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REVIEW

Mesoporous Silica Nanoparticle as a Potential Nanocarrier to Improve the Effectiveness of Antiobesity Drugs

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Abstract: Obesity is a global health issue characterized by an abnormal or excessive accumulation of body fat, defined as a body mass index (BMI) that exceeds 30 kg/m². Many antiobesity drugs, such as orlistat and quercetin, are often limited by poor solubility and bioavailability. These physicochemical limitations can lead to poor gastrointestinal absorption, erratic plasma drug concentrations, and ultimately, suboptimal therapeutic efficacy. This review employed a narrative approach with a structured literature search to summarize current advances in the use of mesoporous silica nanoparticles (MSNs) as drug delivery systems to improve the dissolution and pharmacological profiles of antiobesity compounds. The literature search was conducted using PubMed and Scopus databases with the keywords "obesity OR antiobesity AND mesoporous silica". The search included free full-text articles from the past ten years. A total of 106 articles were screened, and 11 were selected based on relevance to MSN-based delivery in in vitro or in vivo obesity studies. MSNs enhanced the dissolution profile of various antiobesity compounds, including orlistat, quercetin, epigallocatechin gallate, and liraglutide. In vitro assays showed improved lipase inhibition, adipogenesis suppression, and DPP-4 enzyme inhibition. In vivo studies demonstrated significant improvements in triglyceride levels, blood glucose levels, body weight reduction, and food intake suppression. Functionalization of MSNs further enabled targeted and pH-responsive delivery, enhancing bioavailability and reducing systemic side effects. MSNs offer a promising nanocarrier platform to overcome limitations of conventional antiobesity therapies by improving drug solubility, stability, and targeted pharmacological activity. These findings support the potential of MSN-based formulations as innovative strategies in obesity treatment and need for further studies.

Keywords: antiobesity, mesoporous silica, nanocarrier, dissolution, bioavailability

Introduction

Obesity is a major global health issue, with the World Obesity Foundation (2024) reporting that one billion individuals are obese and 2.5 billion have elevated body mass index (BMI) levels. It is characterized by an abnormal or excessive accumulation of body fat, typically diagnosed when BMI exceeds 30 kg/m².[1,2] Treatment includes using medication in addition to lifestyle changes.[3] Antiobesity medications (AOMs), including intra gastrointestinal medications (orlistat), centrally acting medications (phentermine, phentermine-topiramate, naltrexone-bupropion), and nutrient-stimulated hormone-based medications (liraglutide, semaglutide, tirzepatide), have been developed to support weight loss by addressing appetite dysregulation.[4–6] However, their clinical use is often limited by issues such as modest long-term efficacy, gastrointestinal side effects, lean mass loss, high costs, and societal misconceptions about obesity treatment.[4,7] Furthermore, certain AOMs, such as orlistat, exhibit low aqueous solubility, categorized under BCS Class II, which further restricts their therapeutic potential.[8,9]

Mesoporous silica nanoparticles (MSNs) have emerged as a promising nanocarrier to enhance the effectiveness of antiobesity medications by addressing solubility and bioavailability limitations. MSNs can enhance drug solubility, prevent

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medications from early degradation, and facilitate targeted and controlled delivery of drugs because to their high surface area, large pore volume, and adjustable surface characteristics.[10–12] Compared to other nanocarriers commonly explored in obesity research, such as liposomes, polymeric nanoparticles, and lipid-based systems, which often faces challenges like structural instability, rapid systemic clearance, low drug-loading capacity, or complex formulation requirement, MSNs offer superior thermal and chemical stability, tunable pore size for precise drug loading, and enhanced control over drug release kinetics. These features make MSNs a more versatile and robust platform for overcoming the solubility and bioavailability challenges associated with antiobesity medications.[13–15] Through targeted delivery, MSNs have the potential to increase therapeutic efficacy of AOMs while minimizing systemic side effects, offering a strategic solution to the limitations faced by conventional antiobesity therapies.[16] Therefore, this review aims to present current insights, summarize, and elucidate the mechanism of antiobesity drugs within MSNs, focusing on the improvements in dissolution profiles, in vitro, and in vivo activity to highlight their potential as innovative strategies for advancing obesity treatment.

Methodology

Briefly, a literature search using the (1) PubMed database using the keywords obesity OR antiobesity AND mesoporous silica within Abstract, free full text, in the last 10 years, and resulted in n = 14; (2) in the Scopus database using the same keywords within All fields, resulted in n = 92, with a total of all publications found through these searches were reviewed. The authors retrieved and evaluated all documents that met the inclusion criteria, such as using MSN for in vitro or in vivo study in treating obesity. Finally, 11 articles were selected for review, as depicted in Figure 1.

Pathophysiological Pathway of Obesity

The pathophysiological pathway of obesity is presented in Figure 2. At its core, one of the factors that causes overweight, and obesity is chronic imbalance between energy intake and expenditure.[17–19] A diet high in fats and calories, when combined with insufficient physical activity, disrupts the body's energy balance, ultimately leading to excessive fat accumulation in adipose tissue, including in the heart, pancreas, and kidneys.[20–22]

As adipose tissue expands, it initiates a series of physiological disturbances, notably affecting the hormonal regulation of appetite.[25] Appetite-regulating hormones are critical for maintaining energy homeostasis through the modulation of hunger and satiety signals directed to the central nervous system. In the context of obesity, this regulatory system becomes markedly impaired, primarily due to the development of leptin resistance and elevated ghrelin secretion.[26] Leptin, a hormone secreted by adipocytes, ordinarily acts to suppress appetite and signal energy sufficiency to hypothalamic center.[27] However, individuals with obesity experience attenuated central leptin signaling despite elevated leptin levels, which results in diminished satiety perception and persistent hyperphagia. At the same time, ghrelin, a strong hunger hormone produced by the gastric mucosa, stays unusually high, which increases the urge to eat even more.[23,28] This hormonal dysregulation perpetuates excessive food intake, promotes further adipose tissue expansion, and accelerates the progression of metabolic dysfunction.[29]

The chronic overconsumption of energy-dense foods contributes to elevated levels of saturated fatty acids and promotes insulin resistance, a key metabolic abnormality wherein cells become less responsive to insulin, resulting in hyperglycemia.[30,31] This metabolic issue is strongly connected to ongoing low-level inflammation, which is marked by higher levels of pro-inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). These cytokines interfere with insulin signaling pathways and contribute to endothelial dysfunction, collectively exacerbating the risk of obesity-related complications.[32,33]

Ultimately, this complex interplay of hormonal imbalance, metabolic dysfunction, and persistent inflammation underlies the development of obesity and its associated comorbidities, including atherosclerosis, type 2 diabetes mellitus (T2DM), and various liver diseases such as non-alcoholic fatty liver disease (NAFLD).[24,34] Importantly, this conceptual framework shifts the understanding of obesity from being seen solely as a result of lifestyle choices to recognizing it as a complex systemic disorder with wide-ranging health impacts.[35] As a result, effective prevention and management of obesity require comprehensive, multidisciplinary approaches that address not only behavioral changes but also the underlying hormonal imbalances and inflammatory processes.[24]

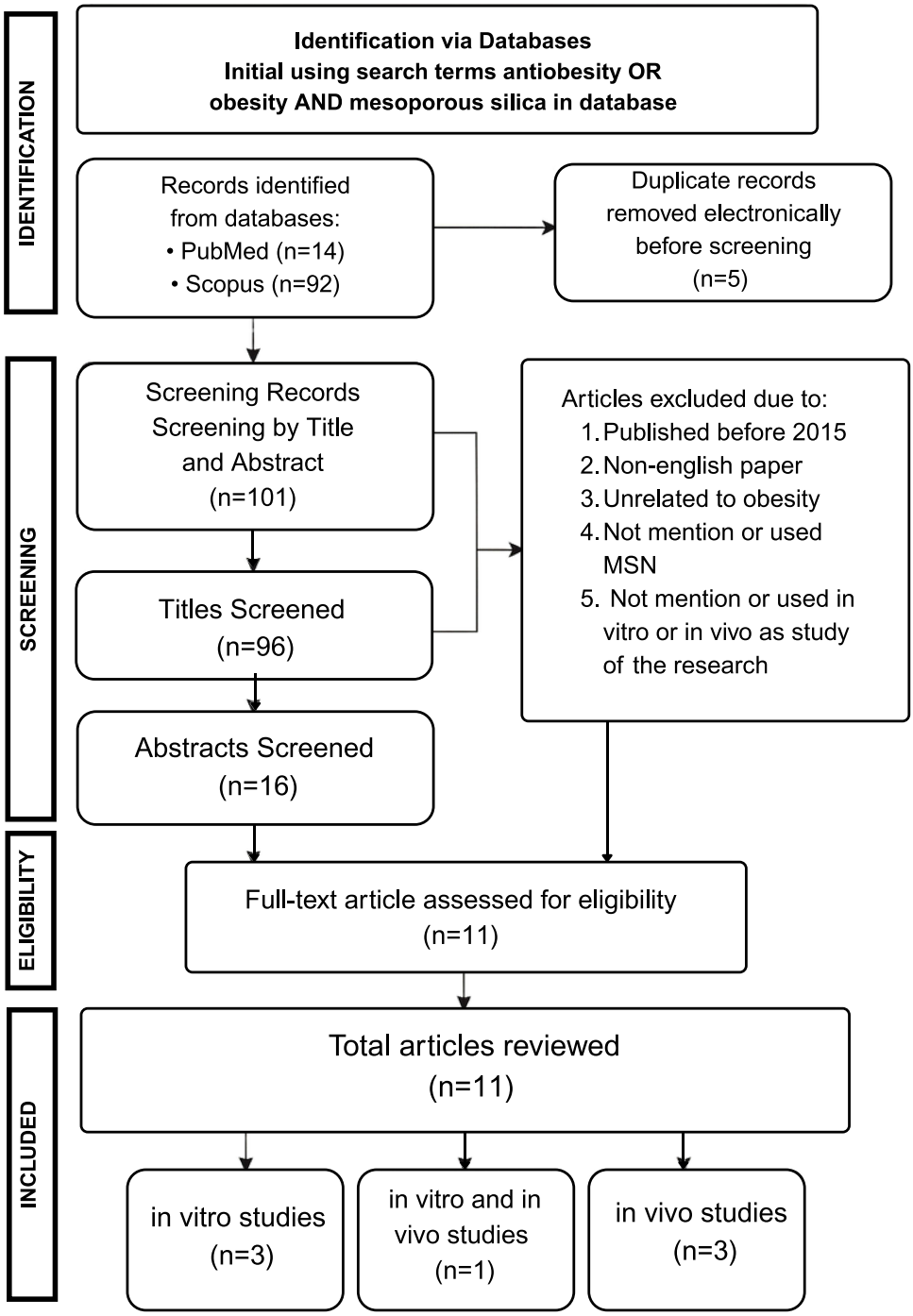

Figure 1 Flow chart of the methodology.

Mesoporous Silica Nanoparticles (MSNs)

Formulation development strategies to improve the solubility of oral drugs have been carried out, including salt formation, cocrystals, emulsion systems, nanotechnology, amorphous solid dispersions, and mesoporous silica nanoparticles.[36,37] Mesoporous silica nanoparticles (MSNs) have become highly effective carriers in medicinal applications because of their distinct structural and functional properties. According to in vivo investigations on its absorption, distribution, and excretion, silica is "Generally Recognized as Safe" (GRAS) by the FDA and exhibits excellent biocompatibility for oral and intravenous uses.[38,39] Amorphous silica is preferred in pharmaceuticals over crystalline

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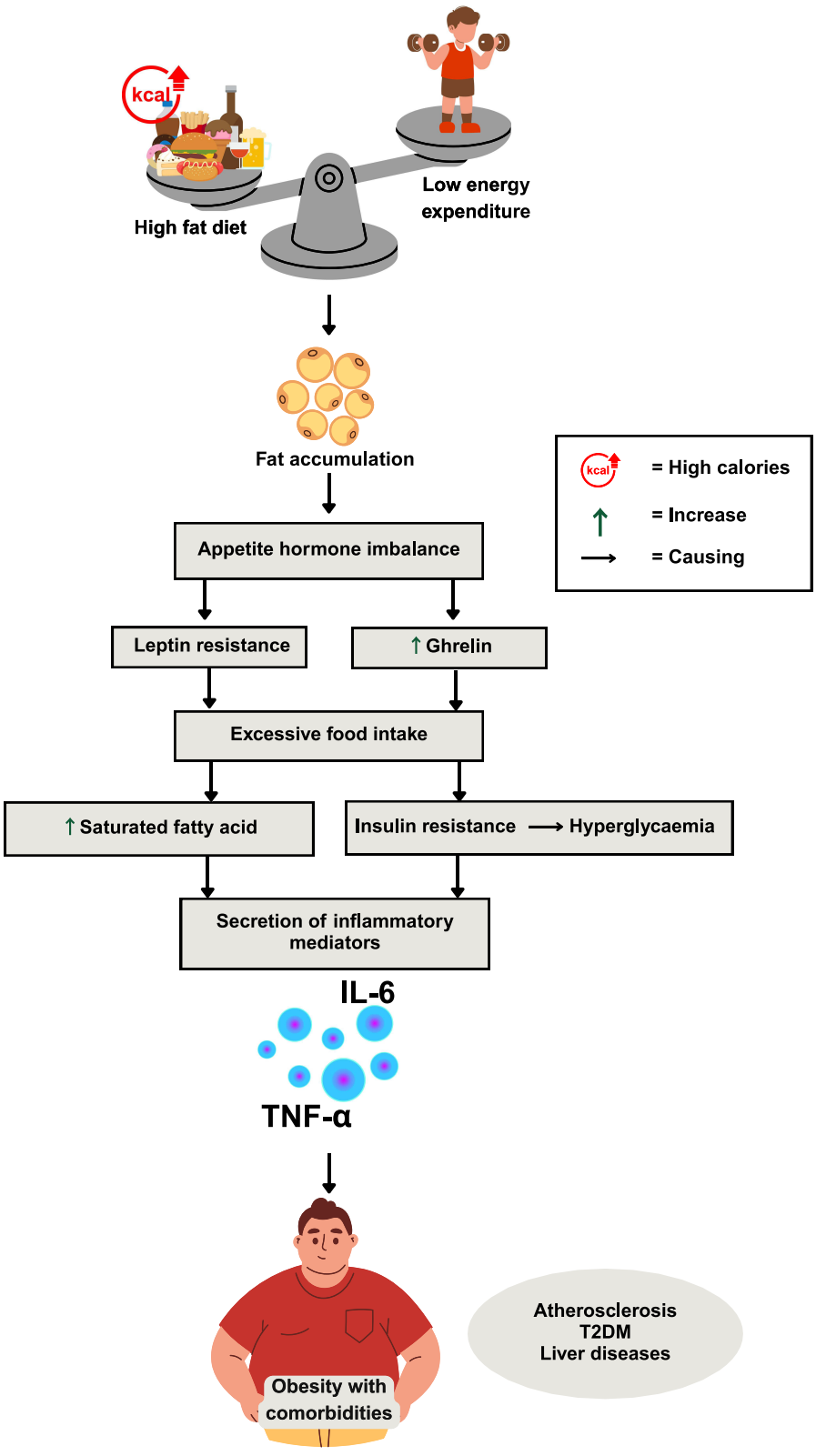

Figure 2 Pathophysiology pathways of obesity and its associated comorbidities.[19,23,24]

silica due to its reduced toxicity and enhanced capacity for controlled drug loading and release, facilitated by a high surface area (>700 m^2/g) and large pore volume (>1 cm^3/g).[38,40] MSNs may load various compounds, including proteins, genes, and medicines, owing to their controlled properties, which include rich silanol groups, low-density solids, variable selectivity, and changeable surface activity.[41] Additionally, to improve loading capacity and optimize release profiles, these nanoparticles can be functionalized with certain groups.[42] Furthermore, drug loading, release characteristics, and targeted delivery efficiency can be optimized through the functionalization of MSNs' outer surface as well as their interior cylindrical pores.[43,44] These nanoparticles are versatile in terms of their synthesis conditions, enabling the creation of different mesoporous carriers like MCM-41, MCM-48, SBA-15, and SBA-16, each of which has distinct morphological and structural characteristics appropriate for particular uses.[42,43]

Mesoporous silica is a promising material for improving the dissolution rates of poorly water-soluble drugs.[10,11] Drugs can be contained in its pores in a stabilized amorphous form, preventing crystallization by nanoconfinement, because of its high surface area, which frequently exceeds 300 m^2/g, and special porous architecture.[11] Drug molecules are kept in an amorphous state by spatial confinement, which prevents crystallization via both thermodynamic equilibrium and kinetic barriers, especially when pore widths are less than the critical nuclei size.[10,45] Additionally, drugs can more easily adsorb onto MSNs' surface due to its high surface-free energy, which stabilizes the system by lowering its free energy state. When the encapsulated medication is exposed to water, it quickly separates from the silica surface and forms supersaturated solutions, which greatly accelerate the rate of dissolution.[45] The presence of silanol groups on the MSN surface enables further surface modifications to optimize drug interactions and enhance dissolution behavior.[11]

Previous studies have demonstrated the potential of MSN in improving the bioavailability of poorly water-soluble drugs. In a proof-of-concept clinical study, Bukara et al (2016) evaluated the bioavailability of fenofibrate, comparing a formulation loaded onto ordered mesoporous silica (OMS) with a commercially available micronized formulation. Results showed a significant enhancement in pharmacokinetic parameters: a 54% increase in AUC0–24h/dose, a 77% increase in Cmax/dose, and a reduction in Tmax by 0.75 hours for the OMS-based formulation.[46] This study indicated that administration of an ordered mesoporous silica-based formulation of fenofibrate resulted in an increased rate and extent of absorption when compared to a marketed product, demonstrating the bioavailability-enhancing potential of this novel formulation. Similarly, Laine et al (2016) investigated the oral delivery of celecoxib using mesoporous silica co-loaded with a precipitation inhibitor. This novel formulation achieved a 15-fold solubility increase in vitro and a 1.35-fold increase in Cmax in vivo after oral dosing in rats, compared to the crystalline celecoxib.[47] Besides its ability to increase medication bioavailability, experimental studies have also shown that mesoporous silica can enhance pharmacological activity. A study conducted by Elbially et al (2020) shows that antitumor activities against HepG2 and HeLa cells of curcumin-loaded PEGylated MSNs (mesoporous silica nanoparticles) increased more than free curcumin. The cytotoxicity results showed that Cur-loaded PEGylated MSNs (Cur concentration = 36 mg mL^{-1}) had cell viability of less than 10% and about 7% after 24 and 48 hours, respectively, whereas HepG2 cells treated with free Cur had cell viability of less than 76% after 48 hours at the same concentration of Cur (Cur concentration = 36 mg mL^{-1}).[48] This approach represents a novel formulation strategy to maximize in vivo exposure to poorly soluble drugs that are critical for discovery.

Antiobesity Compound Loaded into Mesoporous Silica Nanoparticles

Previous studies have reported the loading of antiobesity compounds into mesoporous silica as shown in Table 1.

Characterization

Common Methods

Various analytical techniques are commonly used to characterize drug-loaded mesoporous silica nanoparticles (MSNs). Differential scanning calorimetry (DSC) characterizes drug-loaded MSNs by analyzing melting behavior. Encapsulation lowers the drug's melting point and glass transition temperature, and complete confinement prevents recrystallization, ensuring an amorphous state.[38] Nitrogen adsorption-desorption analysis is a widely used technique for characterizing mesoporous materials, providing key information on surface area, pore volume, and pore diameter of mesoporous silica nanoparticles (MSNs).[60,61] This method precisely quantifies the amount of gas adsorbed onto the material, offering direct insights into its porosity and structural properties.[38] Thermogravimetric analysis (TGA) determines drug content in MSNs by measuring mass

Table 1 The Studies of Antiobesity Compound Loaded MSN

No	Antiobesity Compound	Type of MS	Preparation Method	Dissolution Study	Antiobesity Activities		Ref
					In vivo	In vitro	
1	Orlistat	• SBA-15) • SBA-15_LP (SBA-15 with large pores) • Neusilin® UFL2 • Neusilin® US2 • MCM-41	Supercritical melt-adsorption (SCMA) method using CO_2	For all types of mesoporous silica used, drug release was markedly enhanced in formulations with an orlistat loading ratio below 40% compared to 60%	Serum triglyceride (TG) concentration significantly decreased in the rat administered amorphous orlistat-loaded Neuisilin®UFL2 compare to the commercial product	Lipase inhibition of orlistat-loaded mesoporous silica increased compared to raw orlistat. Oil adsorption capacity increased with specific surface area of mesoporous silica, thus reducing the side effects of orlistat.	[49]
2	Quercetin (QUER)	Fluorescent mesoporous silica nanoparticles (FMSNs) coated with polydopamine (PDA)	PDA coating was applied to the QUER-loaded FMSNs (FMSNs-QUER) through the oxidative polymerization of dopamine under alkaline conditions	FMSNs-QUER showed higher release fraction than pure QUER. FMSNs-QUER @PDA showed a release fraction of ~75% within 24 h, indicating the most delayed release compared to MSNs-QUER (91%), and FMSNs-QUER (85%)	–	QUER loaded onto FMSNs showed an increase in adipogenesis inhibition with increasing concentrations and FMSNs-QUER @PDA demonstrated superior adipogenesis inhibitory	[50]
3	1,3 - oxathiolane steroid derivatives	Micro-emulsion technique by TEOS (tetraethyl-ortho-silicate) dropped gradually on PVA (poly vinyl alcohol)	Solvent evaporation (methanol as the solvent)	After 672 hours, the release rate of compound 11 loaded into silica nanoparticle was very high (reaching almost 90%)	Besides decreased body weight, cholesterol, triglyceride, and LDL levels, there was a significant change ($P<0.05$) in the body weight, chest circumference of the mice treated mesoporous silica-encapsulated compound 11 (8.8 cm) compared to the group of mice given the free drug (9.7 cm).	–	[51]

(*Continued*)

Table 1 (Continued).

No	Antiobesity Compound	Type of MS	Preparation Method	Dissolution Study	Antiobesity Activities		Ref
					In vivo	In vitro	
4	Epigallocatechin gallate (EGCG)	FMSNs (fluorescent mesoporous silica nanoparticles) consisting APTMS-FITC (3-aminopropyl-trimethoxysilane and fluorescein isothiocyanate) coated with PDA (polydopamine)	Solvent evaporation (DMSO as the solvent)	FMSNs-EGCG @PDA shows an accelerated release rate compared to pure EGCG	–	FMSNs-EGCG @PDA was observed of lipids stained with Oil Red O. The FMSNs-EGCG@PDA group show adipogenesis inhibition shown by decreasing red intensity. PDA coating enhance inhibition compared to the non coated EGCG group	[52]
5	Liraglutide (Lira) and pFGF21	Amino-functionalized and embedded dual-mesoporous silica nanoparticles (N-EDMSNs)	Absorption method (mixing, stirring, centrifuging, washing)	The total release of Liraglutide from N-EDMSNs/Lira is about 15% within 48 hours at a neutral pH of 7.4 means N-EDMSNs/Lira exhibit pH-sensitive drug release properties	Compared with both pFGF21 and liraglutide, N-EDMSNs/pFGF21/Lira treatment significantly reduced the food intake, body weight, and blood glucose; increased the energy expenditure and improved hepatic insulin resistance in high-fat diet (HFD)-fed mice.	–	[53]
6	Glimepiride (GLM)	Gelatin-coated mesoporous hollow silica nanospheres (GSN)	Absorption method (mixing, stirring, centrifuging, washing)	The mesoporous improves the dissolution of GLM. Pure GLM shows a low dissolution rate of 33.6% ± 2.01% after 1 hour, whereas GLM-GSN and GLM-MSN exhibits 40% and 80.6% of drug release at 1h, respectively.	Mice treated with GLM-GSN exhibited improvement in lowering blood glucose level, weight loss and decreased food intake compared to marketing preparation (GLM capsules)	–	[54]

(*Continued*)

Table 1 (Continued).

No	Antiobesity Compound	Type of MS	Preparation Method	Dissolution Study	Antiobesity Activities		Ref
					In vivo	In vitro	
7	16-hydroxycleroda-3,13-dine-16,15-olide (HCD)	Surface functionalization of Mesoporous silica nanoparticles with amine groups ((MSN)-NH_2)	Solvent evaporation (methanol as the solvent)	–	MSN-HCD lowered blood glucose of mice almost similar to the control (no treatment) group.	MSN-HCD had higher DPP-4 inhibition 5-fold of pure HCD. The inhibition is time- and dose-dependent	[55]
8	Atorvastatin	SBA-16	Atorvastatin loaded into nano-porous cavities of silica via in vivo application	–	The atorvastatin loaded nanoparticles significantly lowered the body weight of rats. The rats group receiving SBA-16 silica nanoparticles alone showed improvement in hyperlipidemia and oxidant status than the group treated with SBA-16 silica together with atorvastatin	–	[56]
9	Heparin	Periodic mesoporous silica nanoparticles (PMS)	Absorption method (mixing, stirring, centrifuging, washing)	–	Intravenous injection of PMS-HP to mice enabled targeted LDL adsorption (6.5 ± 0.73 vs 8.6 ± 0.76 mM, $p < 0.001$) without affecting other plasma constituents, contributing to reducing intravascular plaque formation (3.66% ± 1.06% vs 1.87% ± 0.79%, $p < 0.05$) on the aortic wall and inhibiting vascular remodeling	Compared to PMS, PMS-HP has the ability to adsorb a greater amount of LDL while having minimal impact on HDL-C and TP levels	[57]

(*Continued*)

Table 1 (Continued).

No	Antiobesity Compound	Type of MS	Preparation Method	Dissolution Study	Antiobesity Activities		Ref
					In vivo	In vitro	
10	Simvastatin	Hyaluronic Acid-Functionalized Mesoporous Silica Nanoparticles (HA-MSN) MCM-41-type MSN	SIM was successfully loaded in MSNs by solvent impregnation	–	–	Downregulating Effects on Inflammation: SIM@HAMSN treatment led to the lowest level of TNF-α and IL-6 at 514.12 and 273.62 pg/mL, respectively. Both are Proinflammatory cytokines in the pathogenesis of atherosclerosis	[58]
11	Rosuvastatin	MSN-NH_2	Solvent evaporation	–	Mice treated by CD9-HMSN@RSV showed significantly higher distribution and stronger binding capability in atherosclerotic lesions compared to IgG-HMSN @RSV. In a separate experiment, CD9-HMSN@RSV reduced the senescent cells and mitigated further atherosclerosis	The subsequent layer-by layer coating with PGA, PLL, and HA via electrostatic interaction ensures prolonged circulation of the drug in the blood and enhances biocompatibility of the delivered cargo	[59]

loss during controlled heating, which reflects drug degradation and desorption of volatile components.[62] Powder X-ray Diffraction (PXRD) confirms drug amorphization after encapsulation in MSNs. A successfully loaded drug exhibits a halo pattern without diffraction peaks, while the pure crystalline drug shows sharp peaks specific to its lattice structure.[38] FTIR is used to determine drug-silica interactions and analyze the chemical state of drugs in MSNs. It identifies functional groups by detecting peak distributions caused by infrared radiation.[38,63,64] Microscopic techniques, including Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM), provide structural characterization, with SEM analyzing surface morphology with nanometer resolution,[65] while TEM provides atomic-scale imaging, revealing internal microstructures. Both can be used separately or together; they offer comprehensive structural insights into MSNs.[38,65,66]

Dynamic Light Scattering

Dynamic Light Scattering (DLS) is a technique used to characterize particle size, size distribution, and the degree of agglomeration within a system. This method measures the intensity of scattered light at a fixed angle for different sample concentrations and compares it with the scattering pattern of a standard.[67] However, DLS has limitations, including low resolution and inefficiency in analyzing highly concentrated samples.[68]

Researchers commonly use DLS to determine the hydrodynamic diameters of mesoporous silica nanoparticles (MSNs), which provides both the frequency distribution and the cumulative particle-size distribution. Research by Jin et al (2024) found that heparin-modified mesoporous silica nanoparticles (MSN-HP) and unmodified MSNs exhibited no significant difference in size, indicating that functionalization did not alter the particle size. Moreover, DLS is also useful for assessing the successful adsorption of LDL onto MSN-HP, as evidenced by the significant increase in particle size.[57]

Photoluminescence (PL) Spectroscopy

Photoluminescence (PL) spectroscopy is used to study optical properties of ~1 nm-sized silica layers and electronic properties of MSNs. This technique provides insights into the radiative recombination process in MSNs (Glinka et al, 2002). PL spectroscopy has been employed to confirm successful surface modifications and investigate the structural properties of MSNs. For instance, the grafting of fluorescent mesoporous silica nanoparticles (FMSNs) and the subsequent polydopamine (PDA) coating (FMSNs-PDA) were confirmed by distinct emission peaks in the PL spectra. Additionally, the presence of the PDA layer partially absorbs and blocks the fluorescent light emitted by FMSNs upon excitation. Moreover, PL spectroscopy enables real-time fluorescent monitoring of drug delivery routes and can confirm the successful transport of the drug to the target area.[50]

Zeta Potential

The zeta potential (ZP), which measures the electrostatic attraction or repulsion between nanoparticles, is frequently used to evaluate surface charge and colloidal stability by quantifying the particle's electrical charge.[38,67] A general threshold for distinguishing between unstable and stable suspensions is ±30 mV, with particles having zeta potentials beyond these limits typically considered electrostatically stable.[69] This method is widely applied in the preparation of MSNs to ensure stability, verify successful modifications, and prevent aggregation.[38] The successful heparinization modification of MSNs was confirmed by a significant shift in surface potential.[57]

XPS

X-ray photoelectron spectroscopy (XPS) is a surface-sensitive analytical technique that involves bombarding a material's surface with X-rays and measuring the kinetic energy of emitted electrons.[70] This method is widely employed to evaluate surface interactions between grafted compounds and silica nanoparticles. By providing quantitative information on the elemental composition and chemical states of material surfaces, XPS serves as a crucial tool for characterizing surface modifications and functionalization.[71] Jin et al (2024) utilized XPS to analyze potential interactions in heparin-modified periodic mesoporous silica nanoparticles (PMS-HP) during LDL adsorption. The analysis revealed the emergence of a distinct peak following LDL adsorption, indicating that N–H and O–H bonds played a key role in the adsorption process.[57]

Dissolution Study

The dissolution study assessed the behavior of medicines in antiobesity drug-loaded MSNs following dispersion in dissolution media. The dissolution study revealed that MSNs significantly enhanced the rate of antiobesity drugs dissolving compared to the drugs alone. Understanding dissolution behavior is crucial for solid formulation development and regulatory assessment. Yu et al found that the release of glimepiride (GLM) from mesoporous hollow silica nanospheres (MSNs) was significantly higher and faster (80.6% in 15 min) compared to GLM alone, which was only 33.6% in 1 hour. This shows that the MSNs significantly improve the releasing rate of the antiobesity drug. MSNs can be nanocarriers that have pH-responsive drug release behavior. A study by Geng et al showed the cumulative amount of liraglutide (Lira) released from MSNs is approximately 15% within 48 h in a neutral environment (pH 7.4), while it can reach 30% at pH 5.0.[53]

In vitro Study

Lipase Inhibition and Oil Adsorption Test

The most attractive and safe target for antiobesity treatment is to alter lipid metabolism by inhibiting dietary fat using pancreatic lipase.[72,73] Pancreatic lipase is the main lipolytic enzyme secreted by the pancreas and plays an important role in fat digestion. Agents that can inhibit the action of gastrointestinal lipase will reduce fat absorption.[74] In clinical

practice, orlistat is the only treatment used as a pancreatic lipase inhibitor.[72,75,76] Orlistat inhibits gastric and pancreatic lipases and carboxylesterases by reacting with the catalytic serine residues of these enzymes.

Park et al conducted an in vitro study on lipase inhibition and compared raw orlistat, commercial products, and orlistat encapsulated in mesoporous silica; the results showed a significant increase in orlistat encapsulated in mesoporous silica in inhibiting lipase. Compared with raw orlistat and commercial products, orlistat encapsulated in mesoporous silica showed 53% and 12% more lipase inhibition, respectively. This decrease is in line with the dissolution results, where samples with high dissolution rates will inhibit lipase activity more efficiently.[49]

In addition, the use of mesoporous silica not only provides a higher lipase inhibitory effect on orlistat, but mesoporous silica can also inhibit the side effects of orlistat by absorbing undigested lipids in the digestive tract after the drug is released from mesoporous silica and absorbed in the body and excreted through feces so that it has the potential to reduce fat absorption and help lose weight.[77] Park et al conducted an in vitro oil absorption test on orlistat encapsulated with various types of mesopores that have different specific surface areas, including Neusilin®UFL2, Neusilin®US2, MCM-41, SBA-15, and SBA-15 large pores. The results indicated that mesoporous silica with the largest surface area, namely MCM-41, had the highest oil absorption capacity.[49] Therefore, studies have shown that MSN inhibits the side effects of orlistat on the gastrointestinal tract by absorbing undigested lipids. The mechanism of orlistat and MSN containing orlistat in inhibiting lipase and absorbing undigested lipids in the body by mesoporous silica can be seen in Figure 3.

Adipogenesis Inhibition

The main target in overcoming obesity is adipogenesis, or the process that causes fat accumulation. Synthetic compounds primarily possess strategies to inhibit adipogenesis. The ability to modulate cellular signaling pathways related to

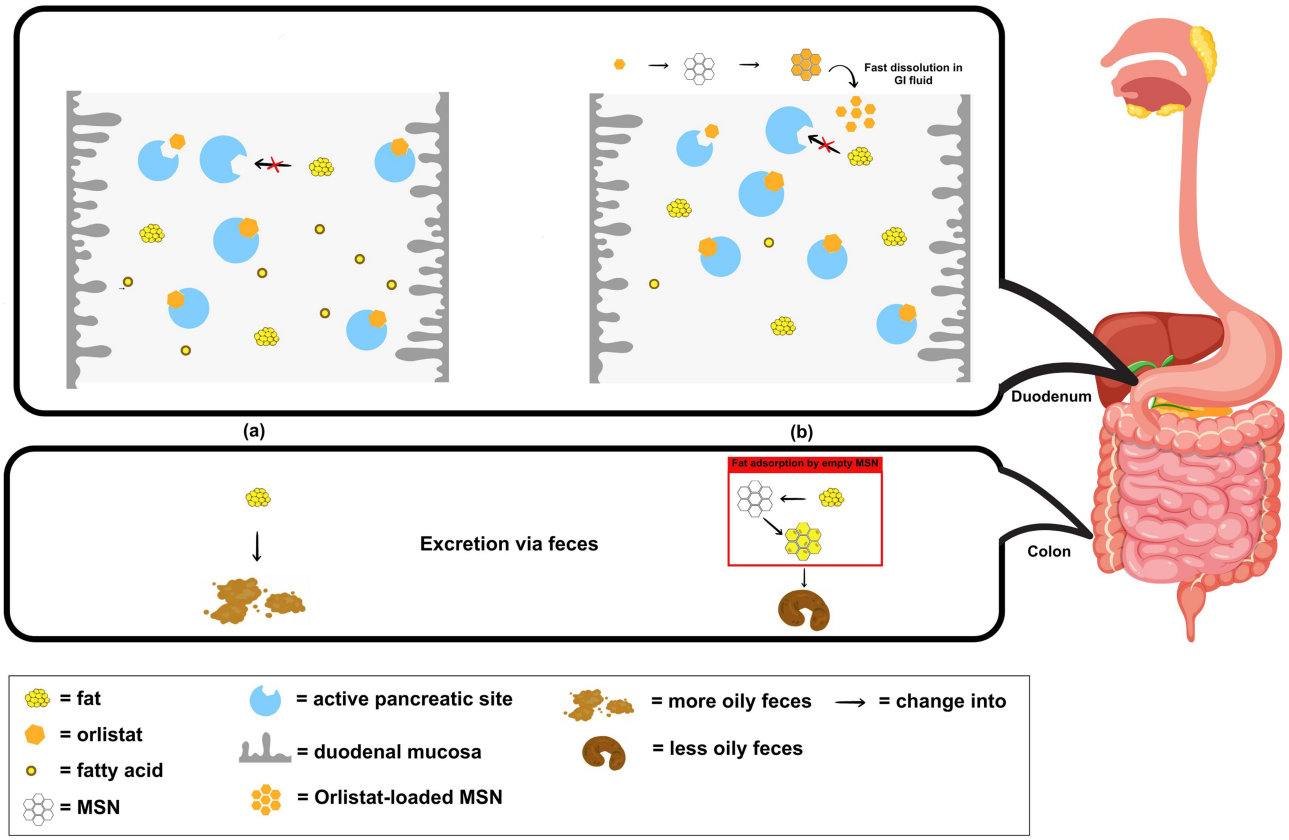

Figure 3 The (**a**) Orlistat mechanism in the body and (**b**) Orlistat encapsulated mesoporous silica mechanism in the body.[49,78] Mesoporous silica nanoparticles not only enhance orlistat's lipase inhibition, but also help minimize its side effects by absorbing unprocessed lipids in the digestive tract. After orlistat is released from the mesoporous silica, absorbed by the body, and eventually excreted in feces, the silica continues to reduce fat absorption, offering potential benefits for weight loss.

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adipogenesis inhibition is one of the properties that make compounds effective candidates to overcome obesity problems. Kim et al reported that encapsulation of quercetin in fluorescent mesoporous silica nanoparticles (FMSN) coated with polydopamine (PDA) (quercetin concentration 2.5–10 μM) showed superior adipogenesis inhibition efficacy compared to free quercetin and FMSN-quercetin. Inhibition of adipogenesis was tested by oil red O staining to compare the level of adipocyte differentiation that would form lipid droplets where the lipophilic oil red O dye marked with red color would dissolve in lipids (Yuan et al, 2019). The results showed a 27% decrease in red intensity in quercetin samples encapsulated in FMSN and coated with PDA (FMSN-quercetin-PDA) compared to pure quercetin. This finding indicates an increase in adipogenesis inhibition in FMSN-quercetin-PDA samples. In conclusion, the use of nanoparticles and PDA coating can increase particle absorption, which allows higher concentrations of quercetin to be maintained in cells so that the efficacy of therapy with natural compounds such as quercetin can be more optimal.[50]

DPP-4 Activity

DPP-4 (dipeptidyl peptidase-4) inhibitors are drugs that prevent DPP-4 from breaking down and inactivating GLP-1, a hormone that stimulates insulin secretion, inhibits glucagon secretion, slows gastric emptying, and suppresses appetite, which indirectly has a weight loss effect. Thus, GLP-1 can last longer in the body, and its effectiveness is increased. Evaluation of DPP-4 enzyme activity using hydroxycleroda (HCD), a secondary metabolite from *Polyalthia longifolia*, was investigated. The results showed that the time-dependent inhibition of DPP-4 by MSN-HCD was better (5-fold) than pure HCD. Based on the in vitro DPP-4 inhibitory activity test, it can be concluded that MSN-HCD can produce more significant inhibition of the DPP-4 enzyme than pure HCD; this is in line with the results of increased solubility and more efficient drug release.[55]

In vivo Study

Biochemical Parameters

Triglyceride

Triglycerides are composed of a glycerol base and three fatty acids. Triglycerides are the main component of fats found in plants and animals and the main form of fat stored in our bodies. Measuring total triglyceride levels in the blood can help diagnose metabolic problems. Obesity and metabolic disorders are largely caused by excessive triglyceride intake.[31]

Park et al, in their study, measured serum triglycerides (TG) after oral administration of orlistat. Orlistat inhibits the breakdown of dietary fat by binding to lipase. The results indicated that the mesoporous silica formulation containing orlistat experienced a faster and more significant decrease in triglycerides compared to the raw orlistat and commercial product groups. This effect can be seen from the levels of ΔTG produced; when compared to raw orlistat, ΔTG in samples encapsulated into MSN was 77.3%, while when compared to the commercial product, ΔTG was 84.9%. The decrease in triglycerides was due to the increased solubility and dissolution rate of orlistat-containing mesoporous silica, resulting in higher drug concentrations in the gastrointestinal tract.[49]

Low Density Lipoprotein (LDL)

Lipoproteins are complex particles with a hydrophobic core made mostly of triglycerides and cholesterol esters, which are nonpolar lipids. A hydrophilic membrane made of phospholipids, free cholesterol, and apolipoproteins encloses this hydrophobic core. LDL is derived from very low-density lipoprotein (VLDL) and is further enriched with cholesterol. Small, dense LDL particles are abundant in people with type 2 diabetes (metabolic syndrome patients), obesity, and diabetes. High-density lipoprotein (HDL) is anti-atherogenic due to its significant role in the reverse transport of cholesterol from peripheral tissues to the liver for excretion.[79]

A study conducted by Jin et al proposed a new method using MSNs to create heparin-modified MSNs (MSN-HP), which allows selective removal of LDL from the blood. The results indicated that functionalized MSNs (MSN-HP) showed selective LDL uptake, which had no effect on HDL and protein levels in blood compared to MSNs that showed non-selective lipid uptake. This is because LDL is composed of triglycerides, cholesterol esters (CE), and unesterified cholesterol (UC). ApoB-100, which has the ability to bind heparin and cause LDL precipitation, primarily composes its

surface. This binding occurs through electrostatic interactions between the positive and negative charge regions in the molecule.[57]

Blood Glucose

Glucose, a type of sugar found in the blood, is derived from carbohydrates and stored in skeletal muscles and the liver in the form of glycogen. Obesity is a feature of metabolic syndrome, insulin resistance, fasting hyperglycemia, lipid disorders, and high blood pressure. Excess body weight can lead to alterations in cellular function, making the body's cells resistant to insulin. Thus, increase blood glucose.[80]

Yu et al, in their study, prepared gelatin-coated mesoporous hollow silica nanospheres (GSN) as drug carriers to increase solubility and regulate the release rate of glimepiride (GLM). The results indicated that the marketing product, GLM, exhibited a rapid hypoglycemic effect with a short duration of action, causing blood glucose levels to spike frequently during the drug administration interval, potentially leading to liver damage. The GLM-GSN group provided a safer hypoglycemic effect because it was moderate, showed a prolonged effect, and did not cause a decrease in blood sugar levels.[54]

Anthropometric Measurements

The anthropometric measurements are associated with adiposity and its distribution. Anthropometric measurement indices can be used for risk identification, intervention, or impact evaluation on nutritional status or health. Body weight is the most widely used anthropometric index to estimate the overall body fatness.[81]

Geng et al conducted a study on weight loss in mice given liraglutide, pFGF-21, liraglutide encapsulated with amino-functionalized and embedded dual-mesoporous silica nanoparticles (N-EDMSNs/Liraglutide), pFGF-21 encapsulated with amino-functionalized and embedded dual-mesoporous silica nanoparticles (N-EDMSNs/pFGF-21), and pFGF-21 and liraglutide encapsulated with amino-functionalized and embedded dual-mesoporous silica nanoparticles (N-EDMSNs/pFGF-21-Liraglutide). The results showed a decrease in body weight in all test groups when compared to the control (saline). The group given N-EDMSNs/pFGF-21-Liraglutide experienced the greatest decrease, reaching 1.39%.[53] Similar results were also found in the study of encapsulation of 16-hydroxycleroda-3,13-dine-16,15-olide (HCD) in mesoporous silica nanoparticles as a natural dipeptidyl peptidase-4 inhibitor that improved hypoglycemia in diabetic rats. In the treatment group, the average weight loss was 4–6 g in HCD and HCD encapsulated MSN (10 mg/kg B.wt)., while the body weight in the untreated group (control and diet-induced obesity) continued to increase.[55]

Food Intake

Food intake is associated with excess calorie consumption that causes weight gain and burdens abdominal fat. In addition, increased abdominal fat gain can increase blood leptin concentrations, leading to leptin resistance.[82] Yu et al, in their study, combined the body weight and food intake of each group every day. The glimepiride group loaded into gelatin-coated mesoporous hollow silica nanospheres (GLM-GSN) experienced a slight decrease in food consumption compared to the marketing preparation, from 77.92.5 to 75.92.9 g/kg/day, while the food intake of the model group was 87.1.3 g/kg/day.[54]

Fat Excretion

Fat excretion via feces can be a measurement to determine the sterol contents of the diets via lipid extraction, saponification, and capillary gas chromatography. Body mass was recorded weekly, while food intake and feces production of group-housed mice were recorded during the first and the last week of the feeding trial.[83]

Park et al divided the mice into four groups: control, raw orlistat, commercial products, and orlistat-loaded mesoporous silica. The result was that the fat content in the feces of mice fed high-fat food without orlistat (control group) was 30.97 ± 6.43 mg/g. After administration of raw orlistat, commercial products, and orlistat-loaded mesoporous silica, the fat content in the feces increased significantly to 45.15 ± 7.64, 45.37 ± 8.18, and 49.71 ± 4.01 mg/g, respectively. This finding implies that orlistat inhibits lipase activity. Therefore, dietary triglycerides are not hydrolyzed into absorbable free fatty acids and are excreted as undigested free oils in the feces.[49]

Undigested Lipids

In a study conducted by Park et al, an oily spotting number test was conducted to confirm the results of the in vitro oil adsorption test by mesoporous silica, namely to see the capacity of mesoporous silica in reducing the side effects (one of which is oil spotting) of orlistat. The results of the study showed something interesting, namely the group given mesoporous silica filled with orlistat experienced a decrease in the number of mice with oily spotting (9 mice) compared to the group given raw orlistat (17 mice) or commercial products (18 mice). This result can be obtained because all types of mesoporous silica used as adsorbents in this study can absorb undigested oil in the intestinal tract through empty mesoporous silica after the release of orlistat in the body.[49]

Collagen

Collagen is a major component of the connective tissue surrounding adipocytes. Collagen cross-linking affects adipose remodeling, which is critical for maintaining the function and metabolic homeostasis of adipose tissue.[84] Obesity can cause changes in collagen metabolism and connective tissue structure, which can affect cardiac function.[85] A study conducted by Jin et al determined the collagen content in plaques in the aortic root area using Masson staining. In the control group treated with phosphate-buffered saline (PBS), a large amount of dark blue collagen was observed in the plaque, indicating a high collagen content of 38.3% ± 1.99%. Compared with the control group, mice treated with heparin-loaded mesoporous silica showed a lower collagen content in the plaque of 27.2% ± 6.55%. Data analysis indicated that PMS-HP treatment effectively reduced the collagen content in the plaque.[57]

Discussion and Author Perspective

Studies showed that mesoporous silica enhance activity of antiobesity drug through some mechanisms as seen in the Figure 4. The pancreas and intestine play a crucial role in the antiobesity effects of the compounds studied as illustrated in the Figure 4(a). Several compounds demonstrated the ability to inhibit digestive enzymes such as pancreatic lipase,

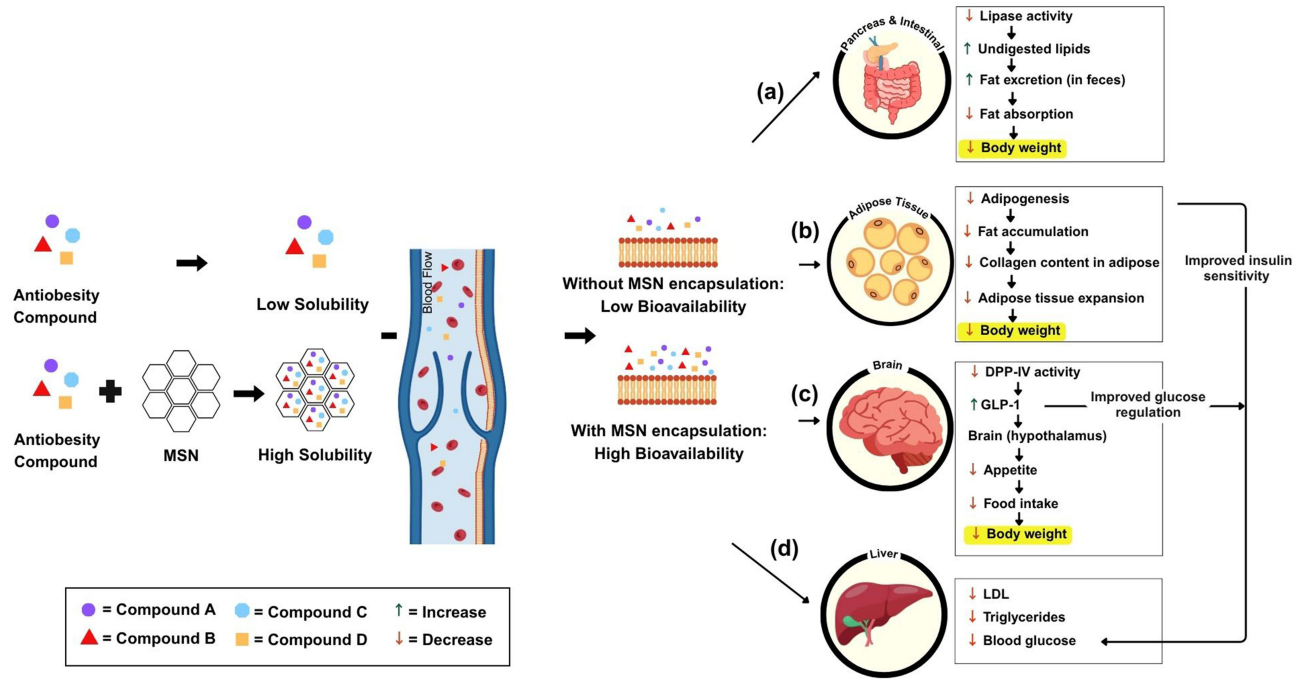

Figure 4 The speculated mechanism of the improvement of the antiobesity activity of MSN-encapsulated compounds. MSN loading significantly improves the solubility, cellular uptake, and systemic absorption of the compounds, resulting in enhanced antiobesity effects at multiple physiological targets: (**a**) Pancreas and intestinal tract: MSN-encapsulated compounds inhibit lipase activity, leading to reduced fat absorption, increased lipid excretion, and a consequent decrease in body weight. (**b**) Adipose tissue: These compounds downregulate adipogenesis and fat accumulation, reduce collagen content in adipose tissue, and limit tissue expansion, collectively contributing to weight reduction. (**c**) Brain (hypothalamus): Encapsulation increases GLP-1 secretion and decreases DPP-IV activity, promoting appetite suppression and improved glycemic control, resulting in reduced food intake and body weight. (**d**) Liver: The compounds lower LDL, triglyceride, and blood glucose levels, contributing to improved metabolic profiles and enhanced insulin sensitivity.

which reduces the breakdown and absorption of dietary fats. This inhibition leads to an increase in undigested lipids that are excreted through the feces, thereby decreasing overall fat absorption and energy intake.[86] Additionally, DPP-4 inhibition was observed, which prolongs the activity of incretin hormones like GLP-1. GLP-1 enhances insulin secretion, slows gastric emptying, and contributes to appetite suppression. Through these mechanisms, the intestinal and pancreatic pathways collectively reduce nutrient absorption and promote metabolic improvements, supporting body weight control and lowering blood glucose levels.[6]

In Figure 4(b), the antiobesity compounds primarily act by inhibiting the adipogenesis process. Adipogenesis is the differentiation of preadipocytes into mature adipocytes, contributing to fat storage. The inhibition of this process results in a reduced formation of new fat cells and a decrease in lipid accumulation within existing adipocytes.[87] Furthermore, some studies reported that treated animals exhibited reduced collagen content associated with adipose tissue, suggesting an improvement in tissue remodeling and possibly mitigating fibrosis that often accompanies obesity. By directly targeting adipose tissue expansion, these compounds help to limit fat storage and contribute to overall weight reduction.[88]

The brain, particularly the hypothalamus, is central to the regulation of appetite and energy homeostasis. The Figure 4 (c), show the compounds indirectly influence the hypothalamic signaling pathways through DPP-4 inhibition and the subsequent increase in GLP-1 levels. GLP-1 acts on the brain to promote satiety and reduce hunger, leading to a significant decrease in food intake.[89] By modulating the hormonal signals that control appetite, the compounds can create a negative energy balance, supporting long-term weight management. This brain-mediated pathway highlights the importance of hormonal crosstalk between peripheral organs and the central nervous system in achieving antiobesity effects.[90] By modulating the hormonal signals that control appetite, the compounds can create a negative energy balance, supporting long-term weight management. This brain-mediated pathway highlights the importance of hormonal crosstalk between peripheral organs and the central nervous system in achieving antiobesity effects.[90]

The liver is critically involved in lipid and glucose metabolism, and its function is often impaired during obesity. As shown in the Figure 4(d), several studies indicated that treatment with the antiobesity compounds resulted in improved blood lipid profiles, including reductions in low-density lipoprotein (LDL) cholesterol and triglycerides, as well as better regulation of blood glucose levels. These improvements suggest that the compounds enhance hepatic lipid metabolism and potentially alleviate insulin resistance.[91] By the liver is critically involved in lipid and glucose metabolism, and its function is often impaired during obesity. Several studies indicated that treatment with the antiobesity compounds resulted in improved blood lipid profiles, including reductions in low-density lipoprotein (LDL) cholesterol and triglycerides, as well as better regulation of blood glucose levels. These improvements suggest that the compounds enhance hepatic lipid metabolism and potentially alleviate insulin resistance. By reducing the metabolic burden on the liver and preventing lipid accumulation, these interventions may also lower the risk of developing non-alcoholic fatty liver disease (NAFLD), a common complication associated with obesity.[92,93]

After confirming that the compound was already loaded into the MSNs through characterization, the dissolution study was used to analyze the release. The outcome demonstrated that, in comparison to their pure forms, MSNs have a considerable potential to greatly increase the dissolving rates of different compounds. The unique characteristics of mesoporous silica, such as its large surface area and tunable pore size, are responsible for this enhancement. Compounds dispersed monomolecularly within the MSNs. The dissolution medium was added immediately after the compound was dispersed in the MSNs. After being divided into monomolecules, the substance dissolves rapidly and releases into the solvent used for bulk dissolution. A high concentration or supersaturation level formed in the dissolution media as a result of the compound's quick dissolution. These characteristics aid in the improved release and dispersion of compounds that are encapsulated. The more soluble form of a compound can be confined in MSNs, most likely because of the nanostructure of the compound's constituents. This study demonstrates how compound-loaded MSNs with mesoporous morphologies can load a complicated multicomponent mixture in a more soluble state, ideally increasing the bioavailability. Additionally, the medications' adsorption onto the MSNs improves wettability and expands the surface area that can dissolve, which speeds up drug release. Strong connections between certain chemicals and the mesoporous silica structure lead to this effect, which may cause some of the chemicals to get partially trapped inside the tiny holes.

Although the use of mesoporous silica nanoparticles (MSNs) offers significant advantages in enhancing drug solubility and bioavailability, several limitations remain. In orlistat study, fat excretion in mice that were administered orlistat-loaded MSN was significantly decreased compared to the control group, but not in comparison with groups administered raw orlistat and the commercial product. In some studies, formulations were evaluated following a single administration, limiting therapeutic efficacy regarding their long-term efficacy and safety under repeated dosing. The limited drug-loading capacity of compounds such as 16-hydroxycleroda-3,13-dine-16,15-olide may also hinder optimal dosing strategies. Other concerns include the preliminary safety evaluations, the lack of long-term stability data; potential systemic and organ-specific toxicities of MSN, insufficient studies on biodegradation kinetics and biodistribution, and the risk of interactions with concurrently administered agents. The mechanistic pathways underlying the observed therapeutic effects have not been fully elucidated and require further validation. Moreover, challenges in purification and the accurate quantification of in vivo performance persist. These gaps call for more detailed pharmacokinetic, mechanistic, and toxicological investigations to support future therapeutic applications.

Conclusion and Future Perspective

The encapsulation of antiobesity compounds within mesoporous silica nanoparticles (MSNs) effectively enhances their solubility, dissolution rate, and stability, addressing key challenges associated with poor water solubility. Characterization studies using DSC, XRD, FTIR, TGA, SEM, and nitrogen adsorption–desorption confirm the successful loading of these compounds into MSNs, with transformations from crystalline to amorphous states contributing to improved dissolution. Furthermore, dissolution studies demonstrate that MSN-loaded formulations significantly accelerate compound release, leading to increased dispersion and prolonged retention in solution. The improved pharmacological activity of MSN-loaded antiobesity compounds is attributed to enhanced dissolution and controlled release mechanisms. Studies on various compounds, including orlistat, quercetin, EGCG, and statins, indicate greater enzyme inhibition, lipid metabolism regulation, and glucose homeostasis when formulated with MSNs. These findings highlight the potential of MSNs as an advanced drug delivery system to optimize the therapeutic effects of antiobesity drugs by improving their physicochemical properties and sustained activity. These improved therapeutic effects can help treat obesity by improving drug availability at target sites, assuring regulated release, sustaining pharmacological activity, and minimizing systemic side effects. MSNs strengthen the efficacy and durability of antiobesity interventions in preclinical models by modulating key physiological pathways, such as lipid absorption, adipogenesis, and insulin sensitivity. These underscore the translational potential of MSN-based systems as a viable strategy to address the complex pathophysiology of obesity, including metabolic dysregulation and its associated comorbidities.

Despite these promising results, additional research is important to facilitate the transition to clinical implementation. Future research should investigate the long-term efficacy and safety of MSN-based formulations with repeated dose, evaluate pharmacokinetics, biodistribution, and potential organ-specific toxicity, and confirm mechanisms of action in advanced animal models or clinical trials. Challenges such as formulation scalability, biodegradation behavior, and potential drug–drug interactions must also be considered. Advancing these investigations will be essential to facilitate the practical application of MSNs and fully exploit their promise in obesity treatment.

Data Sharing Statement

The data generated in the present study may be requested from the first author upon reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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