



The Trend of Organic Based Nanoparticles in the Treatment of Diabetes and Its Perspectives

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Abstract

Diabetes is an untreatable metabolic disorder characterized by alteration in blood sugar homeostasis, with submucosal insulin therapy being the primary treatment option. This route of drug administration is attributed to low patient comfort due to the risk of pain, distress, and local inflammation/infections. Nanoparticles have indeed been suggested as insulin carriers to allow the drug to be administered via less invasive routes other than injection, such as orally or nasally. The organic-based nanoparticles can be derived from various organic materials (for instance, polysaccharides, lipids, and so on) and thus are prevalently used to enhance the physical and chemical consistency of loaded bioactive compounds (drug) and thus their bioavailability. This review presents various forms of organic nanoparticles (for example, chitosan, dextran, gums, nanoemulsion, alginate, and so on) for enhanced hypoglycemic drug delivery relative to traditional therapies.

Key Words: Diabetes mellitus, Treatment, Organic nanoparticles, Nanoemulsions, Drug delivery systems

INTRODUCTION

Diabetes is a chronic metabolic syndrome characterized by hyperglycemia that has spread widely worldwide (Konda *et al.*, 2020; Mukhtar *et al.*, 2020). Diabetes can result in several health problems such as loss of limbs, vision loss, renal failure, and cardiovascular problems. Since the most recent International Diabetes Federation (IDF) data, nearly 463 million individuals globally are presently being suffered by the diabetes. Diabetes will affect 578 million individuals by 2030 if adequate steps do not restrict the diabetic pandemic (Reddi Nagesh *et al.*, 2020; Sirdah and Reading, 2020).

By 2045, the figure will have risen to 700 million (Verma *et al.*, 2021). The World Health Organization stated that there are 1.5 million deaths annually worldwide, making one of the leading causes of mortality in developed nations due to various factors (for example, stress, minimal physical exercise, unhealthy diet, overweight, genetic inheritance, age, as well as inflammatory processes), which can be believed to be due to an increase the percentage of adults over the age of 65 as well as a sedentary lifestyle (Cho *et al.*, 2018; Sirdah and

Reading, 2020). Diabetes is classified into two types based on pathology: type 1 diabetes (5%) (T1D), as well as type 2 diabetes (95%) (T2D) (Eberle and Stichling, 2021).

T1D pathology is insulin insufficiency caused by apoptotic cell death and a low level of insulin-secreting pancreatic β -cells damaged by the autoimmune system's T cells and B cells. As of now, there is no cure for T1D (Law *et al.*, 2018). T2D is a highly complicated metabolic disease due to insulin resistance in the liver and muscles and increased hepatic glucose output attributed to abnormally high glucagon levels (Amalan *et al.*, 2016; Heindel *et al.*, 2017). Unfortunately, there seems to be no remedy for T2D. The primary therapeutic approaches for T2D include sufficient physical activity, appropriately limited carbohydrates, and adherence to a lengthy medication regimen, including the ingestion of synthetic antidiabetics and insulin administration (da Silva Rosa *et al.*, 2020). Most diabetes treatments, on the other hand, enhance excess weight, gastro-intestinal disturbances, diarrhea, kidney problems, hypersensitivity, and there is a reasonable and fair risk of low blood sugar when used to accomplish tight blood sugar control (Emerenziani *et al.*, 2019).

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A further significant impediment seems to be drug resistance. For instance, Sulfonylureas lose efficiency after 6 years of therapy, about 44% of people with diabetes (Bowman *et al.*, 2018). Thus, discover a new anti-diabetic agent with a drug delivery system with increased protection but fewer adverse effects. Traditional drug delivery systems continue to have many constraints, such as inappropriate and ineffective drug concentration, minimal effectiveness, and limited selectivity for the destination, resulting in severe side effects in all other organ systems (Amalan and Vijayakumar, 2015; Verma *et al.*, 2021). Comparable constraints exist while using organic ingredients of nutritional and functional involvement in the management of diabetes. Loading insulin, as well as other drugs into nanoparticles has recently proposed as a much more suitable, non-invasive, as well as safe and secure approach via substitute route of administration (Wang *et al.*, 2021).

Nanoparticles provide particular challenges for biological cells because of their increased surface area, surface chemistry, and reactivity. As a result, it is important to construct these particles and their nanomaterials in a way that makes them noncytotoxic and biocompatible. In recent years, interest has grown in how nanomaterials affect the body. Nanoparticles are intriguing and prospective medication delivery systems because of their distinctive physicochemical characteristics. However, depending on the size, shape, charge, and surface chemistry of the particle, interactions between these particles and blood constituents and cells can have a variety of effects (Souto *et al.*, 2019). Protein binding occurs as soon as a particle enters the systemic circulation, and this further determines the destiny of nanoparticles inside the body. To improve drug delivery to the target tissues, an ideal nanoparticle should be compatible with blood, stable in the physiological milieu, and able to circulate. There is a need for characterization of nanotechnology constructs and production of nanomaterials.

A number of nanoparticle-based delivery systems have been proposed in order to solve enzymatic hydrolysis in the abdomen and hence enhance permeability through gastrointestinal system and hence strengthen following oral uptake and circulation throughout the body (Amalan *et al.*, 2015; Viswanathan *et al.*, 2017). This review discusses the trends and perspectives of organic mediated nanoparticles for diabetes treatment. Since, the nanoparticles may enhance the paracellular absorption of anti-diabetic agents.

NANOTECHNOLOGY IN MEDICATIONS

The phrase “Nanotech” refers to manipulating molecular, atomic, and supramolecular levels at which distinctive quantum theory effects occur (Madkour, 2019). Hence, lowering at least one dimension just at nano-sized (1-100 nm) particles entails the configuration, fabrication, characterization, and application of different nano-sized components in different potential areas, resulting in innovative technological progress (Akhavan *et al.*, 2018). Nanoparticles have such several superior properties compared to parent structures because nano-materials seem to be more completely reliant on shape, size, and interactions that are easily accessible (Kinnear *et al.*, 2017; Natesan and Kim, 2021). The application of nanomaterials and nanodevices in health and pharmaceuticals has paved the way for developing unique nanoscience and nanomedicine areas (Nasrollahzadeh *et al.*, 2019). Nanotechnol-

ogy progressions in treatments can be categorized as follows.

DRUG ADMINISTRATION/THERAPEUTICS:

The production of novel nanoparticle delivery systems intends to reach controlled and targeted pharmacological drug release and bio-distribution. Nanoparticles are also used in drug design to improve absorption rate (Nasrollahzadeh *et al.*, 2019). For instance, numerous drugs are moderately soluble in water. At the same time, some are rapidly absorbed but then eliminated from the body as squandering even before bioactive components attain their optical accumulation, rendering therapies inefficient (Zhou *et al.*, 2016). Moreover, nanotechnology has sparked interest owing to its capacity to produce particles that are fascinated to specific cell types. Several nanoparticles have distinctive characteristics that enable them to be used effectively in therapy (Chenthamara *et al.*, 2019).

The NPs approach a cell membrane; they interact to plasma membrane as well as outer membrane proteins and pass through the membrane, primarily via endocytosis, direct diffusion, phagocytosis, adhesive interactions, and micropinocytosis. Endocytosis involves NPs being engulfed in membrane vesicles, finally budding as well as squeezing off just to establish endocytic vacuoles, which will then be transported to specialized cytoplasmic trafficking chamber. Endocytosis is divided into various types depending on the cell type as well as the peptides, fats, and some other substances associated with the process. Phagocytosis, macropinocytosis, clathrin-mediated endocytosis, clathrin or caveolae-independent endocytosis, and caveolin-mediated endocytosis are the major endocytosis processes. Pinocytotic processes seem to be more prevalent in several types of cells than phagocytosis, which also occurs primarily in competent phagocytes. Nanoparticles can penetrate the cell through phagocytosis, adhesive interactions, endocytosis, micropinocytosis, and direct diffusion (Fig. 1). Behzadi *et al.* (2017) also demonstrated that too many nano-sized components can pass cell membrane via passive mechanisms including diffusion as well as adhesive relations, at which heat blood capillaries waves along with line tension contribute significantly in influencing nanoparticle entrance into the cells. The physicochemical characteristics of nanoparticles, including size, composition, shape, and surface charge influence how they are internalized by cells. The drugs are then delivered and controlled by nanoparticles via biological stimuli (Matrix metalloproteinases: MMPs) as well as light activation.

DIABETIC TREATMENT WITH NANO-DRUG DELIVERY SYSTEMS

Because of their distinctive in-vivo properties, such as good design flexibility, nanoparticle-based drug delivery systems emerged as a potential framework for improving the oral bioavailability of organic drugs (Purohit *et al.*, 2017). The organic drugs can be loaded with nanoparticles to improve their consistency in the gastrointestinal tract. Furthermore, nanoparticles can help organic drugs cross the mucosal barrier and epithelial cell layer, increasing their oral bioavailability in the bloodstream (Brown *et al.*, 2020; Amalan *et al.*, 2021). Numerous endeavors have been undertaken to develop oral peptide

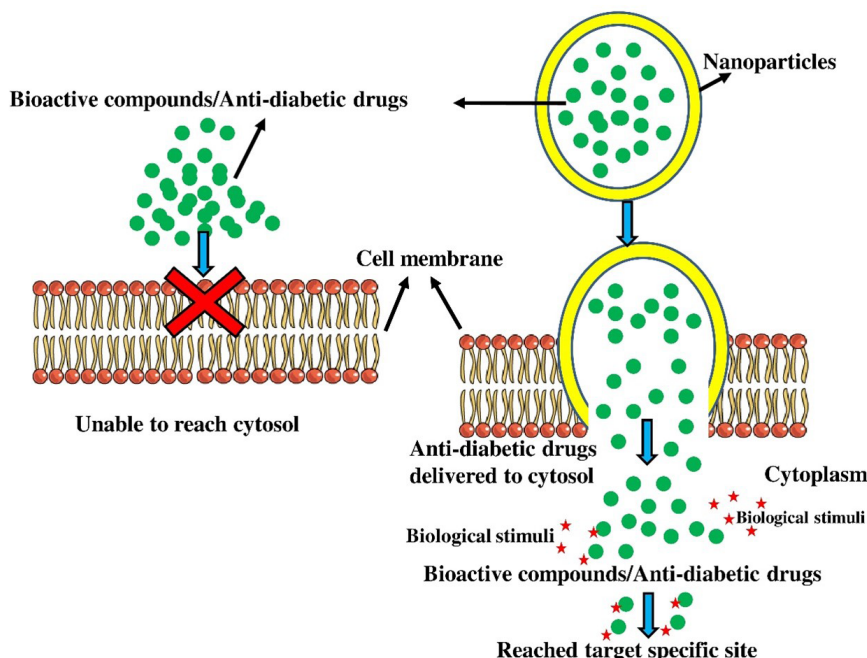


Fig. 1. Nanoparticles based anti-diabetic drug delivery system. The nanoparticles move through the membrane largely by endocytosis, direct diffusion, phagocytosis, adhesion contacts, and micropinocytosis. They interact with the plasma membrane as well as outer membrane proteins.

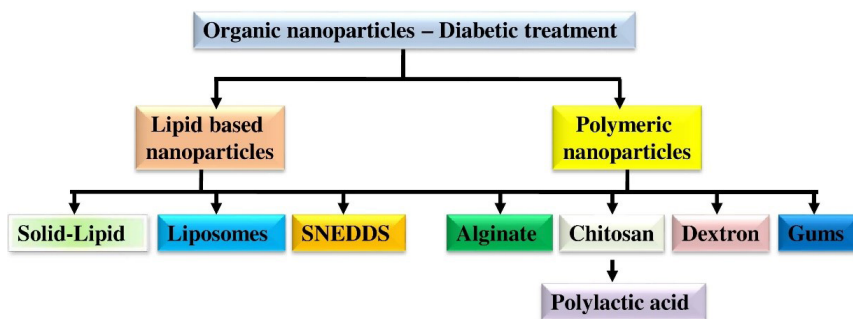


Fig. 2. Various form of organic nanoparticles for diabetic treatment. Natural organic polymers key benefits over inorganic alternatives are their non-toxicity and biocompatibility. Anti-diabetic medications have been successfully delivered using naturally occurring polymers such alginate, dextran, chitosan, gum arabica, gum rosin, sodium, and gum rosin.

drugs NPs for diabetes mellitus treatment. Several natural product based nanoparticles have been investigated as conventional dosage forms for the treatment of diabetes (Ramakrishnan and Vijayakumar, 2017; Durán-Lobato *et al.*, 2020).

ORGANIC NANOPARTICLES

Natural organic polymers-based nanoparticles are low in the production process and cost and abundant in nature. The key benefits of natural organic polymers over inorganic polymers are non-toxicity and biocompatibility (Mansoori *et al.*, 2020). Naturally available polymers such as chitosan, gum rosin, sodium alginate, dextran, and gum arabica have been established to deliver anti-diabetic drugs (Fig. 2) (Nie *et al.*,

2020).

CHITOSAN MEDIATED NANOPARTICLES

Chitosan, a type of polycationic carbohydrate biopolymer, is created through chitin alkaline deacetylation, obtained from microbial cell walls (fungi), insect cuticles, and crustacean exoskeletons (Philibert *et al.*, 2017; Amalan *et al.*, 2022). Because of its ease of surface functionalization, ability to mix with diverse polymeric materials, non-immunogenicity, non-toxicity, as well as significant suitability with tissues and cells, chitosan is perhaps the most widely used in the shipment of anti-diabetic drugs/bioactive (Fig. 3) compounds (Table 1, 2) (Allawadhi *et al.*, 2021). Chitosan-based nanoparticles encap-

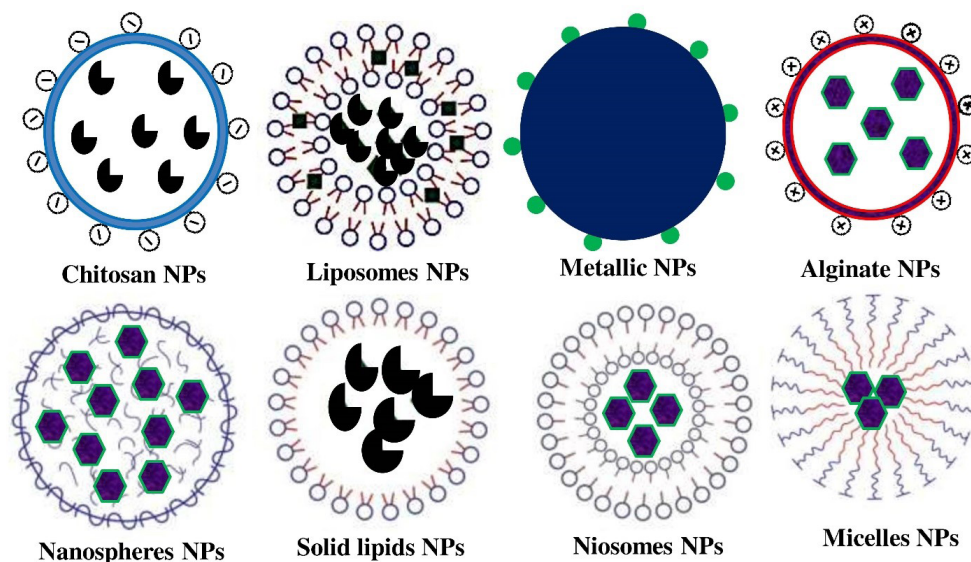


Fig. 3. Pictorial representation of nanoparticles used to deliver the anti-diabetic drugs to treat the diabetes. Chitosan's high positive charge makes it ideal for delivering anti-diabetic drugs because it increases cell absorption and promotes adhesion to surfaces with opposing charges on membranes.

ulating ferulic acid and curcumin were developed through a bottom-up ionic gelation technique. Chitosan's strong positive charge makes it perfect for antidiabetic drug delivery since it improves adherence to oppositely charged membranes surfaces and enhances cell absorption (Vijayakumar and Subramanian, 2010a; Wu *et al.*, 2020). Furthermore, the chitosan OH and NH₂ active groups are susceptible to chemical responses. The inhibitory action of α -glucosidase decreases in the order of catechin-g-chitosan>catechin>acarbose>chitosan, and the α -amylase inhibitory effect decreases in the order of acarbose>catechin-g-chitosan>catechin>chitosan.

One of the biologically useful flavonoids in the human diet is catechin, which is mostly found in red wine, broad beans, black grapes, apricots and tea. Catechin has been shown to possess a number of biological qualities, including antioxidant, antimutagenic, anticarcinogenic, antidiabetic, anti-inflammatory, and antibacterial effects. Antioxidant and anti-diabetic properties of chitosan were improved by grafting catechin onto it using Vc and H₂O₂ as redox initiators in acetic acid solution. Numerous instrumental techniques were used to describe the produced catechingrafted chitosan (catechin-g-chitosan) to ensure conjugation. Additionally, catechin-g-anti-inflammatory chitosan's and anti-diabetic properties were identified (Zhu and Zhang, 2014).

Even though it has favorable biocompatibility, it is very seldom used for oral administration of drugs since chitosan can act as a carrier and prone to leaking from the encapsulated bioactive compounds due to its ease of dissolution in acidic environments (Muzzarelli *et al.*, 2015; Natesan and Kim, 2022).

ALGINATE AND CHITOSAN MEDIATED NANOPARTICLES

Alginate is also another natural organic polymer desired

after chitosan. Alginate seems to be a water-soluble anion exchange copolymer widely distributed in brown algae cell walls (Abedini *et al.*, 2018). Alginate's broad pharmaceutical suitability stems from its distinctive tendency to construct hydrogel in the liquid phase or at minimal pH in the occurrence of Ca²⁺ ions (Abasalizadeh *et al.*, 2020). Electrostatic attraction among oppositely charged groups allows alginate and chitosan to establish polyelectrolyte structures (Fig. 3). The low pH dissolution rate of the alginate channel reduces the high pH solubilization of chitosan, which is far poor dissolvable at elevated pH and stabilizes the alginate (Wasupalli and Verma, 2018).

The alginate and chitosan blend helps protect the encapsulated drug and is efficiently and slowly released compared to chitosan and alginate alone (Table 1, 2). For example, the *in vitro* study revealed that the chitosan and alginate blend considerably increased the releasing period of curcumin around 40 min under fluid (gastric) stimulation and decreased curcumin deficit by 20% (Nalini *et al.*, 2019). Furthermore, the chitosan and alginate blend prepared curcumin nanoemulsion had around a 30% greater glucose reduction effect than chitosan alone (Laha *et al.*, 2019). Maity *et al.* (2017) developed innovative alginate covered chitosan core-shell nanoparticles carrier system that was efficient in drug administration of naringenin for diabetic prompted rats. Since the major-shell renovation had developed to reduce size of particles as well as ensuring proper preventative measures of encapsulated naringenin from high metabolism through protecting within the core of nanoparticles (Abdullah *et al.*, 2019).

Accordingly, Mukhopadhyay *et al.* (2018) prepared pH-based polymeric nanoparticles with corona morphological features for embedding with quercetin, using succinyl chitosan as well as alginate. Because of the existence of carboxyl groups on their structure, succinyl chitosan as well as alginate have high pH sensitivity. In both *in vitro* and *in vivo* experiments, the circular nanoformulation can accomplish a pH-sensitive con-

Table 1. Organic nanoparticles based bioactive compound treatment of diabetes

Antidiabetic organic compound	Drug delivery system	Size (nm)	Concentration (mg kg of body weight)	Activity/mechanism	References
Ferulic acid	Chitosan NPs	119.5	10	Increasing Antihyperlipidemic, bioavailability, and glucose reducing effects, hepatic glycogen, and curcumin deposition in the liver	Maity <i>et al.</i> , 2017; Mukhopadhyay <i>et al.</i> , 2018; Nie <i>et al.</i> , 2020
Naringenin, Quercetin, and Curcumin	Chitosan-alginate nanoparticles	50-216.44	50-100	Increasing glucose reducing effects, control hepatic and pancreatic abnormalities	Maity <i>et al.</i> , 2017; Mukhopadhyay <i>et al.</i> , 2018
Better gourd seed oil, berberine, sage essential oil, and α -tocopherol	Nanoemulsion	85-143.2	25-100	Increasing glucose reducing effects, liver function maintenance, pancreatic tissue regeneration, free radicals scavenging effects, and bioavailability	Nait Bachir <i>et al.</i> , 2019; Xu <i>et al.</i> , 2019
Curcumin	PEG-PLA nanoparticles	117	20	Increasing glucose reducing effects, anti-inflammatory effects and plasma insulin content	El-Naggar <i>et al.</i> , 2019; Nie <i>et al.</i> , 2020
Glycyrrhizin and thymoquinone	Chitosan and rosin gum nanoparticles and nanocapsules	70-181	20-90	Increasing glucose reducing effects and antihyperlipidemic effect	Rani <i>et al.</i> , 2018
Resveratrol, polypeptide-k, curcumin, cinnamic (trans) acid	SNEDDS	40-800	28-336	Increasing glucose reducing, antihyperlipidemic effects, and bioavailability	Rani <i>et al.</i> , 2018; Nie <i>et al.</i> , 2020
Berberine, resveratrol, and myricitrin,	SLNs	50-150	1-100	Free radicals scavenging, Increasing glucose reducing effects, decrease insulin tolerance, increase islet activity, increase bioavailability	Ahangarpour <i>et al.</i> , 2018; Mohseni <i>et al.</i> , 2019
Ursolic acid, berberine, gymnemic acids, and betulin	Nanosuspensions	20-400	73-246	Increasing glucose reducing, antihyperlipidemic effects, decrease insulin tolerance, and increase bioavailability	Singh <i>et al.</i> , 2019; Nie <i>et al.</i> , 2020
Betain	Liposomes	40	20	Increasing glucose reducing, antihyperlipidemic effects, decrease insulin tolerance, stop renal, pancreas, and liver damages	Amjadi <i>et al.</i> , 2019

SNEDDS, self-nanoemulsifying drug delivery systems; SLNs, solid lipid nanoparticles; PLA, poly lactic acid; PEG, poly ethylene glycol; PLGA, poly lactic-co-glycolic acid.

Table 2. Commercially available anti-diabetic drugs loaded nanoparticles to treat diabetes mellitus (Souto *et al.*, 2019)

Anti-diabetic drug	NPs used for drug delivery	Mechanisms involved in treatment	Mode of administration
Insulin	Alginate NPs	Reduction in BSL: longtime hypoglycemic effect	Oral
	Chitosan NPs	Reduction in BSL: Bio-distribution- kidney, both intestine, and urinary bladder	
	Dextran NPs	Reduction in BSL: longtime hypoglycemic effect	
	PAA NPs	Effective on Caco2 cells	
	PLA NPs	Reduction in BSL: longtime hypoglycemic effect. Distributed at heart, kidney, lungs, spleen, and liver	
Metformin	PLGA NPs	Reduction in BSL: longtime hypoglycemic effect	Oral
	CPP NPs	Reduction in BSL	
Gliclazide, insulin metformin, repaglinide pioglitazone	Liposomes NPs	Hypoglycemic effect	Oral
	Niosomes NPs	Enhanced bioavailability for insulin	
Pancreatic insulin (Bovine and human); Calcitonin Porcine and human insulin (lyophilized)	Dendrimers NPs	Improved glucoregulatory activity	Subcutaneous
	Micelles NPs	Enhanced bioavailability for insulin	

trolled delivery of quercetin and exhibit an anomalous trend (Rehman *et al.*, 2020). In STZ-induced diabetic rats, both core-shell nanoparticles had significant hypoglycemic effects and effectively maintained glucose tolerance when compared to organic compounds. Furthermore, neither nanoparticle was toxic *in vivo* (Mukhopadhyay *et al.*, 2018).

GUMS, GUM AND CHITOSAN MEDIATED NANOPARTICLES

Organic gums such as locust bean, guar, karaya, gellan, acacia, xanthan, and konjac gel gums have been widely used in developing safe drug delivery applications (Tahir *et al.*, 2019). While exposed to water, they established hydrogels and showed excellent stability over a wide pH range. Gum rosin is a naturally occurring anionic polymer obtained from pine plant (Table 1). Rani *et al.* (2018) used the nano-precipitation technique, also known as a solvent displacement technique, to establish with thymoquinone-loaded gum based rosin nanocapsules (Nie *et al.*, 2020). Thymoquinone nanocomposites encapsulated half of the quantity of administered as organic thymoquinone but outperformed in T2D rats in terms of antihyperglycemic activity (Vijayakumar and Subramanian, 2010b; Rani *et al.*, 2018).

DEXTRAN MEDIATED NANOPARTICLES

Dextran is a polysaccharide with a negative charge easily soluble in water. It is mostly made up of linear -1,6-linked glucopyranose residues with 1.3-branching. Dextran is derived mainly from *Lactobacillus* and *Streptococcus* cultures grown in a sucrose-enriched environment (Rosenberg *et al.*, 2011). Drug encapsulation appears to be difficult due to the poor affinity among water-soluble polymeric (matrix) and lipophilic bioactive compounds. Berberine-loaded O-hexadecyl-dextran nanoparticles were effective as berberine to avoid raised glucose-stimulated cell damage, mitochondrial damage, and reduction of apoptosis in *in vitro* experiments on hepatocytes (Mortazavi *et al.*, 2020). Despite being extremely degradable, the constraint of organic polymers is related to batch-to-batch significant variation since they are typically retrieved from distinct species, provinces, and climates, making them less appealing than synthetic polymers, which are more adaptable and efficacious (Vijayakumar, 2014; Choudhary *et al.*, 2020).

ADVANCEMENTS IN NANOPARTICLES BASED DRUG DELIVERY SYSTEM

Nanoemulsion based drug delivery system

Organic nanoemulsions are colloidal carriers that include an oily phase, an emulsifier, and an aqueous phase. It is still debatable in nanoemulsions with structured size values and a maximum limit fixed at 100, 200, and 500 nm (Shaker *et al.*, 2019). As the size of the oil phase declines, the energy content needed to break them down raises, indicating that a large amount of energy is required to create nanoemulsions (Sivakumar *et al.*, 2014; Ramakrishnan *et al.*, 2016). Nanoemulsions are drug delivery systems capable of entrapping both hydrophobic and hydrophilic substances. Momordica

charantia seed oil was emulsified with a minimal surfactant to oil (0.65) ratio using a 2 stage homogenization method for nanoemulsions preparation (Ramya *et al.*, 2015; Rahman *et al.*, 2020). *M. charantia* seed oil based nanoemulsions substantially decreased hyperglycemia and oxidative stress in T2D rats induced with alloxan. About 0.5% (w/v) of *M. charantia* seed oil based nanoemulsions demonstrated significant therapeutic efficiency as compared to similar doses of *M. charantia* seed oil traditional emulsion, as well as 1% (w/v) *M. charantia* seed oil nanoemulsion, potentially owing to enhanced bioavailability (Xu *et al.*, 2019). The nanoemulsions (Table 1) increased the absorption of berberine *in vivo* by about 212.02% to controls and lowered diabetic mice's blood sugar levels by threefold (Xu *et al.*, 2019).

Furthermore, the therapeutic efficacy of berberine nanoemulsion on diabetes was superior to metformin. A creative delivery mechanism, cyclodextrin-mediated nanospheres, comprises excitable cyclodextrins linked in a tri-dimensional network. They have the potential to outperform organic cyclodextrins (Xu *et al.*, 2019). Their outstanding traits are due to their sponge-like and nanoporous structure, which would be advantageous for the encapsulation of complex hydrophilic and lipophilic bioactive compounds (Mohammadi *et al.*, 2020). To improve the biocompatibility as well as consistency of herb essential oil. Nait Bachir *et al.* (2019) synthesised 2 engineered nanoemulsions. The first one was stabilized by organic α -cyclodextrin using a physical techniques, as well as the 2nd through α -cyclodextrin nanospheres through C₁₀H₆(CO₂H)₂ as both a cross-linking compound as well as a poly-condensation technique (Nait Bachir *et al.*, 2019)

The *in vivo* anti-diabetic activity of nanoemulsion stabilized with cyclodextrin nanospheres outperformed that of nanoemulsion stabilized through natural and organic cyclodextrin and free herb essential oil (Nait Bachir *et al.*, 2019). Hatanaka

et al. (2010) used a micro fluidizer to prepared through three nanoemulsion of tocopherol at various (10%, 30%, and 50%) concentrations (Hatanaka *et al.*, 2010). In streptozotocin stimulated diabetic rats, 10% tocopherol blended nanoemulsion had a 2.6-fold enhanced bioavailability *in vivo* and a more substantial antioxidant properties influence on the several organ systems, particularly the liver when compared with the control (oil and -tocopherol). Nevertheless, whenever the α -tocopherol substance of the nanoemulsion had been 30% or greater, extreme droplet agglomeration took place during prolonged storage (Hatanaka *et al.*, 2010).

The main limitation that prevents nanoemulsion from being widely used is its stability. Nanoemulsions are both thermodynamically as well as catalytically volatile systems. In other words, if nanoemulsions are given enough time, phase transition will occur (Damarla *et al.*, 2018). Flocculation maturation is the primary mechanism of nanoemulsion destabilization (Singh *et al.*, 2017). This was revealed that just by determining the size, emulsifier, and oil densities during storage as well as application, the consistency of nanoemulsion might be retained against environmental parameters such as pH and temperature (McClements, 2018).

Self-nanoemulsifying drug delivery systems (SNEDDS)

SNEDDS, unlike nanoemulsions, do not contain any liquids, making them more physically and chemically reliable, enabling them to be stored for a lengthy period (Khan *et al.*, 2012). Furthermore, the free energy needed to design SNEDDS seems to be extremely low, as well as the formulation is thermally dynamic. Anhydrous isotropic blends of surfactant, oil, co-surfactant, and drug are called SNEDDS (Sailor, 2021). *In vivo*, these processes are dissolved by gastrointestinal fluids. Afterward, with mild agitation offered by the gastrointestinal motility of the stomach and intestine, they can establish perfect oil-

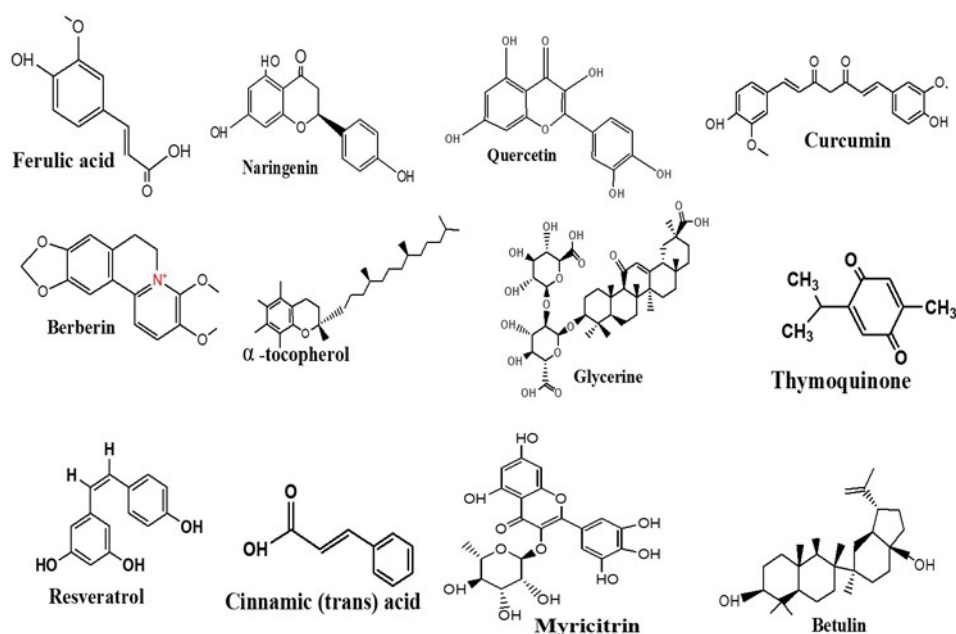


Fig. 4. Structure of anti-diabetic bioactive compounds used with nanoparticles based drug delivery process. The unique attributes of nanoparticles are a result of their nanoporous, sponge-like structure, which is beneficial for encapsulating sophisticated hydrophilic and lipophilic bioactive chemicals.

in-water nanoemulsions with an enormous surface area for improved drug absorption (Rostamabadi *et al.*, 2019). Thus, among the most important aspects of SNEDDS seems to be the alteration whenever bodily secretions neutralize the system following administration (Čerpnjak *et al.*, 2013). Thus, it is important to determine effective self-emulsification areas and select the best emulsifier, co-surfactant, and oil densities to prepare stable SNEDDS. Garg *et al.* (2019) created SNEDDS of peptide chain k and curcumin to improve antidiabetic efficiency in diabetic rats induced by STZ (Table 1, Fig. 4). A pseudo-ternary stage model was created using oil, surfactant, and co-surfactant (Garg *et al.*, 2019).

The liquid formulation had been optimized using the Box–Behnken layout depending on outcomes of drug loading percentage, zeta potential, polydispersity index, and average droplet size (Thapa *et al.*, 2018). The absence of phase transition and drug precipitation under conditions of pH, dispersion, and temperature fluctuations recommended that the optimized formulation was stable (Sipponen *et al.*, 2020). The proportion of emulsifying agents is an important metric for determining emulsification effectiveness. *In vitro*, the ideal methodology resveratrol SNEDDS self-emulsified in 27 ± 0.8 s without precipitation (Abou Assi *et al.*, 2020). A 10 mg/kg resveratrol nanocomposite had substantial hypolipidemic and hypoglycemic impacts on Streptozotocin and glucose-induced-diabetic mice, comparable to a higher dosage (20 mg/kg) of pure resveratrol (Balata *et al.*, 2016).

In another investigation, the roughly comparable in-vivo bioavailability of trans-cinnamic acid (TCA) based SNEDDS was nearly 246% compared to TCA dispersion, denoting that SNEDDS possess such an exceptional ability to improve bioavailability (Wang *et al.*, 2015). These observations can be determined by various mechanisms, including minimized intra-enterocyte biochemical activity via cytochrome P450, reduced P-gp electron transport activity, and circumvented hepatocellular first-pass metabolic activity via lymphatic assimilation. Trans-cinnamic acid improved its anti-diabetic effectiveness in alloxan-stimulated diabetic rats, which can be equivalent to metformin (Wang *et al.*, 2015). SNEDDS have several advantages, nevertheless, they often have had some drawbacks. Characterization and conceptualization concerns include the significant relation between *in vitro* and *in vivo* experiments, the use of a substantial quantity of surfactant, bioactive compound *in vivo*, lipid oxidation possibilities, and the uncertainty of reduced encapsulation, and so on (Chatterjee *et al.*, 2016). To compensate for their inadequacies, researchers are now focusing on emerging applications of SNEDDS, including self-double emulsions, solid SNEDDS, sustained release SNEDDS, completely saturated SNEDDS, and focused SNEDDS (Rehman *et al.*, 2017). The histopathological, biochemical, and hematological results of streptozotocin-stimulated diabetic rats demonstrated that polypeptide-k packed SNEDDS had a greater anti-diabetic efficiency than the naïve form.

CONCLUSION

The bioactive compounds derived from biological sources are promising anti-diabetic agents because they are abundant, have substantial therapeutic benefits, and have few adverse effects. In general, bioactive bounds have 4 low blood

sugar mechanisms: they reduce carbohydrate breakdown as well as glucose absorption, they promote glucose metabolism in the body, they enhance insulin action as well as sensitivity, and they have free radical scavenging and anti-inflammatory properties. Nevertheless, traditional orally ingested of anti-diabetic phytoconstituents has some flaws. Nanoparticle drug delivery processes for bioactive compounds to cure T2D preserve the benefits of orally administered and resolve the disadvantages of previous drug delivery. This review discussed organic bioactive compound coated oral nanoparticles drug delivery systems for T2D therapy, including organic polymeric nanoparticles, lipid-based nanostructures, vesicles structures, and nanoemulsions. According to research, oral nanoparticle drug delivery processes for T2D cure do have the following benefits:

- 1) Encapsulating drugs in organic nanoparticles delivery methods can enhance their stability and defend them from enzyme-mediated degradation in the gastrointestinal system.
- 2) Nano delivery methods act just at the bio-molecular range to enhance cells drug absorption or perhaps to restrict drug efflux processes such as the P-glycoprotein pump, improving the pharmacodynamic and pharmacokinetic nature of anti-diabetic substances.
- 3) First-pass hepatocellular metabolic activity can drastically reduce oral drug bioavailability. Lymphatic drug transfer is the best approach for enhancing drug delivery by avoiding first-pass metabolic activity. Nano delivery method can transfer drugs into the lymphatic system via M cells and enhance drug release in the circulatory system.
- 4) Customizing nanocarrier advancements achieves drug release control, demand for these products prevention, and targeted drug delivery system.

2 Bioactive compounds have demonstrated improved antidiabetic efficiency in nanoparticles-based drug delivery processes with improved absorption, significantly reduced toxic effect, target-specific, as well as reduced dosages and medicating regularity due to the benefits listed above.

Nevertheless, there are some gaps in current studies. On the hand, it is important to note that perhaps the large number of studies do not include a control set prescribed with a non-loaded nano carrier, implying that the drug-independent influence of a carrier can also be overlooked. Most substances used throughout the formulation of nano delivery methods are typically derived from inorganic compounds or synthetic materials via a somewhat more complex and time-consuming synthesis method, which might undoubtedly lead to considerable toxicity. Though organic materials are used as nanocarriers, organic bioactive may very well be initiated into the preparation requirements, and protection is of the utmost importance. However, most published literature comes from cellular and animal prototypes rather than a clinical investigation. Because animal toxicological investigation has boundaries, and clinical trials are eventually critical. Just curcumin nanocapsules have undergone clinical trials as an excellent anti-diabetic nano-drug. Despite the reality that only a few extreme side effects have been noted during therapies, prolonged human toxicity testing investigation has still been underwhelming. The FDA recently released guidelines to aid in nanoparticle-based clinical products' secure progression. Too much clinical study is necessary. Above all, nanoparticle-based drug delivery methods for T2D treatment are quite a viable anti-diabetic drug delivery strategy. One such review could provide scientists with exciting anti-diabetic organic-based drug delivery methods to investigate further pharmacotherapy opportunities.

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