and enhanced protectivity. This can limit the drug loading efficiency to patients and will be developed as a future medicine with lower carrier toxicity to diabetic patients.

Nano-baicalin

Baicalin is a novel antidiabetic bioactive compound that is found specifically in certain plants, namely scutellaria, and it has potential bioactivity against T2DM.[118–123] These bioactive compound are highly hydrophobic, which limits their bioavailability through oral delivery systems and in turn limits their functional activity. Many novel delivery approaches have been developed to improve its bioavailability.[124,125] Recently, a nano-based delivery approach was carried out to improve the bioavailability by using a NLC delivery system. A baicalin-loaded nano-lipid carrier delivery system was developed with a uniform particle size of ~92 nm, and it showed higher antidiabetic activity than conventional baicalin, which in turn will limit the drug dosage levels.[17] Similarly, another approach was done to improve the bioavailability of those compounds through NLC systems with a particle size of ~244 nm, which showed a sustained release of the bioactive compound with improved activity.[59] A baicalin nanoemulsion was also studied for its bioavailability through oral delivery. Baicalin-loaded nanoemulsion showed a 7 times increase in bioavailability than the free suspension, which could be useful for various treatments including T2DM. The storage stability of the baicalin-loaded nanoemulsion was also studied for 6 months, and the results showed greater stability with a uniform particle size.[126] In another study, baicalin-loaded nanoliposome with a particle size of ~375 nm showed a higher bioavailability in many target organs, including kidney, liver, and pancreas.[127] Various nanodelivery approaches show that baicalin can be successfully delivered using novel oral delivery systems in the future to treat chronic diseases, including T2DM.

Nano-curcumin

For centuries, curcumin has been used in food and medicine Asia due to its efficacy against T2DM.[128–131] However, it has low potential through oral delivery due to the low water solubility and stability in gastrointestinal environment.[132–136] Nanodelivery systems are an alternative approach that can improve the stability of those compounds with improved bioavailability of curcumin.[137–150] Curcumin-loaded PLGA NPs were constructed with a particle size of 281 nm, and these have shown a higher bioavailability through oral delivery in the diabetic rat model, delaying cataracts.[151] The self-nanoemulsifying curcumin delivery system was developed, has a particle size of ~213 nm, and has shown improved protection of diabetic neuropathy through oral delivery systems in male Sprague Dawley rats.[152] Several other nanodelivery systems have shown a higher bioavailability for curcumin, delaying

the progression of T2DM. Recently, a curcumin-loaded food grade nanoemulsion for oral delivery developed with a particle size of 110 nm showed a higher bioavailability at lower dosage levels.[153] In another study, curcumin-loaded PLGA NP was prepared for oral delivery with a particle size of ~158 nm, and it showed enhanced solubility and bioavailability. The oral bioavailability of nano-formulated curcumin showed a 22 times increase over conventional curcumin.[154] Curcumin nano-micelles were also constructed for oral delivery with a particle size of ~17 nm, and these showed a 2 times increase in bioavailability.[155] Nevertheless, further research is necessary to assess the efficacy of the highly bioavailable nano-curcumin in T2DM.

Nano-emodin

Emodin is a novel natural antidiabetic compound that is found in many herbs, including Japanese knotweed, buckthorn, and rhubarb, and it has an effective therapeutic effect in diabetes-associated diseases.[156–162] Emodin also plays an active role in treating diabetic nephropathy and neuropathy at earlier stages. However, due to the high first pass metabolism and greater hydrophobicity of emodin, it cannot be efficiently delivered through oral means, limiting the bioavailability and bioaccessibility of the compound.[163–169] A novel delivery approach was carried out using various delivery technologies, including nanoemulsions and nanotransfers, and some showed efficient delivery of emodin through oral means, which in turn enhances its efficacy. Recently, emodin-loaded magnesium hollow silicate nanocarriers were studied for their efficacy in treating angiogenesis associated with diabetic retinopathy. The NPs, with an average mean size of ~400 nm, showed higher efficacy in delivery and greater protective characteristics against angiogenesis.[170] Emodin-loaded nano-transferosome was also studied against obesity, a causative factor for T2DM. The size of emodin loaded nano-transferosome was of ~292 nm with encapsulation efficacy of ~69%, and these showed a relatively higher effect in terms of antiobesity activity,[171] which is an alternative approach to reduce the risk for T2DM. A few other nanodelivery approaches have also been conducted to improve the oral stability of emodin-like nanoemulsion. The emodin-loaded nanoemulsion was constructed with a particle size of ~10–30 nm, and it showed sustained release in vitro, which could be a possible alternative delivery approach for a functional compound, such as emodin.[172] The same research group also studied the bioavailability of an emodin-loaded nanoemulsion in rats. The distribution of nano emodin was found to be higher in the liver and lung,

whereas lower in the brain with a higher mean resident time.[173] The above approach can be used for nanodelivery systems to improve the bioavailability of emodin in various target organs, thereby enhancing its bioactivity against chronic disease, such as T2DM.

Nano-naringenin

Naringenin is a flavonoid compound that is present in many citrus fruits and their related beverages, and it has shown a high antidiabetic potential in many cellular and animal models.[174–180] Due to their higher potential activity in many chronic diseases, they are widely used to prepare novel beverages. However, due to the limited oral bioavailability and stability of those compounds, alternative nano-based delivery technologies have been recently studied to assess their efficacy.[181–185] A naringenin-based nanoemulsion was developed with a particle size of ~50 nm, showing the enhanced bioavailability of naringenin through oral delivery. The enhanced bioavailability of naringenin was most likely due to its higher solubility through self-emulsion nanodelivery systems, which can improve its therapeutic application.[186] Naringenin-loaded NPs were prepared with a mean particle size of ~66 nm, and these showed a higher bioavailability through oral delivery, thereby improving its hepatoprotective activity in rat models.[187] Similarly, naringenin-loaded solid lipid NPs were constructed with particle sizes ranging from ~60 to 80 nm, and these showed a higher cellular uptake.[188] In another study, naringenin-loaded chitosan nanoparticles were constructed with a particle size of ~407 nm, and these showed higher encapsulation efficiency of ~70% with improved antioxidant activity for in vitro cell models.[184] Although many nanodelivery approaches were accessed for their oral bioavailability potential in various related disease models, their potential for T2DM animal model and its related diseases is still limited.

Nano-morin

Morin is a phyto-derived bioflavonoid seen in many fruits, vegetables, and herbs, and it has shown multiple potential activities against diabetes and its associated diseases.[189–193] Its potential activities include reducing lipogenesis, oxidative stress, gluconeogenesis, and inflammation. A higher hepatoprotective activity was also reported for morin in certain studies, which indicated it can reduce hyperlipidemia. In addition, morin has an insulin-mimetic effect, and it is widely accepted to be a naturally derived antidiabetic drug.[194,195] Due to its poor oral solubility, its bioavailability is limited, resulting in lower effects. However, an increased

dosage may result in toxicity. To overcome such disadvantages, novel nanodelivery approaches have been studied to improve its bioavailability through oral delivery.[196–198] Recently, morin-loaded self-nanoemulsifying nanodelivery systems were developed and studied for their oral bioavailability. The improved oral bioavailability of these compounds was observed to lead to an improved bioactivity to treat many chronic diseases.[197] In another approach, morin was successfully formulated using mixed micelles with a particle size of ~90 nm. The nanosized morin-loaded mixed micelles showed a 3.6 times increase in cellular uptake compared to native compounds, with a higher permeability rate of by ~2.4 times, which in turn improves the bioavailability in systematic circulation.[199] In another approach, morin-loaded solid lipid nanoparticles were studied for their efficacy in the oral bioavailability, confirming that a lower particle size improves the permeability of the compound through an intestine membrane with a prolonged release of the compound.[200] Many successful, nanoscale techniques have been used to improve the bioavailability of morin during oral delivery; this helps researchers to study their potential in chronic disease models, includes type 2 diabetes and its associated diseases.

Nano-genistein

Genistein is a soy isoflavonoid with potential antidiabetic activities through various actions, including antioxidant activity, glucose-stimulated insulin secretion, estrogen receptor agonist, and β-cell proliferation at various concentration levels.[201–207] Regular consumption of genistein-rich foods has shown improved beneficial activities in many chronic diseases. Soy isoflavone-incorporated health drinks are permitted in the US for their improved beneficial actions.[208,209] However, the lower solubility and loss of bioactivity through oral delivery has led to less bioavailability of genistein in various animal studies. In addition, a higher dosage leads to other complications and toxicity.[209,210] In recent years, a few nanoscale techniques have been implemented to overcome the toxicity and higher dosage effects, improving the oral delivery of genistein.[211–213] Genistein-loaded polymeric micelles showed a higher bioavailability for genistein through oral delivery, with a particle size of ~27.76 nm. The bioavailability of the genistein micelles was greatly improved through oral delivery, and it was most likely due to the higher solubility of the compound and improved permeability.[214] In another approach, the oral delivery of genistein was successfully improved through self-emulsifying phospholipid preconcentrates of genistein

with sizes ranging from 165 to 425 nm, showing a higher permeability rate of ~12%, which in turn improved the bioactivity.[215] An alternative approach co-loading two natural bioactive compounds, such as curcumin and genistein, was studied in an NLC delivery system, and it showed significant activity with higher stability and solubility of each compound. Although many approaches have been carried out to improve the bioavailability of genistein in many chronic diseases, but the applicability to type 2 diabetes mellitus animal model is still limited.

Nano-hesperidin

Hesperidin is another phyto-derived flavonoid compound that possesses multiple antidiabetic activities through controlled glucose and lipid levels along with higher antioxidant activities, thereby reducing the cellular damage and insulin resistance levels.[216–220] This compound is highly bioavailable in lemon fruits and their juices. The lower bioavailability of those compounds through oral delivery leads to lower beneficial effects at higher doses.[221–223] Many nanotechnological approaches have been carried out to improve their bioavailability, thereby improving the beneficial antidiabetic effects of those compounds. Hesperidin nanocrystals were prepared with a particle size of 3.96 nm, and these showed an improved stability that could be useful in many functional applications.[224,225] In another approach, hesperidin-loaded solid lipid nanoparticles and NLCs were successfully developed with a lower particle size, and these showed improved stability in functional food that could be useful to treat various diseases through their functional activities.[224] Furthermore, hesperetin-loaded NPs with a particle size of ~55–180 nm were also studied for their efficacy in sustained release of the compound.[226] The in vitro cell study showed that hesperetin had sustained release of the compound with a higher antioxidant activity.

Nano-daidzein

Daidzein is another potential antidiabetic compound from soy-based food products, and in various animal studies, it exerted its antidiabetic activity by enhancing the glucose and lipid metabolism.[227–234] Due to their limited bioavailability through high hydrophobicity, nanolipid carrier-based technologies have been recently used to improve the bioavailability for oral delivery. A lipid-based nanodelivery approach was recently developed to improve the effect of daidzein through oral delivery, and the daidzein-loaded lipid carrier was found to have a 6.8 times increase in bioavailability.[235] In another approach, a daidzein-loaded self-assembly

nanodelivery system showed higher bioavailability than in free suspension.[236] The above research shows that potential antidiabetic compounds with lower gastric bioavailability can be successfully delivered orally by using lipid-based nanodelivery systems.

Conclusion

In this review, we have discussed various food grade nanodelivery systems to effectively deliver antidiabetic compounds with a much more novel approach in treating T2DM. This has been used to overcome many complications in traditional treatment of phyto-derived bioactive compounds with a lower potential antidiabetic effect due to the lower stability of those compounds in gastrointestinal systems and during absorption. Phyto-derived bioactive compounds have been loaded into nanoparticles for oral delivery in various antidiabetic animal models, and the results have shown improved stability, bioavailability, and sustained antidiabetic effects. Certain studies confirm that the coadministration of two or more antidiabetic compounds through nanodelivery systems lowers the drug load and provides improved beneficial activities, without altering the stability and bioaccessibility between those compounds. In addition, most carriers used in the delivery of phyto-based bioactive compounds are highly biodegradable because they contain natural materials, and this can reduce the toxicity of the carrier systems. Several phytobioactive compounds loaded into nanodelivery systems are currently in clinical trials, and once these compounds are commercially marketed, nano phyto-based bioactive compounds will be available as novel medicines to treat many chronic diseases, including T2DM. This review confirms that most phyto-derived antidiabetic compounds can be successfully formulated using various nanodelivery approaches to improve the efficacy and provide sustained beneficial effects.

Acknowledgment

Disclosure

The authors report no conflicts of interest in this work.

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