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Recent Advances in Nanoencapsulation of Phytochemicals to Combat Obesity and Its Comorbidities

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Abstract

An increasing epidemic of obesity has become a serious public health concern primarily because it contributes to pathogenesis of many chronic diseases including type 2 diabetes, cardiovascular disease, hepatobiliary disease, obstructive sleep apnea, kidney disease, some types of cancer, among others. Consumption of a variety of phytochemicals has emerged as a promising potential for combating obesity and its comorbidities. However, the generally low aqueous solubility, stability, bioavailability, and target specificity of phytochemicals, along with their side-effects and toxicity seen when used at high doses, have restricted their clinical applications. As a solution, phytochemicals can be encapsulated into nanoparticles to increase their stability and solubility, enhance their bioavailability, protect them from premature degradation in the body, prolong their circulation time, and thus enhance their antiobesity activity. In this perspective,

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we summarize the problems and limitations of the prominent phytochemicals (epigallocatechin gallate, *trans*-resveratrol, curcumin, and quercetin), the major biocompatible and biodegradable nanoparticles, and the efficacy of nanoencapsulated forms of these phytochemicals in combating obesity and its comorbidities.

Keywords

obesity; nanoparticles; epigallocatechin gallate; trans-resveratrol; curcumin; quercetin

INTRODUCTION

Obesity prevalence continues to increase steadily in the United States and worldwide. When energy intake exceeds expenditure, excess energy is stored in the form of fat in adipose tissue, increasing fat mass and body weight. Obesity often leads to a chronic low-grade inflammation, which contributes to pathogenesis of many chronic diseases and conditions including type 2 diabetes, insulin resistance, hypertension, hyperlipidemia, myocardial infarction, heart failure, stroke, gallbladder disease, nonalcoholic fatty liver disease, obstructive sleep apnea, kidney disease, some types of cancer, among others.[1,2] Weight control is critical for preventing and alleviating these diseases.

Weight loss can be achieved by reducing energy intake and/or increasing energy expenditure. Current methods for weight loss include lifestyle intervention, pharmacotherapy, and surgery.[3] The latter one has high efficacy but is highly invasive and expensive and is the last-line option for obesity. Pharmacotherapy utilizes orally administered drugs. Most Food and Drug Administration (FDA) approved drugs target energy intake by either suppressing appetite (phentermine) or decreasing nutrient absorption (orlistat). Orally administered drugs have the highest compliance but are beset with major problems such as a high level of hepatic metabolism (the first-pass effect) and low target specificity, leading to significant side effects and toxicity. Additionally, patients may have obesity relapse after stopping drug therapy. Lifestyle intervention is commonly recommended due to its noninvasiveness, low cost, convenience to practice, and low side effects. It includes medical nutrition therapy, exercise, and behavioral modification. Low-calorie diets and enhanced physical activity can result in short-term weight loss. Behavioral modification can enhance weight loss. However, long-term maintenance of weight loss is challenged by adhesion to the intervention programs and body offset response.[3] Therefore, other approaches to combat obesity and its comorbidities are greatly needed.

Enhancing consumption of fruits and vegetables helps with weight control.[4] This is directly related to the antiobesity functions of phytochemicals, the bioactive compounds which are abundant in these fruits and vegetables. Many cell-based and animal studies have demonstrated that phytochemicals have antiobesity activity via suppressing adipocyte proliferation, decreasing preadipocyte differentiation, promoting adipocyte apoptosis, inhibiting lipogenesis, enhancing lipolysis and fatty acid beta (β)-oxidation, and diminishing inflammation.[4–6] Human studies have also indicated that phytochemicals can maintain metabolic health, but there is no consistent evidence supporting their antiobesity efficacy.[7–9]

The major factors that are commonly blamed include phytochemicals' low aqueous solubility, poor stability, trivial bioavailability, and quick metabolism by enzymes in the gastrointestinal tract, liver, kidneys and other tissues.[10]

Nanoencapsulation opens up a new avenue in overcoming the aforementioned problems.[2,5] Phytochemicals can be encapsulated into biocompatible and biodegradable nanoparticles to improve their bioavailability, aqueous solubility, and stability.[11] Indeed, early results have suggested that enough doses of these phytochemicals, when encapsulated, could be delivered to the targeted organs and cells such that they could effectively promote fat loss and improve overall metabolism status.[2] These early evidence, although preliminary, may herald a new strategy, which potentially is also highly compliant, in coping with the prevalence of obesity. To attract more research interests in this promising area, in this perspective, we will survey the biocompatible and biodegradable nanoparticles that are suitable for carrying phytochemicals and then review the available evidence on the efficacy of these phytochemical-loaded nanoparticles in combating obesity and its comorbidities. However, first we will give an overview on the great potentials of several phytochemicals and point out their practical problems.

PHYTOCHEMICALS: POTENTIALS AND PROBLEMS

Data from three prospective cohort studies, Nurses' Health Studies, the Nurses' Health Study II, and the Health Professional's Follow-up Study, show that increased intakes of fruits and nonstarchy vegetables were negatively associated with weight change over a 24-year period.[7] Additional human cohort studies also confirm this inverse association.[12] Beneficial effects of these diets are attributed for the most part to the significant amounts of phytochemicals with recognized anti-inflammatory, antiproliferative, and antioxidant properties. These phytochemicals modulate signaling pathways including peroxisome proliferator activator receptor gamma (PPARγ), CCAAT/enhancer binding protein α (C/EBPα), AMP-activated protein kinase (AMPK), PPARγ activator 1-alpha (PGC-1α), sirtuin-1 (Sirt1), sterol regulatory element binding protein-1c (SREBP-1c), uncouple protein (UCP)-1 and UCP-2, and nuclear factor-kappa B(NF-κB), which further regulate adipogenesis, lipogenesis, browning and brown adipose tissue activity, and antioxidant and anti-inflammatory responses.[4] Concomitantly, phytochemicals can reduce fat mass and body weight through decreasing adipocyte formation and lipid accumulation, increasing lipolysis, thermogenesis, and energy expenditure, and suppressing inflammation and oxidative stress.[4,13,14]

Although phytochemicals have great potential to address the obesity challenge, their low levels of bioavailability and high levels of metabolism in the body, however, restrain their antiobesity bioactivity. Phytochemical metabolism in the body involves absorption, metabolism, distribution, and excretion, and each of these processes may affect their biological activity.[15] Initially, ingested phytochemicals need to be dissolved in gastrointestinal fluids and endure a wide range of pH throughout the gastrointestinal tract. Subsequently, they may be subjected to degradation and metabolism by intestinal enzymes like glycosidase, esterase, oxidases, and hydrolyases.[16] Another absorption barrier is the intestinal epithelium. Enterocytes have membrane-bound ATP-binding cassette (ABC)

transport proteins, which can facilitate phytochemical transportation in both directions, i.e., to the basolateral side (into blood) or to the apical side (back into the intestinal lumen).[15] Genetic variations and polymorphisms in these transporter proteins may alter the absorption rate of phytochemicals.[17] After free phytochemicals are absorbed into the circulation system, they further undergo extensive modifications through methylation, sulfation, and glucuronidation in the liver and other tissues, which further reduce blood concentrations of free phytochemicals.[18] Moreover, phytochemicals themselves do not have target specificity and therefore cannot target adipose tissue. Enzymes in the liver and other tissues metabolize most of the circulating phytochemicals, which are then excreted in urine and bile.[15,19]

This perspective will focus on the four most promising phytochemicals, *trans*-resveratrol, curcumin, epigallocatechin gallate (EGCG), and quercetin (Figure 1). Not incidentally, these phytochemicals violate the “Lipinski’s rule of five” and thus have low bioavailability. Their low solubility and stability, together with the additional factors such as intestinal wall barrier, active efflux in enterocytes, and degradation and metabolism by microbiota, intestinal, and hepatic enzymes, make these phytochemicals much less bioavailable.[10,19,20] Indeed, after oral ingestion of free *trans*-resveratrol, curcumin, EGCG, and quercetin, their concentrations in blood and adipose tissue are extremely low.[21] They are eliminated into urine and bile as their metabolites.[15,19] The low bioavailability and quick metabolism of these phytochemicals significantly limit their bioactivities in the body to trivial levels. Thus, solutions are in great need to circumvent these restrictions and boost their antiobesity efficacy to levels that meet clinical requirements.

BIOCOMPATIBLE AND BIODEGRADABLE NANOPARTICLES

Nanoparticles are particles having a size range of 1–100 nm in at least one dimension.[2] The pathological expansion of adipose tissue in obesity states enhanced permeation and retention effect, by which these nanoparticles exhibit highly differential uptake efficiency in the expanded adipose tissue over other tissues. Nanoparticles can also increase antiobesity efficacy through preventing phytochemicals from prematurely interacting with the biological environment in the body and improving cellular uptake in the adipose tissue.[2] Major nanoparticle characteristics include nanoparticle size, Zeta potential (surface charge), polydispersity index (size homogeneity), physical and chemical stabilities, encapsulation efficiency, and loading capacity. They are key factors to determine nanoparticles’ stability, bioavailability, biodistribution, and metabolism.[22] In the broad fields of nanomedicine, many organic and inorganic materials have been investigated to construct nanoparticles with a variety of structures and morphologies and functions for diagnosis and treatment of malignant tumors and other fatal diseases. However, in combating chronic diseases such as obesity, the compositions of nanoparticles should be based on those biocompatible and biodegradable materials that are safe to humans with trivial side effects. Therefore, this perspective will only cover liposomes, lipid and polymeric nanoparticles, micelles, and nanoemulsions that can be synthesized from biocompatible and biodegradable materials (Figure 2).

Liposomes.

A liposome is a spherical vesicle consisting of one or multiple lipid bilayers. Most often, liposomes are composed of phospholipids, such as phosphatidylcholine. Phospholipids have a hydrophilic head and two hydrophobic fatty acid tails, which self-organize into the conventional lipid bilayer structure in an aqueous solution. The common liposome synthesis methods include extrusion, sonication, freeze–thawing, ether injection, microemulsification, and microfluidization.[23–25] With its composition flexibility and various preparation methods, the liposome can be fabricated into different types such as the small unilamellar liposome vesicle, the large unilamellar vesicle, and the multilamellar vesicle, with sizes from the nanoscale to microscale.

Since a liposome has an aqueous solution core surrounded by its lipid bilayer, hydrophilic molecules can be dissolved in the core and cannot readily pass through the bilayer, unless the latter is fused with other bilayers such as a cell membrane, where the hydrophilic solute will then be delivered to this cell. Similarly, hydrophobic molecules can also be loaded into the lipid bilayer of the liposome for protective delivery. Due to this capability and its biosafety, the liposome has been used as a vehicle for administration of nutrients and medicines. In 1995, FDA approved liposome-based product Doxil drug for treating ovarian cancer. After that, many liposomal products have been approved by the FDA, including DaunoXome for advanced HIV-associated Kaposi's sarcoma and Amphotec and Ambisome for the treatment of fungal infections. In the food industry, liposomes have also been used for carrying and delivering flavors, nutrients, and enzymes.[26]

With its versatility in loading both hydrophilic and hydrophobic molecules and its biocompatibility, the liposome is also a good vesicle to carry phytochemicals in combating chronicle diseases including obesity. Hydrophilic phytochemicals like EGCG can be encapsulated into the hydrophilic core of liposomes, while hydrophobic phytochemicals like *trans*-resveratrol, curcumin, and quercetin can be incorporated into the hydrophobic domain of their phospholipid tails.[27] Encapsulation of these phytochemicals into liposomes will increase their stability, aqueous solubility, bioavailability, and antiobesity bioactivity.[2,28,29] Importantly, multiple phytochemicals with synergistic effects can be encapsulated into the same liposome vesicle. Target ligands can be further conjugated on the surface of liposomes to enhance targeted delivery of phytochemicals to specific cells with improved therapeutic efficacy.[30] Other functional modifications of the liposome structure can also be made. For example, polyethylene glycol (PEG) can be grafted on the liposome surface to prolong its circulation time in the blood.[31]

Instability might be a concern for liposomes in certain applications. They also suffer from a low loading efficiency for hydrophobic phytochemicals.[32] However, the aforementioned many advantages render the liposome as a good vehicle for delivering drugs, phytochemicals, and other agents.[33] We consider that the liposome is a very promising technique for phytochemical delivery in combating obesity and its comorbidities.

Lipid Nanoparticles.

Lipid nanoparticles can be categorized into solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). The difference lies at their core structure, which leads to different loading capacities. With a lipid core, lipid nanoparticles are suitable for encapsulating hydrophobic molecules.

As the first generation of lipid nanoparticles, SLNs are composed of a monolayer of phospholipids and a hydrophobic lipid core, which is solid at body temperature. Fatty acids, triglycerides, waxes, or mixtures of the above lipids have been used as solid lipids to make the hydrophobic core. One or more surfactants are usually used to stabilize the SLN structure.[34] SLNs have many advantages including protection of encapsulated phytochemicals from enzymatic degradation and metabolism and improvement of their solubility, stability, bioavailability, and bioactivity. Nevertheless, SLNs suffer from their low drug loading capacity due to the “brick wall” structure in the hydrophobic core formed by a single solid lipid. To overcome the low loading issue, NLCs were developed. They have a mixture of solid and liquid lipids in their hydrophobic cores, which provide a less ordered crystalline structure, resulting in the high loading capacity of hydrophobic phytochemicals.[35] The common preparation methods include hot/cold/high-pressure homogenization, ultrasonication, solvent evaporation/emulsification, and phase inversion.[36]

Even though NLCs have some issues related to their thermodynamical instability, aggregation, and sedimentation,[32] their increased drug stability and loading capacity and reduced drug expulsion have attracted much interest in developing NLC delivery systems for various routes of administration.[37] With increased number of patented NLC products and updated knowledge on NLC’s transport, biodistribution, and working mechanisms, the clinical application of NLCs in combating chronic diseases, including obesity and its comorbidities, is expected to speed up in the near future.

Polymeric Nanoparticles.

Polymeric nanoparticles are made of polymers. Commonly used biodegradable polymers include synthetic polymers [poly(lactide) (PLA), poly(*ε*-caprolactone) (PCL), poly(lactide-coglycolide) (PLGA), and poly(ethylene glycol) (PEG)], and natural polymers (chitosan and alginate). Phytochemicals can be conjugated to polymers or encapsulated into polymeric nanoparticles to increase their bioavailability and improve their sustained and controlled release manner.[38] The common preparation methods for polymeric nanoparticles include emulsification–diffusion, nanoprecipitation, and solvent evaporation methods.[2]

trans-Resveratrol,[39] EGCG,[40] and curcumin[41] have been encapsulated into PLGA nanoparticles for improving their characteristics and bioactivities. PLGA is a FDA-approved material for making medical devices.[2] PLGA is synthesized via copolymerization of two monomers, glycolic acid and lactic acid. Different ratios of glycolic acid to lactic acid can produce different types of PLGA. It can be metabolized naturally to yield glycolic acid and lactic acid in the body.[42] Another commonly used biocompatible polymer is PEG, which is highly hydrophilic, and has negligible immunogenicity. PEG has been widely used as the

nanoparticle's hydrophilic shell for prolonging their circulation time and increasing their stability. The unique surface chemistry of polymeric nanoparticles can adsorb, entrap, or covalently attach therapeutic phytochemicals to offer a significant delivery improvement.[43] However, for treatment of chronicle diseases, the metabolism and long-term safety of polymeric nanoparticles require further investigation.

Micelles.

Micelles are a group of amphiphilic colloids made of amphiphilic monomers. The common amphiphilic monomers include phospholipids, PEG, and poly(*N*-vinyl-2-pyrrolidone) (PVP). The common preparation methods for micelles include solvent evaporation, oil in water emulsion, dialysis, filtration, and solid dispersion.[44,45] Micelles have a hydrophobic core and many hydrophobic phytochemicals can be encapsulated into it. Specific targeting ligands can be grafted on the micelle surface to generate "targeting micelles" to disease cells and tissues.[46] Micelles are easy to synthesize and have a long circulation time, high stability, and increased cellular uptake,[32,47] but they suffer from a high surfactant content and low encapsulation efficiency and loading capacity.[32]

Nanoemulsions.

Nanoemulsions can be oil-in-water (O/W) or water-in-oil (W/O) dispersion of two immiscible liquids stabilized by surfactants and cosurfactants.[48] O/W nanoemulsions are formed by dispersing oil into an aqueous phase. On the contrary, W/O nanoemulsions are formed by dispersing an aqueous solution into an oil phase.

O/W nanoemulsions are commonly used in nanomedicine research, which have a hydrophobic core, and many hydrophobic phytochemicals, like *trans*-resveratrol,[49] quercetin,[50] and curcumin,[51] can be encapsulated into the core.[52] In order to stabilize the emulsion structure, amphiphilic surfactants/emulsifiers are needed for synthesizing nanoemulsions.[2] Homogenization and sonication are the common preparation methods for nanoemulsions in a laboratory scale. Industry uses high-pressure homogenization and microfluidization for producing a large amount of nanoemulsions.[2] To improve the target specificity of nanoemulsions, many targeted nanoemulsions have been developed by incorporating targeting ligands including peptides[53] and antibodies[54] on the surface of nanoemulsions. Nanoemulsions are easy to prepare and have high loading capacity and tunable rheology, which render them as excellent delivery vesicles for phytochemicals.[32,55] The disadvantages of nanoemulsions include thermodynamic instability and easy aggregation and creaming.[32]

NANOENCAPSULATED PHYTOCHEMICALS IN COMBATING OBESITY AND ITS COMORBIDITIES

Trans-resveratrol, curcumin, EGCG, and quercetin are the most extensively researched phytochemicals in their nanoformulations. Relevant researches were determined via a systematic search of MEDLINE (Pubmed) and Web of Science Core Collection databases. Search keywords included phytochemical classes in combination with different nanoencapsulation techniques and obesity and related comorbidities.

trans-Resveratrol.

trans-Resveratrol is a natural polyphenolic compound particularly enriched in various berries, red grapes, and other foods of plant origins.[56,57] *trans*-Resveratrol is increasingly recognized to have beneficial effects against obesity and obesity-related insulin resistance, inflammation, and hyperlipidemia by inhibiting adipogenesis and lipogenesis,[58] stimulating lipolysis, improving glucose uptake in adipocytes,[59] and increasing fatty acid oxidation and thermogenesis[60] in cell-based and animal studies. Emerging evidence suggests that *trans*-resveratrol may induce beige adipocyte formation in white adipose tissue that will further bring up subsequent beneficial activities by enhancing mitochondria biogenesis and uncoupling protein 1 expression by activating AMPK.[61]

Although a large body of *in vitro* and *in vivo* studies point to the antiobesity benefit of *trans*-resveratrol, evidence from human studies is limited and inconclusive.[62] The primary factors for this limitation include its low aqueous solubility (<0.1 mg/mL), trivial bioavailability (peak plasma *trans*-resveratrol concentration <10 μM after high-dose oral administration), and lack of targeting specificity.[63] Although the absorption of *trans*-resveratrol after oral consumption is nearly 75%, most of *trans*-resveratrol is trapped and metabolized in the liver and the major metabolites are glucuronides and sulfates of *trans*-resveratrol.[64] One approach to overcoming the aforementioned restrictions is to encapsulate *trans*-resveratrol into biocompatible and biodegradable nanoparticles. Oral bioavailability of *trans*-resveratrol after nanoencapsulation showed an 8- to 19-fold increase in several studies.[65,66] *trans*-Resveratrol-loaded liposomes and lipid nanoparticles have been investigated to enhance its solubility and antiobesity bioactivity.[28] However, liposomes in circulation can be rapidly captured and removed by the mononuclear phagocyte system. To prolong its circulation and integrity, the liposome surface was modified by using PEG, which protected liposomes by its shielding effect against opsonin recognition and consequent liposome phagocytosis upon binding.[67] Chitosan is another widely used polymer for modifying liposomes in order to bypass the acidic stomach environment and allow the release of *trans*-resveratrol in the intestines.[68] *trans*-Resveratrol was also reported to be loaded into polymeric nanoparticles such as PEG—PLA nanoparticles,[69] and PLGA nanoparticles.[39] Polymeric nanoparticles increased oral delivery efficacy of *trans*-resveratrol due to their small particle size, controlled delivery, and high encapsulation efficiency.

Effects of nanoencapsulated *trans*-resveratrol on obesity, type 2 diabetes, and inflammation have been investigated (summarized in Table 1). In our study, we demonstrated that *trans*-resveratrol-encapsulated lipid nanoparticles and liposomes had the advantage over free *trans*-resveratrol in enhancing gene expression of UCP-1 and beige marker CD137 and decreasing white adipose tissue specific marker (insulin growth factor binding protein 3) gene expression in 3T3-L1 white adipocytes.[28] We also developed ligand-coated *trans*-resveratrol-loaded nanoparticles that target adipose stromal cells (ASCs) via binding to their glycanation site-deficient decorin receptor. When administered intravenously to obese mice, nanoencapsulated *trans*-resveratrol significantly increased the targeted delivery of *trans*-resveratrol to ASCs in subcutaneous white adipose tissue and induced UCP-1 expression, resulting in enhanced white adipose tissue browning and fat loss. These results suggest that *trans*-resveratrol nanoencapsulation approach may have a promising clinical

potential for combating obesity and improving metabolic health. Mechanistic studies have explored the involvement of gut microbiota in the antiobesity effect of *trans*-resveratrol. It was proposed that *trans*-resveratrol and its metabolites might promote white adipose tissue browning through inducing remodeling of gut microbiota and Sirt1 signaling appeared to play a key role in this “gut microbiota-adipose tissue” axis.[70] In summary, *trans*-resveratrol has an antiobesity potential, but its clinical application is greatly limited by its low level of solubility, stability, and bioavailability as well as a high level of hepatic metabolism. Encapsulating *trans*-resveratrol into biocompatible and biodegradable nanoparticles represents a potentially effective approach for overcoming these limitations and thus improving its antiobesity bioactivity.

EGCG.

EGCG, a polyphenol, is the most abundant green tea catechin. EGCG has anti-inflammatory, antioxidant, antibacterial, and antiviral properties.[71] Studies have indicated that EGCG exerts its antiobesity and antidiabetic activities via inhibiting adipocyte proliferation, decreasing preadipocyte differentiation, promoting adipocyte apoptosis, reducing lipogenesis, enhancing lipolysis and β-oxidation, improving insulin sensitivity, and suppressing inflammation. [6,71,72] In preclinical studies with animal models, EGCG has been shown to be beneficial in managing obesity and improving its related metabolic diseases/disorders including insulin resistance, dyslipidemia, diabetes, and nonalcoholic fatty liver disease.[73–76] In contrast, these results for the large part have not been reproduced in humans. The allowable doses of EGCG used in human studies are usually much lower than those in animal studies. EGCG has low stability, bioavailability, and target specificity and a high rate of enzymatic metabolization in tissues, primarily liver and kidneys. All these factors are blamed for its low effectiveness in antiobesity activity.[77]

EGCG bioavailability is relatively low. The peak plasma EGCG concentrations are in the range of high nanomolar to low micromolar levels after EGCG or green tea consumption in humans and animals.[6] For example, in a human study, after oral administration of 3 g of decaffeinated green tea, the peak plasma concentrations of EGCG, epigallocatechin (EGC), and (—)-epicatechin (EC) were 0.57, 1.60, and 0.6 μM, respectively.[78]

Moreover, EGCG in water and physiological fluids is not stable;[2] EGCG in the body can be quickly metabolized/transformed by enzymes in the liver, kidneys, and other tissues.[2] The major EGCG metabolic transformations include glucuronidation, methylation, sulfation, and oxidative degradation.[2] Encapsulating EGCG into biocompatible and biodegradable nanoparticles, such as liposomes, lipid nanoparticles, and chitosan-coated lipid nanoparticles, can solve these problems.[71,79] Lipid, liposomes, and polymeric nanocarriers are the most commonly used nanoparticles for EGCG delivery.[71,72] Its stability and bioactivity are significantly enhanced after encapsulated into liposomes or lipid nanoparticles.[80–82] In one study, after EGCG-loaded nanoparticles were added to the simulated digestive fluids, the majority of EGCG (>60%) remained entrapped in the nanoparticles, so that EGCG absorption by the intestinal mucosa was enhanced.[83]

Nanoencapsulation can also improve EGCG’s bioactivity. Compared to free EGCG, nanoencapsulated EGCG increased EGCG stability, decreased macrophage inflammation

and cholesterol accumulation, and prevented atherosclerosis development (Table 1).[80,81] Ligand-coated EGCG lipid nanoparticles, which target intimal macrophages, were shown to increase macrophage EGCG content, which coincided with diminished macrophage monocyte chemoattractant protein (MCP)-1 mRNA expression and protein secretion, and reduced lesion areas of aortic arches in mice.[77] In one study, rabbits were given oral administration of 100 mg/day EGCG in the free or the nanoparticulated form. It was found that EGCG nanoparticles relative to free EGCG significantly decreased blood concentrations of triglyceride, total cholesterol, and low density lipoprotein (LDL)-cholesterol and reduced atherosclerotic lesion development.[84] Nanoencapsulation of EGCG into polymeric nanoparticles can enhance antiatherosclerosis and antitumor bioactivity.[71,83] So far, no information is available regarding the application of EGCG nanoparticles in treating obesity or type 2 diabetes, but the gap is expected to be filled soon given the developing groundwork discussed above.

Curcumin.

Turmeric spice has been used for medicinal purposes for thousands of years in Asia, and curcumin is a primary bioactive ingredient in turmeric and gives it the yellow color.[85] Curcumin is hydrophobic phenolic compound with antioxidant properties, and it was first extracted from *Curcuma longa Linn*. by Vogel et al.[85] In recent decades, investigators have demonstrated that curcumin has a variety of pharmacological activities in preventing and treating chronic metabolic and inflammatory diseases such as cardiovascular diseases, type 2 diabetes, rheumatoid arthritis, Alzheimer's disease, and multiple sclerosis as well as cancer.[86–89] These effects of curcumin are well in line with, its anti-inflammatory, antitumorigenic, antiangiogenic, and antioxidant properties.[90] Studies have also discovered that curcumin has antiobesity bioactivity via inhibiting preadipocyte differentiation and lipogenesis, increasing fatty acid β-oxidation, and suppressing inflammation in adipose tissue, while improving lipid metabolism and insulin sensitivity.[2,91] It can further increase insulin sensitivity, and this effect may be related to activation of nuclear factor erythroid-2-related factor 2 (Nfr2) and PPAR-β and inhibition of NF-κB and Wnt/β-catenin pathways, plasminogen activator inhibitor-1 (PAI-1), and tumor necrosis factor (TNF)-α expressions.[92–94] In addition, curcumin has been reported to suppress inflammation via inhibiting proinflammatory enzymes cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS).[95] As with the cases of resveratrol and EGCG, the antiobesity activity of curcumin is largely observed in cell-based and animal studies,[92–95] while the evidence from human studies is limited and inconsistent.[96,97] Likewise, its low solubility and bioavailability as well as the complexity of human diets may be the factors responsible for the disappointing results in human trials. Furthermore, complex pharmacological features, pharmacokinetics, and possible side effects at high doses present challenges in clinical application of curcumin for obesity management.[98]

Curcumin has a very low aqueous solubility (0.6 μg/mL).[99,100] Free curcumin undergoes rapid chemical degradation in alkaline aqueous conditions and crystallization in acidic aqueous conditions. Curcumin stability is further affected by pH alteration, that is the case when it travels through the gastrointestinal tract.[101] Furthermore, curcumin is quickly metabolized by hepatic enzymes resulting in very low blood concentrations that may not be

adequate to produce a therapeutic effect.[102] In a study by Shoba et al., peak serum curcumin concentration was only 1.35 μg/mL at 1 h after oral administration of 2 g/kg curcumin to rats, and in contrast, extremely lower serum concentration (0.006 μg/mL) was found in healthy males (50–75 kg) after receiving a single dose of 2 g curcumin.[103] Similarly, other studies reported that oral administration of 3.6–8 g of curcumin to humans resulted in the peak plasma curcumin concentrations at 0.004–0.644 μg/mL.[104,105]

Nanoparticles appear to be a promising solution for the poor bioavailability and retaining of curcumin in human body. Nanoencapsulation can increase curcumin's solubility, stability, and bioavailability. It has been reported that encapsulating curcumin into micelles or PLGA nanoparticles increased both its aqueous solubility and stability.[106,107] Nanoencapsulation of curcumin into SLNs, nanoemulsions, and PLGA nanoparticles enhanced its bioavailability by more than 2-fold.[2,107–109]

Accordingly, nanoencapsulation is shown to increase curcumin's antiobesity bioactivity.[2] In a study by Lee et al., high fat diet fed mice were given oral administration of free curcumin or curcumin-loaded nanoemulsions three times per week for 9 weeks.[110] Even though curcumin-loaded nanoemulsions contained 5% of curcumin as in the free curcumin treatment, mice in two groups showed similar results in reducing the weight gain.[110] Additionally, compared to mice fed free curcumin, those fed with curcumin-loaded nanoemulsions had lower lipogenesis and adipogenesis mediated through inhibition of SREBP-1, PPARγ, cleaved caspase-3, and poly(ADP-ribose) polymerase (PARP) in the liver.[110] This study indicates that nanoemulsions can reduce the therapeutic dose of curcumin (Table 1).[110] In another animal study, metabolic syndrome was induced in male Wistar rats using a high carbohydrate and high fat diet for 8 weeks.[111] After that, four groups of rats were given oral administration of curcumin PLGA nanoparticles (5 mg/kg/day), blank nanoparticles, free low dose curcumin (5 mg/kg/day), and free high dose curcumin (100 mg/kg/day), respectively, for an additional 8 weeks. Even though the curcumin nanoparticle group had significantly higher food intake than the free curcumin group, no significant differences in body weight were found between these two groups.

The reported effects of nanoencapsulated curcumin on oxidation, inflammation, glucose homeostasis are inconsistent. Some studies demonstrated that curcumin nanoparticles compared to free curcumin, improved antioxidant, anti-inflammatory and antidiabetic bioactivities,[112,113] but others did not find such difference.[114–116] Other studies also indicated that nanoencapsulated compared to free curcumin improved blood lipid profiles and cardiovascular health. Considering the many health benefits of curcumin, more studies are warranted for definitive evaluation to ascertain whether nanoencapsulation can enhance its antiobesity and other bioactivities.

Quercetin.

Quercetin is a flavonoid compound found in various types of food such as onions, berries, citrus fruits, apples, brassica vegetables, nuts, seeds, and tea.[2] In addition to widely reported anti-inflammatory, antiviral, and antioxidant properties,[6] quercetin has been shown to have antiobesity activity.[6,117,118] It increases fatty acid β-oxidation by stimulating mitochondrial biogenesis and promotes lipolysis by elevating cyclic adenosine monophosphate (cAMP)

levels and hormone sensitive lipase (HSL) activity.[119,120] Furthermore, quercetin suppresses lipogenesis by inhibiting fatty acid synthase and acetyl-CoA carboxylase and adipogenesis by inhibiting PPARγ and C/EBPα.[98] Quercetin's antiobesity bioactivity is largely based on results from cell-based and animal studies, but evidence in human studies is limited and inconclusive,[6,121] which is partly attributed to its low solubility and bioavailability and high levels of metabolism and excretion.[6,20] Quercetin is insoluble in cold water, poorly soluble in hot water, but quite soluble in alcohol and lipids.[120,122] Quercetin's solubility in water differs from 0.00215 g/L at 25 °C to 1.49 g/L at 140 °C in anhydrous or dihyrate forms. The solubility of quercetin in ethanol is approximately 2 g/L at 25 °C.[122] Quercetin is an aglycone and undergoes the first-pass metabolism in the gastrointestinal tract and liver after oral administration. After a single dose of ingestion, bioavailability of quercetin is around 2%. In the glucoside form, the absorption rate was found between 3 and 17% with ingestion of 100 mg in healthy human subjects.[120] Unabsorbed quercetin is rapidly metabolized by gut microbiota and excreted from the colon.[120]

Studies have demonstrated that nanoencapsulation can increase quercetin's stability, aqueous solubility, bioavailability, and bioactivities.[123–126] The aqueous solubility of quercetin can be increased by 110-fold using nanomicelles[127] and 1000-fold using NLCs.[122] NLCs can also increase quercetin's stability and bioavailability.[2,122] Furthermore, nanoencapsulation may prolong quercetin's circulation time and prevent its degradation and metabolism in the body.[2]

Few studies have been published concerning the use of nanoencapsulated quercetin in obesity, type 2 diabetes, cardiovascular disease, and inflammation. In one study, diabetic rats were given 10 mg/kg free quercetin daily or 10 mg/kg nanoencapsulated quercetin every 5 days for 8 weeks via abdominal subcutaneous injections for 8 weeks, and it was found that nanoencapsulated compared to free quercetin had a better and prolonged glycemic control.[128] Similarly, other animal studies demonstrated similar antidiabetic outcomes with different nanoformulations of quercetin (Table 1).[11,129,130] Nanoencapsulation is also shown to improve anti-inflammatory properties of quercetin. After giving rats intravenous injection of free quercetin and quercetin-loaded liposomes at a dose of 5 mg/kg once a week for 4 weeks, quercetin-loaded liposomes compared to free quercetin significantly lowered the concentrations of inflammatory factors including TNF-α, IL-1β, and IL-6 in bronchoalveolar lavage fluid.[131] Another study using quercetin-loaded polymeric nanoparticles demonstrated that nanoencapsulated compared to free quercetin increased mitochondrial integrity, size, and functions.[132]

Quercetin has a potential in suppressing lipogenesis, adipogenesis, and inflammation and therefore may help in obesity treatment; however, its rapid metabolism and low solubility, stability, and bioavailability diminish its efficacy in these effects. Biodegradable and biocompatible nanoparticles have emerged to be a potential solution to overcome these issues and increase the opportunity of its future clinical application in combating obesity and its comorbidities.

SUMMARY AND FUTURE PERSPECTIVES

Many phytochemicals are promising in the prevention and treatment of obesity and its comorbidities. However, their low stability, solubility, and bioavailability together with high metabolism rates prevent their application in these fields. This is true for EGCG, *trans*-resveratrol, curcumin, and quercetin, the most intensively studied phytochemicals with the best potentials in combating obesity and its comorbidities. A considerable amount of studies has demonstrated that biocompatible and biodegradable nanoparticles can effectively deliver phytochemicals, improve their bioavailability and bioactivities, and even increase synergistic effects by carrying multiple phytochemicals in one nanoparticle system.

There are several biocompatible nanoparticle systems that could be used to deliver these phytochemicals for combating obesity and other chronic diseases. Each nanoparticle has its own characteristics, loading capacity, and other pros and cons. Selection of nanoparticles for delivery of a particular phytochemical requires the match between the carrier and the load as well as consideration of effective doses, administration routes and frequency, their side effects, and toxicity among others.

Since most phytochemicals are administered via the oral route, a major challenge in designing biocompatible and biodegradable nanoparticles is how to minimize their digestion, absorption, and metabolism in the body before reaching the target tissues. Many biodegradable components in the nanoparticles can be digested by enzymes in the gastrointestinal tract. Even though nanoparticles, in their integral forms, can protect the encapsulated phytochemical cargo, gastrointestinal digestion may change the integrity, characteristics, and pharmacokinetics of nanoparticles themselves, thus diminishing their protection capability.[2] Future studies should focus on developing nanoparticles which avoid gastrointestinal digestion and enter into the bloodstream in intact forms. Functionalizing the nanoparticle surface to extend their blood circulation duration for sustainable delivery and/or target delivery to the right tissues are some of the crucial research subjects.

Safety is a major concern for nanoparticle medical applications in general and for treatment of obesity and other chronic diseases in particular. The side effects of nanoparticles must be trivial when compared to its benefits. In order to produce commercially feasible nanoparticles, using generally recognized as safe (GRAS) food ingredients and good manufacturing practice is necessary.[32] Target ligands, surfactants, cosurfactants, and emulsifiers in the nanoparticles may lead to hepatoxicity, nephrotoxicity, and immunotoxicity.[2] The photochemical doses are also a major concern. Even though nanoencapsulation gives phytochemicals dose advantages via increasing the phytochemicals' stability, bioavailability, target delivery, and bioactivities, the safe dose ranges of nanoencapsulated phytochemicals must be determined through rigorous studies.[2] Additionally, some nanoparticles may have off-target effects, and nanoencapsulated and free phytochemicals may have completely different tissue biodistribution, pharmacokinetics, and metabolism. Both short- and long-term safety of nanoparticles and encapsulated phytochemicals need to be intensively evaluated. Currently, there are no standardized tests and guidelines available for determining side effects and toxicity of nanoparticles. Future

research should focus on developing suitable in vitro and in vivo models, standardized safety tests, and guidelines.

Even though encouraging groundworks have demonstrated the potential of biocompatible and biodegradable nanoparticles in boosting the antiobesity activities of several phytochemicals, most of these studies have been conducted at the preclinical level with cells and animals as the tested subjects. We therefore recommend that future studies in this promising area might focus on (1) fundamental studies to understand the metabolism and antiobesity mechanisms and efficacy of nanoencapsulated phytochemicals and (2) the safety study of the phytochemical-loaded nanoparticle system. The fundamental understandings on these areas will lay a solid foundation to move the studies forward to clinical stages in near future, toward the ultimate goal of using natural phytochemicals in combating obesity and its comorbidities. Until efficacy and safety of any phytochemical-loaded nanoparticles are rigorously evaluated and approved by FDA, a diet rich in phytochemicals may still be helpful for combating obesity and its comorbidities.

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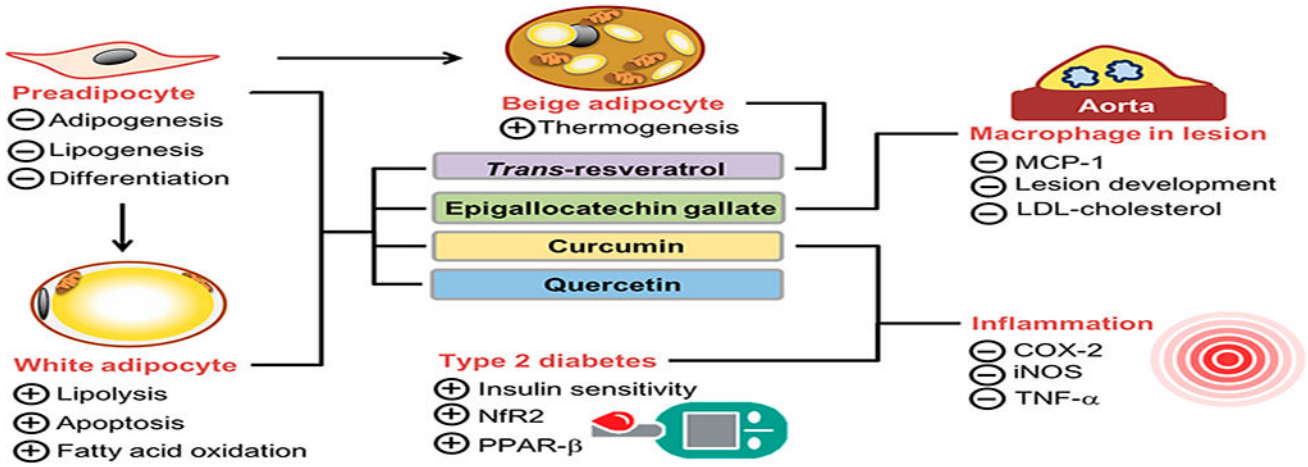

Figure 1.

Potential actions of phytochemicals, particularly *trans*-resveratrol, EGCG, curcumin, and quercetin on obesity and its comorbidities. Abbreviations: EGCG, epigallocatechin gallate; MCP-1, monocyte chemotactic proteins-1; LDL, low-density lipoprotein; COX-2, cyclooxygenase-2; iNOS, inducible nitric oxide synthase; TNFα, Tumor Necrosis Factor; Nrf2, nuclear factor erythroid-2-related factor 2; PPAR-β, peroxisome proliferator-activated receptor-β. (+): Stimulate; (−): Inhibit.

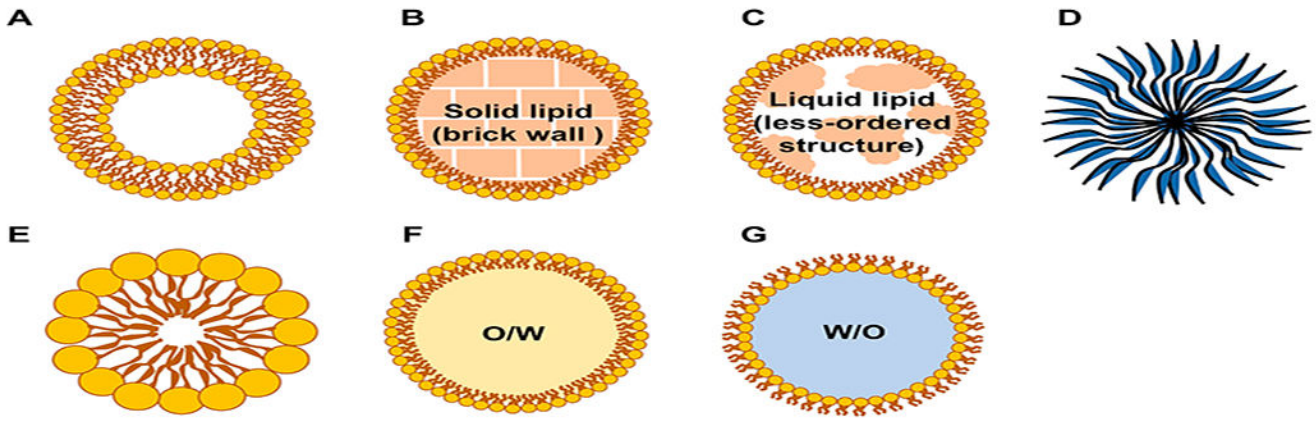

Figure 2.

Schematic structure of biocompatible and biodegradable nanoparticles: (A) liposome, (B) solid lipid nanoparticle (SLN), (C) nanostructured lipid carriers (NLC), (D) polymeric nanoparticle, (E) micelle, (F) nanoemulsion (oil-in-water, O/W), and (G) nanoemulsion (water-in-oil, W/O).

Table 1.

Characteristics and Bioactivities of Phytochemical-Encapsulated Nanoparticles[a]

phytochemicals	nanoparticles			experiments		
name	name/components	size (nm)	EE	model/treatments	main outcomes	refs
trans-resveratrol	solid lipid nanoparticles	248	79.9	model: Wistar male diabetic rats	↓ fasting glucose sugar	133
				treatment: oral administration of 10 mg/kg/day of resveratrol in SLN form or free form for 1 month	↓ insulin resistance	
					↓ serum oxidative stress status	
					↓ Snap23, Stx4 and Vamp2 level in muscle	
	PLGA nanoparticles	176	97.2	model: HepG2 hepatocytes	↑ stability, water solubility and bioactivity of resveratrol	134
				treatment: 12.5, 25, 50, and 100 μM of resveratrol in PLGA form or free form for 24h.	↓ lipogenesis	
					↓ lipolysis	
					↓ hepatocellular proliferation and lipid accumulation	
	galactosylated PLGA nanoparticles	108.4	97.2	model: Caco-2 cells for uptake study	↑ Caco-2 cellular uptake of resveratrol	135
				mouse macrophage cell line RAW 264.7 for anti-inflammation study	↓ TNF-α and IL-6 expressions	
				treatment: 20 μg/mL of resveratrol in PLGA form or free form.		
EGCG	lipid nanoparticles; phosphatidylcholine, kolliphor HS15, a-tocopherol acetate, EGCG, and 1-(palmitoyl)-2-(5-keto-6-octene-dioyl) phosphatidylcholine (KOdiA-PC)	108	96.0	model: human monocytic	↑ EGCG stability	80
				THP-1 cells	↑ sustained release of EGCG	
				treatment: free or nano-EGCG at EGCG dose of 5, 10, 20, and 40 μg/mL in combination with 40 μg protein/mL of oxLDL for 18 h	↑ binding affinity to and uptake by macrophages	
					↑ macrophage EGCG content	
					↓ macrophage MCP-1 mRNA levels and protein secretion	
	chitosan–tripolyphosphate nanoparticles of EGCG (EGCG is encapsulated into self-assembled nanoparticles made of chitosan and aspartic acid)	100	25.0	model: male New Zealand white rabbits	↓ TC	84
				treatment: free or nano-EGCG (7 mL of 0.5% aqueous acetic acid) at EGCG dose of 100 mg/day for 5 weeks.	↓ TG	

phytochemicals	nanoparticles			experiments		
name	name/components	size (nm)	EE	model/treatments	main outcomes	refs
					↓ HDL	
					↓ LDL	
	soy lecithin, glyceryl tridecanoate, glyceryl tripalmitate, and Kolliphor HS15	45- 50	99.0	model: THP-1-derived	↑ EGCG stability	81
				macrophages	↑ sustained release of EGCG	
				treatment: free or nano-EGCG at EGCG dose of 5 μM, 10 μM and 20 μM were tested	↑ cellular bioavailability of EGCG	
					↓ TC content in macrophages	
					↓ MCP-1 expression in macrophages	
	soy PC, surfactant Kolliphor HS15, and (+)-α-tocopherol acetate	104	95.0	Model: male 6-week old LDLr$^{-/-}$ mice	↓ secretion of inflammatory factors in mouse peritoneal macrophages	77
				treatment: free or nano-EGCG at EGCG dose of 25 mg/kg/ body weight EGCG per week for 22 weeks	↓ lesion surface areas of aortic arches	
curcumin	turmeric extract-loaded nanoemulsions	136–138	88.0	Model: Balb/c mice	↓ SREBP-1	110
				treatment: oral administration of free or nanocurcumin at a curcumin dose of 300 mg/kg/day 3 times/week for 9 weeks	↓ PPARγ2	
					↓ Cleaved caspase-3	
					↓ PARP in the liver	
	polylactide-poly(ethylene glycol) (PLA–PEG) copolymer nanoparticles	100–150	98.3	model: albino rats (STZ-induced diabetic)	↓ NF-κB activation	113
				treatment: oral administration of free or nanocurcumin at a curcumin dose of 20 mg/kg/day	↓ COX-2 and TGF-β expression	
					↑ PPARγ expression	
	PLGA based nanoparticles	237 ± 6	66.0	model: Sprague–Dawley rats (STZ induced diabetic)	↓ CRP, IL-6, TNF-α	136
				treatment: oral administration of nanocurcumin at a curcumin dose of 100 mg/kg/day for 15 days.	↓ plasma TG and TC	
					↑ HDL-cholesterol	
quercetin	succinylated chitosan-alginate core—shell-corona nanoparticles	91.58 ± 1.14	95.0	model: Male Wistar rats (STZ induced diabetic)	↓ TG	11
				treatment: oral administration of free or nanoquercetin at a quercetin dose of 100 mg/kg/day for 28 days	↓ TC	
					↓ AST, ALT and ALP levels	

phytochemicals	nanoparticles			experiments		
name	name/components	size (nm)	EE	model/treatments	main outcomes	refs
	PLGA nanoparticles	179.9 ± 11.2	86.0	model: Sprague–Dawley rats (STZ induced diabetic) treatment: oral administration of free or nanoquercetin at a quercetin dose of 150 mg/kg every day for free group and every 5th day for NP group for 15 days	↓ blood glucose levels (similar effect to free quercetin although with a lower dose and frequency)	129

[a]Abbreviations: SLN, solid lipid nanoparticles; EE, encapsulation efficiency; EGCG, epigallocatechin gallate; oxLDL, oxidized low density lipoprotein; MCP-1, monocyte chemotactic proteins-1; NP, nanoparticle; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PC, phosphatidylcholine; Snap23, synaptosomal-associated protein 23; Stx4, Syntaxin4; Vamp2, vesicle-associated membrane protein 2; R, resveratrol; SREBP1c, sterol regulatory element-binding protein-1c; PPAR, peroxisome proliferator-activated receptors; PARP, poly(ADP-ribose) polymerase; STZ, streptozotocin; NF-κB, suppressing nuclear factor-kappa B; COX-2, cyclooxygenase-2; TGF, tumor growth factor; CRP, C-reactive protein; IL-6, interleukin-6; TNFα, Tumor Necrosis Factor; TG, triglycerides; TC, total cholesterol; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase.