Review Paper

# Nanopolyphenols: a review of their encapsulation and anti-diabetic effects

**Theresa F. Rambaran**[1]

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**Abstract**
Polyphenols are believed to possess numerous health benefits and can be grouped as phenolic acids, flavonoids or non-flavonoids. Research involving the synthesis of nanopolyphenols has attracted interest in the areas of functional food, nutraceutical and pharmaceutical development. This is in an effort to overcome current challenges which limit the application of polyphenols such as their rapid elimination, low water-solubility, instability at low pH, and their particle size. In the synthesis of nanopolyphenols, the type of nanocarrier used, the nanoencapsulation technique employed and the type of polymers that constitute the drug delivery system are crucial. For this review, all mentioned factors which can influence the therapeutic efficacy of nanopolyphenols were assessed. Their efficacy as anti-diabetic agents was also evaluated in 33 publications. Among these were phenolic acid (1), flavonoids (13), non-flavonoids (17) and polyphenol-rich extracts (2). The most researched polyphenols were quercetin and curcumin. Nanoparticles were the main nanocarrier and the size of the nanopolyphenols ranged from 15 to 333 nm with encapsulation efficiency and drug loading capacities of 56–97.7% and 4.2–53.2%, respectively. The quantity of nanomaterial administered orally ranged from 1 to 300 mg/kg/day with study durations of 1–70 days. Most studies compared the effect of the nanopolyphenol to its free-form and, in all but three cases, significantly greater effects of the former were reported. Assessment of the polyphenol to understand its properties and the subsequent synthesis of its nanoencapsulated form using suitable nanocarriers, polymers and encapsulation techniques can result in effective therapeutic agents for the treatment of diabetes.

**Keywords** Nanopolyphenols · Nanoencapsulation · Nanomedicine · Nanocarrier · Diabetes

## 1 Introduction

Phenolics are compounds having one or more aromatic rings which possess at least one hydroxyl group. Polyphenols are a group of secondary metabolites with phenolic structural features and is a general term used to refer to several sub-groups of phenolic compounds. These ubiquitous compounds are the largest group of phytochemicals and have been suggested to play critical roles in the growth and reproduction, color, and also the defense mechanism of plants against pathogens, parasites and predators [1, 2]. These compounds are also stated to be beneficial to health and are believed to be the most abundant group of compounds in the diet with an average adult being estimated to have a total dietary intake of 1 g polyphenol/day [3].

Numerous biological properties have been suggested for polyphenols and included among these are antioxidant, antimicrobial, anti-cancer, anti-inflammatory and anti-diabetic effects [4–8]. For this review we will however focus only on their anti-diabetic activity. Polyphenols are believed to be able to confer anti-diabetic effects via various mechanisms through their ability to: increase insulin secretion, insulin sensitivity and insulin-dependent

✉ Theresa F. Rambaran, theresa.rambaran@umu.se | [1]Department of Public Health and Clinical Medicine, Section of Sustainable Health, Umeå University, 90187 Umeå, Sweden.

glucose uptake, inhibit glucose absorption in the intestine by sodium-dependent glucose transporter 1 (SGLT1), reduce hepatic glucose output, and influence the gut microbiome [9–12]. These effects have been observed in basic research using animal models and have been confirmed in some clinical trials [13–15].

The ability of dietary polyphenols to regulate glucose homeostasis would suggest that they can be used for the prevention and management of diabetes. There are however several challenges in achieving this outcome. While positive effects of polyphenols (as it relates to their anti-diabetic effect in both healthy and diseased subjects), have been suggested in numerous basic research and clinical trials, this outcome is inconsistent. These inconsistencies are due to several factors including: the quantity of polyphenols used in vitro and in vivo to demonstrate effects are usually significantly higher than the amount generally contained in the human diet; and more importantly, the ability of the compounds to exert their effect in target tissues is significantly reduced due to their low bioavailability in humans [16, 17]. While there are several extrinsic factors which can impact the bioavailability of polyphenols such as food matrix, gut microbiota and rapid elimination, some of the main challenges include intrinsic factors such as their low water-solubility, instability at low pH, and the particle size of the compounds [18–20]. The synthesis of nanomaterials to improve the bioavailability of polyphenols is therefore a trending area of study. Methods which have been utilized in the preparation of these nanosystems are able to impact the physical and chemical properties of polyphenols. The focus of this study is therefore to review the encapsulation of nanopolyphenols and evaluate their efficacy as anti-diabetic agents. The number of studies in humans are limited and so the evaluation of the anti-diabetic potential of nanopolyphenols was done using in vivo diabetic models. The general framework of this review is schematically represented in Fig. 1.

## 2 Classification of polyphenols

Polyphenolic compounds are diverse in chemical structure and this is one basis on which classification can be achieved. The most common variations in the chemical skeleton include the degree of oxidation, hydroxylation, methylation and glycosylation. The main classes of polyphenols include phenolic acids, flavonoids and non-flavonoids with subclasses of the latter including stilbenoids, lignans, tannins, and diarylheptanoids (Fig. 2). Less common subclasses of non-flavonoid polyphenols include

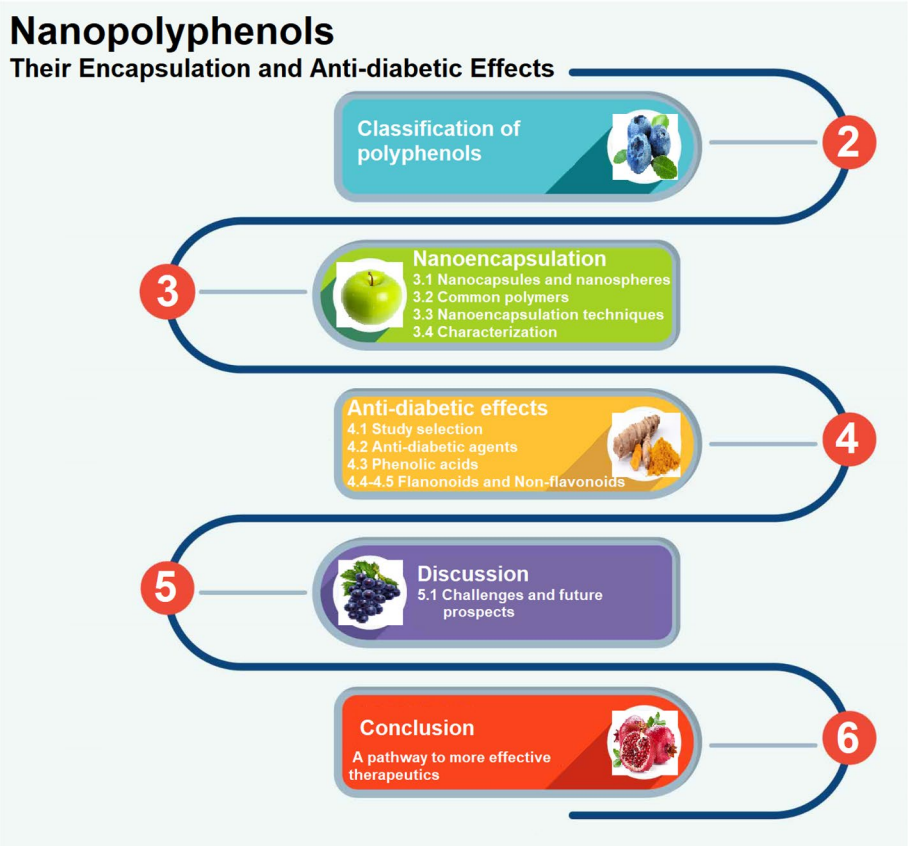


**Fig. 1** Schematic representation of the topics covered in the review

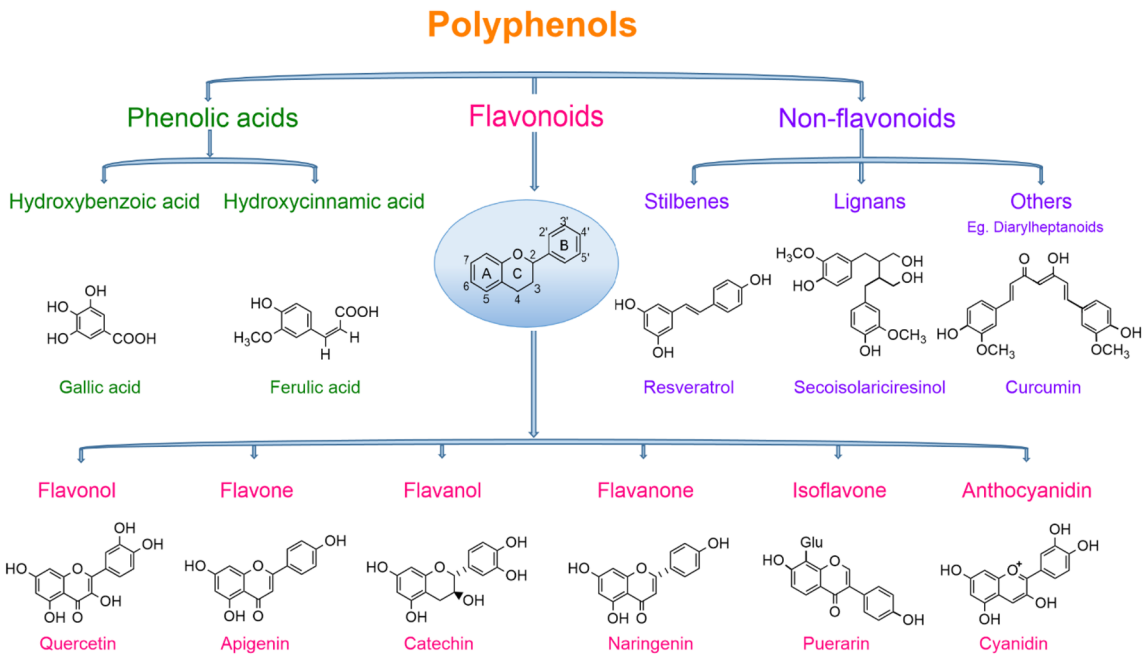


**Fig. 2** Classification of polyphenols

polyphenolic amides and anthraquinones. There are several accounts of the anti-diabetic effects of each class of polyphenol outlined [21–26].

About one-third of dietary polyphenols are phenolic acids and these—which can be categorized as hydroxybenzoic or hydroxycinnamic acids—are present in both their bound and free-forms in plants [27]. Among the benzoic acid derivatives are compounds such as ellagic acid, *p*-hydroxybenzoic acid, protocatechuic acid, vanillic acid and gallic acid while among the cinnamic acid derivatives are *p*-coumaric acid, caffeic acid, ferulic acid and sinapic acid [27, 28].

Of all the phenolics in our diet, approximately two-thirds are estimated to be flavonoids [1]. These compounds have a general structure that consists of two aromatic rings (A and B rings) that are linked by 3 carbons that are usually in an oxygenated heterocycle ring, or C ring. Variations in the heterocyclic ring can result in several flavonoids and these can be categorized as flavonols, flavones, flavanols, flavanones, anthocyanidins and isoflavonoids. According to Puupponen-Pimiä et al. [29], flavonols and flavones are the most common phenolics in plant-based food.

Tannins are a subclass of non-flavonoid polyphenols and are comprised of both proanthocyanidins, which are condensed non-hydrolysable tannins, and hydrolysable tannins which are esters of gallic acid, gallotannins, ellagic acid and ellagitannins [6, 30]. The lignan subclass of non-flavonoids are derived from phenylalanine and, along with isoflavone, is one of the major classes of phytoestrogens [31]. Common examples of lignans are enterolignans, enterodiol, enterolactone and secoisolariciresinol. Stilbenoids are hydroxylated derivatives of stilbenes and are classified as phytoalexins [32]. The most popular stilbenoid is resveratrol. Another non-flavonoid subclass is diarylheptanoids which consists of two aryl groups joined by a seven carbon chain. They can be classified into linear and cyclic diarylheptanoids; for example, curcumin and myricanone, respectively.

## 3 Nanoencapsulation

### 3.1 Nanocapsules and nanospheres

Nanomaterials are commonly defined to be of a diameter in the range of 1-100 nm; however, in principle, these materials have a length of 1-1000 nm in at least one dimension [33]. Nanoencapsulation is defined as the technology of packaging nanomaterials of an active ingredient in the form of a solid, liquid, or gas, also known as the core or active, within a secondary material, named the matrix or shell, to form nanocapsules [34]. A similar technology can lead to the formation of nanospheres where the bioactive compound is uniformly dispersed in a matrix system [35]. The core (depending on design) is generally released by diffusion or as a response to triggers such as shear, pH, or enzyme action, consequently enabling their controlled and timed delivery to a targeted site [36, 37]. The nanocapsules or nanospheres can be used as a carrier

for hydrophilic or lipophilic bioactive compounds and are shown in Fig. 3.

It is important to note that while nanoencapsulation is often used to describe the trapping of bioactive materials in nanoscale carriers, substances that are not therapeutically active can also be encapsulated to determine the impact of this process on dynamic behavior, electrical properties, phase transitions and so on [38, 39].

### 3.2 Common polymers constituting nanomaterials

Like the core of the nanomaterial, the external polymeric membrane is also of paramount importance in their synthesis. Physicochemical properties of the selected polymer play a crucial role on the responsiveness of the nanomaterial and so a number of factors have to be taken into consideration before deciding on a polymer. These include whether the polymer and its degraded products are safe and also whether the polymer possesses the necessary properties to enable achievement of the drug delivery goals; e.g. a suitable controlled release profile [40]. A critical requirement, as it relates to the safety of the material, is the need for the polymer and its degraded products to be non-toxic, non-immunogenic, and also to be biodegradable or at least be totally eliminated from the body in a short period of time so repeat administration is possible without any risk of uncontrolled accumulation [41].

The most commonly used natural biopolymers in the preparation of nanoencapsulated materials are chitosan, gelatin, sodium alginate and albumin [41–43]. These natural polymers offer a number of advantages which include being biodegradable (thus after the drug is depleted the carrier is broken down to components that are readily re-absorbed or eliminated); being biocompatible (and as a result are non-toxic in humans); allowing for adhesion to target tissues (which helps to enhance residence time and consequently the amount of absorbable drug);

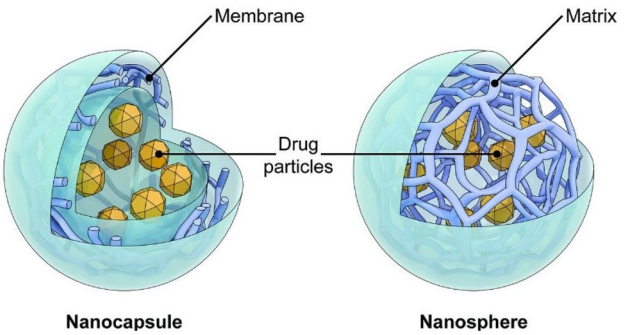


**Fig. 3** A representation of the structure of a nanocapsule and a nanosphere. The image is in the public domain and is credited to the National Institutes of Health/Department of Health and Human Services [131]

possessing specific receptor recognition; allowing for non-specific protein adsorption as they provide neutral coating with low surface energy; and possessing a high amount of hydroxyl groups on their backbone (therefore allowing the incorporation of different specific ligands) [44]. Some disadvantages associated with natural polymers include a great level of variability among those derived from animal sources, complex structures, and complicated and costly extraction processes [45].

There are many synthetic polymers such as polylactides (PLA), polyglycolides (PGA), poly(lactide co-glycolides) (PLGA), and poly(vinyl alcohol) (PVA), to name a few. There are also copolymers such as poly(lactide)-poly(ethylene glycol) (PLA-PEG), and poly(lactide-co-glycolide)-poly(ethylene glycol) PLGA-PEG. The use of polymeric colloidal stabilizers to prevent aggregation is also common in nanoencapsulation processes and some common ones include dextran, polysorbate 20 and polysorbate 80 [41]. Some advantages associated with the use of these synthetic materials include that they offer both greater mechanical and chemical stability, increased reproducibility due to minimized variation between batches, reduced nonspecific protein binding, ease of modification, and tunable properties [46, 47]. Disadvantages, on the other hand, include the possibility of the synthetic polymer being toxic and non-degradable and this is coupled with a complex and costly production process [45].

Along with the use of natural and synthetic materials in the design of nanocarriers, there are a few studies which have focused on the use of the bioactive compounds as the nanocarrier to develop 'self-carrying nanodrug delivery systems' [48]. This approach aims to develop functional carriers and is expected to have better biocompatibility than drug delivery systems derived from synthetic materials and also exhibit intrinsic therapeutic efficacy. The functional molecules can be either chemically attached to the core or shell or physically bound [49]. The advantages derived from this synthesis protocol include increased stability and water solubility, the nanocarrier is not susceptible to compound leakage, and it is also non-toxic with a high carrier-to-drug ratio [50, 51]. The formulation of these self-carrying natural nanocarriers however pose challenges in their synthesis, characterization, purification, mass production, and quality control (uniformity and reproducibility). They are also more costly to produce and these factors, overall, limit their prospects as biomedical therapies [48].

### 3.3 Nanoencapsulation techniques

Nanomaterials can be made using a range of nanocarriers which serve as a transport module for bioactive materials. Pharmaceutical nanocarriers include nanospheres,

nanocapsules, nanoparticles, nanoemulsion, nanoliposomes and nanoniosomes (non-ionic surfactant vesicles). These nanoscale drug delivery systems can be natural or synthetic and can transport either lipophilic or hydrophilic molecules. They can be classified based on their origin (e.g. lipid-based and biopolymer nanocarriers), their method of preparation (e.g. electrospun and electrosprayed nanocarriers) and also based on their composition as outlined in Fig. 4 [52, 53]. The use of inorganic nanomaterials such as silica, gold and carbon-based nanostructures are being used extensively for drug delivery in cancer therapy [54]. Some nanocarriers such as solid lipid nanoparticles (SLNs) (a polymeric nanocarrier) have been further modified over time to improve their stability and loading capacity and this resulted in the formation of nanostructured lipid carriers (NLCs) [55]. The loading capacity of a nanocarrier is the amount of drug loaded per unit weight. This is an important parameter which determines the quantity of drug that can be transported and released after administration. As the size of the nanocarrier decreases, loading capacity also decreases; henceforth, both properties have to be considered in determining the quantity of nanocarrier needed for therapeutic efficacy.

Nanocarriers can be made using several nanoencapsulation techniques which can be divided into physical, physicochemical and chemical methods as outlined in Fig. 5. These techniques result in variations in the resulting drug delivery systems and each has its own advantages and disadvantages which have been outlined in several studies [41, 56]. Nanoencapsulation techniques used to synthesize nanomaterials are either top-down or bottom-up approaches. A top-down approach, as its name suggests, involves the size reduction and structure shaping of the material using specific methods (e.g. emulsification-solvent evaporation) while the bottom-up approach allows for the self-assembly and self-organization of molecules to yield nanomaterials (e.g. coacervation) [57]. Examples of the types of nanomaterials that can be synthesized using the categories of nanoencapsulation techniques outlined in Fig. 5 are as follows. A supercritical anti-solvent processing technique, which is a physical method of nanoencapsulation, can be used for the synthesis of polymeric nanoparticles. This protocol involves the supersaturation and solidification of the nanomaterial following exposure to another solvent (or multiple solvents) in which the material is sparingly soluble. Recovery of the nanomaterial can then be achieved by drying. Interfacial polycondensation has also been used for the synthesis of polymeric nanoparticles. Interfacial polycondensation which is a chemical nanoencapsulation technique is a type of irreversible polymerization at the interface between an aqueous difunctional monomer and an inert immiscible organic solvent containing a complementary difunctional monomer. Nanogels, which can result from physicochemical methods of nanoencapsulation, are a class of nanoparticles which may be synthesized via ionic interactions. This synthesis is derived from innate ionic forces and particle–particle interactions present in a colloidal system which result in a

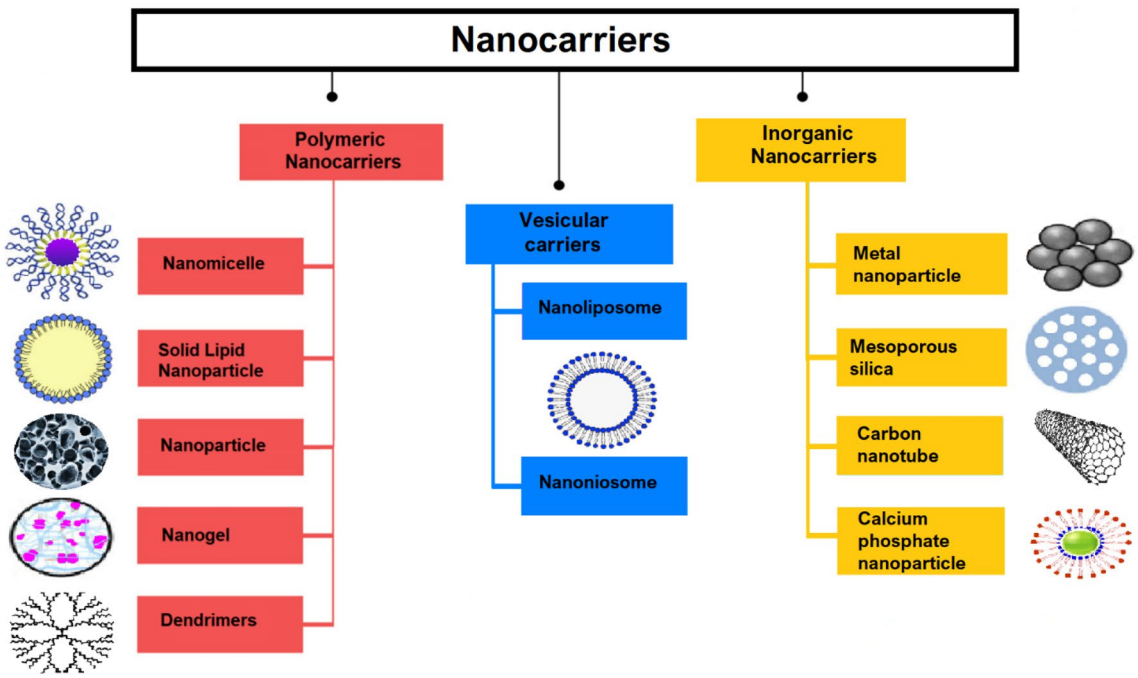


**Fig. 4** Types of nanocarriers

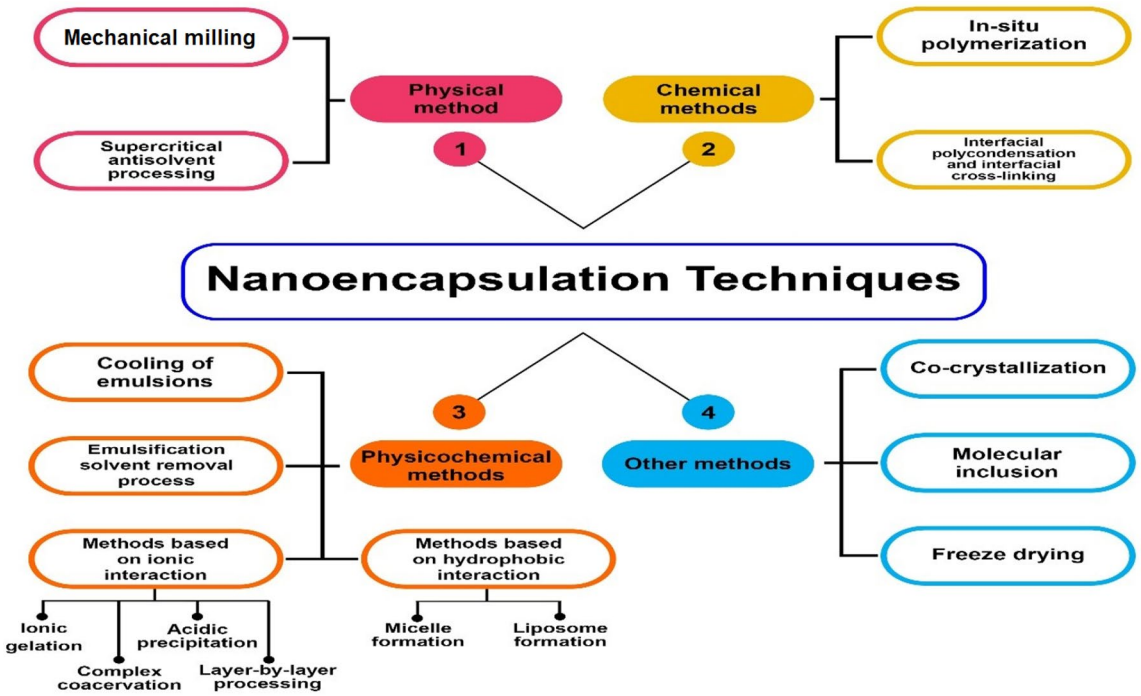


**Fig. 5** Nanoencapsulation techniques

gel network formed by chemical cross-linking [58]. Freeze drying is a good technique to improve the long-term stability of colloidal nanoparticles. This technique lyophilizes the nanomaterial and the conditions that will yield powders that do not aggregate after resuspension and storage are most ideal.

The nanoencapsulation technique and delivery system used in the development of the nanoscale bioactives are able to alter various physicochemical properties of the material such as its particle size, size distribution, surface area, shape, solubility, encapsulation efficiency and releasing mechanism [57]. As a result of this, careful selection of both the type of nanocarrier and the synthesis technique is critical.

The release rate of nanopolyphenols is determined by a combination of diffusion and erosion mechanisms [57]. The materials have low permeability and are absorbed only via active transport mechanisms [59]. Given the challenges outlined previously which result in the low bioavailability of polyphenols, some of the main benefits to be derived from the nanoencapsulation of polyphenols include the ability of these techniques (if carefully selected) to allow for targeted delivery of the compounds through the modification of surface coating or conjugation so the drug is released only when it has reached the site in the body where it is needed. This not only allows for targeted delivery but also allows the rate of delivery to be controlled. These techniques also allow for the modification of surface charge which can promote cell entry, allow for timed release of the encapsulated polyphenols in the body, extend circulation time of the compound through PEGylation and protect the compounds from degradation [56, 57].

### 3.4 Characterization of nanomaterials

The efficacy of a nanomaterial is greatly influenced by its physical and chemical properties. Additionally, its surface characteristics can influence its functional and physicochemical properties, and ultimately, its application. The characterization of nanomaterials is therefore critical to ensure the necessary characteristics which will allow for maximum efficacy and safety are met. There are several characterization techniques which can be used to assess different parameters of a nanomaterial and those presented in Table 1 are some of the most common ones. These techniques vary with regard to relative advantages, disadvantages, cost, efficiency, and complexity and so careful consideration is necessary when selecting one [60, 61].

**Table 1** Characterization techniques for nanomaterials

| Parameter | Main impact on nanomaterial | Analytical technique/calculation |
|---|---|---|
| *Physical properties* | | |
| Morphology | Morphology influences functionality, dispersion and toxicity | TEM, SEM, AFM and CLSM |
| Particle size and size distribution (also covers size of agglomerates/aggregates) | Impacts in vivo distribution, bioavailability, toxicity, targeting and drug loading capacity, drug release, the stability of the nanomaterial and polymer degradation | TEM, SEM, AFM, DLS, SLS, gravitational settling, and LIBD |
| Solubility | Influences bioavailability, toxicity, speciation and drug loading/release | UV–Vis, DLS |
| Optical properties, imaging, color | Influences application | Image processing method, fluorescence microscope, UV–Vis, SPR |
| *Chemical properties* | | |
| Surface chemistry | Surface atoms are in direct contact with solvents and influence dissolution, sorption of molecules and reactivity | XPS, secondary ion mass spectroscopy, auger spectroscopy |
| Surface charge (zeta potential) | This is an indicator of colloidal stability (a critical parameter for many emulsions or dispersions), and is also predictive of the uptake of the nanomaterial by cells | Zeta-potential determination, Laser Doppler electrophoresis |
| Bulk chemical composition | Bulk composition of the nanomaterial impacts its effect in living systems | Mass spectroscopy, X-ray and electron diffraction |
| Surface area | Surface area influences reactivity and surface interactions with ligands | Gas adsorption and use of the BET equation, Electron microscopy |
| Phase transitions, crystallization behavior, melting, molecular structure, interaction bonding, and complex formation | These parameters (like others) can alter the pharmacokinetics, distribution, accumulation, and toxicity of nanomaterials | XRD, DSC, FTIR, and NMR |
| Encapsulation/entrapment efficiency | Impacts the biological activity of the nanomaterial | Headspace gas chromatography, HPLC, UV-Vis |
| *Mechanical properties* | | |
| Hardness, tensile strength, elastic modulus, bending strength, fracture properties, and impact resistance | Useful in determining roles, action mechanisms and the applications of nanomaterials | AFM, in situ TEM, molecular simulation |
| Adhesion and friction | Influences colloidal stabilization, drug delivery and other applications | AFM |
| Movement | Provides deeper understanding of the roles of nanomaterials in specific applications | High-resolution fluorescence microscope, in situ TEM |
| *Thermal properties* | | |
| Thermal conductivity, thermal stability, electrical conductivity, thermoelectric power or Seebeck coefficient, and heat capacity | Provide valuable insight into important physical characteristics of the nanomaterial and influence application | TIM tester, hot disk technique, laser flash technique, TGA, PPMS, Seebeck coefficient and electrical resistance measurements, Calorimetry |

AFM, Atomic force microscopy; BET, Brunauer–Emmett–Teller; CLSM, Confocal laser scanning microscopy; DLS, Dynamic light scattering; DSC, Differential scanning calorimetry; FTIR, Fourier-transform Infrared spectroscopy; LIBD, Laser-induced breakdown detection; NMR, Nuclear magnetic resonance; PPMS, Physical property measurement system; SEM, Scanning electron microscopy; SLS, Static light-scattering; TEM, Transmission electron microscopy; TGA, Thermogravimetric analysis; TIM, Thermal interface material; UV–Vis, Ultraviolet–visible spectroscopy; XPS, X-ray photoelectron spectroscopy; XRD, X-ray powder diffraction

## 4 Efficacy of nanopolyphenols in diabetic models

### 4.1 Study selection

The use of nanoencapsulated polyphenols in the treatment of diabetes was studied using several databases. These include PubMed/MEDLINE, CINAHL (EBSCO), Scopus and Web of Science. The search strategy used to retrieve literature from PubMed was: ((polyphenol OR flavonoids OR flavanones OR flavanone OR flavones OR phenols OR flavonols OR kaempferol OR quercetin OR catechin OR myricetin OR rutin OR proanthocyanidin OR tannins OR resveratrol OR "isoquinoline flavonoid" OR flavanolignan OR stilbene OR "phenolic acid" OR anthocyanin OR anthocyanidin OR extract) AND (nano OR nanoparticle OR nanocapsule OR nanoconjugate OR nanocolloid OR nanomicelle OR nanoemulsion OR nanocomposite OR nanostructure OR nanoencapsulate OR nano-encapsulation) AND (glucose OR glycemia OR glycemic OR "blood sugar" OR "glycated hemoglobin" OR hba1c OR "glycosylated hemoglobin" OR insulin OR "glucose metabolism disorders" OR "metabolic disorders" OR "metabolic profile" OR hyperglycemia OR hyperglycemic OR "glucose intolerance" OR diabetes OR t2d OR t1d OR "prediabetic state" OR prediabetes)).

The search results were further refined and filtered by advanced search options, sorting by relevance and limiting search by language (English). References of the selected articles were further checked to identify relevant articles. Studies that included other biologically active components other than nanopolyphenols were included only if the nanopolyphenol was also assessed individually. Additionally, the nanoencapsulated material had to have a dimension less than 1000 nm to qualify as a nanopolyphenol. Data extracted from the resulting 33 studies include general study characteristics (polyphenol type and (sub)class, type of nanocarrier, size of the nanomaterial, the main components of the drug delivery system, quantity of nanopolyphenol administered, the encapsulation and/or drug loading capacity and the study duration), and the effect assessed along with the efficacy/outcome results (Table 2).

### 4.2 Nanopolyphenols as anti-diabetic agents

Several types of polyphenols and nanocarriers have been utilized in the synthesis of nanopolyphenols for the assessment of their effects in diabetic models. Of the 33 studies, outcome measures included the ability of the bioactive material to: confer anti-diabetic, hypoglycemic, anti-hyperglycemic effects or relieve oxidative stress associated with diabetes (n = 20), impact diabetic wound healing (n = 2), inhibit diabetic neuropathic pain (n = 3) and impact other complications associated with diabetes such as inflammation (n = 3), diabetic cardiomyopathy (n = 2), diabetic cataract or retinopathy (n = 2), diabetic nephropathy (n = 1) and diabetes-induced learning and memory impairment (n = 1). In all studies, streptozotocin-induced diabetic rats were used (Type 1 DM model, predominantly) with the exception of 2 studies which used alloxan-induced [62, 63] (Type 1 DM model) and 2 others that used sodium arsenite induced hyperglycemic rats [64] (Type 2 DM model) and a db/db mouse model [65] (Type 2 DM model).

Nanocarriers used were mostly nanoparticles (n = 22), while solid lipid nanoparticles/nanostructured lipid carriers (n = 4), nanoemulsions (n = 3), nanomicelles (n = 2) nanospheres (n = 1) and nanorods (n = 1) were used to a lesser extent. None of the included studies outlined in Table 2 used a 'self-carrying nanodrug delivery system'. The smallest particle sizes (15 and 17 nm) were obtained for nanorods prepared by use of a magnetic field [62] and nanospheres prepared by anti-solvent precipitation, respectively [66]. Both natural and synthetic polymers were used in the synthesis of the nanomaterials along with polymeric colloidal stabilizers. A few studies also incorporated inorganic species such as selenium and iron oxide into their matrix to assess for synergistic effects [67–69].

The quantity of nanomaterial administered orally ranged from 1 to 300 mg/kg/day. Nanopolyphenols were also administered via intravenous and topical delivery. The encapsulation efficiency and drug loading capacity of the prepared nanomaterials were within the range of 56–97.7% and 4.2–53.2%, respectively. A decrease in particle size resulted in a similar decrease in drug loading capacity in all but one study for which this data was available [70]. Study durations ranged from 1 to 70 days for drugs administered orally. The effect of the nanopolyphenols was determined in relation to the free-form of the drug for 73% of the included studies (n = 24). Efficacy was also determined through comparisons with the drug-free nanocarrier (n = 2), different administered quantities of the nanopolyphenol (n = 2), other nanoencapsulated bioactive materials (n = 2), the effect of the nanodrug in treated versus untreated diabetic rats (n = 2) and established pharmaceuticals (n = 1). A few studies used an experimental design which allowed for comparisons on several of the noted premises; however, that relating to the effect of the free-form of the drug versus its nanoencapsulated counterpart was prioritized.

**Table 2** *In vivo* anti-diabetic effects of nanopolyphenols

| Polyphenol ((sub) class) | Nanocarrier | Size (nm) | Drug delivery system main components | Dose (mg/kg/day) | EE or DLC (%) | Study duration (days) | Effect Assessed | Efficacy of nanopolyphenol[a] | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| Ferulic acid (phenolic acid) | Polymeric nanoparticle | 240 | PLGA,<br>Pluronic® F-68<br>Carbopol 980 (for topical hydrogel preparation) | A: 13 (oral)<br>B: 2.3% (topical) | EE: 88.8<br>DLC: 19.9 | 14 | Wound healing | ↑Wound epithelialization<br>↑Hydroxyproline content<br>↑Sustained release | [72] |
| Naringenin (flavanone) | Polymeric nanoparticle | 150–300 | Chitosan, sodium alginate | 50 | DLC: 15.9 | 19 | Anti-diabetic effect | ↓Blood glucose<br>↑ and regenerated structural complexity of Langerhans cells<br>Revived hepatic tissue architecture<br>↓Free iron content<br>↓Arachidonic acid and deoxyribose degradation reactions | [76] |
| Baicalin (flavone) | Nanostructured lipid carrier | 92 ± 3 | Precirol,<br>miglyol,<br>pluronic surfactant | 200 | EE: 85 ± 3 | 28 | Anti-diabetic effect | ↓FBG<br>↓HbA1c<br>↓TG levels | [77] |
| Scutellarin (flavone) | Polymeric nanoparticle | 150–250 | Chitosan,<br>EDC,<br>CDI,<br>vit B12,<br>FITC | 40 | – | 56 | Diabetic retinopathy | ↑Cellular uptake<br>2-3 times higher bioavailability<br>Down-regulated CRA resistivity index and the expression of angiogenesis proteins<br>of retinas<br>No significant changes in blood glucose levels | [78] |

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**Table 2** (continued)

| Polyphenol ((sub) class) | Nanocarrier | Size (nm) | Drug delivery system main components | Dose (mg/kg/day) | EE or DLC (%) | Study duration (days) | Effect Assessed | Efficacy of nanopolyphenol[a] | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| Myricitrin (flavonol) | Solid lipid nanoparticle | 76 | Compritol, oleic acid, Tween 80, Span 20 | A: 1<br>B: 3<br>C: 10 | EE: 56.2<br>DLC: 5.6 | 28 | Anti-diabetic effect | ↑SOD, CAT, Glut4 gene expression in skeletal muscle<br>↓Blood glucose concentration<br>Nanodrug more potent than metformin in some instances<br>(Comparison between different concentrations) | [80] |
| Rutin (flavonol) | Polymeric nanoparticle | 56 | PVA, palmitic acid | 10% w/w (topical) | – | 16 | Diabetic Foot Ulcer (Wound healing) | ↑Wound contraction and wound closure<br>↑Antioxidants<br>↑Hydroxyproline content<br>↑Regeneration of dermal tissues, capillary vessels and thickness of granulation tissues | [81] |
| Rutin and puerarin (mainly flavonol and isoflavone) | Polymeric nanoparticle | 120 | PLGA–PEG, DOTAP, pluronic® F-68 | 125 | EE: 89.4 rutin<br>EE: 90.6 puerarin | 14 | Hypoglycemic effect | ↑Bioavailability<br>Demonstrated multiple anti-diabetic effects<br>↑Pancreatic function<br>↑Glucose utilization by adipocytes | [69] |
| Quercetin (flavonol) | Nanosphere | 17 | Use of anti-solvent followed by vacuum drying | A: 10<br>B: 20 | – | 49 | Anti-diabetic effect | ↓Hyperglycemia<br>↓Oxidative stress<br>Dose of 20 mg/kg had maximum inhibition of lipid profile, hepatic enzymes and oxidative stress<br>(Comparison between different concentrations) | [66] |

**Table 2** (continued)

| Polyphenol ((sub) class) | Nanocarrier | Size (nm) | Drug delivery system main components | Dose (mg/kg/day) | EE or DLC (%) | Study duration (days) | Effect Assessed | Efficacy of nanopolyphenol[a] | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | Nanorods | 15 | Use of a magnetic field followed by vacuum drying | 20 | – | 28 | Anti-diabetic effect | Amelioration of lipid peroxidation, and protein carbonylation<br>↓FBG, G6Pase and FBPase activity<br>↑SOD, CAT, GSH<br>↓AST, ALP, and ALT<br>(Comparison to untreated diabetic rats) | [62] |
| | Nanomicelle | 88 | Soluplus®, pluronic® F-127 | 50 | EE: 70.7 | 15 | Anti-diabetic effect | ↑Bioavailability of 1676%<br>↓Glucose levels<br>↑SOD and CAT | [82] |
| | Inorganic nanoparticle | 30–50 | $FeCl_3$ anhydrous, $FeCl_2$, dextran | 25 | DLC: 42 | 35 | Diabetes-induced learning and memory impairment | Both free and nanodrug prevented changes in weight and decreased blood glucose levels<br>↑Memory performance | [68] |
| | Polymeric nanoparticle | 180 ± 11 | PLGA, PVA | 150 | EE: 86<br>DLC: 10 | 15 (every 5$^{th}$ day) | Anti-diabetic effect | ↑CAT and SOD levels compared to control<br>Nano quercetin decreased blood glucose levels to a greater extent<br>↓Drug doses of nanoquercetin required | [83] |
| | Polymeric nanoparticle | 92 | Succinyl chitosan, alginate | 100 | EE: 95 | 28 | Anti-diabetic effect | ↓Serum AST, ALT and ALP levels<br>↓Cholesterol and triglyceride levels<br>↑Hypoglycemic effect and efficient maintenance of glucose homeostasis | [84] |

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**Table 2** (continued)

| Polyphenol ((sub) class) | Nanocarrier | Size (nm) | Drug delivery system main components | Dose (mg/kg/day) | EE or DLC (%) | Study duration (days) | Effect Assessed | Efficacy of nanopolyphenol[a] | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | Polymeric nanoparticle | 32 | BLG, PEG-$NH_2$, ε-benzyloxycarbonyl-L-lysine | 10 | DLC: 53.2 | 56 | Diabetic nephropathy | Downregulation of ICAM-1 expression<br>↓Blood glucose levels | [70] |
| Berberine (isoquinoline flavonoid) | Nanostructured lipid carrier | 160 | Oleic acid, glyceryl distearate, Tween 80, $Na_2SeO_3$, vit C | 50 | EE: 90 | Single dose | Hypoglycemic effect | ↑Sustained release and oral bioavailability<br>↓Blood glucose<br>Synergistic relation between selenium and berberine | [67] |
| | Nanoemulsion (freeze dried) | < 60 | Cyclohexane/dichloromethane/diethyl ether | A: 2.5<br>B: 100 | EE: 95.5-97.7 | 7 | Anti-diabetic effect | ↑Oral bioavailability<br>↓Blood glucose | [94] |
| | Solid lipid nanoparticle | 77 | Glycerol tripalmitate, soybean phospholipid, labrasol, pluronic® F-68, mannitol | A: 50<br>B: 100 | EE: 58<br>DLC: 4.2 | 28 | Hypoglycemic effect | ↓Body weight, FBG, HOMA-IR<br>Ameliorated impaired glucose tolerance and insulin tolerance | [65] |
| Silybin (flavanolignan) | Polymeric nanoparticle | 185 | PLGA, pluronic® F-127, chitosan | 50 | EE: 92.1 | 28 | Anti-diabetic effect | ↑Serum insulin and antioxidant characteristics<br>↓HbA1c, AST, ALT, ALP, cholesterol and triglyceride<br>↑SOD, CAT and GSH | [95] |
| Resveratrol (stilbene) | Nanoemulsion | < 100 | – | 20 | – | 30 | Anti-diabetic effect | ↓Serum glucose<br>↑Serum insulin<br>↑Nitric oxide,<br>↓SOD, CAT, GPx and GST<br>↓Glutathione<br>(Comparison to another bioactive) | [96] |

**Table 2** (continued)

| Polyphenol ((sub) class) | Nanocarrier | Size (nm) | Drug delivery system main components | Dose (mg/kg/day) | EE or DLC (%) | Study duration (days) | Effect Assessed | Efficacy of nanopolyphenol[a] | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| Curcumin (diaryl-heptanoid) | Polymeric Nanoparticle | – | PEG-PLGA<br>PVA | 150 | – | 20 | Antioxidant activity | Nanocurcumin enhanced anti-oxidative enzymes<br>↓Oxidative stress induced in diabetes | [63] |
| | Nanomicelles | 333 ± 6 | Pluronic® F-108 | 100 | EE:87.8-91.2 | 14 | Anti-diabetic effect | ↑Upregulation of Pdx-1 and NKx6.1 gene expression<br>-Optimum redox balance<br>Alleviation of STZ-induced β-cell damage<br>40% insulin positive cells (10% more than its free-form counterpart) | [97] |
| | Nanoparticle | 32 | Use of ultrasonication and evaporation | 15 | – | 21 | Gene expression of insulin (Hypoglycemic effect) | Nanodrug and Diamicron normalized blood sugar level<br>↑Gene expression of insulin and insulin receptor<br>(Comparison to negative control, untreated diabetic rats and Diamicron) | [98] |
| | Polymeric Nanoparticle | – | PEGMA-DMAEMA-MAO | 16 | DLC: 25 | 70<br>with 2 dosages given<br>(the 7$^{th}$ and 8$^{th}$ week) | Diabetic neuropathic pain | ↓Up-regulated IL-1β and Cx43 expression<br>↓p-Akt<br>↓Up-regulation of the P2Y12 receptor on SGCs<br>↓Mechanical and thermal hyperalgesia<br>(Comparison to nanocarrier) | [99] |

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**Table 2** (continued)

| Polyphenol ((sub) class) | Nanocarrier | Size (nm) | Drug delivery system main components | Dose (mg/kg/day) | EE or DLC (%) | Study duration (days) | Effect Assessed | Efficacy of nanopolyphenol[a] | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | Nanoemulsion (SNEDDS) | 214 | Gelucire, labrasol, vit E TPGS, PEG, HPMC E5 | A: 30<br>B: 100<br>C: 300 | – | 14 | Diabetic neuropathic pain | ↓Neuroinflammation<br>↑Antioxidant defence<br>↑Protection in diabetic neuropathy | [100] |
| | Basic nanoparticle | 200 | Sodium bicarbonate buffer | 300 | – | 56 | Diabetic cardiomyopathy | ↓Serum CK-MB, LDH, and insulin compared to an aged garlic extract<br>↓Triglycerides, and AST<br>Non-significant effect on glucose, insulin, and total cholesterol<br>(Comparison to untreated diabetic rats) | [101] |
| | Polymeric nanoparticle | 30 | BLG, $H_2N$-PEG-$NH_2$ | 20 | – | 56 | Diabetic cardiomyopathy | ↑$H_2S$<br>↑CaSR<br>↑CSE<br>↑CaM | [102] |
| | Polymeric nanoparticle | 117 | PLA-PEG copolymer | 20 | – | 60 | Liver inflammation | Ameliorated negative changes in NF-κB, hepatic COX-2, TGF-β1, and hepatic PPAR-γ<br>↓Inflammation | [103] |
| | Polymeric nanoparticle | 300 | PLGA | A: 25<br>B: 50<br>C: 100 | – | 28 | Inflammation and apoptosis in pancreatic β-cells | ↓Glucose levels<br>↓Islet/β-cell death<br>↓8-oxo-20-deoxyguanosine | [104] |

**Table 2** (continued)

| Polyphenol ((sub) class) | Nanocarrier | Size (nm) | Drug delivery system main components | Dose (mg/kg/day) | EE or DLC (%) | Study duration (days) | Effect Assessed | Efficacy of nanopolyphenol[a] | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | Polymeric nanoparticle | 237 ± 6 | PLGA, PVA | 100 | – | 15 | Anti-diabetic effect | ↓CRP, IL-6, total cholesterol, TNF-α, ↓Plasma triglycerides ↑HDL (Comparison to another bioactive) | [105] |
| | Polymeric nanoparticle | 283 ± 6 | PLGA, PVA | 2 mg/day | EE: 56 | 70 | Diabetes induced cataract | Both nano and free-form of drug failed to reduce glucose and increase insulin levels Effective against osmotic stress caused by hyperglycemia ↓Formation of AGE in soluble protein fraction ↑Soluble protein Potentially manage diabetic cataract | [106] |
| Emodin (anthraquinone) | Polymeric nanoparticle | – | PEGMA-DMAEMA-MAM | 5 mg/ml per rat (containing 1 mg pure emodin) | – | 7 (Every other day for a total of 3 injections) | Neuropathic pain | ↓Upregulation of P2X3 receptor and TNF-α protein ↓Phosphorylation and activation of ERK1/2 (Comparison to nanocarrier) | [114] |

**Table 2** (continued)

| Polyphenol ((sub) class) | Nanocarrier | Size (nm) | Drug delivery system main components | Dose (mg/kg/day) | EE or DLC (%) | Study duration (days) | Effect Assessed | Efficacy of nanopolyphenol[a] | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| *Syzygium cumini* (L.) (polyphenol-rich extract) | Polymeric nanoparticle | – | Polysorbate 80, PCL, sorbitan monooleate | 100 | – | 21 | Antioxidant activity in diabetic rats | ↓Blood glucose, cholesterol, creatinine, serum and pancreatic AOPP and renal TBARS levels<br>↓NAG activity | [119] |
| | Polymeric nanoparticle | 122 | PLGA, polyoxyethylene-polyoxypropylene | A: 10<br>B: 20 | – | 56 | Hyperglycemic effect | ↓Blood glucose<br>↓ HbA1c<br>Nanosized drugs were able to pass the blood–brain-barrier | [64] |

AGE, advanced glycation end products; ALP, alkaline phosphatase; ALT, alanine transaminase; AOPP, advanced oxidation protein products; AST, aspartate aminotransferase; BLG, γ-benzyl-L-glutamate; CaSR, calcium-sensing receptor; CaM, calmodulin; CAT, catalase; CDI, *N,N′*-carbonyldiimidazole; CK-MB, creatine kinase-isoenzyme; COX-2, cyclooxygenase-2; Cx43, connexin43; CRA, central retinal artery; CRP, C-reactive protein; CSE, cystathionine gamma-lyase; DLC, drug loading capacity; DMAEMA, dimethylaminoethyl methacrylate; DOTAP, 1,2-dioleoyl-3-trimethylammonium propane; EDC, N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride; EE, encapsulation (or entrapment) efficiency; ERK, extracellularly regulated kinases; FBG, fasting blood glucose; FBPase, fructose-bisphosphatase activity; FITC, fluorescein isothiocyanate; G6Pase, glucose-6-phosphatase; Glut-4, glucose transporter type 4; GSH, glutathione; GPx, glutathione peroxidase; GST, glutathione S transferase; Hb, hemoglobin; HbA1c, glycated hemoglobin; HDL, high density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; HPMC, hydroxypropyl methylcellulose; ICAM-1, intercellular adhesion molecular-1; IL-1β, interleukin 1 beta; IL-6, interleukin 6; LDH, lactate dehydrogenase; MAM, poly(methyl methacrylate)-poly(butyl acrylate)-poly(methyl methacrylate); MAO, methyaluminoxane; NAG, β-N-acetylglucosaminidase; NF-κB, nuclear factor-kappa B; $NH_2$-PEG-$NH_2$, diamino-terminated polyethylene glycol; p-Akt, phosphorelated-protein kinase B; PCL, polycaprolactone; PEGMA, poly(ethylene glycol) methacrylate; PEG, poly(ethylene glycol); Pdx-1, insulin promoter factor 1; PEG-$NH_2$, poly(ethylene glycol) amine; PLA, polylactide; PLGA, poly(lactic-co-glycolic acid); PPAR-γ, peroxisome proliferator-activated receptor gamma; PVA, poly(vinyl alcohol); P2X3, purinoceptor 3; SGCs, satellite glial cells; SNEDDS, self-nanoemulsifying drug delivery systems; SOD, superoxide dismutase; STZ, streptozotocin; TBARS, thiobarbituric acid reactive substances; TG, triglyceride; TGF-β1, transforming growth factor beta 1; TNF-α, tumour necrosis factor alpha; TPGS, D-α-tocopheryl polyethylene glycol succinate
–Information not available

[a]Efficacy of nanopolyphenol in relation to its free-form unless otherwise stated

### 4.3 Phenolic acids

Anti-diabetic effects of phenolic acids have been suggested in several studies [71]. Ferulic acid, which is a hydroxycinnamic acid, was nanoencapsulated and its impact on diabetic wound healing and hypoglycemia studied [72]. It was found that nanosized ferulic acid (with significantly increased sustained release) was able to promote wound healing significantly in diabetic rats compared to free-formed ferulic acid. This was effected through an increase in wound epithelization and hydroxyproline content. Hydroxyproline is a basic component of collagen. An increase in hydroxyproline content is an indication of increased cellular proliferation and therefore increased collagen synthesis [73]. This increase in collagen synthesis and turnover provides strength to repaired tissues and stimulates healing; thereby indicating the mechanism of action of the nanopolyphenol [74].

### 4.4 Flavonoids

There are 6 subclasses of compounds within the category of flavonoids as outlined in Fig. 2. Of these subclasses, included among the resulting 33 studies are flavanone (n = 1), flavones (n = 2), flavonols (n = 9) and one study which used a mixture of compounds from 2 different subclasses (flavonol and isoflavone) (Table 2). While the structures of these flavonoids are similar, structure–activity relationship causes changes to the chemical structure at particular regions to significantly impact functionality. The type of sugar moiety attached and the degree of hydroxylation and glycosylation (among other factors) can therefore influence the efficacy of the flavonoid [75]. This was corroborated by Sarian et al. [23] who outlined that the total number and configuration of hydroxyl groups existing on the compounds increased the antioxidant and anti-diabetic effects of flavonoids.

#### 4.4.1 Flavanone and flavone

The flavanone studied was naringenin [76] while the flavones included baicalin and scutellarin [77, 78]. A glucose lowering effect was obtained for naringenin and baicalin; however, scutellarin did not produce a similar effect in neither its free nor nanoencapsulated form. This effect of naringenin may be due to its ability to suppress the absorption of glucose from the intestine of diabetic rats [79]. While a hypoglycemic effect of scutellarin was not reported, in its nanoencapsulated form it caused an increase in cellular uptake and a two-threefold increase in bioavailability. Furthermore, the nanoencapsulated scutellarin also down-regulated both central retinal artery resistivity index and the expression of angiogenesis proteins which promote abnormal retinal blood vessel growth and contribute to diabetes-related vision loss. Other effects obtained for naringenin and baicalin included increasing and regenerating the structural complexity of Langerhans cells, and lowering glycated hemoglobin (HbA1c); respectively.

#### 4.4.2 Flavonol

Compounds studied among the flavonols included myricitrin, rutin and quercetin. While the effect of nanomyricitrin was not determined by comparison to its free-form, a clear increase in efficacy was seen with an increase in the concentration of the nanodrug [80]. The resulting outcomes included antioxidant and anti-diabetic effects which were evidenced by an increase in the activity of the endogenous antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT); and through hypoglycemic effects. Nanoencapsulated rutin effectively improved wound contraction in diabetic foot ulcer rats by causing significant wound contraction when applied topically [81]. There was also increased antioxidants and hydroxyproline content in the rats treated with the nanoencapsulated drug compared to the rats treated with the free-form of the drug (on the 16th day). Oxidative stress is implicated in the progression of diabetic complications including diabetic foot ulcer and so an increase in antioxidants can reduce progression. Efficient regeneration of dermal tissues, capillary vessels and thickness of granulation tissues was also noted in rats treated with rutin nanoparticles.

Quercetin was the most researched flavonol with a total of 7 of the included 33 studies focusing on this polyphenol. The nanoencapsulated form of the drug varied between nanospheres, nanomicelle, nanorods, and nanoparticles. The effects of nanoquercetin were determined by comparison to its free-form in 5 studies [68, 70, 82–84]. Of the remaining studies, one compared different concentrations of the nanoencapsulated drug [66], and in the other, the effects of the nanodrug were determined in treated versus untreated diabetic rats [62]. A decrease in glucose concentration was observed after administration of the nanoencapsulated quercetin in all instances. An increase in the activity of the endogenous antioxidant enzymes SOD, CAT and glutathione (GSH) was also obtained for several studies and this resulted in a concomitant reduction in oxidative stress [62, 66, 82, 83].

Accounts of other activities of nanoencapsulated quercetin included a decrease in aspartate transaminase (AST), alkaline phosphatase (ALP), alanine transaminase (ALT), glucose 6-phosphatase (G6Pase), fructose bisphosphatase (FBPase), downregulation of intercellular adhesion molecular-1 (ICAM-1) expression; amelioration of lipid peroxidation; and protein carbonylation [62, 70,

84]. The glucose metabolic enzymes G6Pase and FBPase, and the liver enzymes AST, ALP and ALT showed higher activity in diabetic subjects than their normoglycemic counterparts. Changes in the activity of liver enzymes can be a normal physiological phenomenon; however, it may also reflect potential liver injury [85]. Elevation of liver enzyme activity can be due to leakage of the enzymes from liver cytosol into the bloodstream due to hepatic injury. The administration of nanoquercetin restored the activities of both the glucose metabolic and liver enzymes towards normal via mechanisms including its radical scavenging abilities and also its ability to protect tissue function [62].

An improvement in memory performance and diabetic nephropathy by nanoquercetin were also communicated in one study each [68, 70]. Oxidative stress plays a crucial role in the development of diabetes and is also involved in neuronal damage and cognitive decline [86]. Quercetin is able to confer antioxidant effects, due to the presence of two pharmacophores inside its structure, and thereby reduce oxidative stress [87]. Quercetin also reduces neuro-inflammation by inhibiting the NF-κB pathway and reducing pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 which are associated with impaired cognition [88, 89]. Other properties of quercetin which enable its positive impact on memory performance include its ability to increase the expression of cAMP response element-binding protein (CREB) (since a reduction in the expression of this protein in the brain of diabetics can result in cognitive decline), and its inhibitory effects on acetylcholine esterase (AChE) which can result in cognitive dysfunction if induced in diabetic brains [90, 91].

As it relates to the effect of nanoquercetin on diabetic nephropathy, it was stated that the quercetin nanoparticle complex can attenuate diabetic nephropathy by down-regulating the expression level of ICAM-1 (which may play a role in the development of diabetes and diabetic nephropathy) on endothelium [70, 92]. Along with these therapeutic effects of nanoencapsulated quercetin, significant increase in bioavailability (of 1676%) and significantly lower drug doses of the nanodrug produced greater effects than its free-form.

The isoflavonoid, puerarin, was administered in combination with rutin in the only study that used two different subclasses of polyphenols [69]. These compounds were able to demonstrate multiple anti-diabetic effects and increase pancreatic function and glucose utilization. These outcomes could be due to the previously outlined effects of rutin in addition to the ability of puerarin to elevate insulin expression and maintain metabolic homeostasis in STZ-diabetogenic mice [93].

### 4.5 Non-flavonoids

Polyphenols of a non-flavonoid classification were the subject of 19 of the 33 included studies. The groups of polyphenols included isoquinoline flavonoid (n = 3), flavanolignan (n = 1), stilbene (n = 1), diarylheptanoid (n = 11), anthraquinone (n = 1) and a crude polyphenol-rich extract (n = 2).

#### 4.5.1 Isoquinoline flavonoid, flavanolignan and stilbene

The major pharmacological targets of the nanoencapsulated non-flavonoid polyphenols were the same as those of the nanoflavonoids outlined previously; that is, blood glucose levels, antioxidant status by determination of SOD, CAT and GSH levels, HbA1c, and the activity of the liver enzymes AST, ALT and ALP. The isoquinoline flavonoid (berberine) [65, 67, 94], the flavanolignan (sylibin) [95], and the stilbene (resveratrol) [96], impacted these pharmacological targets in a similar way as the flavonoids (Table 2). Additionally, nanoencapsulated berberine prepared in a nanostructured lipid carrier (NLC) and another which existed as a freeze dried nanoemulsion both resulted in increased oral bioavailability while the former also caused an increased sustained release. The berberine NLC was compared to both its free-form and a selenium-coated NLC berberine and a synergistic relationship was found between berberine and selenium.

#### 4.5.2 Diarylheptanoid

The diarylheptanoid, curcumin, was the most studied non-flavonoid. Comparison of the effect of the nanoencapsulated polyphenol was done with the polyphenol-void nanocarrier, other bioactives/pharmaceuticals, and also with its free-form. The biological effects and conditions assessed included anti-diabetic and antioxidant activity [63, 97, 98], diabetic neuropathic pain [99, 100], diabetic cardiomyopathy [101, 102], inflammation [103–105], and cataract in a diabetic rat model [106]. It was reported that nanoencapsulated curcumin produced anti-diabetic effects by increasing the number of insulin positive cells and the gene expression of insulin, alleviating STZ-induced β-cell damage and increasing the upregulation of the transcription factors pancreatic and duodenal homeobox 1 **(**Pdx-1), which play a critical role in pancreatic development, and NKx6.1 which is required for the development of β-cells [97, 98]. One possible mechanism through which these effects could have been produced include curcumin inhibiting phosphodiesterases (PDEs) which degrade cyclic adenosine monophosphate (cAMP) [107].

This allows for the intracellular production of cAMP and a consequent enhancement of pancreatic β-cell function and insulin secretion.

Nanocurcumin produced desirable results against diabetic neuropathic pain by decreasing the upregulated IL-1β and connexin43 (Cx43) expression, decreasing phosphorylated-protein kinase B (p-Akt), decreasing the upregulation of the P2Y12 receptor on satellite glial cells (SGCs), decreasing neuro-inflammation and increasing antioxidant defence [99, 100]. The upregulated expression of IL-1β and Cx43 contributes to the induction and/or maintenance of pain [108, 109]. The impact of nanoencapsulated curcumin on these proteins explains possible mechanisms through which neuropathic pain can be reduced. P2Y12 and p-Akt are involved in the initiation and maintenance of neuropathic pain [110, 111]. A reduction of their activity therefore alleviates pain.

The effect of nanocurcumin on diabetic cardiomyopathy was evidenced through a reduction in AST. There were however non-significant effects on glucose and insulin compared to untreated diabetic rats [102]. Increases in the following parameters were also reported: hydrogen sulfide ($H_2S$), CaSR, CSE and CaM [101]. Diabetic cardiomyopathy is a type of cardiovascular damage in diabetic patients that is independent of the coexistence of ischemic heart disease or hypertension. Damage to the heart muscle enhances the release of AST in diabetic subjects; therefore, a reduction in AST by nanocurcumin is indicative of a positive effect. Intracellular calcium is involved in several vital biochemical processes and an increase in its concentration can enhance the activity of CaM and regulate a variety of physiological functions. In turn, $Ca^{2+}$/CaM can regulate the activity of CSE and the formation of $H_2S$ [102]. Exogenous $H_2S$ improves cardiac function and attenuates cardiac hypertrophy and myocardial fibrosis in diabetic mice via the forkhead box protein O1 (FOXO1) pathway [112]. This protein plays important roles in the regulation of gluconeogenesis and glycogenolysis by insulin signaling; hence, by increasing exogenous $H_2S$, protective effects against diabetic cardiomyopathy are attained.

For the studies which assessed the anti-inflammatory effects of nanoencapsulated curcumin [103–105], the drug showed strong anti-inflammatory effects by inhibiting C-reactive protein (CRP), IL-6 and TNF-α release. Nanocurcumin also ameliorated negative changes in NF-κB (which plays a role in many inflammatory processes), hepatic COX-2 (an enzyme responsible for inflammation), and hepatic peroxisome proliferator activated receptor (PPAR)-γ (which inhibits the expression of inflammatory cytokines), while lowering 8-oxo-20-deoxyguanosine [113]. This oxidized derivative of deoxyguanosine is a biomarker of oxidative damage and its concentrations are elevated in diabetic subjects. A reduction of this clinical marker by nanocurcumin is therefore an indication of antidiabetic effects.

The efficacy of curcumin nanoparticles in delaying diabetes-induced cataract in rats was the focus of one study [106]. Efficacy was determined by comparing the activity of the nanoencapsulated drug to its free-form. It was communicated that both the nano and free-form of curcumin failed to reduce glucose and increase insulin levels; however, an effect against osmotic stress caused by hyperglycemia was observed. A delay in the progression of diabetic cataract was also attributed to the ability of nanocurcumin to mediate the biochemical pathways of disease progression such as protein insolubilization, the polyol pathway (a contributor to diabetic retinopathy), protein glycation, and crystallin distribution.

#### 4.5.3 Anthraquinone

The sole anthraquinone polyphenol reported among the included studies was emodin [114]. Nanoencapsulated emodin was assessed for its effect against diabetic neuropathic pain. The effects reported include a decrease in the upregulation of purinoceptor 3 (P2X3) receptor and TNF-α protein, and a reduction of the phosphorylation and activation of extracellular signal-regulated protein kinases 1 and 2 (ERK1/2). A reduction in the activity of these proteins result in a decline in diabetic neuropathic pain since P2X3 is involved in acute, inflammatory, neuropathic, visceral and cancer pain; TNF-α plays a role in the peripheral mediation of neuropathic pain; and ERK (which are activated in spinal glial cells and lead to the synthesis of proinflammatory/pronociceptive mediators) can enhance and prolong pain [115–117]. There are other studies, however, for which different roles have been reported for ERK1/2. These include controlling the phosphorylation and protein level of CREB and positively impacting glucose-mediated β-cell survival [118]. Given these roles, a reduction of ERK1/2 could therefore influence the negative effect of nanocurcumin on glucose and insulin levels.

#### 4.5.4 Crude polyphenol extract

The crude polyphenol extract of java plums was nanoencapsulated and their antioxidant and hypoglycemic effects determined [64, 119]. Compared to the free-form of the drug, it was found that the polymeric nanoparticles were able to effect changes in lowering blood glucose, cholesterol, creatinine, serum and pancreatic advanced oxidation protein products (AOPP). Additionally, there were reductions in renal thiobarbituric acid reactive substances (TBARS) levels, β-N-acetylglucosaminidase (NAG) activity and HbA1c, and nanosized drugs were able to pass the blood-brain-barrier.

## 5 Discussion

Polyphenols are ubiquitous in nature and have numerous proposed health benefits. The low bioavailability of polyphenols however poses a great challenge in their therapeutic efficacy. Nanotechnology has proved to be a promising field which can allay these challenges by improving bioavailability and allowing for targeted drug delivery and sustained drug release while lowering the required drug dose. The utilization of nanotechnology potentiates the beneficial effects of polyphenols in diabetes treatment in vivo via several mechanisms. Of the 24 studies that compared the activity of the nanoencapsulated polyphenol to its free-form, it was found that effects were significantly greater for the former in all but one study [68] where similar effects were reported for both forms of the drug for selected parameters and in two other instances where both forms failed to reduce blood glucose concentrations [78, 106].

The polyphenols studied were found to be effective as hypoglycemic, anti-hyperglycemic, anti-diabetic and antioxidant agents while also producing positive effects in diabetic wound-healing, diabetic neuropathic pain, diabetic retinopathy and cataract, diabetic nephropathy, diabetic cardiomyopathy, and diabetes-induced learning and memory impairment.

There were great variations among the type of polyphenol, the nanocarrier and nanoencapsulation technique used, the size of the nanomaterials, the drug delivery system, the dose of nanopolyphenol administered, the encapsulation efficiency and loading capacity of the resulting nanomaterials and the study duration. With these variations, superior anti-diabetic effects of the nanopolyphenols were still evident in all but 4 of the 33 included studies [68, 78, 101, 106]. Of these 4 studies, 3 compared the efficacy of the nanodrug to its free-form while the other did a comparison with untreated diabetic rats.

The design of a suitable drug delivery system requires the properties of the polyphenol to be taken into consideration. Different polyphenol subgroups can differ significantly in chemical stability [2]. Resveratrol, for example, is sensitive to pH, and so degradation increases significantly above pH 6.8 [120] while the highest degradation of quercetin is at pH 2 at 60 °C [121]. The processing conditions and environment are therefore dependent on sound knowledge of the polyphenols to ensure their efficacy is unaltered.

The variations seen in the drug delivery systems used are of note due to the integral role they play in the advancement of drug delivery technology and the fact that they are tailored to exert distinct biological functions [122]. Environmentally-responsive polymers, or smart polymers, are a class of materials composed of a diversity of linear and branched (co)polymers or cross-linked polymer networks that are able to undergo a dramatic physical or chemical change in response to an external stimulus [123]. The polymeric systems can be activated by physical stimuli (such as temperature, ultrasound, light, and magnetic and electrical fields) or chemical stimuli (such as pH, redox potential, ionic strength, and chemical agents) and these systems have been the focus of several research [40, 123].

Depending on the type of external stimuli, that is, whether physical or chemical, the effect induced on the polymer system can directly modulate the energy level of the polymer/solvent system and induce a polymer response at some critical energy level or it can induce a response by altering molecular interactions between polymer and solvent or between polymer chains, respectively. The resulting behavioral change on the polymer system can include transitions in solubility, hydrophilic-hydrophobic balance, and conformation [124]. The majority of responsive polymers for drug delivery can be broadly categorized as hydrogels, micelles, polyplexes, or polymer-drug conjugates [123]. Of the drug delivery systems outlined in Table 2, there were two nanomicelles and several polymer-drug conjugates with great variations among the latter. While PEG is not a smart polymer, it can be grafted with other polymers such as poly(methacrylic acid) to form a responsive-polymer [123, 125]. Two more popular responsive polymers are polyacrylic acid (PAA) (carbopol) which was used in one of the included study and is a pH sensitive smart polymer; and the commercially available Pluronic® (non-proprietary name "poloxamer") which is a nonionic tri-block copolymer consisting of a central hydrophobic polypropylene oxide (PPO) block flanked by hydrophilic polyethylene oxide (PEO) blocks; that is, PEO-PPO-PEO [126]. Pluronics® were used in seven of the included studies, as outlined in Table 2, and are temperature sensitive smart polymers. All studies that used a smart polymer reported positive results. The mechanism of action of different types of smart polymers however varies and since their physical and chemical properties impact their utilization, care should be taken in selecting a suitable one.

### 5.1 Challenges and future prospects

The application of nanotechnology in medicine can significantly impact human health as it relates to the prevention, diagnosis, and treatment of diseases. The use of this technology aims to increase therapeutic efficacy, decrease the therapeutically effective dose, and/or reduce the risk of systemic side effects. Achieving these outcomes however present several challenges. These can be categorized

as biological challenges, challenges associated with biocompatibility and safety, large-scale manufacturing, intellectual property (IP), government regulations, and overall cost-effectiveness in comparison to current therapies [127].

Some challenges associated with the biological properties, biocompatibility and safety of nanopolyphenols include inadequate understanding of the interaction of nanomaterials with tissues and cells, limited understanding of the biological interaction of these materials with the biological environment in the body of patients, inadequate information on the degree of accumulation of nanomedicines in target organs, tissues, and cells, the need for the development of more specialized toxicological studies for nanomedicines, and required structural stability of the nanomaterials following in vivo administration [127, 128]. Potential challenges arising from the large-scale manufacture of nanopolyphenols and the cost-effectiveness of their production include difficulties in their large-scale production according to GMP standards to ensure quality control and reproducibility in physicochemical properties on a batch-to-batch basis [129]. Additionally, the cost of the raw materials involved in the synthesis of nanopolyphenols are also obstacles for their scale-up and manufacture. In order to compensate for the high costs of the development and manufacture of these nanomedicine products, the clinical therapeutic effect of the drugs has to be much more advanced than conventional therapeutics [128]. Intellectual property and government regulation associated challenges include a lack of clear regulatory guidelines specific for nanoparticulate nanomedicines, and the complexity of nanomedicine patents and IP [127].

Approaches to use nanotechnology in the particle design and formulation of nanomedicines derived from polyphenols are beginning to expand the nutraceutical and pharmaceutical markets. These growing nanomedicine industries are expected to have a significant impact on the economy and medical care of the society. Currently, nanomedicines are used unanimously to improve the lives of patients suffering from a number of illnesses and this review has outlined the efficacy of nanopolyphenols as anti-diabetic agents. The safety of these drug delivery systems is therefore critical. Presently, a significant number of research has been conducted using smart polymers in the synthesis of nanopolyphenols. Smart polymers that have been approved by the US Food and Drug Administration as a safe drug delivery system (e.g. Pluronics®) should be carefully selected and used in the design of nanomaterials. Most of the polymers used in the drug delivery systems of the included studies are synthetic in origin and while their short-term use in vivo is regarded as being safe and non-toxic, the effect of prolonged exposure of large quantities in human subjects is not known [130]. Nanomaterials which are comprised of inorganic species are also of concern as it relates to possible toxic effects. Self-carrying nanodrug delivery systems which functionalize the nanocarrier by utilizing the polyphenol as the nanocarrier would eliminate the possibility of toxicity from a nanocarrier and should therefore be further explored.

## 6 Conclusion

The nanoencapsulation of polyphenols can be achieved using polymeric, vesicular or inorganic nanocarriers. Several physical, chemical, physicochemical and a few other nanoencapsulation techniques are also available. The groups of polyphenols studied included phenolic acids (hydroxycinnamic acid), flavonoids (flavonol, flavone, flavanone and isoflavone) and non-flavonoids (isoquinoline flavonoid, flavanolignan, stilbene, diarylheptanoid and anthraquinone). The most studied polyphenols were the flavonol, quercetin, and the diarylheptanoid, curcumin. Anti-diabetic effects were noted for all groups of polyphenols and several studies reported significantly higher effects for the nanopolyphenol compared to its free-form.

It can be concluded that the diversity of processes involved in the manufacture and analysis of nanopolyphenols impacts them differently. This in turn influences their physical nature, chemical behavior, biological interactions, analytical properties and efficacy which consequently may introduce some constraints to their applications. With a deeper understanding of the physicochemical properties of polyphenols, the use of smart polymers in the development of cost-effective and efficient self-carrying nanodrug delivery systems, and the stabilization of nanomaterials to facilitate site-specific targeting, nanoencapsulated polyphenols can play a critical role in the push towards safer and more effective therapeutics to counter the rise of lifestyle diseases.

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### Compliance with ethical standards

**Conflict of interest** The author reports no conflicts of interest in this work.

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