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REVIEW

Nanophytochemicals for the treatment of type II diabetes mellitus: a review

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Abstract

Type II diabetes mellitus is one of major lifestyle disorders worldwide. Despite numerous therapeutic interventions, cases and adverse health effects are still rising. Many plant substances, known as phytochemicals, display potential to treat diabetes, yet their clinical application is actually limited by inefficient delivery. In this review, we show that recent nano-delivery systems such as liposomes, niosomes, solid–liquid nanoparticles, nanostructured lipid carriers, nanomicelles and nanoparticles improve pharmacokinetic properties of entrapped phytochemicals for the treatment of diabetes and associated vascular complications.

Keywords Phytochemicals · Nanotechnology · Type II diabetes mellitus · Drug delivery

Introduction

Diabetes mellitus is perceived to be one among the prevalent threats for public health in the twenty-first century and is mentioned as one of the top ten diseases triggering death (Hu et al. 2018). Diabetes mellitus is a chronic metabolic dysfunction of elevated blood glucose level, which precipitates either due to a deficit in secretion of a hormone termed as insulin or as a result of pancreatic β-cell injury or because of insulin, the tendency to non-utilize owing to insulin resistance (Matzinger et al. 2018). Type I diabetes mellitus and type II diabetes mellitus are two subgroups of diabetes mellitus, and they differ in pathophysiology from each other. Cytotoxic lymphocyte auto-antibodies and the T-helper cells contribute to autoimmune destruction of pancreatic β-cells, which reduces the secretion of insulin and leads to type I diabetes mellitus (Vitak et al. 2017). Whereas due to a cumulative impact of drop in insulin secretion and insulin resistance, type II diabetes mellitus occurs (Acharjee et al. 2013).

The prevalence of type II diabetes mellitus is increasingly growing, and it is estimated that by 2045 approximately 629 million people are expected to have diabetes mellitus. The principal clinical intervention in diabetes mellitus has been known to be glycemic modulation. However, countless risk factors for diabetes, fatal complicacies and the development of vasculopathy prior to diagnosis entail the development of new treatment techniques for successful diabetes management (Dewanjee et al. 2018). Contributing to side effects, the available clinical antidiabetic therapeutics discourage both doctors and patients, gradually turning the emphasis into the innovation of novel antidiabetic treatment strategies, whereas in preclinical studies certain naturally occurring phytochemicals have demonstrated tremendous implications for diabetes and diabetic complications through hitting several targets.

Phytochemicals have been shown to display antidiabetic effects through several pathways, including glucose absorption reduction, β-cell functional mass regeneration, recovery of insulin expression, reversal of insulin resistance, improvement in glucose consumption and modulation in metabolism of lipid and carbohydrate (Bhattacharjee et al. 2016). In addition, the

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biocompatibility of these phytochemicals makes them an apt choice to be exploited as therapeutic negotiators. The associated poor biopharmaceutical and pharmacokinetic properties largely limit their clinical utility as therapeutic agents (Padhi et al. 2015). To improve their conformity and clinical effectiveness, many pharmaceutical researches have been conducted. In this aspect, the utilization of nanotechnology has been regarded as the best path for enhancing compliance and therapeutic effectiveness through addressing the pharmacokinetic and biopharmaceutical hurdles associated with the conventional therapeutic agents (Padhi et al. 2018). Such nanoformulations provide distinct benefits over conventional delivery system such as stability, high precision, controlled release, high entrapment efficiency, enhanced solubility and bioavailability (Behera and Padhi 2020; Saka and Chella 2020). Herbal drugs are regarded as safe, cheap and popular in comparison with the synthetic drugs. Globally 800 plant species are known to have hypoglycemic properties out of which 450 are the most known to be mostly used for research (Han et al. 2019). Main phytochemicals along with their plant origin are enlisted in Table 1.

This review article presents an overview of the pharmaceutical advantages conferred by the nanoformulations entrapping various phytochemicals recommended in the treatment of diabetes mellitus and its associated complicacies.

Nanotools for the treatment of type II diabetes mellitus

Nanotechnology has gained enormous attention in both diagnosis and treatment in medical research in the past few years (Verma et al. 2017). It has been showcased that certain unique physical, chemical and biological attributes are gained by nanoscaled materials, making them suitable for numerous biomedical applications (Behera et al. 2020; Khuroo et al. 2014).

It has been ascertained that the engineering of nanocarriers like polymeric nanoparticles, metallic nanoparticles, liposomes, niosomes, micelles, dendrimers, nanostructured lipid carriers and nanofabricated structures has achieved considerable acceptance over contemporary drug delivery systems with respect to potency, durability, bioavailability, bio-distribution and drug release as represented in Fig. 1. In addition, functionalized nanocarriers with suitable ligands end up in targeted drug delivery with improved therapeutic efficacy (Padhi and Behera 2020). The progress and efficacy of nanoenabled formulations of antidiabetic therapeutic agents from plant sources (phytochemicals) are highlighted in the following portion of this article.

Liposomes

Liposomes are the vesicular structure containing one or more phospholipid bilayers, which are naturally non-toxic phospholipids and cholesterol. They are capable of transporting the active drug molecules to the targeted site within the biological system (McClements 2010). Liposomes fuse with the lipid membrane of the cell and thus discharge the liposomal content into the cytoplasm. Liposomes can entrap both lipophilic and hydrophilic drugs to deliver the target-specific drug with maximum efficacy and safety. Drug delivery through the nano-liposome systems entrapping phyto-bioactive compounds with antidiabetic properties was reported to be significantly improved (Gunasekaran et al. 2014).

In a research study, liposome of quercetin was evaluated in streptozotocin-induced diabetic nephropathy rat model. The in vivo study was conducted by administering quercetin (50 mg/kg), polyethylene glycol 4000 (150 mg/kg) and quercetin liposomes (200 mg/kg) by intragastric route in the group of rats. The study showed high levels of quercetin were present in plasma and kidney tissues in groups treated with quercetin-loaded liposome as compared to free-quercetin-treated group within 60 min. Quercetin liposomes or free quercetin were able to avoid loss of body weight, reduced renal hypertrophy index, decreased blood glycemic levels and decreased secretion of urinary protein for 24 h, but the liposomal quercetin formulation indicated superior therapeutic efficacy as compared to that of quercetin alone (Tang et al. 2020).

Resveratrol is considered to be a potent antioxidant with an insulin-like effect on diabetic cells (Arora and Jaglan 2017). It has proven efficacy in diabetes care, and it majorly acts by decreasing oxidative stress and glucose levels as well as protecting the β-cells accountable for the secretion of insulin. Cytotoxicity study of resveratrol liposomes was carried in β-TC pancreatic cell lines by 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay and the study indicated that inhibitory concentration (IC_{50}) of resveratrol to be 50.69 µg/ml. Resveratrol liposomes increased the levels of glutathione peroxidase and superoxide dismutase demonstrating the antioxidant activity. Significant differences were observed when compared to insulin levels of resveratrol solution and liposome formulations entrapping resveratrol ($p < 0.001$). In diabetic cell groups synchronous with increasing insulin levels, the resveratrol liposomes reduced glucose levels and demonstrated sustained antioxidant activity against oxidative stress for a time period of 24 h relative to the resveratrol in solution form (Yücel et al. 2018).

Hyperglycemia, hepatotoxicity, and nephrotoxicity in diabetic mice are more effectively alleviated by

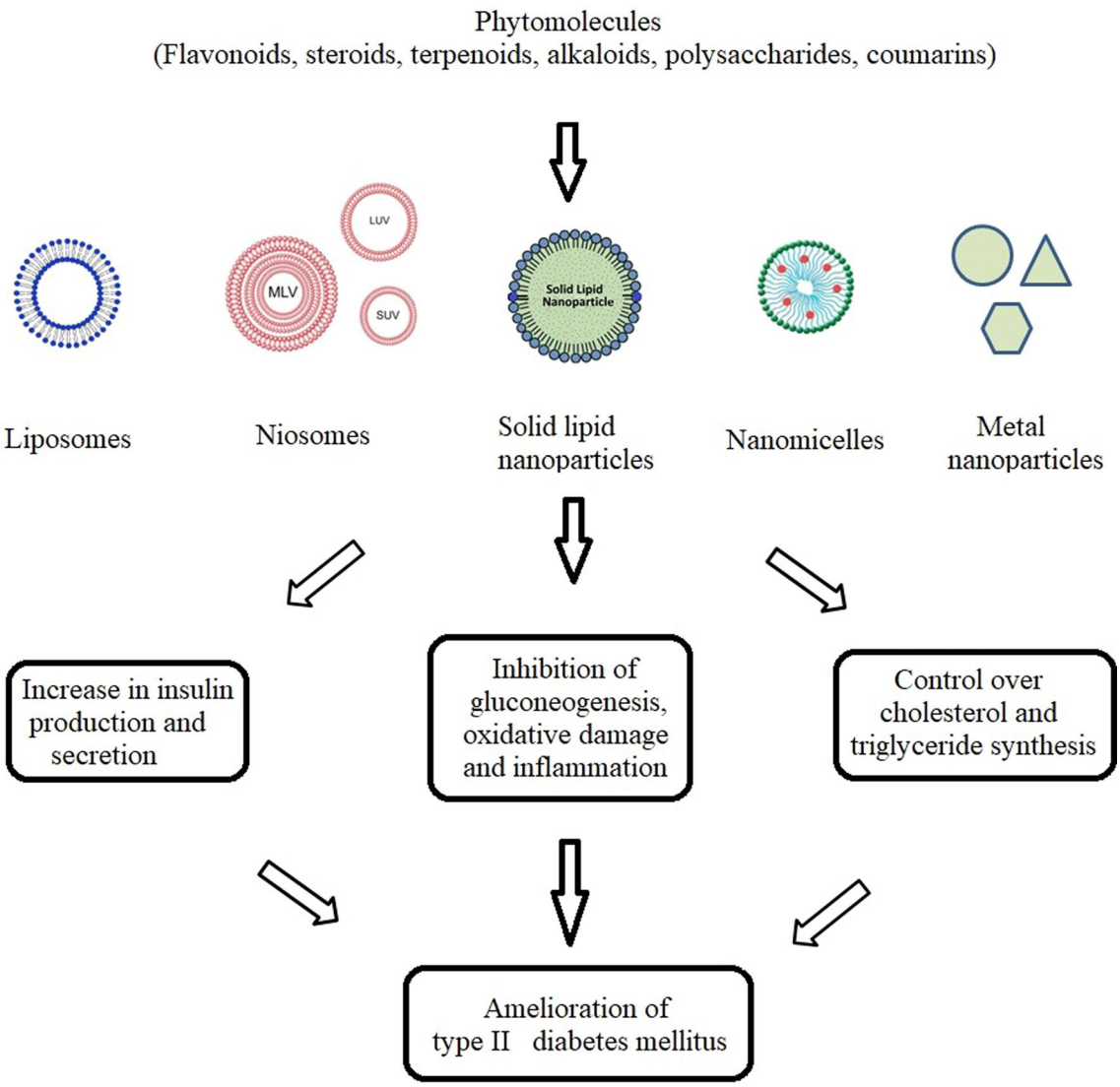

Fig. 1 Nanotools for the delivery of phytomolecules for amelioration of type II diabetes mellitus. Phyto-constituents entrapped in nano-delivery systems such as liposomes, niosomes, nanostructured lipid carriers, nanomicelles and nanoparticles, ameliorate symptoms of type II diabetes mellitus by increasing the insulin production and secretion, inhibiting gluconeogenesis, reactive oxygen species, oxidative damage, inflammation and controlling cholesterol and triglyceride synthesis. MLV—multilamellar vesicles, SUV—small unilamellar vesicles, LUV—large unilamellar vesicles

thymoquinone-encapsulated nanosized liposomes in comparison with free thymoquinone (Khan et al. 2018). The structural integrity of pancreatic β-cells was seen to be preserved by the liposomal formulation.

Betanin, a bioactive component, has a proven antioxidant activity. In spite of its therapeutic potency and efficacy, stability issues and incomplete oral absorption limit its clinical application. In view of these limitations, betanin nanoliposomes were formulated, which showed a sustained release profile in the simulated intestinal and gastric fluids. The plasma glucose level dropped to 185.11 ± 27.27 mg/dl post-treatment with betanin nanoliposomes, which was lower as compared to pre-treatment plasma glucose levels of diabetic rats (≥ 250 mg/dl). In addition, histopathological research found that damage in the tissues of liver, kidney and pancreas was decreased in betanin-loaded nanoliposome-treated diabetic rats. Hence based on the illustrated results, it can be stated that nanoliposomes are ideal carriers for enhancing the therapeutic efficacy and stability of betanin (Amjadi et al. 2019).

Table 1 Phytochemicals for the treatment of diabetes mellitus and their biological sources

Phytochemicals	Sub-class	Biological source	Parts of the plant	References
Phenolics				
Polyphenols				
1. Flavonoids				Lamba et al. (2000), Bacanli et al. (2019), Aba and Asuzu (2018), Salehi et al. (2019)
Flavonols	Isorhamnetin	*Papaver rhoes L*	Leaves	
		Hippophae rhamnoides, Oenanthe javanica, Ginkgo biloba		
	Kaempferol	*Jindai soybean, Ginkgo biloba*	Leaves	
		Ficus racemosa	Bark	
	Myricetin	*Papaver rhoeas L*	Leaves	
	Rutin	Buck wheat, Oranges, grapes, limes, lemons, berries and peaches	Grains Fruits	
		Rheum species	Leaves and petioles	
		Asparagus		
	Quercetin	*Papaver rhoeas L*	Leaves	
		Bauhinia perpurea L	Leaves	
		Bauhinia variegate L var.canidida Roxb/ Leguminisae		
		Ficus racemosa	Bark	
		Onion, berries, nuts, Brassica	Fruit	
	Resveratrol	Grapes	Peels	
	Epicatechin	*Pterocarpus marsupium Roxb* / Leguminosae	Bark	
Flavanones	Hesperidin	Lemons, sweet orange (*Citrus sinensis* Linn.)	Peels	
	Naringenin	*Ficus racemosa*	Bark	
	Naringin	Grapefruit, sour orange, tomatoes, tart cherries, bergamot, greek oregano, cocoa, water mint, beans	Fruits	
	Mangiferin	*Mangifera indica, Anemarrhena asphodeloides*	Fruit, Rhizomes	
Flavones	Apigenin, Acacetin (derivative of Apigenin)	Chamomile plants	Flowers	
		Chamomile tea	Leaves	
		parsley, celery, celeriac		
	Chrysin	Honey	–	
		Propolis	–	
		Passiflora caerulea	Flower	
		Passiflora incarnate		
	Luteolin	*Mentha spicata L*	Fresh or dried leaves	
Isoflavones	Daidzein, Genistein	Soyabeans and soya products	Whole	

Table 1 (continued)

Phytochemicals	Sub-class	Biological source	Parts of the plant	References
Tannins	Gallotannins	*Caesalpinia spinosa,*	Fruit	Aba and Asuzu (2018), Hostetler et al. (2017)
		Pistacia lentiscus	Leaves	
		Quercus infectoria	Fruit	
	Ellagitannins	Species of Onagraceae, Lythraceae, Myrtaceae, Trapaceae, Melastomataceae	wholeplant	
	Complex Tannins	*Quercus infectoria*	Gall Whole	
	Condensed Tannins	Cereals, legumes, oilseeds, finger millet, field bean, sunflower seed, drumstick	Grain and leaves	
		Amaranth		
Simple Phenol				
1. Phenolic acids	Hydroxy cinnamic acids	Tea, cocoa and wine	Beverages	Morandi Vuolo et al. (2019)
		Plums, blueberries, apples, pears, cherries, kiwis	Whole fruit	
	Hydroxibenzoic acids	Carrots (*Daucus carota*)	Whole fruit	
		Oil palm (*Elaeis gueneensis*)		
		Grapes (*Vitis venifera*)		
2. Coumarins	Simple coumarins	Dipteryx odorata	Seeds	Li et al. (2017a, b)
	Furanocoumarins	*Ammi majus*, parsnip, giant hogweed	Sap of plant	
	Dihydrofurano coumarins			
	Pyranocoumarins	*Clausena excavate*	Roots	
	Phenylcoumarins	Strawberries, black currant, apricots and cherries	Edible parts of the plants	
	Bicoumarins	Rutaceae and Umbelliferone	Plant (fruits, roots, stem and leaves)	
Alkaloids	Berberine	*Coptis chinensis*/Ranunculaceae	Aerial parts	Lamba et al. (2000), Aba and Asuzu (2018), Salehi et al. (2019)
	Dioscoretine	*Dioscorea dumetorum* Pax/Dioscoreaceae	Tuber	
	Galegin	*Galega officinalis Linn*/Leguminosae	Seeds	
	Lathyrines	*Lathyrus japonicas Sic*/Leguminosea	Seeds	
	Lepidine	*Lepidium ruderale L*/Cruciferea	Aerial parts	
	1, 2 substituted pyrrolidines	*Tinospora cordifolia Miers*/ Menispermaceae	Whole plant	
	Tecomine and Tecostamine	*Tecoma stans Juss*/Bignoniaceae	Whole plant	
	Vindoline	*Vinca rosea Linn*/Apocyanaceae	Leaves	

Table 1 (continued)

Phytochemicals	Sub-class	Biological source	Parts of the plant	References
Glycoside/steroids/ terpenoids	β-Sitosterol	*Coffea arabica*/Rubiaceae	Green beans	Lamba et al. (2000), Aba and Asuzu (2018), Salehi et al. (2019)
		Acacia arabica / Mimosaceae	Seeds	
	β-Sitosterol 3-β-D-glucoside	*Centauria seridis L.var.maritima*/compositae	Aerial parts	
		Ficus religiosa O/moraceae	Bark	
	Bassic acid	*Bumelia sartorum Mart*/ Sapotaceae	Root bark	
	E-Senega saponins, Z-Senega saponins and Senegins II, III, IV	*Polygala senega L. var.latifolia Torrey et Gray*/Polygalaceae	Rhizomes	
	Elatoside E and F	*Aralia elata Seem*/Araliaceae	Roots	
	Ginsenoside RbI and RgI	*Panax ginseng Mey*/Araliaceae	Roots	
	Ginsenoside Rb2	*Panax ginseng Mey*/Araliaceae	Roots	
	Iridoidal glycosides	*Gardenia jasminoids Ellis*/Rubiaceae	Leaves	
	Stevioside	*Stevia rebaudiana* Bertoni	Leaves	
	Oleanolic acid	*Cornus officinalis Sieb.et Zucc*/Cornaceae	Seeds	
		Momordica cochinchinensis Spreng / Cucurbitaceae	Tuber	
	Oleanolic acid glycosides	*Aralia elata Seem*/Araliaceae	Root	
	Pelargonidin glycoside	*Ficus bengalensis* Linn/Moraceae	Barks	
	Prunin	*Prunus davidiana Fr*/Rosaceae	Fruits, Stems	
	Timosaponin AIII	*Anemarrhena asphodeloids Bunge*/ Liliaceae	Rhizomes	
	Saponin triterpenoidal glycoside Christinin A	*Ziziphus spina-christi* Wild/ Rhamnaceae	Leaves	
	Saudin	*Cluytia richardiana* L/Euphorbiaceae	Leaves	
	Steroidal glycoside	*Polygonati rhizome*/ Liliaceae	Rhizomes	
	Steroid Saponins	*Balanites aegyptiaca Del*/Balatinaceae	Fruits	
	Sesquiterpene glycosides polyhydroxylated triterpenoids	*Eriobotrya japonica Linde*/Rosaceae	Leaves	
	Tormentic acid	*Poterium ancistroides Desf*/Rosaceae	Aerial parts	
	Ursolic acid	*Cornus officinalis Sieb.et Zucc*/Cornaceae	Seed	
Polysaccharides and proteins	Aconitans A, B, C, D	*Aconitum carmichaeli Debx*/ Ranunculaceae	Roots	Lamba et al. (2000), Aba and Asuzu (2018), Salehi et al. (2019)
	Arborans A and B	*Aloe arborescens Mill*. var. natalensis/ Liliaceae	Leaves	
	Atractans A, B, C, D	*Atractyloids japonica Koidz*/Compositae	Rhizomes	
	Coixans A, B, C		Seeds	

Table 1 (continued)

Phytochemicals	Sub-class	Biological source	Parts of the plant	References
		Coix lachryma-jobi L. var. mayuen Stapf/ Gramineae		
	Dioscorans A, B, C, D, E, F	*Dioscorea japonica* Thunb/Dioscoreaceae	Tubers	
	Eleutherans A, B, C, D, E, F, G	*Eleutherococcus senticosus* Maxim/Araliaceae	Roots	
	Ephedrans A, B, C, D	*Ephedra distachya* Linn/Ephedraceae	Aerial parts	
	Ganoderans A, B, C	*Ganoderma lucidum* Karsten/ Polyporaceae	Fruits	
	Lithospermans A, B, C	*Lithospermum erythrohizon* Zucc/ Boranginaceae	Roots	
	Moran A	*Morus alba* L/Moraceae	Root barks	
	Oryzabrans A, B, C, D	*Oryza sativa* L/Gramineae	Roots, External seed coats	
	Neutral polysaccharide	*Malva verticilata* L/Malvaceae	Seeds	
	Panaxans A, B, C, D, E	*Panax ginseng* Mey/Araliaceae	Roots	
	Quinquefo-lans A, B, C	*Panax quinquefolium* L/Araliaceae	Roots	
	Saccharans A, B, C, D, E, F	*Saccharum officinarum* L/Gramineae	Aerial plant	
	Trichosan A, B, C, D, E	*Trichosanthes kirilowii* Maxim/ Cucurbitaceae	Roots	
Miscelaneous	Allicin	*Allium cepa* linn *Allium sativum* linn/Liliaceae	Bulb	Lamba et al. (2000), Aba and Asuzu (2018), Salehi et al. (2019)
	Curcuminoids	*Curcuma longa*	Rhizomes	
	Masoprocol	*Larrea tridentate*		
	4-hydroxy isoleucine	*Trigonella foenum-graecum*	Seeds	
	Ginseng polypeptides	*Panax ginseng*	Roots	
	Marsupsin Pterostilbene Pterosupin	*Pterocarpus marsupium* Roxb/ leguminosae	Heartwood	
	Swerchirin	*Swertia chirayita Karst*/Gentianaceae	Whole plant	
	Ferulic Acid	*Curcuma longa*	Leaves and seeds	

Niosomes

Niosomes are the surfactant-based nanocarriers and categorized as vesicular delivery systems. Uniqueness of vesicular system of niosomes is the presence of nonionic surfactants in aqueous phase, and it is more advantageous than liposomes with respect to drug-loading efficiency, use of less cholesterol and better capability in crossing the biological barriers due to enhanced permeability (Kazi et al. 2010). Niosomes may be classified on the basis of size, number of bilayers as multilamellar vesicles, large unilamellar vesicles, small unilamellar vesicles, proniosomes and bola niosomes (Khoee and Yaghoobian 2017).

Niosomes can entrap hydrophilic and lipophilic drugs and can deliver the drugs in a controlled way at the targeted site. Niosomes are superior than other vesicular systems as they are chemically stable, biodegradable, biocompatible, require low production cost, less toxic and easy to store and handle (Khoee and Yaghoobian 2017). The universality of niosomes can be applicable for designing the drug delivery for oral, pulmonary, nasal, transdermal, ocular and gene delivery (Khan and Irchhaiya 2016).

Lycopene, a potent bioactive of *Lycopersicum esculentum*, has potential application in diabetes, but its high sensitivity to light, heat and oxidants proves to be a hurdle in its therapeutic applications. In such a scenario, lycopene niosomes were formulated to preserve its activity. The antidiabetic function of the formulation showed a substantial reduction in blood glucose levels. In the treated groups, biochemical markers such as total cholesterol, total glycerides, low-density lipoprotein and very-low-density lipoprotein were substantially reduced relative to the control groups. The overall results indicated that niosomes loaded with lycopene are efficient nanotools against diabetes. For broader applications that can play an important role in drug delivery and formulation science, the niosome formula appeared to be much encouraging (Sharma et al. 2017).

Solid lipid nanoparticles

The solid lipid nanoparticles are considered to be an optimum carrier system for the treatment of type II diabetes mellitus and diabetes-induced oxidative stress in mice through the oral delivery of myricitrin. Myricitrin-encapsulated solid lipid nanoparticles accomplished a continual release from the nanoformulation of myricitrin and demonstrated exceptional therapeutic outcomes in concurrent hyperglycemia, insulin tolerance, myotubal deficiency of glucose absorption and in vitro and in vivo pancreatic apoptosis. Myricitrin solid lipid nanoparticles have been shown to be more efficacious at a much lower dosage than metformin. The stated formulation was also capable of attenuating oxidative stress, fibrosis, inflammation and apoptosis induced by hyperglycemia in high-glucose-exposed in vitro mouse model (Ahangarpour et al. 2018).

Another research study evaluated the efficacy of myricitrin-encapsulated solid lipid nanoparticles on streptozotocin–nicotinamide-induced type II diabetes mellitus of the mouse and hyperglycemic myotube. The in vitro and in vivo studies showed better diabetes conditions and improved hyperglycemia complications. Hence, it can be inferred that the nano-entrapment of myricitrin was able to showcase better antioxidant, antidiabetic and antiapoptotic effects in the mouse and myotube cells (Ahangarpour et al. 2018).

In order to improve the efficacy of resveratrol after oral therapy in diabetic rats, resveratrol-loaded solid lipid nanoparticles were fabricated. The formulation initially showed an initial burst release accompanied by a slow release under standard conditions with an enhanced resveratrol oral bioavailability. The formulation was proved to be substantially advantageous over free resveratrol in overcoming insulin resistance via the stimulation of synaptosomal-associated protein 23 (Snap23), syntaxin-4 (Stx-4), and vesicle-associated membrane protein 2 (Vamp2) mRNAs in tissues of muscle as well as decrease of oxidative stress in type II diabetic rats (Mohseni et al. 2019).

Madureira and co-workers designed physicochemically safe and biologically compatible rosmarinic acid solid lipid nanoparticles using carnauba waxes. Oral delivery of rosmarinic acid could be possible by the nanoformulations as it was found to be stable and biocompatible (Madureira et al. 2015). Additionally, rosmarinic acid solid lipid nanoparticles displayed no signs of in vitro genotoxicity or cytotoxicity as evidenced in the published report (Reis et al. 2016).

Compared to the berberine in native form, berberine-loaded solid lipid nanoparticles were noted to maximize the oral bioavailability, stability as well as antidiabetic potency (Wang et al. 2011). The oral administration of the nanoformulations substantially decreased hyperglycemia, gain of body weight and insulin tolerance in type II diabetes-induced mice (Xue et al. 2013). Furthermore, berberine-entrapped solid lipid nanoparticles had reached maximal liver drug concentration by approximately 20 times more than in plasma and dramatically depleted hepatosteatosis caused by type II diabetes (Xue et al. 2015).

Chitosan-conjugated silybin solid lipid nanoparticles have been identified to be more stable, with notable mucoadhesive properties, continuous release, improved absorption and cellular internalization of silybin after oral

absorption (Piazzini et al. 2019). Bixin-loaded solid lipid nanoparticles have been reported to improve their therapeutic potential by improving stability, tissue localization at target sites and controlled release of drug by passive diffusion mechanism and profound cellular internalization of bixin (Rao et al. 2014).

Nanostructured lipid carriers

Nanostructured lipid carrier is a type of lipid-based nanodelivery system having some anchored advantages over solid lipid nanoparticles, like smaller particle size and increased loading capability to accomplish efficient delivery of phytochemicals in type II diabetes mellitus treatment (Ni et al. 2014).

Numerous studies have displayed superior antihyperglycemic effects of baicalin, which acts by inhibition of lipid peroxidation. Baicalin, being a low hydrophilic drug with poor absorption after oral administration, suffers from widespread therapeutic application. In such a pursuit, baicalin-loaded nanostructured lipid carrier was synthesized by using precirol as the solid lipid and miglyol as the liquid lipid and further evaluated for antidiabetic effects. It was noted from the in vivo results that baicalin-loaded nanostructured lipid carriers significantly decreased the fasting blood glucose level, glycosylated hemoglobin, total cholesterol and total glycerides in diabetic group in comparison with the normal control group, implying the fact that the nanoformulation-entrapping baicalin has significant hypoglycemic effect and has a pivotal role in regulating lipid metabolism in type II diabetes mellitus (Xu et al. 2016).

Nanostructured lipid carriers loaded with baicalin have been showcased to be safe for delivery by oral route, providing baicalin by continuous release, and have been shown to improve the hypoglycemic potency of baicalin. At the same dosage, relative to free baicalin and metformin, the regulation of hyperglycemia and hyperlipidemia was found to be more significant in the nanostructured lipid complex of baicalin in diabetic rats (Xu et al. 2016).

Berberine-entrapped selenium-coated nanostructured lipid carriers have been recognized to cause the therapeutic effectiveness of berberine in the treatment of diabetes relative to berberine-entrapped nanostructured lipid carriers and free berberine. Increased absorption in intestine, bioavailability by oral administration and controlled release of berberine were elicited due to selenium modulation of the nanostructured lipid formulation. The selenium-entrapped berberine nanostructured lipid carriers improved the uptake of glucose in diabetic rats by increased diffusion of the phytochemical into enterocytes (Yin et al. 2017).

Oral bioavailability of ferulic acid was found to be increased in ethyl oleate-nanostructured lipid carriers than solid lipid nanoparticles (Zhang et al. 2016). There are reports indicating significant antioxidant and antidiabetic properties of astaxanthin, a natural keto-carotenoid. The ability to boost stabilization and increase the antioxidant function of astaxanthin was demonstrated by astaxanthin-assembled nanostructured lipid carriers (Bhuvaneswari and Anuradha 2012).

Nanomicelles

Micelles are core–shell-type nanostructures containing hydrophobic core and the hydrophilic outer layer to form the shell. They are produced by self-assembling of amphiphilic co-polymers at a critical micellar concentration. The hydrophobic core acts as a suitable carrier for hydrophobic drugs used for antidiabetic treatment (Ahmad et al. 2014).

Silymarin-entrapped nanomicelles were evaluated for its efficacy and mechanism of action in lowering glucose level in streptozotocin-induced diabetic rats. Silymarin-loaded pluronic nanomicelles were fabricated, which were noted to improve antioxidant, antihyperglycemic and antihyperlipidemic activities as compared with free silymarin. The observed effect may be due to sustained release pattern and superior bioavailability conferred by silymarin nanomicelles. Treatment with silymarin nanomicelles showed a high degree of downregulation of fasting blood glucose levels from the initial week following significant suppression of blood glucose levels from the second week of treatment ($p < 0.001$, $p < 0.0001$ respectively) as compared to the control group. In particular, silymarin nanomicelles therapy was shown to restore fasting glucose levels to a near-normal range by the end of the second week of therapy and also proved to be better than native silymarin in this aspect (El-Far et al. 2016).

Furthermore, curcumin-loaded pluronic nanomicelles were also evaluated for the treatment of diabetes. The hypoglycemic activity of curcumin nanomicelles was largely attributable to the major upregulation of expression of Pdx-1 and NKx6.1 genes and the optimum redox balance was achieved, contributing to exacerbation of β-cell damage by streptozotocin through up-regulating gene expression for insulin shown by reverse transcriptase polymerase chain reaction studies and the existence of 40% insulin-positive cells through confocal pancreatic microscope pictographs (El-Far et al. 2017).

Morin, a phyto-derived bioflavonoid, has potential benefits that include lowering lipogenesis, gluconeogenesis, inflammation and oxidative stress. Additionally, morin showed insulin-mimetic activity, so believed to be a natural antidiabetic drug (Paoli et al. 2013). Its bioavailability is

limited owing to its poor oral solubility, resulting in lower therapeutic benefits. An increased dose, however, can result in toxicity patterns. In such a pursuit, morin was fabricated as mixed micelles with an average particle size of approximately 90 nm. Compared to the native drug, the morin-loaded mixed nanomicelles displayed a 3.6-fold improvement in cellular penetration, with an improved permeability rate of approximately 2.4 times, which enhanced the bioavailability in the systemic circulation (Choi et al. 2015).

It has been noted in in vivo experiments that the lack of bioactivity and lower solubility by oral administration contributed to lower bioavailability of genistein. In particular, administration of higher dose was related to emergence of other risks and toxicity patterns. In recent decades, several nanoscale methods have been applied to address toxicity and higher dose effects, enhancing genistein oral distribution (Wu et al. 2016). In such a scenario, genistein-loaded polymeric micelles administered by oral delivery showed an enhanced bioavailability. The observed effect may be attributed to the increase in solubility of the drug with a better permeability (Kwon et al. 2007).

Hyperglycemia, hyperlipidemia, oxidative stress, and hypoinsulinemia have been shown to be attenuated by curcumin-entrapped pluronic nanomicelles administered orally by restricting β-cell injury, fostering β-cell regeneration and activating PDX-1 and NK6 homeobox-1 (NKx6.1) gene activation beyond the results depicted by control group (El-Far et al. 2017).

A nanosystem comprising of apigenin-loaded nano-micelles involving soluplus and pluronic F127 polymers has been reported to achieve sustained release with quadruple bioavailability and reinforce absorption of apigenin gastrointestinal tract as compared to free apigenin in rats. Nano-mixed micelles of apigenin greatly increased the water solubility and cellular uptake of apigenin (Zhang et al. 2017).

As compared to suspension of baicalin in rats, baicalin-encapsulated nanomicelles incorporating pluronic P123 copolymer and sodium taurocholate demonstrated an increase in absorption, circulation time and oral bioavailability by approximately > 1.5 times as compared to native baicalin and can thus contribute as a potential approach to oral delivery of baicalin (Xu et al. 2016).

Self-assembled phospholipidic nanomicelles loaded with mangiferin have been demonstrated to enhance the biopharmaceutical characteristics of mangiferin (Khurana et al. 2017). Following the study, the same research group designed a self-assembled phospholipidic nanomixed micelles system co-loaded with vitamin E-D-alpha-tocopheryl polyethylene glycol 1000 succinate, which also increased the intestinal permeability as well as oral bioavailability of mangiferin (Khurana et al. 2018).

Nanoparticles

Nanoparticles are the most widely used nanomaterial for administration of antidiabetic drugs due to enhanced drug utility and decreased adverse effects. Surface modification can further help in more target-specific delivery of the antidiabetic drugs to control the hyperglycemic conditions (Ponnappan and Chugh 2015).

More recently, the neuroprotective roles of flavonoids are extensively examined in neurodegenerative disorders. Quercetin is a phytoderived bioactive flavone, which has multitude of therapeutic applications. However, it has restricted blood–brain barrier permeability, low oral bioavailability, weak aqueous solubility and fast gastrointestinal digestion, which contribute to high-dose quercetin administration in clinical use. In order to overcome the stated limitations, quercetin was conjugated with superparamagnetic iron oxide nanoparticles and was further tested in streptozotocin-induced diabetic rats for assessing its benefit as an antidiabetic treatment modality and improving diabetes-related memory impairment. Quercetin–iron oxide nanoparticles and free quercetin induced a substantial decrease in blood glucose level in diabetic rats. Quercetin-loaded super-paramagnetic iron oxide nanoparticles displayed significantly improved efficacy than free quercetin on the upgrading of memory performance (Ebrahimpour et al. 2018).

Carbohydrate biopolymers such as chitosan and alginate were utilized for successful entrapment of a flavanone drug, naringenin. In vivo studies indicated appropriate hypoglycemic effect after oral delivery of the nanoformulations to streptozotocin-induced diabetes in rats. The significant antidiabetic effect is attributed to the stimulatory action of naringenin, which acts by regeneration of β-cell islets, which in turn improves the diabetic condition in rats. The research findings indicated that polymeric formulations entrapping the flavonoids were too effective in the treatment of dyslipidemia; hyperglycemia and hemoglobin iron induced oxidative stress in the type I diabetic paradigm (Maity et al. 2017).

Gallic acid, a phenolic compound, is widely known for its antidiabetic activity. However, because of its deterioration during the absorption process, the use of this compound delivers unsatisfactory outcomes. The approach proposed to solve the problem is to encapsulate it in chitosan nanoparticles that leverage freeze-drying technique to shield the bioactive compound from degradation, improve solubility, and deliver the bioactive compound to the target site. Results of the inhibition test revealed that gallic acid-conjugated chitosan nanoparticles at 50 ppm

were able to inhibit alpha-glucosidase activity. It can thus be inferred that gallic acid can be encapsulated in chitosan nanoparticles and has been shown to suppress alpha-glucosidase enzyme (Purbowatiningrum et al. 2017).

Ferulic acid, a hydroxyl cinnamic acid, has a variety of medicinal properties, which may be due to its strong antioxidant ability, including antidiabetic impact. However, its medicinal uses have remained stagnant owing to its poor bioavailability and clinical efficacy. In the current research, ferulic acid-encapsulated chitosan nanoparticles were produced in order to boost ferulic acid bioavailability. Extended plasma retention time was shown by the encapsulated ferulic acid, and maximum plasma concentration was registered at 60 min. There was a marked drop in blood glucose in the group of rats treated with free ferulic acid and ferulic acid nanoparticles, respectively, though no pronounced decrease was observed in insulin levels.

More interesting findings were reported for rats treated with ferulic acid nanoparticles, where a substantial drop in glucose levels in blood was found over the whole duration of the study relative to all diabetic control groups and glibenclamide-treated rats. Ferulic acid nanoparticles were also evaluated on streptozotocin-induced diabetic Wistar rats and was shown to mitigate the symptoms related to diabetes. Ferulic acid nanoparticles also showed an increase of body weight, a drop in glucose levels in blood and a controlling effect on diabetic rats' blood lipid profile. The positive effect of ferulic acid nanoparticles on the improvement of the hyperglycemic syndrome prevailing in diabetic rats could offer new avenues for diabetes mellitus care and potentially prevent drug-related secondary complications (Panwar et al. 2018).

Glycyrrhizin is an active phytoconstituent of *Glycyrrhiza glabra*'s roots and rhizomes and has proven antidiabetic effects. Glycyrrhizin- and metformin-loaded nanoparticles employing the biocompatible polymers gum arabic and chitosan were evaluated in vivo for their antidiabetic ability in type II diabetes in rats. As compared to the control group, rats treated with glycyrrhizin-loaded nanoparticles at a similar dose of 20 or 40 mg/kg containing 4.2 or 8.4 mg/kg of glycyrrhizin, respectively, demonstrated a substantial dose-dependent drop in blood glucose levels ($p < 0.001$) as implied by the q values, 22.04 and 23.53, respectively. Similarly, the groups treated with metformin (40 mg/kg) and glycyrrhizin (20 and 40 mg/kg) revealed a substantial drop in blood glucose levels ($p < 0.001$) relative to rats treated with native metformin. It can be concluded that glycyrrhizin nanoparticles had superior anti-hyperglycemic benefits even though they encompassed only a quarter of the dose compared to the free drug (Rani et al. 2017).

Another research report suggested that curcumin-treated rats displayed slightly higher levels of insulin and insulin receptor gene expression, relative to positive and negative controls. These findings indicated that nano-curcumin could be employed in streptozotocin-induced diabetic rats as antidiabetic treatment, to cause hypoglycemia and to improve gene expression of insulin and insulin receptors. In order to explain the precise mechanism of action of nano-curcumin relating the upregulation of gene expression, further investigations are necessary (Gouda et al. 2019).

Antidiabetic activities have also been demonstrated by berberine, an isoquinoline derivative of alkaloid. Nevertheless, its poor oral bioavailability limits its medicinal use. Nanosuspension of berberine was developed comprising of berberine and D-alpha-tocopheryl polyethylene glycol 1000 succinate. In streptozotocin-induced diabetic C57BL/6 mice, antidiabetic efficacy of berberine nanosuspension was compared to bulk berberine. Superior hypoglycemic and total cholesterol and body weight lowering results were achieved by berberine nanosuspension when administered at a dose of 50 mg/kg by oral route relative to the comparable dosage of bulk berberine and metformin (metformin at a dose of 300 mg/kg). These results suggest that a low dose of berberine nanosuspension in type II diabetic C57BL/6 mice lowered blood glucose and increased lipid metabolism. These observations indicate that delivery of berberine nanosuspension may be a striking approach for the treatment of type II diabetes (Wang et al. 2015).

The connection between diabetes and zinc homeostasis dysfunction enabled nanoparticles of zinc oxide an enticing therapeutic alternative. In diabetes mellitus, the glucose-phosphorylating enzyme glucokinase and the glucose transporter 2 were involved in the regulation of glucose metabolism. Pleiotropic actions on a diverse variety of molecular benchmarks are seen by curcumin, the key polyphenolic phyto-constituent of rhizomes of turmeric. Curcumin exhibits hypoglycemic impact by multiple pathways, including gene expression of glucokinase and glucose transporter 2 in diabetes mellitus. The present research evaluated curcumin nanoparticles, zinc oxide nanoparticles and curcumin–zinc oxide composite nanoparticles on the possible efficacy in streptozotocin-induced diabetic rats. The most potent antidiabetic behavior was shown by curcumin–zinc oxide composite nanoparticles, and the histopathological results confirmed the biochemical and molecular evidence suggesting curcumin–zinc oxide composite nanoparticles as a possible antidiabetic agent (Raslan et al. 2018).

Vicenin-2 gold nanoparticles were also evaluated their effect on the glucose utilization efficiency in 3T3-L1

adipocytes. When incubated with vicenin-2 gold nanoparticles, a concentration-dependent increase in glucose uptake was noted in 3T3-L1 adipocytes. A close interaction of vicenin-2 with the protein-tyrosine phosphatase 1B and 5' adenosine monophosphate-activated protein kinase binding pockets was unveiled in the docking results. This indicated that the developed vicenin-2 gold nanoparticles could facilitate the use of cellular glucose regulated by intracellular vicenin-2 accessibility, which may serve as a novel nano-drug for diabetes treatment (Chockalingam et al. 2015).

Stevia rebaudiana has become a lead candidate for diabetes treatment owing to its hypoglycemic and antihyperlipidemic properties. The result demonstrated for the first time that the titanium dioxide–*Stevia rebaudiana* nanoformulation at a dose of 20 and 30 μM was able to reverse the alloxan-induced hyperglycemic effect. In addition, the insulin, glycosylated hemoglobin, cholesterol and triglyceride concentrations demonstrated a substantial recovery from baseline values. Hence, it can be inferred that titanium dioxide could also be used as an appropriate vehicle for the sustained release of active compounds for the treatment of diabetes mellitus (Langle et al. 2015).

In improving the therapeutic efficacy and bioavailability of different drugs, biodegradable polymers have been used for innovative drug delivery systems, which gained considerable attention (Parhi, 2020). 14-Deoxy 11, 12-didehydro andrographolide-entrapped polycaprolactone nanoparticles were synthesized and the confocal microscopy experiments with rhodamine 123-loaded polycaprolactone nanoparticles showed a time-dependent internalization of the nanoparticles in L6 myoblasts. For 14-deoxy 11, 12-didehydro andrographolide-entrapped polycaprolactone nanoparticles, a maximum uptake of 108.54 + 1.42% at 100 nM on L6 myotubes, a dose-dependent rise in glucose uptake was observed, confirming its antidiabetic efficacy (Kamaraj et al. 2017).

Nanophytochemicals for the treatment of complications associated with type II diabetes mellitus

In patients with type I and II diabetes mellitus, the associated complications are typical and are also accountable for remarkable morbidity and mortality. The complications are notably divided into microvascular and macrovascular where the former includes neuropathy, nephropathy and retinopathy and the later includes cardiovascular disease, stroke and peripheral artery diseases (Papatheodorou et al. 2018). The other related complications include dental disease, reduced resistance to complications and birth complications that are not included under the above-mentioned categories rather included under gestational diabetes (Papatheodorou et al. 2018; Deshpande et al. 2008). Diabetes-induced cataract also proved to be a major cause of blindness in a number of subjects. The risks of cataract were noted to be higher in type II diabetes mellitus patients as compared to the non-diabetic ones (Li et al. 2014). Some other complications include diabetic wounds, severe hypoglycemia and higher risk of cardiovascular disease (Papatheodorou et al. 2018).

A typical associated complication is diabetic peripheral neuropathy, which precipitates with risk of age, smoking, disease period, hypertension, elevated triglyceride levels, alcohol intake, higher body mass index and taller height. Polyneuropathy, a form of diabetic peripheral neuropathy, leads to weakness of muscles, sensory loss and pain including burning sensation and lack of sensation in feet. Patients with diabetic peripheral neuropathy are often noted with a risk of foot ulceration (Li et al. 2014).

Diabetic nephropathy or persistent proteinuria with patients without urinary tract infections or other diseases may be noticed in individuals with type II diabetes mellitus. People with type II diabetes mellitus and diabetic nephropathy are more likely to develop stroke and coronary heart disease than the people with only diabetes (Deshpande et al. 2008).

Retinopathy is associated with prolonged hyperglycemia. The impairment of vision in patients with diabetes increases with age, and women are more prone to the disability than men (Deshpande et al. 2008).

Ischemic heart disease and stroke enlist for higher proportion of morbidity in diabetes mellitus (Deshpande et al. 2008). Cardiovascular disease is the most prevalent case of morbidity and mortality in diabetes mellitus. In diabetic patients, the risk associated with cardiovascular diseases like obesity, dyslipidemia and hypertension is common (Leon 2015).

Peripheral vascular diseases may lead to injuries that do not heal which proceeds to gangrene and then amputation. This is caused due to narrowing of blood vessels carrying blood to different parts and organs of the body. In case of diabetic patients, peripheral vascular disease increases with age, duration of diabetes and presence of neuropathy (Deshpande et al. 2008).

Table 2 Nanophytochemicals for the treatment of complications associated with type 2 diabetes mellitus

Type of diabetic complication	Name of the biomolecule	Types of nanodelivery system	Mechanism of action	Pharmacological output	References
Diabetic cardiomyopathy	Curcumin and garlic extract	Nanoparticles	Downregulation of gene expression of receptor for advanced glycation end products up to 1.79 times by garlic extract Nano-curcumin and garlic extract normalized the integrity of structures of monocytes in heart of diabetic models	Garlic extract enhanced the insulin level and reduced the activities of serum glucose level, creatine kinase-isoenzyme, lactate dehydrogenase enzyme activities Nano-curcumin reduced the serum levels of triglycerides, creatine kinase- MB, lactate dehydrogenase, and aspartate aminotransferase Accumulation of transcript quantity of manganese-superoxide dismutase gene by 3.25 and 3.87 times in heart tissues with nano-curcumin and garlic extract suspension, respectively	Abdel-Mageid et al. (2018)
Diabetic complications	Curcumin and coenzyme Q10	Polymeric nanoparticles–coenzyme Q10 and curcumin-loaded poly lactic–co-glycolic acid nanoparticles	Coenzyme Q10 nanoparticles reduced C reactive protein levels Curcumin nanoparticles reduce C reactive protein levels, interleukin-6 and tumor necrosis factor-α levels	Enhanced the bioavailability of coenzyme Q10 and curcumin Increase in antioxidant and anti-inflammatory efficacy Reduction of plasma triglycerides, total cholesterol and increase in high-density lipoprotein cholesterol	Devadasu et al. (2011)
Diabetic cataract	Curcumin	Polymeric nanoparticles—poly lactic–co-glycolic acid nanoparticles	Nano-curcumin delays progression by interfering the biochemical pathways such as protein insolubilization, polyol pathway, protein glycation, crystalline distribution and oxidative stress	Reduction in body weight (198 $\pm$ 5.22 g) in diabetic animals treated with nano-curcumin in comparison with the control group (320 $\pm$ 3.65 g) A remarkable percentage of delay was showcased in cataract progression, i.e., 0.379 with standard error of mean 0.080	Grama et al. (2013)
Diabetic peripheral neuropathy	Curcumin	Microspheres—curcumin loaded poly-(ethylene glycol) methacrylate—2-(dimethylamino)-ethyl-methacrylate-Methylaluminoxane microspheres	Reduction in up-regulating gene expression of connexin43 and interleukin-1β Reduction of phosphorylated protein kinase B levels in the dorsal root ganglia of diabetic rats Inhibition of satellite glial cells along with its anti-inflammatory effects decreasing the expression of up-regulated calcitonin gene-related peptide in the neurons at dorsal root ganglia	The results of the phosphorylated protein kinase B to protein kinase B-integrated optical densities were found to be increased significantly in comparison with the control group Curcumin-encapsulated nanoparticles decreased the ratio of phosphorylated–protein kinase B to protein kinase B-integrated optical densities in treated group as compared to the untreated group	Jia et al. (2018)
		Self-nano-emulsifying drug delivery	Self-nano-emulsifying drug delivery of curcumin acts effectively for proper nerve functioning and decrease in inflammatory proteins like tumor necrosis factor-α and interleukin-6	Increase in bioavailability with increase in maximum plasma concentration by 1632.1% and area under curve by 7411.1% and increased half-life of 10.1 h than naïve curcumin Appreciable results were observed against functional, behavioral and biochemical deficiencies in diabetic neuropathy, enhancing protection	Joshi et al. (2013)

Table 2 continued

Type of diabetic complication	Name of the biomolecule	Types of nanodelivery system	Mechanism of action	Pharmacological output	References
	Emodin	Microspheres—poly-(ethylene glycol) methacrylate-(dimethylamino)-ethyl-methacrylate—methyl-methacrylate microspheres	Decrease in phosphorylation and activation of extracellular signal-regulated protein kinase ½ in dorsal root ganglia Inhibition of signals in human embryonic kidney cell lines HEK293 transfected with the P2X3 targeted by P2X3 agonist α, β-methylene ATP	Up-regulation of P2X3 receptor, tumor necrosis factor-α protein and even the phosphorylation of extracellular signal- regulated protein kinase 1/2 in dorsal root ganglia of type II diabetes mellitus-induced rats Decrease in hyperalgesia and in type II diabetic rats, indicating alleviation of diabetic peripheral neuropathy was observed	Li et al. (2017a, b)
Diabetic retinopathy	Scutellarin	Polymeric nanoparticles—scutellarin-loaded amphiphilic chitosan derivative with deoxycholic acid and vitamin B_{12} nanoparticles	Increase in permeation of nanoparticles in human colorectal adenocarcinoma Caco-2 cells High cellular uptake ensuring the increase in efficacy by oral delivery Down-regulation of expression of angiogenesis proteins with potential for treatment of diabetic retinopathy	The chitosan derivative nanoparticles chitosan–deoxycholic acid–vitamin B_{12} and chitosan–deoxycholic acid showed decreased toxicity in human colorectal adenocarcinoma Caco-2 cells at a concentration of 250 μg/ml with cell viability being 85.02 ± 4.34% and 85.09 ± 3.29% respectively	Wang et al. (2017)
	Quercetin	Solid lipid nanoparticles—propylene glycol with poloxamer 188 as surfactant	Reduction of plasma homocysteine content showing ameliorative effect on relative weight ratio of retinal tissue in streptozotocin-induced diabetic vascular complications Controlling different functions of the cell-like decrease in free radical, increase in function of mitochondria, maintain the polarity of the cell membrane and biosynthesis of reduced glutathione	Improvement in the vascular complications in streptozocin induced diabetes and also improved the levels of optokinetic motor response, startle response, phototactic response and escape response in zebrafish model of diabetic retinopathy	Wang et al. (2020)
	Resveratrol	Gold nanoparticles	Reduction in expressions of retinal mRNA of vascular endothelial growth factor-1, tumor necrosis factor, monocyte chemotactic proteins-1, intercellular adhesion molecule-1 and interleukin-6, interleukin-1β Reduction in streptozotocin-induced growth and phosphorylation of nuclear factor kappa B p65 Decrease in phosphorylation of extracellular signal regulated kinase 1 or 2	More vasculature in the outer nuclear layer, inner nuclear layer and ganglion cell layer in streptozotocin-induced diabetic rats Decrease in vessels was observed with gold nanoparticles (300 mg/kg)	Dong et al. (2019)

Table 2 continued

Type of diabetic complication	Name of the biomolecule	Types of nanodelivery system	Mechanism of action	Pharmacological output	References
Diabetic nephropathy	Quercetin	Polymeric nanoparticle—quercetin-loaded poly (ethylene glycol)–*b*-(poly (ethylenediamine l-glutamate)–*g*-poly (ε-benzyl oxycarbonyl-l-lysine nanoparticle	The nanoparticles regulated the expression of intracellular adhesion molecule-1 on endothelium	The nanoparticle in in vitro showed burst release of 15.23% after 4 h, 71.15% following 3 days and 85.43% following five days showing biphase release profile Quercetin in a subcutaneous injection (10 mg/kg) achieved the maximum plasma concentration of 26.78 μg/ml with transport maximum of 2 h, and reduced to baseline content within 10 h, whereas in case of quercetin nanoparticles, the maximum plasma concentration reached 17.85 μg/ml at transport maximum of 8 h, and declined to baseline content in 5 days showing a sustained release pattern Quercetin nanoparticles reduced diabetic nephropathy through suppression of expression of inflammatory cell infiltration and intracellular adhesion molecule-1	Tong et al. (2017)
	Rhein	Core–shell—rhein-loaded lipid nanoparticles consisting with a yolk as shell structure made up of polycaprolactone–polyethyleneimine-based cores and kidney targeting peptide modified lipid layers	Reduction of transforming growth factor-β1 and up-regulation of Smad2/3 expression Progress of diabetic nephropathy by blockade of inflammatory signaling pathways	Reduction of levels of urea nitrogen, serum creatinine and kidney index Improvement in physiological functions of kidney was observed by ameliorating the levels of creatinine clearance rate and urinary creatinine by repressing secretion and accumulation of fibronectin and transforming growth factor-β1	Wang et al. (2019)
Diabetic wound Healing	Berberine	Nanocolloids—hydrogel	Inhibition of expression of nuclear factor kappa B, tumor necrosis factor-α and interleukin-6 by berberine nanocolloid hydrogel Increase in expression of free vascular endothelial growth factor, cluster of differentiation 31 and smooth muscle actin by activating nicotinamide adenine dinucleotide-dependent deacetylase Sirtuin-1	Aggregation of cells to clusters was noted Berberine and berberine nanocolloid hydrogel with 100 μg/ml promoted the better migration effect and cell proliferation on human foreskin fibroblast migration	Zhang et al. (2020)

Table 2 continued

Type of diabetic complication	Name of the biomolecule	Types of nanodelivery system	Mechanism of action	Pharmacological output	References
	Curcumin	Microspheres—curcumin nanoparticles–gelatin microspheres-loaded into thermos-sensitive hydrogel	The curcumin nanoparticles enclosed in gelatin microspheres responded to the matrix metalloproteinase that gets overexpressed at diabetic non-healing wound sites Promotion of healing efficacy with antioxidant properties and promotes cell migration	Improvement in bioavailability and therapeutic efficacy of curcumin was noted The nanoparticles resulted in a lower inhibitory concentration, i.e., 5.67 ± 0.1 μg/ml in human foreskin fibroblasts (BJ cells) and 3.01 ± 0.06 μg/ml in human keratinocyte (HaCat cells) as compared to native curcumin Nano-crystallization enhanced drug efficacy in vitro	Liu et al. (2018)
		Curcumin nanoparticle—hydrogel	Improved curing process with complete intact dermo epidermal junction, re –epithelialization and reorganization of the dermis Enhancement in deposition of collagen expression of genes like vascular endothelial growth factor and aquaporin 3 was observed	The wound healing in diabetic rats treated with curcumin nanoparticle hydrogel showed a higher rate of wound closure (93.3%) compared to curcumin hydrogel group (58.3%)	Kamar et al. (2019)
		Nanohybrids scaffold—chitosan curcumin nanoparticles	Complete epithelialization with thick granulation tissue formation was seen in nanohybrid scaffold group Curcumin showed anti-inflammatory, antioxidant, anti-infective, angiogenic and healing properties to nerve endings Chitosan in the nanohybrid scaffold got depolymerized to produce N-acetyl glucosamine which initiates fibroblast proliferation and helps in deposition of collagen	Nanohybrid scaffold exhibited better in vitro properties like better water uptake, biocompatibility and sustained drug release In vivo wound healing by non-hybrid scaffold was faster than the healing of wounds in comparison with the control and placebo scaffold groups	Karri et al. (2016)
		Polymeric micelle-alginate, chitosan, pluronic F127, pluronic P123, maltodextrin with curcumin	Sustained anti-inflammatory and antioxidant effect of curcumin led to scavenging of free radicals leading to decline in oxidative stress at wound site	Different formulation combinations were prepared. The formulation containing chitosan and sodium alginate showed enhanced wound healing as they prevented the wound from infections from bacteria and speeded up healing process	Akbar et al. (2018)

Table 2 continued

Type of diabetic complication	Name of the biomolecule	Types of nanodelivery system	Mechanism of action	Pharmacological output	References
	Curcumin and *Gymnema sylvestre*	Scaffold–graphene oxide polyhydroxy butyrate-sodium alginate curcumin and *Gymnema sylvestre* composite	The combination of *Gymnema sylvestre* and curcumin in graphene oxide scaffold increased the biocompatibility and the pores caused better cell viability by enhancing the proliferation of the cell	75 μg/ml of graphene oxide polyhydroxy butyrate-sodium alginate curcumin and *Gymnema sylvestre* showed a significant increment in cell viability Polyhydroxy butyrate—sodium alginate; graphene oxide-polyhydroxy butyrate-sodium alginate and graphene oxide polyhydroxy butyrate-sodium alginate curcumin and *Gymnema sylvestre* scaffolds showed viability over 80%, 85%, and 95%, respectively, where graphene oxide polyhydroxy butyrate-sodium alginate curcumin and *Gymnema sylvestre* showed the maximum cell viability	Daisy et al. (2020)
	Rosmarinic acid	Polymeric nanoparticles of rosmarinic acid-loaded chitosan nanoparticles	The percentage of wound healing was found to be heightened by enhancing the wound closure efficiency than the rosmarinic acid	The rate of wound closure was faster for rosmarinic acid nanoparticles in comparison with native rosmarinic acid and control group	Wani et al. (2019)
	Resveratrol	Polymeric nanoparticle—carboxy methyl cellulose-based wafer with resveratrol nanoparticles	The stability and solubility of resveratrol increased Exposure of resveratrol in a sustained manner, small size and high surface area to volume ratio accelerated the internalization of the drug and enhanced cell proliferation leading to netter wound healing	The wafer of resveratrol nanoparticles showed 100% of wound healing by day 11 as compared to other groups with normal saline, free wafer and resveratrol wafer which showed 64.47 ± 6.65%, 84.76 ± 3.89%, and 86.18 ± 5.53% of healing, respectively	Amanat et al. (2020)
		Microparticles of resveratrol-loaded hyaluronic acid and dipalmitoyl phosphatidyl choline microparticles	Increase in superoxide dismutase activity by the resveratrol microparticles The pore structure of dermal matrix formulation helped in rapid drainage and absorption of the wound exudates and suitable moisture level is maintained which is ideal for wound healing	Sustained release of resveratrol was noted which showed 70% of release after a time period of 6 h Intense collagen fibers were formed without inflammation Highest healing was observed for dermal matrix impregnated with resveratrol microparticles with an augmented antioxidant activity Controlled release and synergistic effect were found in resveratrol microparticles at collagen laminin dermal matrix as it contained skin components The porous structure of the formulation showed approximately 80% water uptake leading to good absorbent characteristics	Gokce et al. (2017)

Table 2 continued

Type of diabetic complication	Name of the biomolecule	Types of nanodelivery system	Mechanism of action	Pharmacological output	References
	Resveratrol and ferulic acid	Nanofiber scaffold—core shell structure (ferulic acid form shell and resveratrol as core)	Angiogenesis with expression of vascular endothelial growth factor by resveratrol and antioxidant and anti-inflammatory effect of ferulic acid showed enhanced wound healing effect by resveratrol – ferulic acid core shell nanofibrous scaffold	Nanofiber scaffold of resveratrol–ferulic acid core–shell increased the tensile strength of skin by twofold An increase in tensile strength due to deposition of collagen from proliferating fibroblasts in the regenerating tissues at the site of the wound was observed	Poornima and Korrapati (2017)
	Quercetin	Polymeric nanoparticle—quercetin–chitosan tripolyphosphate nanoparticles	Quercetin nanoparticles (0.03%) treatment caused decrease in the tumor necrosis factor-α and increase in expressions of interleukin-10, vascular endothelial growth factor and transforming growth factor-β1 Improved wound healing with quercetin nanoparticles (0.3%) by modulating the growth factors, and cytokines were involved in wound healing in inflammation and proliferative phases	Wound healing with quercetin nanoparticles (0.03%) showed superior quality of healing and maturity due to decrease in inflammation and increase in density of blood vessels, number of myofibroblasts, deposition and arrangement of collagen fibers and re-epithelialization	Choudhury et al. (2020)
		PEGylated graphene oxide-mediated quercetin	Reduction of expression of gene collagen (Col I and Col III) leading to the synthesis of collagen proteins that promotes the wound healing α-smooth muscle actin is a marker for early wound healing. The mRNA expression level of α-smooth muscle actin was decreased leading to formation of mature blood vessels during a later period of wound repair	The scaffold showed biocompatibility, cell-adhesive surface for accelerating mesenchymal stem cell attachment and proliferation with high stability	Chu et al. (2018)
	Bixin	Bixin-loaded polycaprolactone nanofibers	Lowering of in vitro fibroblast proliferation leading to significant reduction in the scar tissue area and a good remodeling effect	Burst release of bixin from the nanofibers within 10 h up to 30–40% 100% bixin was released from the nanofibers within 14 days Reduction of collagen deposition was observed in vivo post-treatment with bixin-loaded polycaprolactone nanofibers compared with pure polycaprolactone nanofibers	Pinzón-García et al. (2016)
Diabetic foot ulcer	Berberine	Nanofibers containing cellulose acetate/ gelatine electrospun mat loaded with berberine	Pro-protein convertase subtilisin/kexin type -9—low density lipoprotein receptor pathway was adjusted by berberine to show anti-inflammatory effect Reduction of the plasma concentration of interferon gamma, tumor necrosis factor-α, interleukins -1α, and 8-isoprostane Berberine reduced interleukin-6 expression, activity, and expression of matrix metalloproteinase-9 Berberine suppressed extracellular signal-regulated protein kinase activation and activator protein-1 DNA-binding activity	The dressings exhibited potent anti-bacterial activity Incorporation of berberine did not negotiate with the physical properties of dressing, while improved the biological activities	Samadian et al. (2020)

Table 2 (continued)

Type of diabetic	complication	Name of the biomolecule	Types of nanodelivery system	Mechanism of action
	Pharmacological output	References		
Quercetin and oleic acid	Nanohydrogel	Quercetin showed anti-inflammatory antioxidant and anti-edematous effects	Nanohydrogel containing quercetin, oleic acid and hyaluronic acid reduced pain and improved tissue visco-elasticity	Gallelli et al. (2019)
		Oleic acid showed immune response in wound healing and showed synergic effect of quercetin and oleic acid in the management of diabetic foot ulcer	Hyaluronic acid accelerated the cell proliferations to the wound site and also contributed to the orientation of the extracellular matrix and fibrous component	
		Oleic acid increases the expression of vascular endothelial growth factor alpha and interleukin-1β		

Different mechanisms involved in amelioration of diabetic microvascular and macrovascular complications by nanophytochemicals are represented in Figs. 2 and 3.

Conclusion

Diabetes mellitus is a complicated metabolic disorder, and owing to its complex pathophysiology, its treatment is often troublesome. Despite the evidence provided over recent decades about the impact on the quality of life and human health by phytochemicals, their efficient delivery stands as a conundrum. Nano-based drug delivery systems have been developed in recent years as one of the key methods for remedying these challenges in order to enhance the effectiveness of herbal extracts in the treatment of diabetes mellitus and its related complications. As demonstrated, nanoformulations of phytomedicines such as nanostructured lipid carriers, solid lipid nanoparticles, colloidal nanoemulsion systems and other formulations have shown a substantial improvement in antidiabetic effects of the phytochemicals as compared to the conventional ones. The results of the discussed studies explicitly illustrate that by different nano-delivery methods, most phytochemicals can be efficiently developed and thus successfully administered to elicit the requisite therapeutic

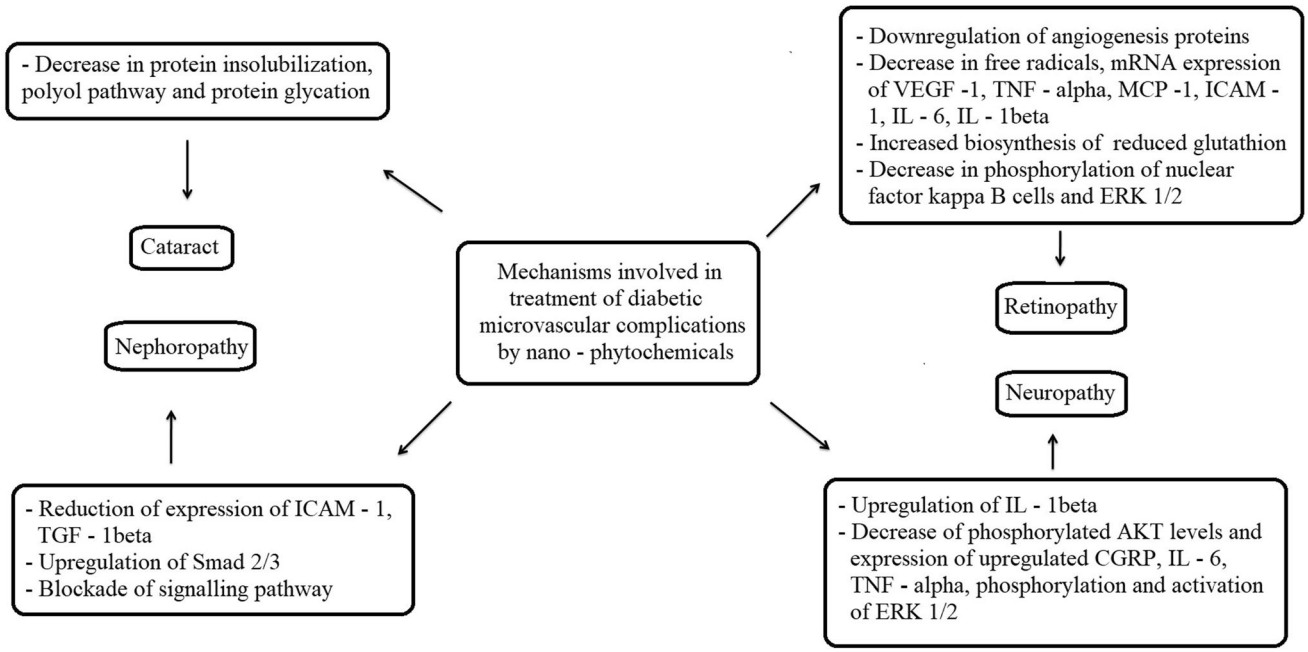

Fig. 2 Mechanisms involved in treatment of diabetic microvascular complications by nano-phytochemicals. Microvascular complications associated with type II diabetes mellitus including neuropathy, nephropathy, retinopathy and cataract are regulated by different intracellular markers. Cataract can be treated by nano-phytomolecules by decreasing protein insolubilization, regulation of polyol pathway and protein glycation. Retinopathy can be treated by downregulation of angiogenesis proteins; decrease in free radical, mRNA expression of vascular endothelial growth factor-1, tumor necrosis factor-α, monocyte chemotactic proteins-1, intracellular adhesion molecules-1, interleukin-6, interleukin-1β; increased biosynthesis of reduced glutathione, decrease in phosphorylation of nuclear factor kappa-light-chain-enhancer of activated B cells and extracellular signal-regulated protein kinase 1/2. Nephropathy can be ameliorated by regulation of expression of intracellular adhesion molecules-1, reduction of transforming growth factor-1β and upregulation of Smad 2/3. Neuropathy can be treated by nano-phytomolecules by upregulation of interleukin-1β, decrease of phosphorylated protein kinase B levels, decrease in upregulated calcitonin gene-related peptide expression, interleukin-6, tumor necrosis factor-α phosphorylation and activation of extracellular signal-regulated protein kinase 1/2. VEGF—vascular endothelial growth factor; TNF—tumor necrosis factor; MCP-1—monocyte chemotactic proteins-1; ICAM—intracellular adhesion molecules; IL—interleukins; TGF—transforming growth factor; ERK—extracellular signal-regulated protein kinase, AKT—protein kinase B; CGRP—calcitonin gene-related peptide]

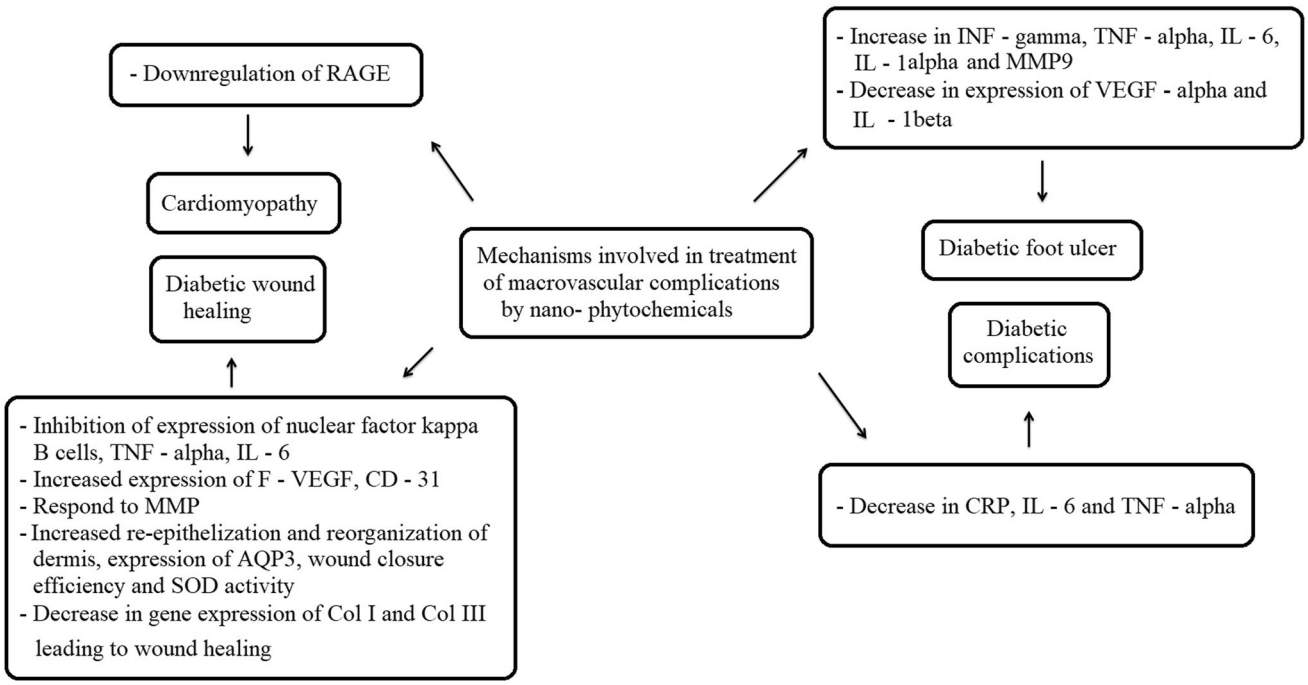

Fig. 3 Mechanisms involved in treatment of diabetic macrovascular complications by nano-phytochemicals [Macrovascular complications of type II diabetes mellitus include cardiomyopathy, diabetic complications, diabetic foot ulcer and diabetic wound healing. Nano-phytoconstituents can ameliorate the cardiomyopathy by downregulation of receptor for advanced glycation end products. Diabetic foot ulcer can be treated by nano-phytoconstituents by increase in interferon gamma, tumor necrosis factor-α, interleukin-1α, interleukin 6 and matrix metallopeptidase 9 and decreased expression of vascular endothelial growth factor-α and interleukin-1β. Diabetic wound healing can be enhanced by inhibition of expression of nuclear factor kappa-light-chain-enhancer of activated B cell, tumor necrosis factor-α, interleukin-6 and increase in expression of vascular endothelial growth factor, cluster of differentiation-31, responding to matrix metallopeptidase 9; increase in re-epithelization and reorganization of dermis; increase in expression of aquaporin 3, increase in wound closure efficiency, increased superoxide dismutase activity, decrease in gene expression of collagen I and collagen III leading to wound healing. Other diabetic complications can be treated by decreasing C reactive protein, interleukin-6 and tumor necrosis factor-α. RAGE—receptor for advanced glycation end products; INF-ϒ—interferon gamma; TNF—tumor necrosis factor; IL—interleukins; MMP9—matrix metallopeptidase 9; VEGF—vascular endothelial growth factor; NF-κB—nuclear factor kappa-light-chain enhancer of activated B cells; CD-31—cluster of differentiation 31; AQP3—aquaporin 3 gene; SOD—superoxide dismutase; Col I and Col III—collagen I and collagen III; CRP—C reactive protein]

outcome. In addition, the targeted distribution of nano-formulated phytochemicals will pave the pathway to integrate conventional medicine with modern pharmaceutical methodologies.

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Declaration

Conflict of interest The authors declare that they have no conflict of interest.

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