Obesity Medicine 61 (2026) 100712

Contents lists available at ScienceDirect

Obesity Medicine

journal homepage: www.elsevier.com/locate/obmed

Nanotechnology-enabled targeted delivery of incretin therapies for the treatment of obesity and metabolic disorders

Daniel Ejim Uti [a,b,*], Josephine E. Egbung [c], Esther Ugo Alum [b], Inalegwu Bawa [a], Samuel Ali Agada [a], Celestine O. Ogbu [a], Okechukwu Paul-Chima Ugwu [b]

[a] Department of Biochemistry, Faculty of Basic Medical Sciences, College of Medicine, Federal University of Health Sciences, Otukpo, Benue State, Nigeria
[b] Department of Biochemistry, Research and Publications, Kampala International University, P.O. Box 20000, Kampala, Uganda
[c] Department of Public Health Science, Faculty of Allied Medical Sciences, University of Calabar, Calabar, Nigeria

ARTICLE INFO

Keywords:
Nanotechnology-based drug delivery
Incretin mimetics
Obesity and metabolic dysfunction
GLP-1 receptor agonists
Targeted nanocarriers
Personalized nanomedicine

ABSTRACT

Obesity is a significant health issue worldwide, and a key risk factor for type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), non-alcoholic fatty liver disease (NAFLD), and related complications. Incretin-based therapies, especially glucagon-like peptide-1 receptor agonists (GLP-1RA) and Incretin-based therapies, particularly *glucagon-like peptide-1 (GLP-1)* and dual or triple agonists targeting glucose-dependent insulinotropic polypeptide (GIP) have enhanced the metabolic regulation and therapy of obesity. Nevertheless, their clinical use is limited by enzymatic degradation, short biological half-life, low bioavailability, frequent administration, and systemic adverse effects. This review looks into the physiological functions of incretin hormones, the primary constraints of the present incretin-based treatment, and how nanotechnology can enhance their administration. It reviews lipid-based, polymeric, biomimetic, and stimuli-responsive nanocarriers looking at the benefits of peptide stability, release control, oral, injectable delivery, and targeting to metabolically important tissues, including the liver, adipose tissue, and brain. Formulation strategies that are included in the review development include polyethylene glycol (PEG) and biomimetic coatings, and newer strategies that include artificial intelligence (AI) are not yet widely explored, but the concepts have been intergraded. On the whole, nanotechnology has the potential to enhance incretin therapy but additional studies on safety, scalable manufacturing and clinical translation are required before such systems can be used in medical care.

1. Introduction

Obesity alongside metabolic dysfunction represent a major worldwide health concerns because medical experts estimate that more than 1 billion people experience obesity, and this disease is associated with metabolic syndrome, exhibiting different complications

* Corresponding author. Department of Biochemistry, Faculty of Basic Medical Sciences, College of Medicine, Federal University of Health Sciences, Otukpo, Benue State, Nigeria.
E-mail addresses: dan4uti@gmail.com, daniel.uti@fuhso.edu.ng, daniel.ejimuti@kiu.ac.ug (D.E. Uti), josephineegbung@gmail.com (J.E. Egbung), esther.alum@kiu.ac.ug (E.U. Alum), bawainalegwu15@gmail.com (I. Bawa), agadasamuel22@gmail.com (S.A. Agada), ogbucele@gmail.com (C.O. Ogbu), ugwuopc@kiu.ac.ug (O.P.-C. Ugwu).

https://doi.org/10.1016/j.obmed.2026.100712
Received 4 February 2026; Received in revised form 8 May 2026; Accepted 8 May 2026
Available online 9 May 2026
2451-8476/© 2026 Elsevier Ltd. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

and other metabolic diseases (Fig. 1) (Jin et al., 2023; Kurul et al., 2025). It is a known risk factor for the development of type 2 diabetes mellitus (T2DM), cardiovascular diseases and non-alcoholic fatty liver disease (NAFLD) and some cancer types (Y. Chen et al., 2023; Kurul et al., 2025; Uti et al., 2025). The weight-related metabolic complications, insulin resistance together with dyslipidemia and hypertension and chronic low-grade inflammation lead to decreased quality of life and elevated mortality rates (Uti et al., 2025). The fight against obesity with life-style interventions, pharmaceutical drugs and bariatric surgery meets ongoing difficulties to sustain ideal weight maintenance goals and control of the ensuing metabolic dysfunctions.

Incretin hormones play a crucial role in maintaining glucose homeostasis, regulating energy balance, and modulating insulin secretion (Angelini et al., 2024; Michałowska et al., 2021; Reed et al., 2024). The two important hormones known as glucagon-like peptide-1 (GLP-1) along with glucose-dependent insulinotropic polypeptide (GIP) function predominantly to balance glucose homeostasis and control energy intake and insulin release, and both of which are secreted by enteroendocrine cells in response to nutrient intake (Angelini et al., 2024; Mehta et al., 2023; Michałowska et al., 2021). The multiple metabolic effects of GLP-1 include stimulating glucose-dependent insulin secretion along with glucagon inhibition and delayed gastric emptying together with lipid metabolism modulation and reduction of inflammation (Kurul et al., 2025). Research indicates that GIP helps stimulate insulin production while playing an essential part in regulating lipid metabolic processes and shows signs of regulating fat tissue stability and body energy management (Quesada-Vázquez et al., 2024; Q. Zhang et al., 2021). Glucagon demonstrates dual metabolic functions through its ability to raise blood glucose levels through hepatic gluconeogenesis and glycogenolysis actions even though it originally obtained recognition for its blood glucose elevation abilities (Kajani et al., 2024; Zeigerer et al., 2021). New pharmacological treatments combine glucagon benefits with those of GLP-1 and GIP in either dual-agonist or triple-agonist combinations for maximizing metabolic control and weight management.

Research is ongoing to establish how incretin drugs affect the effectiveness of obesity treatment. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) alongside dual or triple agonists targeting GLP-1 and GIP receptors and glucagon receptors have demonstrated notable success in treating obesity cases with metabolic issues (Del Prato et al., 2022; Forst et al., 2024; Newsome and Ambery, 2023). Despite their clinical benefit incretin-based therapies have several drawbacks that include their short life span and quick breakdown by DPP-4 and low bioavailability following subcutaneous administration and the negative effects of nausea and vomiting and broad distribution in the body (Psaltis et al., 2025; Saini et al., 2023). Novel therapeutic approaches need to be developed to enhance the stability and bioavailability and targeted delivery of incretin-based drugs since nanotechnology-based drug delivery systems hold promise as alternative.

Medicinal applications of nanotechnology have emerged as a solid solution to address existing delivery challenges (Haleem et al., 2023; Kurul et al., 2025; Puri et al., 2024). In this review, we particularly concentrated on nanotechnology designed to enhance incretin-based therapeutics such as GLP-1 receptor agonists, GIP-based agonists, glucagon-based agonists and dual/triple incretin co-agonists. The focus is on the delivery systems that overcome the key translational limitations of these peptide drugs, specifically enzyme degradation, short plasma half-life, low oral bioavailability, overwhelming injection load, and non-targeted tissue delivery. Lipid-based, polymeric, biomimetic, and stimuli-responsive nanocarriers are therefore addressed in respect to their applicability with regard to incretin stabilization, controlled release, organ targeting, and therapeutic efficacy. In cases where the broader concepts of nanotechnology are referred to, it is only done to emphasize design concepts that may be applicable to incretin delivery, particularly in the areas that are at the preclinical level. The recent trend toward environmentally-friendly materials have given rise to biologically synthesized nanoparticles, and metal-organic frameworks and nanorobotics as tools for specific drug delivery. The safety of these technologies are essential and researchers are evaluating nanoparticle biological interactions to help reduce the hazard.

The clinical application of incretin mimetics as a glycemic and weight control drug faces limitations stemming from stability issues along with bioavailability limitations and patient adherence problems (Bendicho-Lavilla et al., 2022). The development of next-generation incretin mimetics becomes feasible because nanotechnology-based initiatives solve current obstacles through improved pharmacokinetics and targeted delivery together with enhanced patient convenience. The review would explore how

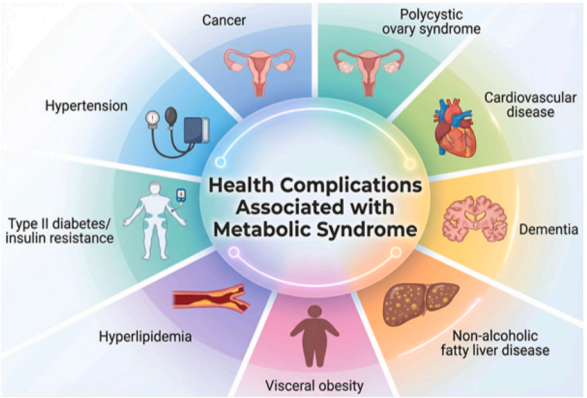


Fig. 1. *Health Complications Associated with Metabolic Syndrome. Adapted and modified from* Mann et al., 2024.*Under open access* Creative Commons Attribution-Non Commercial 4.0 International License (CC BY-NC 4.0) *(Created in* https://BioRender.com**)**.

nanotechnology is revolutionizing the delivery and efficacy of incretin-based therapies (e.g., GLP-1 receptor agonists) for treating obesity and related metabolic disorders.

2. The physiological role of incretin hormones in metabolic regulation

2.1. Glucagon-like peptide 1 (GLP-1)

It is a hormone from intestinal L-cells that are stimulated by nutrients for secretion. Glucagon like peptide helps in glucose homeostasis, insulin secretion, and appetite regulation (Holst, 2022; Kurul et al., 2025). Development of therapeutic agents for type 2 diabetes mellitus (T2DM) and obesity is based on GLP-1 receptor agonists (GLP-1RAs) (Kurul et al., 2025; Mehta et al., 2023). Various mechanisms via which GLP-1 regulates appetite, enhances insulin secretion and maintain glucose homeostasis. These include hypothalamic regulation, it can activate the Arcuate Nucleus (ARC), paraventricular nucleus (PVN), brainstem action, activate the vagal nerve, cause delayed gastric emptying, promote insulin secretion, beta-cell proliferation and survival, and inhibition of glucagon secretion (Kabahizi et al., 2022; Roh and Choi, 2023).

Glucose homeostasis is achieved through multiple mechanisms, such as enhanced glucose uptake in the peripheral tissues, inhibition of hepatic glucose production and suppressions of gastric emptying. Indirectly, GLP-1 improves insulin sensitivity by means of weight loss and reduction in lipotoxicity and therefore insulin resistance (Dimitriadis et al., 2021; Gastaldelli et al., 2016). GLP-1 has shown therapeutic efficacy in diabetes and obesity and consequently, GLP-1 receptor agonists including exenatide, liraglutide and semaglutide have been developed to recapitulate the effect of native GLP-1 by acting on the GLP-1 receptors. They are agents of glycemic control and weight loss. On the contrary, DPP-4 inhibitors work by inhibiting the breakdown of native incretin hormones and hence extending the natural GLP-1 and GIP (Barać and Roganović, 2025; Gunturu, 2024; Hamed et al., n.d.; Kupnicka et al., 2024).

GLP-1 has potential neuroprotective effects for the treatment of neurodegenerative diseases and has, therefore, possible applications for conditions such as Alzheimer's disease (Lv et al., 2024; Siddeeque et al., 2024). Finally, it is stated that GLP-1 plays a key role in maintaining metabolic homeostasis, controlling appetite, insulin secretion, and glucose homeostasis. Five (multi) armed structure of the mechanism and a valuable target in terms of treatment of metabolic disorders including diabetes and obesity. Fresh therapeutic strategies for treating metabolic and neurodegenerative diseases may arise as a result of research on more general physiological effects

Table 1
Physiological roles, mechanisms, and obesity-related modulation of incretin hormones in metabolic regulation.

Regulatory Factor/Axis	Source/ Anatomical Origin	Primary Physiological Role	Key Mechanisms of Action	Relevance to Obesity/Metabolic Dysfunction	Therapeutic/ Translational Relevance	References
Glucagon-like peptide 1 (GLP-1)	Intestinal L-cells	Glucose homeostasis, insulin secretion, appetite regulation	Activates hypothalamic regions (ARC, PVN), brainstem action, vagal nerve activation, delayed gastric emptying, promotes insulin secretion, β-cell survival, inhibits glucagon secretion	Reduced GLP-1 secretion and receptor sensitivity in obesity, leading to impaired glucose homeostasis and appetite regulation	GLP-1 receptor agonists (GLP-1RAs) like exenatide, liraglutide, semaglutide for T2DM and obesity; potential neuroprotective effects	(Alcaino et al., 2024; Drucker, 2018)
Gastric inhibitory polypeptide (GIP)	Enteroendocrine K-cells of the proximal small intestine	Enhances insulin secretion, regulates lipid metabolism, energy balance	Stimulates pancreatic β-cells, increases LPL activity, triglyceride synthesis, enhances lipid storage in adipose tissue	Chronic GIP elevation in obesity contributes to fat accumulation and insulin resistance; GIP receptor activation in brown adipose tissue may enhance energy expenditure	Dual GIP/GLP-1 receptor agonists (e.g., tirzepatide) improve glycemic control, weight loss, lipid metabolism	(Nogueiras, 2021; Quesada-Vázquez et al., 2024)
Glucagon receptor agonists (GRAs)	Pancreatic α-cells	Enhances lipolysis, energy mobilization, and glycemic regulation	Increases cAMP levels, activates protein kinase A (PKA), promotes glycogenolysis, gluconeogenesis, fatty acid oxidation, and thermogenesis	In obesity, glucagon resistance may impair lipid metabolism and increase hepatic steatosis; GRAs can enhance thermogenesis and energy expenditure	GRAs for obesity, T2DM, NAFLD/ NASH, cardiometabolic protection; co-therapy with GLP-1 and GIP agonists for optimal effects	(Novikoff and Müller, 2023; Shepard and Ecelbarger, 2021; Spezani & Mandarim-de-Lacerda, 2022)
Adipose-Liver-Brain Crosstalk	Adipose tissue, liver, brain	Regulates metabolic homeostasis and energy balance	Adipokine and inflammatory cytokine signaling, FFA release, neural pathways	Dysregulated adipokine signaling in obesity contributes to insulin resistance, NAFLD, and metabolic syndrome	Targeting adipokine pathways and neural regulation to improve metabolic disorders	(Azzu et al., 2020; Hemat Jouy et al., 2024; Y. Yao et al., 2020)

of GLP-1 (Tamayo-Trujillo et al., 2024).

2.2. Gastric inhibitory polypeptide (GIP)

Glucose dependent insulinotropic polypeptide (GIP) (Gastric inhibitory polypeptide) is a key incretin hormone released by enteroendocrine K-cells within the proximal small intestine (Guccio et al., 2025; Oteng et al., 2024). Metabolic regulation through stimulation of insulin secretion following nutrient intake plays a very important role. The diabetes and obesity related functions of GIP in relation to glucose homeostasis, lipid metabolism and energy balance have placed GIP beside glucagon-like peptide-1 (GLP-1) as an important therapeutic target (Gaffey et al., 2024; Kurul et al., 2025; Y. Yao et al., 2020). Because GIP acts in two ways, it has been the subject of intense scientific investigation. Despite its insulinotropic effects being beneficial for glucose regulation, the role of glucagon in lipids metabolism has caused controversy in its long term effect on obesity and metabolic diseases (Y. Jiang et al., 2025; Quesada-Vázquez et al., 2024).

The opportunity that exists for treating T2DM and obesity through the interplay between GIP and GLP-1 is a particularly unique one. GIP is a hormone that exerts many physiological effects and the majority of which are involved in anabolic and catabolic metabolic processes. It can broadly be categorized in its effect on glucose and lipid metabolism in metabolic balance. GIP is the key player in postprandial glucose regulation, since it increases glucose induced insulin secretion (Fisman and Tenenbaum, 2021). Pancreatic β cell express GIP receptors and on activation of the GIP receptor, insulin secretion is augmented, but this does not happen in individuals with T2DM, in whom the pancreatic β cells are not responsive to GIP, and is therefore considered to be resistant to GIP (Kurul et al., 2025; Varney and Benovic, 2024). In addition to that, GIP also takes part in lipid metabolism. GIP is not only an insulinotropic hormone, but it also plays an important role in lipid metabolism (Kurul et al., 2025; Nauck and Müller, 2023). It enhances the activity of lipoprotein lipase (LPL) and triglyceride synthesis, and in consequence, it facilitates the uptake and storage of lipid in adipose tissue (Nauck and Müller, 2023). Such action also provides for efficient storage of energy, which in evolutionary terms was another aspect that proved to be an advantage on plenty of food. In the setting of caloric excess, however, there now exists evidence indicating that chronic activation of GIP signaling contributes to obesity and insulin resistance related to fat accumulation (Corbin et al., 2018; Quesada-Vázquez et al., 2024).

Interestingly, other than inhibitory effects on carbohydrate metabolism, GIP may also increase fat oxidation and energy expenditure under certain condition. Agonists at GIPR are suggested to modulate activation of brown adipose tissue, and enhance thermogenesis and the effect of metabolic health (Campbell, 2020; Genchi et al., 2023). In terms of its role as a metabolic regulator, GIP has this paradoxical role in fat accumulation in some tissues and the utilization of fat in other tissues (Chait & den Hartigh, 2020; Fukuda, 2021). Advances in incretin-based therapies have put GIP and GLP1 receptor agonists in good position for therapeutic use for metabolic disorders. More interestingly, after the advent of the dual GIP/GLP-1 receptor agonists, like tirzepatide, have shown considerable improvement of glycemic control, weight loss along with lipid metabolism (Quesada-Vázquez et al., 2024; Thomas et al., 2021). This indicates that single hormone therapies should be an ineffective strategy where one sets out to target and suppress both of the receptors simultaneously.

2.3. Glucagon receptor agonists

Glucagon functions as a metabolic regulatory hormone by supplying catabolic action that activates energy store mobilization as an

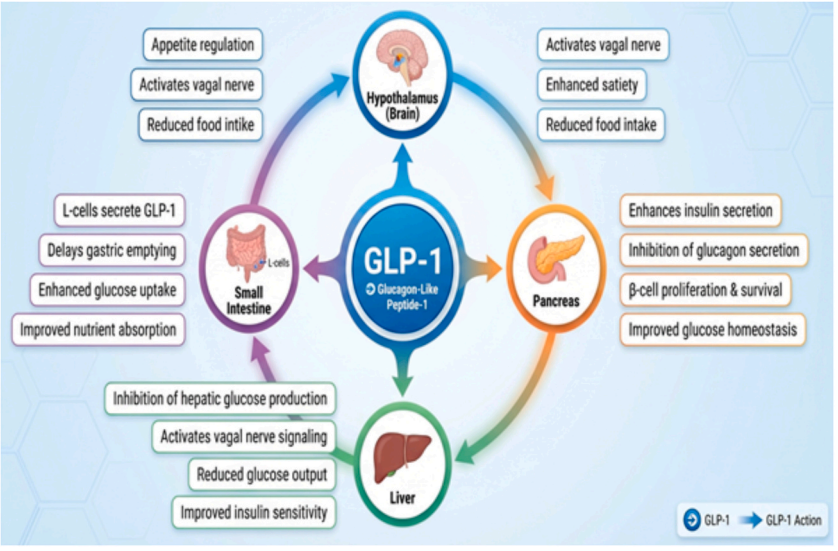


Fig. 2. *Illustrates the physiological role of incretin hormones in metabolic regulation following nutrient intake* (**Created in** https://BioRender.com).

insulin oppositional response (Quesada-Vázquez et al., 2024; J. Zhang et al., 2023). The medical community identifies GRAs as promising therapeutic options for treating all three components of metabolic syndrome alongside obesity and diabetes (Clemente-Suárez et al., 2023; Godoy-Matos et al., 2020). The properties of lipid metabolism control and energy usage together with glycemic regulation make glucagon receptor agonists attractive agents for metabolic syndrome treatment (Conceição-Furber et al., 2022; Muzurović et al., 2022; Quesada-Vázquez et al., 2024). During hypoglycemic events and periods of fasting state pancreatic α-cells produce the 29-amino acid peptide hormone glucagon. As a G-protein-coupled receptor (GPCR), the glucagon receptor (GCGR) primarily works in the liver yet detection exists in adipose tissue and kidneys and in the central nervous system (Capozzi et al., 2022; Chrysavgis et al., 2024). When GCGR receptors become activated, the body produces more adenylate cyclase leading to elevated cyclic AMP (cAMP) levels thus triggering protein kinase A (PKA) signaling that manages glucose and lipid metabolic activities (Gao et al., 2023; Janah et al., 2019).

Glucagon promotes liver processes of glycogen breakdown and gluconeogenic synthesis which together result in rising blood glucose levels in fasting conditions. The use of incretin-based therapies alongside glucagon allows the counteraction of its hyperglycemic effects which results in favorable blood glucose control. Pancreatic islets use glucagon to release insulin based on paracrine mechanisms that work especially well during times of glucose availability (Campbell and Newgard, 2021; Wendt and Eliasson, 2022). The prolonged activation of glucagon receptors reduces insulin levels needed in the body which leads to better insulin sensitivity as well as decreased risk of insulin resistance. The therapeutic potential of GRAs includes their medical application for obesity control as well as their use in type 2 diabetes management and NAFLD and NASH therapy and cardiometabolic protection and neurodegenerative disease treatment (Ferguson and Finck, 2021). Hyperglycemic risks combined with gastrointestinal side effects and cardiovascular risks exist as barriers for successful use of these medications. Upcoming investigations should evaluate how to achieve the best possible level of advantage between glucagon's positive and negative effects during co-therapy with GLP-1 and GIP receptor agonist treatments. Knowledge about how people individually respond to GRAs can create specific treatment protocols for obesity treatment alongside diabetes management.

Achieving optimal therapeutic effects with glucagon receptor agonists proves difficult because of their risks to cardiovascular health and hyperglycemic conditions (Quesada-Vázquez et al., 2024). Researchers need to establish future research directives that involve the creation of more targeted GRAs together with compound therapy evaluation for achieving optimum therapeutic results. Finally, GIP influences glucose and lipid metabolism in a dual manner and is therefore an important component of incretin physiology. These has been summarized in Table 1, and Fig. 2. Consequently, to develop further therapeutic evolution, it will be necessary to understand GIP's subtle contribution to metabolic control.

2.4. The interplay of adipose-liver-brain crosstalk in regulating obesity and metabolic disorders

Several metabolic disorders including type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD) and metabolic syndrome are spreading across the globe because energy regulation between brain, liver and adipose tissue remains unstable. A unique equilibrium between adipose tissue and brain and liver functions serves as the main regulatory system (Fan et al., 2025; Tattoli et al., 2024). This regulatory network consisting of three major components enables metabolic function by using hormonal and neural together with inflammatory signaling pathways (Quesada-Vázquez et al., 2024). Adipose tissue serves as an endocrine tissue which produces bioactive molecules including adipokines and free fatty acids (FFAs) besides inflammatory cytokines that direct metabolic processes throughout the body while enabling communication between adipose tissue and the liver and brain for regulating energy balance (Baldelli et al., 2024; L. Xie et al., 2024). The metabolic regulatory system depends heavily on adipokines such as leptin and adiponectin to function properly because leptin directs hypothalamus activities that suppress hunger and enhance energy use. The development of leptin resistance in obesity causes people to retain excessive hunger while decreasing their energy utilization (Clemente-Suárez et al., 2023).

Both metabolic problems and inflammatory factors lead to obesity through abnormal production of pro-inflammatory cytokines such as TNF-α, IL-6, and MCP-1. The cytokines disrupt insulin receptor signals which leads to insulin resistance while promoting the accumulation of liver lipids (Mehta et al., 2023; Uti et al., 2025; H. Wu and Ballantyne, 2020). Metabolic dysfunction receives additional escalation from the entry of macrophages and other immune cells into adipose tissue (Uti et al., 2025). Glucose and lipid metabolic functions of the liver derive information from both brain signals and adipose tissue signals. Free fatty acids that originate from adipose tissue get transported to the liver thus causing triglyceride buildup that predisposes patients to NAFLD (Bansal et al., 2023; Chadt and Al-Hasani, 2020; X. Li and Wang, 2020). This condition becomes worse due to de novo lipogenesis instigated by insulin resistance combined with very low density lipoproteins (VLDL) secretion impairment and processes activated by cytokines from adipose tissue which lead to mitochondrial dysfunction and oxidative stress that further enhances liver damage and promotes lipid accumulation (Basil et al., 2024; Bo et al., 2024). Blood glucose homeostasis along with hepatic insulin sensitivity experience changes from the liver's management of glucose levels in the blood. High glucose production from poor hepatic glucose control and hyperglycemia develops as a result of insulin resistance in obesity patients who later develop T2DM(Lewis et al., 2021; Mu et al., 2019). The faulty hepatic insulin response results in elevated glucagon activity thus intensifying blood sugar elevation (Hatting et al., 2018). The hypothalamus includes the arcuate nucleus (ARC) which functions as a critical element for energy balance management because it processes signals from peripheral organs through hormonal and neural communications (Pixner et al., 2023). Overconsumption of nutrients causes hypothalamic inflammation which damages leptin and insulin signaling pathways and produces persistent hunger together with decreased energy consumption (Bhusal et al., 2021; C. H. Lee et al., 2020).

Adipose liver brain axis presents a significant biological model in comprehending how incretin-based medications rule on appetite, glucose regulation, lipid metabolism, and insulin sensitivity. With respect to nanotechnology, the crosstalk is applicable since tailored

nanocarriers can enhance the delivery of GLP-1-, GIP-, and glucagon-based therapeutics to metabolically significant tissues, such as the liver, fat tissue, and the central nervous system. Hence, it is only discussed here as a mechanistic background to other sections on tissue-targeted incretin nanomedicine.

3. Limitations of conventional incretin-based therapies

3.1. Short half-life and rapid degradation of peptide-based drugs

The incretin-based therapeutic drugs GLP-1 receptor agonists and DPP-4 inhibitors have brought a major shift in T2DM treatment practices through their ability to enhance β-cell function together with glucose homeostasis. The major limitation of peptide-based drugs in these therapies comes from their short half-life duration along with their fast biological breakdown mechanisms (Quesada-Vázquez et al., 2024; Y. Xie et al., 2023). The primary factor which results in the short half-life of incretin-based drugs is enzyme-mediated breakdown by dipeptidyl peptidase-4 (DPP-4). The incretin hormone GLP-1 displays brief plasma existence of 1-2 min because enzyme DPP-4 rapidly cleaves its N-terminal portion thereby producing nonfunctional products (Mima, 2016). GIP (intestinal polypeptide) together with other incretin hormones becomes degraded after contact with DPP-4 (Deacon, 2019; M. Razavi et al., 2022).

The short length of GLP-1-receptor agonists (GLP-1RA s) as small peptides allows both renal filtration and bloodstream enzymes to reduce their effectiveness (Latif et al., 2024; H. Y. Lee et al., 2024; Mima et al., 2012; Mima et al., 2023). Because small peptides readily pass through the kidneys small peptides need to be provided multiple times per day to sustain therapeutic drug levels in circulation (Mima et al., 2023). Gastrointestinal tract conditions lead to the natural degradation of these peptides so oral accessibility remains restricted (G. Chen et al., 2022; Tasdemiroglu et al., 2022). The rapid proteolytic degradation both in bloodstream plasma and tissue cells shortens the amount of time these medications remain effective which forces patients to take multiple doses each day or use specialized extended-release formulations. Multiple factors arise from short half-life including increased frequency of dosing and poor patient compliance and unstable glycemic control as well as increased cost of development and multiple strategies to counteract the short half-life (G. Chen et al., 2022; L. Wang et al., 2022).

The newer generation GLP-1 receptor agonist (RAs) including Liraglutide along with dulaglutide and semaglutide contain structural modifications which stop DPP-4 degradation and extend their half-life duration (Quesada-Vázquez et al., 2024). Longer half-life becomes possible through albumin and fatty acid conjugation which decreases the amount of these drugs eliminated through the kidneys (Quesada-Vázquez et al., 2024). Drugs delivered through PEGylation along with nanotechnology demonstrate better solubility and proteolytic resistance which extends their effectiveness duration. Scientists investigate oral GLP-1RA s together with non-peptide alternatives to solve the limitations involving DPP-4 sensitivity and renal clearance issues (Mehta et al., 2023; Y. Yao et al., 2020). A big pharmacological hurdle for peptide-based incretin therapies comprises their brief lifetime together with fast breakdown which forces patients to stick to multiple administrations daily while negatively impacting medication adherence (Quesada-Vázquez et al., 2024). Drugs based on incretin therapy have gained more effectiveness and convenience through recent innovations in structural modifications and drug delivery systems and oral formulations to address their initial limitations. Research should concentrate on finding non-peptide components as well as gene therapy applications along with extended-release oral formulations to maximize incretin-based drug treatment effectiveness.

3.2. Suboptimal bioavailability and need for frequent injections

The main issue hindering incretin-based therapy use particularly with GLP-1 receptor agonists exists in their limited bioavailability due to their swift enzyme breakdown and kidney elimination mechanisms. GLP-1 native form becomes degraded rapidly through the enzymatic activity of dipeptidyl peptidase-4 (DPP-4) rendering its half-life shorter than 1-2 min (Farngren and Ahrén, 2019). The short circulatory lifespan of GLP-1 analogs along with their vulnerability to DPP-4 degradation stimulates scientists to create resistant analogs and DPP-4 inhibitory compounds but these developed treatments still demand multiple daily dosages. Acquiring oral absorption of GLP-1 receptor agonists becomes challenging because of three major barriers: degradation in the gastrointestinal tract alongside poor intestinal permeability and inconsistent absorption levels that vary depending on food consumption. DPP-4 inhibitors perform better when taken orally than GLP-1 receptor agonists despite showing limited therapeutic effects (Gallwitz, 2019; Mehta et al., 2023).

Scientists are studying different pharmacologic delivery techniques to enhance incretin-based therapy performance including lipid and nanoparticle carriers together with Rybelsus oral semaglutide administration and intranasal and transdermal applications along with hydrogen-based delivery approaches (Andersen et al., 2021; Nicze et al., 2024). Routine administration becomes essential because patient responsibilities conflict with medication compliance requirements when most short-lived drugs need subcutaneous injections. Profitability along with accessibility issues become barriers since injectable medicine costs exceed those of oral medications specifically in low- and middle-income countries (LMICs) due to restricted diabetes treatment availability in such regions (Aremu et al., 2022; Baryakova et al., 2023; J. Xu et al., 2021). Compulsory self-injection administration requirements for diabetic patients causes major life quality deterioration because of the difficulty in administration together with worries about discomfort and side effects and expensive treatment costs (Ndara and Nuuyoma, 2023; Negash et al., 2023).

Scientists are working to create extended-release versions of GLP-1 analogs besides developing creative delivery methods that involve weekly or monthly GLP-1RA formulations alongside oral semaglutide and implantable or depot-based GLP-1 delivery systems (Kalra and Sahay, 2020; Yu et al., 2018). Future research aims to create better oral GLP-1RA s along with peptide modifications to

extend stability and absorption enhancers for intestinal drug uptake and microencapsulation and nanocarrier systems for enzymatic protection of GLP-1 molecules. Combination therapy strategies for improved outcomes connect GLP-1RA s with different anti-diabetic medications including GLP-1/Glucagon dual agonists for dual weight management and glucose regulation and GLP-1/GIP receptor agonists for additional metabolic advantages is of great importance.

The clinical advancements in T2DM treatment with incretin-based therapies face important roadblocks due to their limited bioavailability and required multiple administration. Researchers are presently working on improving the chemical stability of oral formulations and non-intravenous administration and sustained-release GLP-1 receptor agonists to optimize treatment results by making therapy more accessible to patients while lowering abandonment rates and generating superior diabetes management results.

3.3. Challenges in targeting adipose-liver-brain metabolic pathways

Energy regulation with metabolic homeostasis depends on functional processes between adipose tissue and the liver and brain. Several obstacles stand in the way of creating successful therapeutic methods to target this complicated network (Mehta et al., 2023; Wen et al., 2022). The therapeutic challenges involve the resistance and functional impairment of adipose tissue and liver metabolic disruptions along with neurologic complexities and systemic interactions and off-target consequences and unpredictable long-term process effects (AlZaim et al., 2020; Bettinetti-Luque et al., 2024). The progression of obesity-related conditions includes various factors such as the action of inflammatory mediators, fat tissue placement outside normal locations, multiple adipose tissue types, impaired hepatic metabolism, neuroinflammation with cognitive deficits, systemic interactions with feedback mechanisms and safety issues with unintended side effects along with long-term unexpected outcomes. The next generation of incretin therapy includes dual receptor agonists along with triple receptor agonists and small-molecule GLP-1RAs and personalized medicine and biomarkers with multi-targeted approaches and lifestyle and behavioural interventions which demonstrate stronger metabolic regulatory properties (de et al., 2022; Neto et al., 2023).

These problems underpin the necessity of nanotechnology-based incretin delivery platforms that enhance tissue selective delivery, decrease intoxication and enhance long-term metabolic regulation via the combination of adipose, liver, and brain regenerative metabolisms.

3.4. Market availability and characterization of incretin-based therapies

The current landscape of incretin-based therapies, including GLP-1 receptor agonists (e.g., liraglutide, semaglutide) and dual/triple agonists (e.g., tirzepatide), faces significant market-related challenges and opportunities (Anastasiou et al., 2025; Reddy et al., 2024). Despite promising clinical efficacy, the high cost of these therapies limits their widespread market availability, particularly in low and middle-income countries (LMICs) where access and affordability remain key barriers (Morin et al., 2023). Some medications have been approved by drug regulatory bodies such as the US FDA and EMA and have opened their way to the market, but further characterization based on real-life evidence and pharmacoeconomic studies are needed to maximize their clinical value. Long-acting formulations are more convenient, but injection-related pain is associated with poor patient compliance and adherence. New formulated formulation techniques and development of next generation dual and triple agonists in nanotechnology may enhance tolerability but a detailed market analysis is necessary to define cost effectiveness and competitive positioning. These market barriers are important for the worldwide expansion of incretin-based approaches to the treatment of obesity and metabolic dysfunction.

3.5. Positioning nanotechnology-based incretin delivery relative to current clinical therapies

Though the clinical efficacy of long-acting GLP-1 receptor agonists (e.g., semaglutide, dulaglutide) is outstanding and oral semaglutide is accessible, there are significant therapeutic drawbacks. These are in the form of gastrointestinal (GI) adverse effects, intertransmission variability in the oral absorption, absence of tissue specificity, and chronic administration. Delivery systems based on nanotechnology have been suggested in the control of these unmet requirements but their benefits ought to be compared to the current standards.

The better and more reliable oral delivery is one of the needs that have not been fulfilled. Even though it is novel, oral semaglutide has low and unpredictable bioavailability, as it depends on the absorption enhancements (Abbasi et al., 2026; Solis-Herrera et al., 2024). Alternatively, nanocarriers that are discovered to be effective in protecting incretin peptides against enzymatic breakdown and increase intestinal absorption include pH-responsive, mucoadhesive, and lipid-based nanoparticles. The second huge opportunity is organ specific targeting. The traditional GLP-1 receptor agonists are spread out over the body, and nanoparticles can be used to target the liver, adopting fat, or central nervous system (CNS), potentially enhancing activity and reducing side effects.

In formulation terms, nanotechnology brings about adjustable physicochemical parameters, which are the ones which have direct effect on the performance of the therapeutic activity. As reported, the particle sizes of report systems are usually in the 50-300 nm range, which allows the uptake into cells, allowing extended circulation (Islam et al., 2025). The encapsulation efficiencies tend to be 60-90 percent according to the carrier composition (e.g. lipid-based and polymeric systems). Moreover, controlled release kinetics are also able to maintain the release of drugs during prolonged durations (hours-days) which may have lowered dosing schedule in comparison to the current therapies (Ataide et al., 2023). Preclinical models of biodistribution have shown that surface modified nanoparticles are able to increase the accumulation of the model in target tissues though there is inconsistency in biodistribution across the various models.

Significantly, no studies of head-to-head comparison of systems based on nanotechnology and approved incretin therapies can be

Table 2
Nanotechnology-driven strategies for enhancing incretin drug delivery in obesity treatment.

Therapeutic Cargo	Nanocarrier Type	Targeting Strategy	Route of Administration	Experimental Model/ Application Context	Main Efficacy Outcomes	Safety/Formulation Considerations	Development Stage	References
Nanotechnology-Driven Innovations in Incretin Mimetics Delivery	**Lipid-Based Nanoparticles**	Liposomes, Solid Lipid Nanoparticles (SLNs), Polymeric Nanoparticles (NPs)	Encapsulation for controlled and targeted drug release	Cancer, neurodegenerative diseases, infectious diseases	Enhancing the stability and bioavailability of incretin mimetics for sustained appetite suppression	Possible lipid-related toxicity; formulation stability	Preclinical–early translational	Y. Xu et al. (2020)
	Peptide-Conjugated & Hybrid NPs	RGD, TAT peptides, aniopep-2	Receptor-mediated endocytosis for targeted delivery	Cancer therapy, gene therapy	Directing incretin drugs to adipose and liver tissues for improved metabolic effects	Polymer biocompatibility and degradation concerns	Preclinical	(Ilieş et al., 2024; M. Liu et al., 2021)
Nanocarriers for Enhanced Bioavailability & Stability	**PEGylation**	PEGylation of incretin mimetics	Extends drug stability, minimizes degradation & immune response	Diabetes treatment (exenatide, liraglutide, semaglutide)	Extending the half-life of GLP-1 agonists to reduce dosing frequency and enhance efficacy	Stability and leakage issues	Preclinical	(Poudwal et al., 2021; Y. Yao et al., 2020)
	Biomimetic Coatings	Liposomal encapsulation, cell membrane, mucin-based coatings	Protection against enzymatic degradation & immune clearance	Peptide-based drugs, diabetes therapy	Enhancing incretin drug absorption and stability in the gastrointestinal tract	Scalability and lipid oxidation concerns	Preclinical	(Dash et al., 2020; Lutz et al., 2022)
Stimuli-Responsive Nanoparticles	**pH-Sensitive NPs**	Polymethacrylate-coated, chitosan nanogels	Controlled drug release at specific pH levels	Oral peptide therapeutics	Enabling pH-triggered incretin release in the gut for improved bioavailability	Immunogenicity risk; complex synthesis	Preclinical	(Araújo et al., 2015; X.-Q. Wang and Zhang, 2012)
	Enzyme-Triggered NPs	Trypsin-sensitive, DPP-4-active NPs	Drug release activated by enzymatic interaction	Oral GLP-1-based therapies	Enzyme-responsive incretin release to prevent premature degradation and improve therapeutic effects	Manufacturing complexity	Preclinical	(Pinto et al., 2024; Y. Yao et al., 2020, 2020)
Targeting Adipose-Liver-Brain Crosstalk	**BBB Penetration**	Liposomes, SLNs, polymeric & inorganic NPs	Enabling nanoparticle transport across the blood-brain barrier	Neurodegenerative diseases, metabolic disorders	Delivering incretin drugs to the hypothalamus to regulate appetite and energy balance	Variability in pH response	Preclinical	(W. Zhang et al., 2021; Zhou et al., 2018)
Targeting Adipose-Liver-Brain Crosstalk	Hepatic Targeting	Liposomes, lipid nanoparticles (LNPs), polymeric nanoparticles, and surface-functionalized nanocarriers	Protection of incretin peptides from degradation, prolonged circulation, sustained release, and enhanced hepatic delivery	Obesity, insulin resistance, NAFLD/ NASH	Liver-directed delivery of GLP-1R agonists and incretin co-agonists to improve hepatic lipid metabolism and insulin sensitivity	Variability in enzyme activity	Preclinical	(Peng et al., 2025; Yabut and Drucker, 2023)
Nanoparticles for Gut Microbiome Modulation	**Probiotic-Loaded NPs**	Encapsulation of probiotics in PLGA, chitosan, or lipid-based NPs	Protecting probiotics from degradation and ensuring targeted gut release	Gut microbiome modulation, metabolic health improvement	Enhancing gut microbiota balance to support incretin-mediated metabolic benefits	Potential hepatic accumulation; safety concerns	Preclinical–early translational	(Lopes et al., 2023; S. Razavi et al., n.d.)

found. The evidence available is almost in preclinical stages and most of the variables like optimal dosing schedule, safety and clinical superiority are yet to be determined. Thus, even though nanotechnology presents a promising solution especially in the area of oral delivery and targeted therapy and controlled release the translational benefit of nanotechnology over the existing clinical standards should undergo additional challenging validation.

4. Nanotechnology-driven innovations in Incretin Mimetics Delivery

4.1. Nanoparticle-based drug delivery systems

This section examines three main approaches regarding nanoparticle-based drug delivery: Lipid-Based Nanoparticles, Solid Lipid Nanoparticles (SLNs), Polymeric Nanoparticles for Controlled and Sustained Release, and recently developed Peptide-Conjugated and Hybrid Nanoparticles for Targeted Delivery (L. Xu et al., 2022) (Table 2).

Drug delivery benefits significantly from the usage of lipid-based nanoparticles because they demonstrate both excellent stability and encasing ability for hydrophilic and hydrophobic drugs and besides these benefits they are compatible with biological systems (Mehta et al., 2023). The particles replicate biological membranes to deliver drugs efficiently during controlled release processes. The common varieties of nanoparticles for drug delivery systems are liposomes and solid lipid nanoparticles (SLNs) and polymeric nanoparticles. Spherical vesicles with an aqueous core and one or more phospholipid bilayers make up liposomes as a nanoparticle structure (Mehta et al., 2023, 2023, 2023). These carriers provide several benefits including degraded components that break down easily and are able to compromise with biological systems as well as degrading agent immunity while enabling surface-function-selection processes to reach specific targets and enabling drug substance stability and increased dissolving power (Magadani et al., n.d.; Trucillo, 2024). The medical field utilizes nanoparticles for cancer treatments and antimicrobial drug delivery together with gene therapy and vaccine administration. Submicron lipid-solid carrier systems known as Solid Lipid Nanoparticles (SLNs) use surfactants to maintain their stability while composed of solid lipid materials (Arabestani et al., 2024; Mehta et al., 2023).

The biodegradable structures used in polymeric nanoparticles assist controlled drug release rates through their biocompatible polymers. Three main polymers used for fabricating nanoparticles are poly (lactic-co-glycolic acid) (PLGA) as well as chitosan with polyethylene glycol (PEG)-based polymers (R. Sun et al., 2024). The advantages of these nanocarriers consist of sustained drug release that presents controlled formulation with improved bioavailability and targeted delivery capability and lower number of required doses (Mall et al., 2024). The combination of peptide-related and hybrid nanoparticles has emerged as a modern approach in nanomedicine through specific peptide connections or nanocarrier combinations for precise targeting functions. The system uses RGD (Arg-Gly-Asp) peptides, TAT peptides as well as aniopep-2 for targeting functions (Javid et al., 2024; Y. Zhang et al., 2021). The combination of diverse nanomaterials in hybrid nanoparticles allows for simultaneous access to several benefits such as prolonged stability with precise delivery precision and controlled substance release. These nanomaterials serve different applications in treating cancer and treating neurodegenerative conditions and delivering genetic material (Deivayanai et al., 2024; Drabczyk et al., 2024).

Recent progress in contemporary medicine relies on nanoparticle-based drug delivery technologies that enhance therapeutic efficacy and provide more effective therapy while minimizing possible side effects. The biological characteristics of lipid-based nanoparticles integrate with the controlled release capabilities of polymeric nanoparticles and the targeted precision of peptide-conjugated or hybrid nanoparticles (Elumalai et al., 2024). Future breakthroughs in drug delivery systems via research will enable successful personalized therapy techniques for cancer, neurological diseases, and infection control.

4.2. Nanocarriers for enhanced bioavailability and stability

a. **PEGylation in Incretin Mimetics Delivery:** PEGylation is a measure which could enhance the stability and pharmacokinetic characteristics of peptide therapeutics, whereas extended activities of commercial incretin receptor agonists are not a result of PEGylation per se, but an uncountable number of drug-specific structural and formulation solutions (Santhanakrishnan et al., n.d.; Simberg et al., n.d.). Dulaglutide is a GLP-1 analogue with an amino acid hydrolysis reaction with an amino acid analogue, semaglutide, an GLP-1 analogue with amino-acid substitutions and a lysine-26 side-chain amino acid substitution to extend human plasma levels, oral semaglutide, co-formulated with sodium N-(8-[2-hydroxy (Holler et al., 2025; Peri et al., 2025). In this regard, in case of maintaining the endogenous GLP-1 against degradation, preserving degradation must be addressed in DPP-4 inhibition, rather than in GLP-1 receptor agonism.
b. **Biomimetic Coatings for Protection and Enhanced Absorption:** Biomimetic coatings that derive their design from biological membranes and proteins function as an alternative to PEGylation for enhancing drug stability and accessibility(Y. Yao et al., 2020). Drugs benefit from these materials which duplicate cell-based components to protect medication ingredients and maintain bloodstream durability while enabling pharmaceutical segmentation(H. Liu et al., 2023). The main strategies for drug protection utilize liposomal encapsulation and cell membrane coatings and mucin-inspired coatings. A careful application of liposomal materials results in proteolytic protection of incretin mimetics and the addition of cell membrane coatings leads to improved biocompatibility with natural defense systems. The addition of mucin to hydrogels contributes to the protection of peptides from gastrointestinal enzymes so they become more suitable for oral administration of incretin mimetics(Ferreira-Faria et al., 2022). The applications of these approaches include both protecting peptides from enzymatic breakdown and extending circulation duration and decreasing immune system removal.

4.3. Stimuli-responsive nanoparticles (pH-sensitive, enzyme-triggered release)

The release of medication from stimuli-responsive nanoparticles (SRNPs) occurs according to physiological changes such as pH conditions and enzymatic activity which optimizes drug distribution and lowers adverse effects and delays additional dosing frequency (Ahmadi et al., 2020).

a. **pH-Sensitive Nanoparticles:** The drug release capabilities controlled by pH make nanocarriers an optimal choice to transport incretin mimetics by mouth for intestine-directed release (J. Wang et al., 2023). The nanoparticles maintain stability in regular body fluid conditions then change their shape under either acidic or alkaline solution conditions. French researchers developed a system where the incetins stay protected by a protective layer at acidic conditions but they break down at higher pH values to release the peptide for systemic intake (L. Liu et al., 2017). The delivery of GLP-1 receptor agonists through polymethacrylate-coated nanoparticles serves as an oral treatment while targeting intestinal tissues through chitosan nanogels and utilizing liposomes that respond to pH changes for oral absorption (Ziebarth et al., 2024).
b. **Enzyme-Triggered Nanoparticles:** Drug release through enzyme-responsive nanoparticles (ERNPs) occurs when the nanoparticles experience contact with particular enzymes found in gastrointestinal tracts or bloodstream systems. The systems demonstrate high effectiveness for delivering incretin mimetics to their intended targets while decreasing side effects and the need for multiple dosages (M. Li et al., 2020; Y. Wang et al., 2024). These nanoparticles contain enzyme-sensitive linkers which break down after specific enzymes like proteases or amylases exist. When nanoparticles encounter enzyme proteins they begin to break down while simultaneously releasing incretin mimetics to the specific site. Medical professionals employ trypsin-sensitive nanoparticles for oral delivery of GLP-1 while DPP-4-active nanocarriers function for incretin mimetic treatments and enzyme-triggered hydrogel systems maintain sustained peptide administration (Ren et al., 2022; Q. Zhang et al., 2024). The development of incretin mimetics requires better biocompatible long-term solutions combined with improved methods to scale up production and obtain regulatory requirements and overcome inconsistent bioavailability following oral administration under shifting gastrointestinal conditions. Innovation in nanomedicine along with polymer chemistry development brings forth innovative increase mimetics delivery approaches which promise extended and improved drug formulations that are friendly for diabetic patients

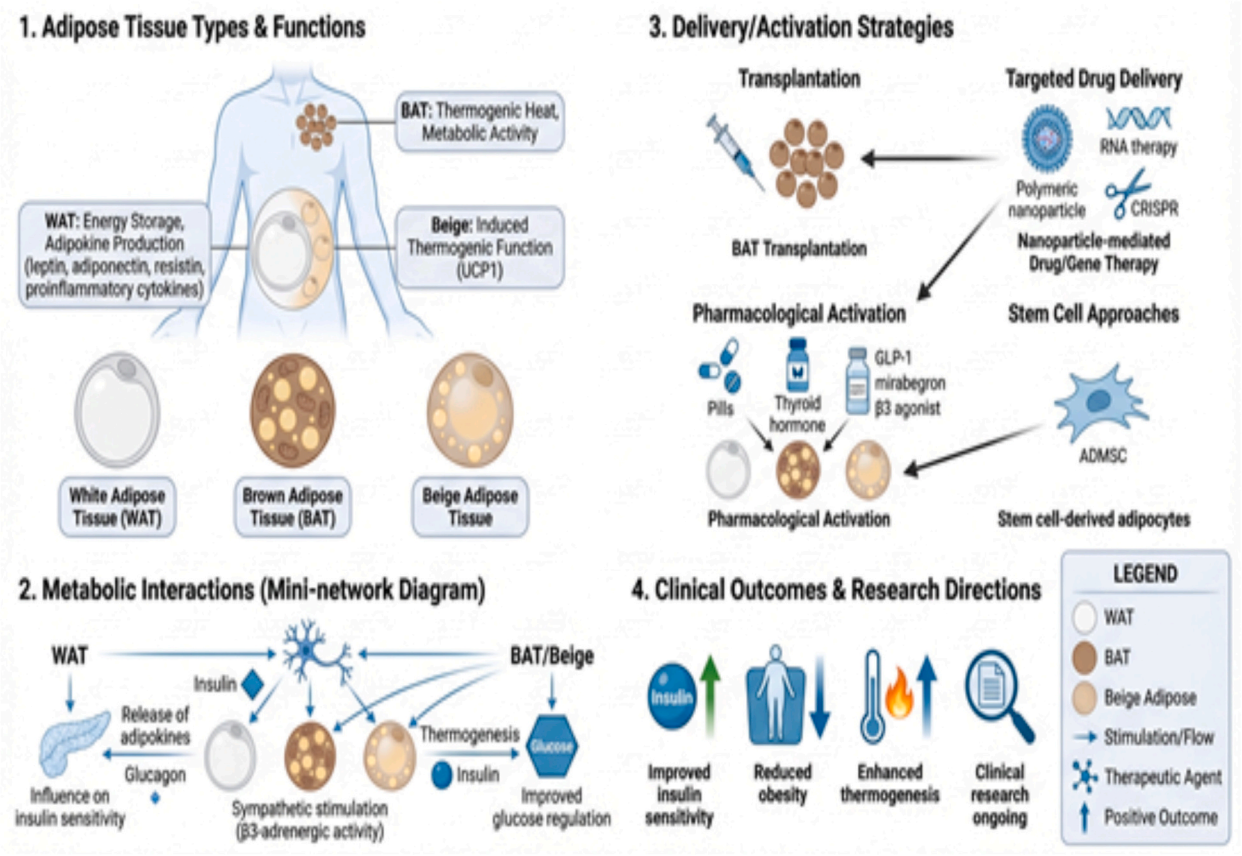


Fig. 3. *Types of Adipose Tissue and Their Interconnections with Metabolic Regulation. (Created in* https://BioRender.com**).**

4.4. Targeting adipose-liver-brain crosstalk

4.4.1. Nanoparticle-facilitated BBB penetration for central appetite regulation

The crosstalk between adipose tissue and liver with brain functions as an essential mechanism for metabolic equilibrium and appetite control and exhibits dysfunctions in cases of obesity and diabetes and NAFLD. Integration of signals originating from peripheral tissues carefully occurs within the hypothalamus and brain through this essential connection (Yang et al., 2024; Y. Yao et al., 2020). Several therapeutic interventions with central nervous system (CNS) targets become ineffective because the blood-brain barrier (BBB) prevents drug entry (Banks et al., 2024; Y. Yao et al., 2020). The adipose tissue represents an endocrine organ since it releases hormones and adipokines that control appetite functions and energy equilibrium mechanisms. Leptin triggers signals to hypothalamus for decreased hunger as well as more energy consumption. Leptin resistance emerges in obesity that diminishes the feedback regulation system. The liver functions through insulin and glucagon signals to control glucose and lipid operations while hepatokines enable brain interactions that affect appetite regulation and metabolic activities. When these pathways suffer regulatory breakdown it causes people to eat in excess and develop metabolic problems (Stefanakis et al., 2024).

The arcuate nucleus (ARC) within the hypothalamus houses two essential neuronal networks that include POMC/CART cells which serve as appetite-reducing elements along with appetite-increasing AgRP/NPY neurons (Jais and Brüning, 2021). Metabolic diseases develop because neuronal circuit dysfunctions occur in the body. The brain endothelial cells of the BBB function as an extensive filtering boundary which blocks the entrance of nearly all medications and proteins. Staggered delivery of therapeutic agents through nanoparticles serves as an innovative method which allows passage through the BBB to directly change appetite-regulatory circuits in the brain (Kochman et al., 2026). A range of nanoparticles have been researched for drug delivery purposes with representatives coming from liposomes and solid lipid nanoparticles (SLNs) together with polymeric nanoparticles and inorganic nanoparticles and magnetic nanoparticles and exosome-mediated delivery (Kadry et al., 2020).

Parameter selection for obesity treatments should focus on utilizing leptin inhibition as well as RNA-based therapies and blocking neuropeptides and modifying the gut-brain axis. Background studies must focus on improving nanoparticle size parameters and surface modification techniques and extended assessments of biocompatibility and safety in addition to obtaining medical authorization for CNS nanoparticle therapies.

4.4.2. Hepatic targeting for improved lipid metabolism and insulin sensitivity

Liver is also a prime target organ in obese-related metabolism disfunction since it controls the gluconeogenesis, and the glycogen metabolism, lipid processing as well as insulin sensitivity (Truong and Lee, 2025). Primarily, hepatic steatosis and hepatic insulin resistance are the potential causes of hyperglycemia, dyslipidemia, and NAFLD/NASH development (Truong and Lee, 2025). This is why polydactic intravenous delivery of incretin-based therapeutics can be effective in enhancing the level of metabolic regulation and minimizing the level of exposure of the body and off-target side effects.

Hepatic targeting is applicable using nanotechnology given the possibility of protecting drugs target to the liver like peptide drugs, including GLP-1 receptor agonists, dual GLP-1/GIP agonists and glucagon-containing co-agonists by protecting those drugs in nanoparticles. Lipid nanoparticles, polymeric nanoparticles, liposomes and surface-functionalized nanocarrier can be designed to enhance hepatic uptake and long-lasting release and intracellular delivery of incretin-related cargo (Uti et al., 2025). They are especially appealing in the field of obesity, insulin resistance, and fatty liver disease whereby the local delivery to the liver was likely to improve lipid metabolism, decrease the hepatic glucose production, and enhance insulin sensitivity.

Nevertheless, the vast majority of nanotechnology approaches applicable in targeting the liver are still at the preclinical phase in regard to incretin therapy. More effort is required to get tissue specificity, long term safety, reproducibility, dose control and translational feasibility of these methods to be included in clinical trials. Therefore, hepatic targeting can be regarded as a good but still developing field of nanotechnology-based incretin therapy.

4.4.3. Adipose tissue delivery for thermogenesis and adipokine modulation

The multiple functions of adipose tissue as an organ consist of energy storage and endocrine signaling and the regulation of body temperature (Mısırlıoğlu, 2025). The tissue participates extensively in controlling metabolic processes that encompass energy balance together with homeostasis. Through adipose tissue delivery approaches using transplantation and targeted drug delivery methods medical teams aim to regulate thermogenic functions and adipokine production for treating metabolic diseases mostly obesity and type 2 diabetes (Cheng et al., 2024). The three basic types of adipose tissue include white adipose tissue (WAT), brown adipose tissue (BAT) alongside beige adipose tissue (Uti et al., 2025), and the general interconnection between the adipose, neuronal network, glucagon, and insulin sensitivity given in (Fig. 3) as earlier shown by Ruud et al. (Ruud et al., 2017). The human body stores triglycerides in WAT to serve as its main form of energy storage until times when additional energy is needed. The excessive growth of WAT tissue leads to obesity alongside insulin resistance along with numerous metabolic diseases. Besides energy storage WAT produces adipokines like leptin and adiponectin together with resistin and pro-inflammatory cytokines that lead to changes in energy balance and systemic inflammation. The quantity of WAT tissue plays a fundamental role in causing metabolic problems with its primary accumulation happening in abdominal spaces (Sakers et al., 2022; Semwal et al., 2022).

Brown adipose tissue (BAT) functions as specialized tissue which produces thermogenic heat to regulate body temperature when staying in cold conditions. BAT activation creates enhanced metabolic energy consumption leading to better glucose control and insulin responsiveness while presenting itself as a valuable therapeutic objective for metabolic diseases including obesity (Maliszewska and Kretowski, 2021). Cold exposure together with physical activity or pharmacological therapy allows beige adipocytes to develop between existing white adipocytes throughout WAT(Magro and Dias, 2024; Scheel et al., 2022). The thermogenic behaviour found in

Table 3
Advances and challenges in nanotechnology-enhanced incretin therapies: Preclinical and clinical insights.

S. No.	Application	Advantages	Shortcomings	Recent Animal Model Studies	Clinical Trials	Future Directions and Personalized Approaches	References
1	**Nanoparticle-based GLP-1 receptor agonists**	Enhanced bioavailability and sustained release.	Limited long-term data.	Improved efficacy and prolonged action in diabetic rats.	No specific named clinical nanoparticle-based GLP-1 formulation or trial identifier is provided in this review; therefore, clinical translation should be regarded as emerging rather than established	Precision nanomedicine for individualized dosing.	(Magro and Dias, 2024; Sharmah et al., 2024)
2	**Nanoparticle-based GIP receptor agonists**	Targeted delivery to tissues, reducing side effects.	Complex manufacturing processes.	Better glucose regulation in obese rodent models.	Clinical evidence remains insufficiently defined in the current manuscript; no named formulation or trial identifier is cited here	Personalized nanomedicine for optimized therapy.	(Mukherjee et al., 2023; Y. Yao et al., 2020)
3	**Nanoparticle-based glucagon receptor agonists**	Potential for weight loss and improved insulin sensitivity.	Risk of immune responses to nanoparticles.	Increased weight loss and glucose homeostasis in animals.	At present, this area should be considered preclinical/early translational in the context of this review unless specific human studies are identified	Exploring combination therapies with other nanomaterials.	(Min, 2024; Palani et al., 2022)
4	**Comparative analysis of nanoparticle-enhanced vs. conventional therapies**	Superior efficacy with fewer side effects in preclinical trials.	High costs of development and production.	Animal models show better results with nanoparticles.	No robust, clearly identified comparative clinical dataset is presented here; claims of clinical superiority should therefore be avoided	Future clinical trials may determine patient-specific benefits.	B. Wang et al. (2024)
5	**Nanotechnology in improving therapy adherence**	Increased patient compliance due to reduced frequency of administration.	Regulatory hurdles for approval.	Animal studies demonstrate better adherence with long-acting formulations.	Human adherence benefit remains hypothetical in the absence of clearly cited clinical studies specific to nano-enabled incretin systems	Potential for home-based self-administration.	Ekpa et al. (2020)
6	**Nanoparticle formulations for combination therapy**	Enhanced therapeutic outcomes when combined with other drugs.	Possible interactions with other medications.	Synergistic effects observed in combination therapy models.	Clinical validation is not yet established in this review	Personalization of combination therapies to address individual patient needs.	Shrestha et al. (2019)
7	**Targeted delivery systems for reduced systemic side effects**	Targeting specific organs and tissues for minimal systemic exposure.	Difficulty in achieving precise targeting in humans.	Studies show precise liver targeting in rodent models.	Translational status remains early; clinical benefit has not yet been demonstrated here with specific named trials	Advances in targeting strategies for better precision.	(Machindra et al., n.d.; Rus et al., 2021)
8	**Enhanced pharmacokinetics and pharmacodynamics**	Extended drug half-life and more controlled drug release.	Risk of altering pharmacokinetic profiles in some individuals.	Animal studies show slower release and improved control over blood glucose levels.	Clinical pharmacokinetic confirmation for specific nano-incretin products is not clearly documented in this manuscript	Personalized dosing strategies based on pharmacokinetic data.	(Pise, 2024; S. Wang et al., 2020)
9	**Nanoparticle-mediated gene delivery for incretin therapy**	Potential for genetic modifications to enhance therapy outcomes.	Ethical concerns and long-term effects.	Gene delivery models show enhanced expression of target incretin receptors.	No clinical trials are identified here for gene-delivery applications in incretin nanotherapy	Research in gene-editing techniques for diabetes management.	(Lourie et al., 2024; Tasyurek et al., 2014)
10	**Nanotechnology in reducing drug resistance**	Ability to bypass cellular	Challenges in identifying all	Animal studies indicate reversal of	Clinical relevance remains speculative	Targeting molecular	(Y. Yao et al., 2020;

(*continued on next page*)

Table 3 (*continued*)

S. No.	Application	Advantages	Shortcomings	Recent Animal Model Studies	Clinical Trials	Future Directions and Personalized Approaches	References
		resistance mechanisms.	potential resistant pathways.	resistance to conventional therapies.	without identified human studies	pathways specific to drug resistance.	X. Zhu et al., 2024)

BAT cells also occurs in beige cells which help boost metabolism and energy expenditure through UCP1 expression. The research potential of beige fat stands out due to its capability to improve thermogenic activity independently from major weight reduction (Magro and Dias, 2024).

Researchers have investigated different delivery methods for adipose tissue because they seek to improve metabolic health through thermogenic enhancement and adipokine secretion management (An et al., 2023; Ghesmati et al., 2024). Research conducted on improving thermogenesis focuses on BAT transplantation alongside beige fat induction procedures and pharmacological activation and gene therapy with cell-based approaches and nanoparticle-mediated drug delivery techniques (T. Zhu et al., 2023). The results from BAT transplant research demonstrate promising potential as obesity and diabetes therapeutic solutions because they increase metabolic function along with insulin sensitivity. Experts use several methods to turn beige fat into thermogenically active beige fat which includes exposing tissues to cold temperatures and exercise and giving substances that stimulate β3-adrenergic receptors or modify genetic expression patterns (S. Lee et al., 2022; Negroiu et al., 2024).

Mirabegron together with thyroid hormone analogs and GLP-1 receptor antagonists and CRISPR-based gene editing as well as stem cell-derived adipocytes and nanoparticle-mediated drug delivery constitute pharmacological approaches to activate thermogenesis (Dąbrowska and Dudka, 2023; X. Sun et al., 2023). Through genetic modification scientists can enhance adipocyte thermogenic potential by changing the genes that direct BAT development as well as those regulating UCP1 expression. ADMSCs alongside other stem cells show potential to become thermogeneic adipocytes that could serve as bases for therapeutic approaches to increase energy consumption and enhance metabolic health (Dowker-Key et al., 2024; X. Yao et al., 2020). Polymeric nanoparticles provide exact regulation of metabolic pathways by carrying tiny molecules with RNA therapies straight to adipose tissue and gene-editing technologies (kapoor et al., 2023). The continued development of this approach requires resolving technical problems regarding long-term effectiveness and patient-oriented medicine solutions and improved delivery methods. These therapies need sustained activation of thermogenesis therapy without detrimental effects so they can become successful treatments. Moving onward with clinical effectiveness in pharmacological treatments requires specific improvements in the stability and delivery system characteristics as well as pharmacological agent bioavailability and selectivity. The regulatory role adipose tissue plays in metabolism remains essential because its potential to influence thermogenesis and adipokine release gives motivation to fight obesity and metabolic disorders effectively. Research must continue to improve methodical delivery systems along with harm assessment while building custom-made treatments to treat obesity-related conditions across the world.

5. Preclinical and clinical advances in nanotechnology-enhanced incretin therapies

A summary of some of the representative preclinical advances and of translation issues in nanotechnology-enhanced incretin therapies is summarized in Table 3. Since the field remains in its early stages of development, the table highlights evidence-of-concept results and opportunities to formulate the field, critical limitations, and the prevailing state of the field translationally, as opposed to suggesting an implied clinical maturity. The analysis explores both advantages and restrictions of GLP-1 GIP and glucagon receptor agonist nanoparticles that compares its attributes with the conventional therapeutic alternatives. This study explores the recent trends in personalized medicine along with the precision nanomedicine methods that strive to induce the most effective results of treatment while dealing with type 2 diabetes, and obesity patients.

6. Challenges, safety considerations, and regulatory perspectives

Nanomedicine shows significant potential as it continues to advance rapidly for treating complex obesity cases along with their linked metabolic problems. The medical implementation of nanoparticles (NPs) requires resolving various crucial problems that stand in the way of global acceptance. Security obstacles together with scaling problems combine with regulatory issues and moral aspects create substantial barriers in the nanomedicine field. This section provides a detailed analysis of essential matters within nanomedicine treatment for obesity.

6.1. Potential toxicity and immunogenicity of nanoparticle formulations

Nanoparticles create major health threats to human beings through their distinctive physical and chemical attributes (Vignesh et al., 2025). The combination of toxic effects includes damage to cells together with tissue deposition and damage to blood vessel walls. The direct toxic effects of nanoparticles stem from their small dimensions which produces big surface contact and strong reactivity that triggers oxidative stress along with inflammatory reactions and DNA alterations (Vignesh et al., 2025). During obesity treatment NPs tend to build up in adipose tissue as well as liver and gut tissue. The prolonged build-up of nanoparticles in liver tissue

and kidneys along with the spleen creates toxicity because these organs become unable to clear them properly from the body. Individuals who have obesity face an increased risk for cardiovascular diseases since endothelial dysfunction generates vascular toxicity and inflammatory processes in blood vessels (Zhaisanbayeva et al., 2024).

The activation of immune responses becomes possible through immune stimulation by foreign nanoparticles which results in toxic immune reactions. The application of polyethylene glycol (PEG) coatings helps reduce immune reactions to NPs yet recurring interactions between NPs and immune cells cause potential harmful effects (Padín-González et al., 2022; Pondman et al., 2023). Nanoparticles' toxicity requires control through essential development initiatives based on testing which incorporates optimization of size and shape as well as surface charge and coatings and use of biocompatible materials.

6.2. *Scalability and cost-effectiveness in pharmaceutical development*

The potential of nanomedicine for obesity treatment encounters major obstacles during large-scale manufacturing together with maintaining economic efficiency (Türeli and Türeli, 2020). The products encounter challenges in large-scale manufacturing because specialized equipment needs along with minimal material availability and stable product stability under unique processing environments (Thursby and Juge, 2017). Nanostructured liposomes together with lipid nanoparticles (LNPs) demand high production costs which prevents their wide clinical use because of their expense (Thursby and Juge, 2017). Nanostructured liposomes and LNPs command production expenses that exceed conventional formulations by several times thus making them inaccessible for broad clinical use. Commercial innovation of nanomedicines requires pharmaceutical businesses to minimize production expenses while sustaining product quality standards (L.-P. Wu et al., 2020). The wide adoption of nanomedicines as obesity treatments depends heavily on two main factors: automated manufacturing improvements and reduced material production expenses. The commercial adoption of nanomedicine treatments for obesity relies on solving the existing obstacles.

6.3. *Regulatory hurdles and translational challenges in clinical applications*

When applied in medical treatment, nanomedicines face many regulatory barriers because they are novel compounds that require regulatory bodies to verify safety and the effectiveness of their benefits (Đorđević et al., 2022). Current guidelines for nanomaterials treatment of obesity prove challenging for researchers because they lack flexibility for adapting to various kinds of nanoparticles used

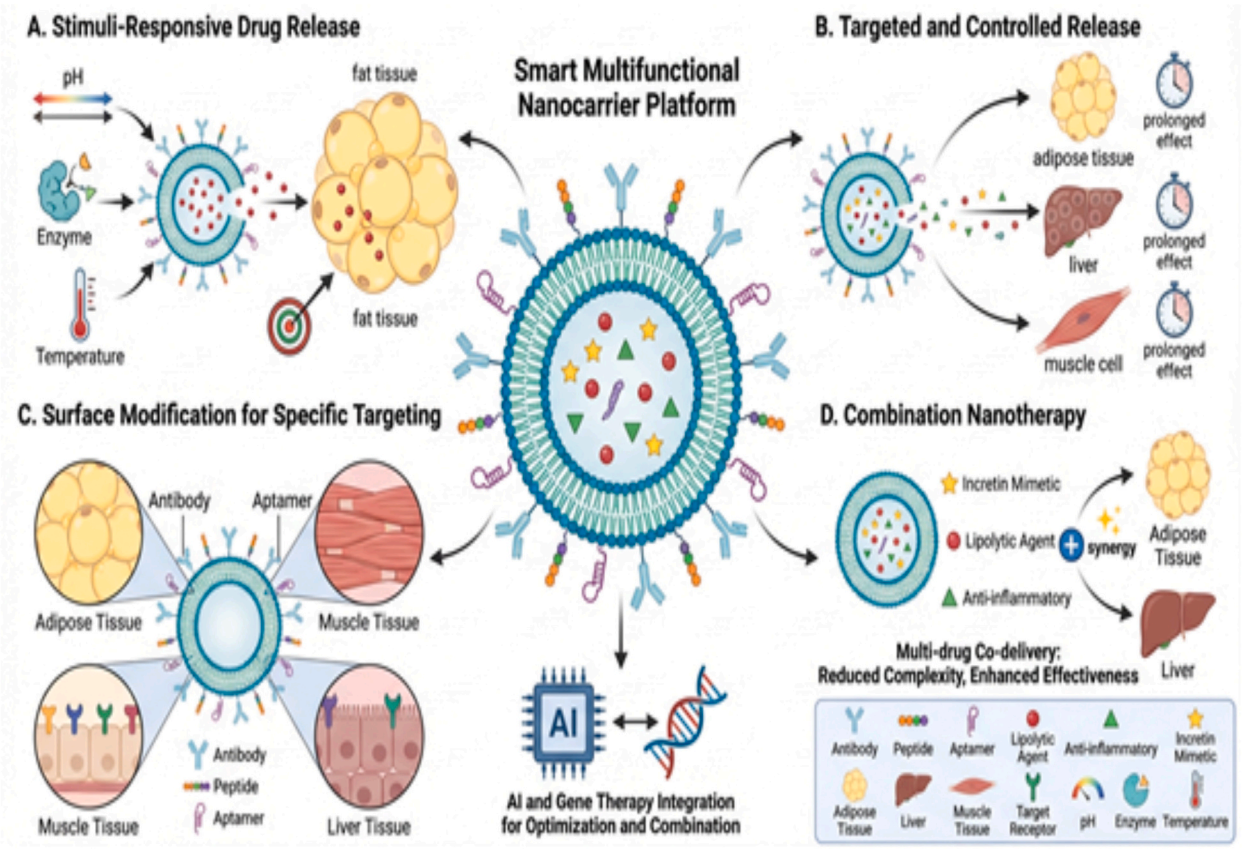


Fig. 4. *Emerging Trends in Smart Nanocarriers and Multi-Functional Drug Delivery Systems* (**created in** https://BioRender.com).

in medical applications (Đorđević et al., 2022). Approval delays frequently occur because nanomedicines do not have enough documented safety data because they represent new medical approaches. Researching the delayed adverse effects of nanoparticles proves difficult because it limits our ability to predict their safety outcomes across extended timescales (Ali et al., 2023). The production of nanoparticles requires maintaining strict consistency between batches because regulatory requirements demand evidence proving that materials maintain minimal changes in their dimensional properties together with their surface features and chemical makeup. Translational efforts face hurdles when interpreting preclinical study results for human trials since metabolic dissimilarities and immune system reactions and distribution patterns between animals and humans pose problems (Ali et al., 2023; Ineichen et al., 2024). Nanoparticles' properties present unique design issues in clinical trials because it necessitates novel approaches for finding correct drug amounts and scheduling of therapy as well as setting measurable outcomes. Off-target impacts together with non-target tissue accumulation create difficulties in understanding trial findings.

6.4. Ethical considerations in the use of nanomedicine for obesity treatment

The implementation of nanomedicine for obesity therapy induces ethical dilemmas since it demands a careful assessment of both the therapeutic advantages and patient and community security hazards (L. Jiang and Carmichael, 2019). Physical approval from patients remains essential when taking nanomedical substances since their advanced scientific concepts exceed basic human understanding. Certain vulnerable populations including children and elderly citizens along with economically disadvantaged people may become susceptible to clinical trial participation and nanomedicine treatment adoption because of inadequate risk comprehension (Quesada-Vázquez et al., 2024). The expense of nanoparticle-based obesity treatments could grow health inequalities because they would likely become available only to upper-class patients and nations (Fathi-karkan et al., 2025; Jia et al., 2023). The importance of global health equity demands nanomedicines to comply with worldwide health priorities so that they can enhance healthcare for lower-income population groups. Applied nanoparticulate medical treatment creates ethical problems regarding their environmental impact. The improper clearance of nanoparticles inside the body might result in their eventual release into the environment. The environmental hazards posed by accumulating nanoparticles require attentive assessment because they affect aquatic ecosystems mainly.

The promise of nanomedicine for obesity treatment advances forward while facing various essential hurdles. The full potential of nanomedicine depends on solving safety problems with nanoparticle formulations and resolving scalability and cost matters and regulatory complexities as well as ethical considerations. The effective use of nanomedicines for obesity management requires mutual cooperation between researchers and regulatory bodies and pharmaceutical industry representatives.

7. Future prospects in nanotechnology for obesity and metabolic dysfunction treatment

A new drug delivery revolution emerged with nanotechnology that offers healthcare professionals the possibility to transform obesity treatment methods together with related metabolic disorders. Combining research on smart nanocarriers with artificial intelligence applications and combination treatments with gene therapy methodologies will have significant impact on breakthroughs in obesity and metabolic disease treatment. The following part examines new trends for smart nanocarriers together with multifunctional delivery systems and AI-based formulation optimization and nanotechnology-gene therapy combinations and

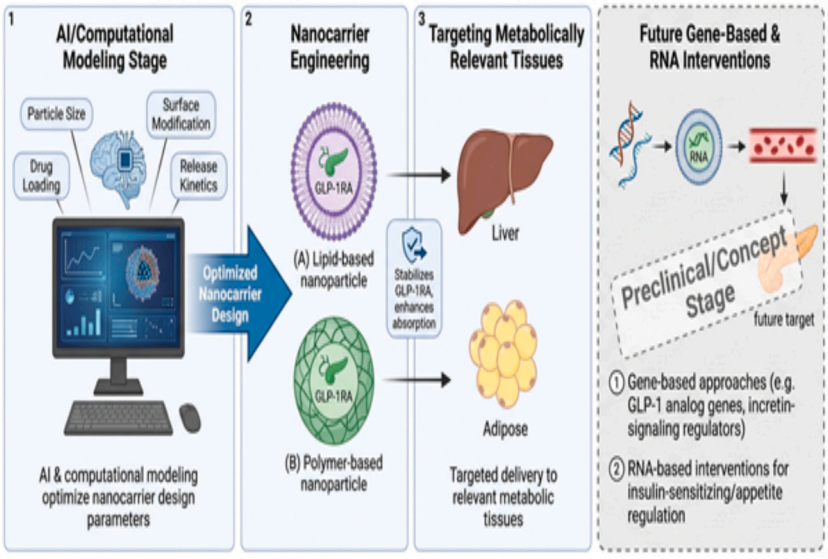


Fig. 5. *Integrating AI and Nanotechnology for Personalized Formulation and Gene Therapy* (**created in** https://BioRender.com**).**

nanotechnology-enhanced incretin mimetics applications.

7.1. Emerging Trends in Smart Nanocarriers and Multi-Functional Drug Delivery Systems

Nanocarriers based on smart design marks a tremendous progress in pharmaceutical drug delivery systems (Fig. 4). The nanocarriers exhibit distinct traits through environmental stimuli conditions which enable controlled drug delivery to the target site without producing unwanted effects and generates superior therapeutic results. Smart nanocarriers have experienced several advancements according to recent trends.

a. **Stimuli-Responsive Nanocarriers:** The release mechanism of stimuli-sensitive nanocarriers operates through specific physiological cues which include pH levels and temperature fluctuations alongside enzyme or antigen recognition (Ahmar, 2024). Smart nanocarriers possess the ability to activate under the specific conditions of fat tissue acidity and adipose cell enzymatic activity in metabolic disorder treatments (Sargazi et al., 2024). Through selective release mechanisms the drug reaches its targeted action site more effectively because off-target effects are minimized and the drug remains bioactive.
b. **Targeted and Controlled Release Systems:** The main hurdle in treating metabolic conditions involves obtaining proper doses to specific target tissues across prolonged periods. Nanocarriers accustomed to controlled incretin mimetic, or lipolytic agent delivery systems demonstrate extended medication effects which enhance medical performance while shortening medication schedule intervals. Nanocarriers having multiple functions as lipid-based nanoparticles and polymeric nanoparticles together with micelles enable simultaneous delivery of various drugs which enhances the therapeutic effect through combined metabolic pathway intervention.
c. **Surface Modifications of Nanocarriers:** Represent an essential strategy to improve their ability to target specific areas. By attaching targeting ligands including antibodies as well as peptides and aptamers to nanocarriers their capability to target receptors expressed within adipose tissues and muscle cells and within the liver gets enhanced (Correia et al., 2021; Fatima et al., 2025). The drug requires vital surface modifications to prevent systemic harm and maintain its action within particular metabolic organs. The therapeutic index of obesity treatment and type 2 diabetes management becomes more effective through targeting receptors mediating insulin resistance and tissue inflammation in adipose tissue.
d. **Combination Nanotherapies:** Scientists are focused on multi-functional drug delivery platforms because these systems effectively provide combined medical treatments for complex metabolic diseases. A nanocarrier system which contains several active ingredients including incretin mimetics and lipolysis-stimulating agents and anti-inflammatory agents enables treatment of obesity along with its various underlying factors. Multiple drug delivery through co-encapsulation reduces medication complications since it reduces treatment complexity and helps patients meet their treatment requirements (Razzaq et al., 2025).

7.2. The role of artificial intelligence and computational modeling in optimizing formulations

The design process of nanocarriers for drug delivery has received significant improvement through the application of Artificial Intelligence (AI) and computational modeling systems especially when treating metabolic diseases such as obesity (Fig. 5). Implementation of artificial intelligence (AI) and gene-based technology into nanotechnology based incretin therapy is a new and highly speculative area with little direct support in incretin systems. AI-based approaches are starting to be pursued in maximizing the design parameters of nanocarrier such as particle size, surface modification, drug loading, and release kinetics. AI may be useful in incretin therapy by predicting interactions between drugs and carriers, refining oral peptide delivery systems, and enhancing system targeting to metabolically viable tissues, including the liver and adipose tissue. Regarding this, the computational modeling can be used to design lipid-based or polymer-based nanoparticles, which will stabilize and absorb GLP-1 receptor agonists better. Nevertheless, the existing applications are mostly preclinical, formulation-oriented and there are no developed AI-directed incretin nanomedicine systems.

Other future strategies in inhibiting or stimulating incretins that have been suggested include gene-based methods, such as using nanocarrier-mediated nucleic acid delivery. Theoretically, a prolonged effect of the treatment using nanoparticles of genes encoding GLP-1 analogs or incretin-signaling regulators may be possible. Also, RNA-based interventions can address the insulin-sensitizing or appetite-regulating pathways. These approaches are however currently, these are concepts and no clinically proven gene therapies on incretin systems through nanotechnology exists. In sum, although AI and gene-based methods have a chance to improve the new evolution of incretin nanomedicine, it is still in its early stages and investigative mode. Safety, efficacy and translation amenable research is yet to be established prior to clinical application.

8. Conclusions

This review assessed the limitations of conventional incretin-based therapies in the management of obesity and metabolic dysfunction, while highlighting the innovative potential of nanotechnology-based delivery systems. The objectives were achieved through a comprehensive analysis of how advanced nanocarrier systems including lipid-based nanoparticles, polymeric nanoparticles, and stimuli-responsive platforms can effectively overcome the challenges of enzymatic degradation, short biological half-life, and systemic side effects associated with current incretin mimetics. In doing so, we underscored the novel and promising intersection of nanotechnology with incretin-based therapies, proposing a next-generation framework that incorporates smart nanocarriers, artificial intelligence-driven formulation strategies, and the potential synergy with gene therapy.

Our findings confirm and extend previous observations on the pharmacokinetic and pharmacodynamic enhancements achievable through nanotechnology, and we provide new insights into targeted delivery to key metabolic organs such as the liver, adipose tissue, and the brain. From these investigations, several future perspectives arose: there is a critical need to prioritize comprehensive safety profiling and biocompatibility testing of nanoparticle systems, to develop scalable and cost-effective manufacturing processes, and to conduct rigorous preclinical and clinical studies that validate both the therapeutic efficacy and the long-term safety of these emerging treatments. Furthermore, the integration of personalized medicine approaches, incorporating omics data and artificial intelligence, holds considerable promise in optimizing patient-specific outcomes. In summary, nanotechnology-enhanced incretin-based therapies represent a transformative avenue for addressing the global burden of obesity and metabolic dysfunction, offering the potential for more effective, targeted, and patient-centered treatment solutions in the years to come.

CRediT authorship contribution statement

Daniel Ejim Uti: Writing – review & editing, Writing – original draft, Validation, Software, Conceptualization. **Josephine E. Egbung:** Writing – review & editing, Writing – original draft, Validation, Software, Conceptualization. **Esther Ugo Alum:** Writing – review & editing, Writing – original draft, Validation, Software, Conceptualization. **Inalegwu Bawa:** Writing – review & editing, Validation, Supervision, Conceptualization. **Samuel Ali Agada:** Writing – review & editing, Writing – original draft, Validation, Conceptualization. **Celestine O. Ogbu:** Writing – review & editing, Visualization, Validation, Conceptualization. **Okechukwu Paul-Chima Ugwu:** Writing – review & editing, Validation, Supervision, Conceptualization.

Consent to publish

Not applicable.

Conflicts of interest

The Authors declare no conflict of interests.

Consent to participate

Not applicable.

Institutional review board statement

NA.

Data availability statement

No new data was generated in the current review.

Ethics declaration

Not applicable.

Clinical trial number

NA.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work the author(s) used Grammarly & Quilbot to frame the grammar and English editing. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

Funding

This review received no external funding or grants from any agency or organization.

Declaration of competing interest

The Authors declare no conflict of interests.

Acknowledgement

Figures presented in this manuscript were created using BioRender. Specifically, *Created in BioRender. Basajja, M. (2026)* https://BioRender.com/s09o0gn. The authors gratefully acknowledge Kampala International University, Kampala, Uganda, for providing institutional subscription access to BioRender, which supported the development of the graphical illustrations in this study.

References

Abbasi, M., Sun, K., Huggins, K.W., Heath, B., DeLoit, H., McGinness, L., Mccamy, K., 2026. Advances in GLP-1 receptor agonists delivery systems for obesity and diabetes. Acta Pharm. Sin. B. https://doi.org/10.1016/j.apsb.2026.01.035.

Ahmadi, S., Rabiee, N., Bagherzadeh, M., Elmi, F., Fatahi, Y., Farjadian, F., Baheiraei, N., Nasseri, B., Rabiee, M., Dastjerd, N.T., Valibeik, A., Karimi, M., Hamblin, M. R., 2020. Stimulus-responsive sequential release systems for drug and gene delivery. Nano Today 34, 100914. https://doi.org/10.1016/j.nantod.2020.100914.

Ahmar, H., 2024. Nonenzymatic electrochemical detection of glucose using screen-printed electrode modified with Pd–Au nanoparticles encapsulated on dendrimer grafted multi-wall carbon nanotubes. Current Applied Sciences 2 (2), 67–78. https://doi.org/10.22034/cas.2022.343533.1019.

Alcaino, C., Reimann, F., Gribble, F.M., 2024. Incretin hormones and obesity. J. Physiol. JP286293. https://doi.org/10.1113/JP286293.

Ali, F., Neha, K., Parveen, S., 2023. Current regulatory landscape of nanomaterials and nanomedicines: a global perspective. J. Drug Deliv. Sci. Technol. 80, 104118. https://doi.org/10.1016/j.jddst.2022.104118.

AlZaim, I., Hammoud, S.H., Al-Koussa, H., Ghazi, A., Eid, A.H., El-Yazbi, A.F., 2020. Adipose tissue immunomodulation: a novel therapeutic approach in cardiovascular and metabolic diseases. Front. Cardiovasc. Med. 7, 602088. https://doi.org/10.3389/fcvm.2020.602088.

An, S.-M., Cho, S.-H., Yoon, J.C., 2023. Adipose tissue and metabolic health. Diabetes & Metabolism Journal 47 (5), 595–611. https://doi.org/10.4093/dmj.2023.0011.

Anastasiou, I.A., Argyrakopoulou, G., Dalamaga, M., Kokkinos, A., 2025. Dual and triple gut peptide agonists on the horizon for the treatment of type 2 diabetes and obesity. An overview of preclinical and clinical data. Curr. Obes. Rep. 14 (1), 34. https://doi.org/10.1007/s13679-025-00623-1.

Andersen, A., Knop, F.K., Vilsbøll, T., 2021. A pharmacological and clinical overview of oral semaglutide for the treatment of type 2 diabetes. Drugs 81 (9), 1003. https://doi.org/10.1007/s40265-021-01499-w.

Angelini, G., Russo, S., Mingrone, G., 2024. Incretin hormones, obesity and gut microbiota. Peptides 178, 171216. https://doi.org/10.1016/j.peptides.2024.171216.

Arabestani, M.R., Bigham, A., Kamarehei, F., Dini, M., Gorjikhah, F., Shariati, A., Hosseini, S.M., 2024. Solid lipid nanoparticles and their application in the treatment of bacterial infectious diseases. Biomed. Pharmacother. 174, 116433. https://doi.org/10.1016/j.biopha.2024.116433.

Araújo, F., Shrestha, N., Shahbazi, M.-A., Liu, D., Herranz-Blanco, B., Mäkilä, E.M., Salonen, J.J., Hirvonen, J.T., Granja, P.L., Sarmento, B., Santos, H.A., 2015. Microfluidic assembly of a multifunctional tailorable composite System designed for site specific combined oral delivery of peptide drugs. ACS Nano 9 (8), 8291–8302. https://doi.org/10.1021/acsnano.5b02762.

Aremu, T.O., Oluwole, O.E., Adeyinka, K.O., Schommer, J.C., 2022. Medication adherence and compliance: recipe for improving patient outcomes. Pharmacy: Journal of Pharmacy Education and Practice 10 (5), 106. https://doi.org/10.3390/pharmacy10050106.

Ataide, J.A., Coco, J.C., dos Santos, É.M., Beraldo-Araujo, V., Silva, J.R.A., de Castro, K.C., Lopes, A.M., Filipczak, N., Yalamarty, S.S.K., Torchilin, V.P., Mazzola, P.G., 2023. Co-Encapsulation of drugs for topical Application—A review. Molecules 28 (3), 1449. https://doi.org/10.3390/molecules28031449.

Azzu, V., Vacca, M., Virtue, S., Allison, M., Vidal-Puig, A., 2020. Adipose tissue-liver cross talk in the control of whole-body metabolism: implications in nonalcoholic Fatty liver disease. Gastroenterology 158 (7), 1899–1912. https://doi.org/10.1053/j.gastro.2019.12.054.

Baldelli, S., Aiello, G., Mansilla Di Martino, E., Campaci, D., Muthanna, F.M.S., Lombardo, M., 2024. The role of adipose tissue and nutrition in the regulation of adiponectin. Nutrients 16 (15), 15. https://doi.org/10.3390/nu16152436.

Banks, W.A., Rhea, E.M., Reed, M.J., Erickson, M.A., 2024. The penetration of therapeutics across the blood-brain barrier: classic case studies and clinical implications. Cell Rep. Med. 5 (11), 101760. https://doi.org/10.1016/j.xcrm.2024.101760.

Bansal, S., Vachher, M., Arora, T., Kumar, B., Burman, A., 2023. Visceral fat: a key mediator of NAFLD development and progression. Human Nutrition & Metabolism 33, 200210. https://doi.org/10.1016/j.hnm.2023.200210.

Barać, M., Roganović, J., 2025. GLP-1 receptor signaling and oral dysfunction: a narrative review on the mechanistic basis of semaglutide-related oral adverse effects. Biology 14 (12). https://doi.org/10.3390/biology14121650.

Baryakova, T.H., Pogostin, B.H., Langer, R., McHugh, K.J., 2023. Overcoming barriers to patient adherence: the case for developing innovative drug delivery systems. Nat. Rev. Drug Discov. 22 (5), 387–409. https://doi.org/10.1038/s41573-023-00670-0.

Basil, B., Myke-Mbata, B.K., Eze, O.E., Akubue, A.U., 2024. From adiposity to steatosis: Metabolic dysfunction-associated steatotic liver disease, a hepatic expression of metabolic syndrome – current insights and future directions. Clinical Diabetes and Endocrinology 10, 39. https://doi.org/10.1186/s40842-024-00187-4.

Bendicho-Lavilla, C., Seoane-Viaño, I., Otero-Espinar, F.J., Luzardo-Álvarez, A., 2022. Fighting type 2 diabetes: formulation strategies for peptide-based therapeutics. Acta Pharm. Sin. B 12 (2), 621–636. https://doi.org/10.1016/j.apsb.2021.08.003.

Bettinetti-Luque, M., Trujillo-Estrada, L., Garcia-Fuentes, E., Andreo-Lopez, J., Sanchez-Varo, R., Garrido-Sánchez, L., Gómez-Mediavilla, Á., López, M.G., Garcia-Caballero, M., Gutierrez, A., Baglietto-Vargas, D., 2024. Adipose tissue as a therapeutic target for vascular damage in Alzheimer's disease. Br. J. Pharmacol. 181 (6), 840–878. https://doi.org/10.1111/bph.16243.

Bhusal, A., Rahman, M.H., Suk, K., 2021. Hypothalamic inflammation in metabolic disorders and aging. Cell. Mol. Life Sci.: CM 79 (1), 32. https://doi.org/10.1007/s00018-021-04019-x.

Bo, T., Gao, L., Yao, Z., Shao, S., Wang, X., Proud, C.G., Zhao, J., 2024. Hepatic selective insulin resistance at the intersection of insulin signaling and metabolic dysfunction-associated steatotic liver disease. Cell Metab. 36 (5), 947–968. https://doi.org/10.1016/j.cmet.2024.04.006.

Campbell, J.E., 2020. Targeting the GIPR for obesity: to agonize or antagonize? Potential mechanisms. Mol. Metabol. 46, 101139. https://doi.org/10.1016/j.molmet.2020.101139.

Campbell, J.E., Newgard, C.B., 2021. Mechanisms controlling pancreatic islet cell function in insulin secretion. Nat. Rev. Mol. Cell Biol. 22 (2), 142–158. https://doi.org/10.1038/s41580-020-00317-7.

Capozzi, M.E., D'Alessio, D.A., Campbell, J.E., 2022. The past, present, and future physiology and pharmacology of glucagon. Cell Metab. 34 (11), 1654–1674. https://doi.org/10.1016/j.cmet.2022.10.001.

Chadt, A., Al-Hasani, H., 2020. Glucose transporters in adipose tissue, liver, and skeletal muscle in metabolic health and disease. Pflügers Archiv 472 (9), 1273–1298. https://doi.org/10.1007/s00424-020-02417-x.

Chait, A., den Hartigh, L.J., 2020. Adipose tissue distribution, inflammation and its metabolic consequences, including diabetes and cardiovascular disease. Front. Cardiovasc. Med. 7. https://doi.org/10.3389/fcvm.2020.00022.

Chen, G., Kang, W., Li, W., Chen, S., Gao, Y., 2022. Oral delivery of protein and peptide drugs: from non-specific formulation approaches to intestinal cell targeting strategies. Theranostics 12 (3), 1419. https://doi.org/10.7150/thno.61747.

Chen, Y., Wang, W., Morgan, M.P., Robson, T., Annett, S., 2023. Obesity, non-alcoholic fatty liver disease and hepatocellular carcinoma: current status and therapeutic targets. Front. Endocrinol. 14. https://doi.org/10.3389/fendo.2023.1148934.

Cheng, Y., Liang, S., Zhang, S., Hui, X., 2024. Thermogenic fat as a new obesity management tool: from pharmaceutical reagents to cell therapies. Biomedicines 12 (7), 1474. https://doi.org/10.3390/biomedicines12071474.

Chrysavgis, L.G., Kazanas, S., Bafa, K., Rozani, S., Koloutsou, M.-E., Cholongitas, E., 2024. Glucagon-like peptide 1, glucose-dependent insulinotropic polypeptide, and glucagon receptor agonists in Metabolic dysfunction-associated steatotic liver disease: novel medication in new liver disease nomenclature. Int. J. Mol. Sci. 25 (7), 7. https://doi.org/10.3390/ijms25073832.

Clemente-Suárez, V.J., Martín-Rodríguez, A., Redondo-Flórez, L., López-Mora, C., Yáñez-Sepúlveda, R., Tornero-Aguilera, J.F., 2023a. New insights and potential therapeutic interventions in metabolic diseases. Int. J. Mol. Sci. 24 (13), 13. https://doi.org/10.3390/ijms241310672.

Clemente-Suárez, V.J., Redondo-Flórez, L., Beltrán-Velasco, A.I., Martín-Rodríguez, A., Martínez-Guardado, I., Navarro-Jiménez, E., Laborde-Cárdenas, C.C., Tornero-Aguilera, J.F., 2023b. The role of adipokines in health and disease. Biomedicines 11 (5), 1290. https://doi.org/10.3390/biomedicines11051290.

Conceição-Furber, E., Coskun, T., Sloop, K.W., Samms, R.J., 2022. Is glucagon receptor activation the thermogenic solution for treating obesity? Front. Endocrinol. 13. https://doi.org/10.3389/fendo.2022.868037.

Corbin, K.D., Driscoll, K.A., Pratley, R.E., Smith, S.R., Maahs, D.M., Mayer-Davis, E.J., Advancing Care for Type 1 Diabetes and Obesity Network (ACT1ON), 2018. Obesity in type 1 diabetes: pathophysiology, clinical impact, and mechanisms. Endocr. Rev. 39 (5), 629–663. https://doi.org/10.1210/er.2017-00191.

Correia, J.H., Rodrigues, J.A., Pimenta, S., Dong, T., Yang, Z., 2021. Photodynamic therapy review: principles, photosensitizers, applications, and future directions. Pharmaceutics 13 (9), 1332. https://doi.org/10.3390/pharmaceutics13091332.

Dąbrowska, A.M., Dudka, J., 2023. Mirabegron, a selective β3-Adrenergic receptor agonist, as a potential anti-obesity drug. J. Clin. Med. 12 (21), 6897. https://doi.org/10.3390/jcm12216897.

Dash, P., Piras, A.M., Dash, M., 2020. Cell membrane coated nanocarriers—An efficient biomimetic platform for targeted therapy. J. Contr. Release 327, 546–570. https://doi.org/10.1016/j.jconrel.2020.09.012.

de, A., Boleti, A.P., de, O., Cardoso, P.H., Frihling, B.E.F., e Silva, P.S., de Moraes, L.F.R.N., Migliolo, L., 2022. Adipose tissue, systematic inflammation, and neurodegenerative diseases. Neural Regen. Res. 18 (1), 38–46. https://doi.org/10.4103/1673-5374.343891.

Deacon, C.F., 2019. Physiology and pharmacology of DPP-4 in glucose homeostasis and the treatment of type 2 diabetes. Front. Endocrinol. 10. https://doi.org/10.3389/fendo.2019.00080.

Deivayanai, V.C., Thamarai, P., Karishma, S., Saravanan, A., Yaashikaa, P.R., Vickram, A.S., Hemavathy, R.V., Kumar, R.R., Rishikesavan, S., Shruthi, S., 2024. A comprehensive review on advances in nanoparticle-mediated cancer therapeutics: current research and future perspectives. Cancer Pathog. Ther. https://doi.org/10.1016/j.cpt.2024.11.002.

Del Prato, S., Gallwitz, B., Holst, J.J., Meier, J.J., 2022. The incretin/glucagon system as a target for pharmacotherapy of obesity. Obes. Rev. 23 (2), e13372. https://doi.org/10.1111/obr.13372.

Dimitriadis, G.D., Maratou, E., Kountouri, A., Board, M., Lambadiari, V., 2021. Regulation of postabsorptive and postprandial glucose metabolism by insulin-dependent and insulin-independent mechanisms: an integrative approach. Nutrients 13 (1), 1. https://doi.org/10.3390/nu13010159.

Đorđević, S., Gonzalez, M.M., Conejos-Sánchez, I., Carreira, B., Pozzi, S., Acúrcio, R.C., Satchi-Fainaro, R., Florindo, H.F., Vicent, M.J., 2022. Current hurdles to the translation of nanomedicines from bench to the clinic. Drug Deliv. Transl. Res. 12 (3), 500–525. https://doi.org/10.1007/s13346-021-01024-2.

Dowker-Key, P.D., Jadi, P.K., Gill, N.B., Hubbard, K.N., Elshaarrawi, A., Alfatlawy, N.D., Bettaieb, A., 2024. A closer look into white adipose tissue biology and the molecular regulation of stem cell commitment and differentiation. Genes 15 (8), 8. https://doi.org/10.3390/genes15081017.

Drabczyk, A., Kudłacik-Kramarczyk, S., Jamroży, M., Krzan, M., 2024. Biomaterials in drug delivery: advancements in cancer and diverse Therapies—Review. Int. J. Mol. Sci. 25 (6), 3126. https://doi.org/10.3390/ijms25063126.

Drucker, D.J., 2018. Mechanisms of action and therapeutic application of glucagon-like Peptide-1. Cell Metab. 27 (4), 740–756. https://doi.org/10.1016/j.cmet.2018.03.001.

Ekpa, E.D., Asuquo, U.R., Elijah, A.A., Ime, S.N.-A., Ini, U.A., Ekpa, E.D., Asuquo, U.R., Elijah, A.A., Ime, S.N.-A., Ini, U.A., 2020. The oral film delivery- application of nanotechnology and potential in medication adherence. GSC Biological and Pharmaceutical Sciences 11 (3), 3. https://doi.org/10.30574/gscbps.2020.11.3.0154.

Elumalai, K., Srinivasan, S., Shanmugam, A., 2024. Review of the efficacy of nanoparticle-based drug delivery systems for cancer treatment. Biomedical Technology 5, 109–122. https://doi.org/10.1016/j.bmt.2023.09.001.

Fan, Y.-H., Zhang, S., Wang, Y., Wang, H., Li, H., Bai, L., 2025. Inter-organ metabolic interaction networks in non-alcoholic fatty liver disease. Front. Endocrinol. 15, 1494560. https://doi.org/10.3389/fendo.2024.1494560.

Farngren, J., Ahrén, B., 2019. Incretin-based medications (GLP-1 receptor agonists, DPP-4 inhibitors) as a means to avoid hypoglycaemic episodes. Metab., Clin. Exp. 99, 25–31. https://doi.org/10.1016/j.metabol.2019.06.016.

Fathi-karkan, S., Nasiri, S., Hasannia, M., Rahdar, A., Nouri, M., Najafi, M., Basiri, A., Tehrani, F.S., Hashemi, S.M., Romanholo Ferreira, L.F., 2025. Green carbon dots and theranostic applications. J. Drug Deliv. Sci. Technol. 108, 106861. https://doi.org/10.1016/j.jddst.2025.106861.

Fatima, I., Khan, A., Rahdar, A., Fathi-karkan, S., Kharaba, Z., Baino, F., 2025. Optimized mesalamine-loaded polyelectrolyte complex nanoparticles for targeted colon delivery in inflammatory bowel disease treatment: a central composite design approach. Next Mater. 8, 100530. https://doi.org/10.1016/j.nxmate.2025.100530.

Ferguson, D., Finck, B.N., 2021. Emerging therapeutic approaches for the treatment of NAFLD and type 2 diabetes mellitus. Nat. Rev. Endocrinol. 17 (8), 484–495. https://doi.org/10.1038/s41574-021-00507-z.

Ferreira-Faria, I., Yousefiasl, S., Macário-Soares, A., Pereira-Silva, M., Peixoto, D., Zafar, H., Raza, F., Faneca, H., Veiga, F., Hamblin, M.R., Tay, F.R., Gao, J., Sharifi, E., Makvandi, P., Paiva-Santos, A.C., 2022. Stem cell membrane-coated abiotic nanomaterials for biomedical applications. J. Contr. Release 351, 174–197. https://doi.org/10.1016/j.jconrel.2022.09.012.

Fisman, E.Z., Tenenbaum, A., 2021. The dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist tirzepatide: a novel cardiometabolic therapeutic prospect. Cardiovasc. Diabetol. 20 (1), 225. https://doi.org/10.1186/s12933-021-01412-5.

Forst, T., De Block, C., Del Prato, S., Armani, S., Frias, J., Lautenbach, A., Ludvik, B., Marinez, M., Mathieu, C., Müller, T.D., Schnell, O., 2024. The role of incretin receptor agonists in the treatment of obesity. Diabetes Obes. Metabol. 26 (10), 4178–4196. https://doi.org/10.1111/dom.15796.

Fukuda, M., 2021. The role of GIP receptor in the CNS for the pathogenesis of obesity. Diabetes 70 (9), 1929–1937. https://doi.org/10.2337/dbi21-0001.

Gaffey, R.H., Takyi, A.K., Shukla, A., 2024. Investigational and emerging gastric inhibitory polypeptide (GIP) receptor-based therapies for the treatment of obesity. Expert Opin. Invest. Drugs 33 (8), 757–773. https://doi.org/10.1080/13543784.2024.2377319.

Gallwitz, B., 2019. Clinical use of DPP-4 inhibitors. Front. Endocrinol. 10. https://doi.org/10.3389/fendo.2019.00389.

Gao, J., Li, H., Xu, H., Liu, Y., Cai, M., Shi, Y., Zhang, J., Wang, H., 2023. High glucose-induced glucagon resistance and membrane distribution of GCGR revealed by super-resolution imaging. iScience 26 (2), 105967. https://doi.org/10.1016/j.isci.2023.105967.

Gastaldelli, A., Gaggini, M., Daniele, G., Ciociaro, D., Cersosimo, E., Tripathy, D., Triplitt, C., Fox, P., Musi, N., DeFronzo, R., Iozzo, P., 2016. Exenatide improves both hepatic and adipose tissue insulin resistance: a dynamic positron emission tomography study. Hepatology 64 (6), 2028. https://doi.org/10.1002/hep.28827.

Genchi, V.A., Palma, G., Sorice, G.P., D'Oria, R., Caccioppoli, C., Marrano, N., Biondi, G., Caruso, I., Cignarelli, A., Natalicchio, A., Laviola, L., Giorgino, F., Perrini, S., 2023. Pharmacological modulation of adaptive thermogenesis: new clues for obesity management? J. Endocrinol. Investig. 46 (11), 2213–2236. https://doi.org/10.1007/s40618-023-02125-0.

Ghesmati, Z., Rashid, M., Fayezi, S., Gieseler, F., Alizadeh, E., Darabi, M., 2024. An update on the secretory functions of brown, white, and beige adipose tissue: towards therapeutic applications. Rev. Endocr. Metab. Disord. 25 (2), 279–308. https://doi.org/10.1007/s11154-023-09850-0.

Godoy-Matos, A.F., Silva Júnior, W.S., Valerio, C.M., 2020. NAFLD as a continuum: from obesity to metabolic syndrome and diabetes. Diabetol. Metab. Syndr. 12 (1), 60. https://doi.org/10.1186/s13098-020-00570-y.

Guccio, N., Alcaino, C., Miedzybrodzka, E.L., Santos-Hernández, M., Smith, C.A., Davison, A., Bany Bakar, R., Kay, R.G., Reimann, F., Gribble, F.M., 2025. Molecular mechanisms underlying glucose-dependent insulinotropic polypeptide secretion in human duodenal organoids. Diabetologia 68 (1), 217–230. https://doi.org/10.1007/s00125-024-06293-3.

Gunturu, S., 2024. The potential role of GLP-1 agonists in psychiatric disorders: a paradigm shift in mental health treatment. Indian J. Psychol. Med. 46 (3), 193–195. https://doi.org/10.1177/02537176241246744.

Haleem, A., Javaid, M., Singh, R.P., Rab, S., Suman, R., 2023. Applications of nanotechnology in medical field: a brief review. Global Health Journal 7 (2), 70–77. https://doi.org/10.1016/j.glohj.2023.02.008.

Hamed, K., Alosaimi, M. N., Ali, B. A., Alghamdi, A., Alkhashi, T., Alkhaldi, S. S., Altowarqi, N. A., Alzahrani, H., Alshehri, A. M., Alkhaldi, R. K., Alqahtani, K. W., Alharbi, N. H., Alhulayfi, H. F., Sharifi, S. Y., & Dighriri, I. M. (n.d.). Glucagon-Like Peptide-1 (GLP-1) receptor agonists: exploring their impact on diabetes, obesity, and cardiovascular health through a comprehensive literature review. Cureus, 16(9), e68390. https://doi.org/10.7759/cureus.68390.

Hatting, M., Tavares, C.D.J., Sharabi, K., Rines, A.K., Puigserver, P., 2018. Insulin regulation of gluconeogenesis. Ann. N. Y. Acad. Sci. 1411 (1), 21–35. https://doi.org/10.1111/nyas.13435.
Hemat Jouy, S., Mohan, S., Scichilone, G., Mostafa, A., Mahmoud, A.M., 2024. Adipokines in the crosstalk between adipose tissues and other organs: implications in cardiometabolic diseases. Biomedicines 12 (9). https://doi.org/10.3390/biomedicines12092129. Article 9.
Holler, N., Ruseska, I., Schachner-Nedherer, A.-L., Zimmer, A., Petschacher, C., 2025. Oral treatment of obesity by GLP-1 and its analogs. Pharmaceutics 17 (12). https://doi.org/10.3390/pharmaceutics17121596.
Holst, J.J., 2022. Glucagon-like peptide-1: are its roles as endogenous hormone and therapeutic wizard congruent? J. Intern. Med. 291 (5), 557–573. https://doi.org/10.1111/joim.13433.
Ilieş, B.D., Yildiz, I., Abbas, M., 2024. Peptide-conjugated nanoparticle platforms for targeted delivery, imaging, and biosensing applications. Chembiochem 25 (10), e202300867. https://doi.org/10.1002/cbic.202300867.
Ineichen, B.V., Furrer, E., Grüninger, S.L., Zürrer, W.E., Macleod, M.R., 2024. Analysis of animal-to-human translation shows that only 5% of animal-tested therapeutic interventions obtain regulatory approval for human applications. PLoS Biol. 22 (6), e3002667. https://doi.org/10.1371/journal.pbio.3002667.
Islam, S., Ahmed, M.M.S., Islam, M.A., Hossain, N., Chowdhury, M.A., 2025. Advances in nanoparticles in targeted drug delivery–A review. Results Surf. Interfaces 19, 100529. https://doi.org/10.1016/j.rsurfi.2025.100529.
Jais, A., Brüning, J.C., 2021. Arcuate nucleus-dependent regulation of Metabolism—Pathways to obesity and diabetes mellitus. Endocr. Rev. 43 (2), 314. https://doi.org/10.1210/endrev/bnab025.
Janah, L., Kjeldsen, S., Galsgaard, K.D., Winther-Sørensen, M., Stojanovska, E., Pedersen, J., Knop, F.K., Holst, J.J., Wewer Albrechtsen, N.J., 2019. Glucagon receptor signaling and glucagon resistance. Int. J. Mol. Sci. 20 (13), 3314. https://doi.org/10.3390/ijms20133314.
Javid, H., Oryani, M.A., Rezagholinejad, N., Esparham, A., Tajaldini, M., Karimi-Shahri, M., 2024. RGD peptide in cancer targeting: benefits, challenges, solutions, and possible integrin–RGD interactions. Cancer Med. 13 (2), e6800. https://doi.org/10.1002/cam4.6800.
Jia, Y., Jiang, Y., He, Y., Zhang, W., Zou, J., Magar, K.T., Boucetta, H., Teng, C., He, W., 2023. Approved nanomedicine against diseases. Pharmaceutics 15 (3), 774. https://doi.org/10.3390/pharmaceutics15030774.
Jiang, L., Carmichael, K.A., 2019. Innovating nanoethics. AMA Journal of Ethics 21 (4), 313–316. https://doi.org/10.1001/amajethics.2019.313.
Jiang, Y., Zhu, H., Gong, F., 2025. Why does GLP-1 agonist combined with GIP and/or GCG agonist have greater weight loss effect than GLP-1 agonist alone in obese adults without type 2 diabetes? Diabetes Obes. Metabol. 27 (3), 1079–1095. https://doi.org/10.1111/dom.16106.
Jin, X., Qiu, T., Li, L., Yu, R., Chen, X., Li, C., Proud, C.G., Jiang, T., 2023. Pathophysiology of obesity and its associated diseases. Acta Pharm. Sin. B 13 (6), 2403. https://doi.org/10.1016/j.apsb.2023.01.012.
Kabahizi, A., Wallace, B., Lieu, L., Chau, D., Dong, Y., Hwang, E.-S., Williams, K.W., 2022. Glucagon-like peptide-1 (GLP-1) signalling in the brain: from neural circuits and metabolism to therapeutics. Br. J. Pharmacol. 179 (4), 600–624. https://doi.org/10.1111/bph.15682.
Kadry, H., Noorani, B., Cucullo, L., 2020. A blood–brain barrier overview on structure, function, impairment, and biomarkers of integrity. Fluids Barriers CNS 17, 69. https://doi.org/10.1186/s12987-020-00230-3.
Kajani, S., Laker, R.C., Ratkova, E., Will, S., Rhodes, C.J., 2024. Hepatic glucagon action: beyond glucose mobilization. Physiol. Rev. 104 (3), 1021–1060. https://doi.org/10.1152/physrev.00028.2023.
Kalra, S., Sahay, R., 2020. A review on semaglutide: an oral glucagon-like peptide 1 receptor agonist in management of type 2 diabetes mellitus. Diabetes Therapy 11 (9), 1965–1982. https://doi.org/10.1007/s13300-020-00894-y.
kapoor, D. u, Garg, R., Gaur, M., Prajapati, B.G., Agrawal, G., Bhattacharya, S., Elossaily, G.M., 2023. Polymeric nanoparticles approach and identification and characterization of novel biomarkers for colon cancer. Results Chem. 6, 101167. https://doi.org/10.1016/j.rechem.2023.101167.
Kochman, U., Sitka, H., Kuźniar, J., Czaja, M., Kozubek, P., Beszłej, J.A., Leszek, J., 2026. Targeted nanoparticles for drug delivery across the blood–brain barrier in early and late stages of alzheimer's disease: a review. Mol. Neurobiol. 63 (1), 75. https://doi.org/10.1007/s12035-025-05417-z.
Kupnicka, P., Król, M., Żychowska, J., Łagowski, R., Prajwos, E., Surówka, A., Chlubek, D., 2024. GLP-1 receptor agonists: a promising therapy for modern lifestyle diseases with unforeseen challenges. Pharmaceuticals 17 (11), 11. https://doi.org/10.3390/ph17111470.
Kurul, F., Turkmen, H., Cetin, A.E., Topkaya, S.N., 2025. Nanomedicine: how nanomaterials are transforming drug delivery, bio-imaging, and diagnosis. Nanotechnology 7, 100129. https://doi.org/10.1016/j.nxnano.2024.100129.
Latif, W., Lambrinos, K.J., Patel, P., Rodriguez, R., 2024. Compare and contrast the glucagon-like Peptide-1 receptor agonists (GLP1RAs). In: StatPearls [Internet]. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK572151/.
Lee, C.H., Suk, K., Yu, R., Kim, M.-S., 2020. Cellular contributors to hypothalamic inflammation in obesity. Mol. Cells 43 (5), 431–437. https://doi.org/10.14348/molcells.2020.0055.
Lee, H.Y., Ko, S.-H., Park, S., Kim, K., Kim, S.-Y., Cho, I.-J., Cho, E.J., Kim, H.C., Park, J.-H., Ryu, S.K., Moon, M.K., Ihm, S.-H., the Korean Society of Hypertension, 2024. The role of glucagon-like peptide-1 receptor agonists (GLP1-RAs) in the management of the hypertensive patient with metabolic syndrome: a position paper from the Korean society of hypertension. Clinical Hypertension 30 (1), 24. https://doi.org/10.1186/s40885-024-00279-4.
Lee, S., Benvie, A.M., Park, H.G., Spektor, R., Harlan, B., Brenna, J.T., Berry, D.C., Soloway, P.D., 2022. Remodeling of gene regulatory networks underlying thermogenic stimuli-induced adipose beiging. Commun. Biol. 5 (1), 1–16. https://doi.org/10.1038/s42003-022-03531-5.
Lewis, G.F., Carpentier, A.C., Pereira, S., Hahn, M., Giacca, A., 2021. Direct and indirect control of hepatic glucose production by insulin. Cell Metab. 33 (4), 709–720. https://doi.org/10.1016/j.cmet.2021.03.007.
Li, M., Zhao, G., Su, W.-K., Shuai, Q., 2020. Enzyme-responsive nanoparticles for anti-tumor drug delivery. Front. Chem. 8. https://doi.org/10.3389/fchem.2020.00647.
Li, X., Wang, H., 2020. Multiple organs involved in the pathogenesis of non-alcoholic fatty liver disease. Cell Biosci. 10 (1), 140. https://doi.org/10.1186/s13578-020-00507-y.
Liu, H., Su, Y.-Y., Jiang, X.-C., Gao, J.-Q., 2023. Cell membrane-coated nanoparticles: a novel multifunctional biomimetic drug delivery system. Drug Deliv. Transl. Res. 13 (3), 716–737. https://doi.org/10.1007/s13346-022-01252-0.
Liu, L., Yao, W., Rao, Y., Lu, X., Gao, J., 2017. pH-Responsive carriers for oral drug delivery: challenges and opportunities of current platforms. Drug Deliv. 24 (1), 569–581. https://doi.org/10.1080/10717544.2017.1279238.
Liu, M., Fang, X., Yang, Y., Wang, C., 2021. Peptide-enabled targeted delivery systems for therapeutic applications. Front. Bioeng. Biotechnol. 9. https://doi.org/10.3389/fbioe.2021.701504.
Lopes, S.A., Roque-Borda, C.A., Duarte, J.L., Filippo, L.D.D., Cardoso, V.M.B., Pavan, F.R., Chorilli, M., Meneguin, A.B., 2023. Delivery strategies of probiotics from Nano- and microparticles: trends in the treatment of inflammatory bowel disease—An overview. Pharmaceutics 15 (11), 2600. https://doi.org/10.3390/pharmaceutics15112600.
Lourie, J., Goraltchouk, A., Fujishiro, A., Berger, N., Rosen, H.G., Hollander, J., Luppino, F., Seregin, A., Zou, K., 2024. 792-P: a novel gene therapy platform using GLP1 and EX4 attenuates hyperglycemia in a preclinical model of type 2 diabetes. Diabetes 73 (Suppl. ment_1), 792. https://doi.org/10.2337/db24-792-P.
Lutz, T.M., Kimna, C., Lieleg, O., 2022. A pH-stable, mucin based nanoparticle system for the co-delivery of hydrophobic and hydrophilic drugs. Int. J. Biol. Macromol. 215, 102–112. https://doi.org/10.1016/j.ijbiomac.2022.06.081.
Lv, D., Feng, P., Guan, X., Liu, Z., Li, D., Xue, C., Bai, B., Hölscher, C., 2024. Neuroprotective effects of GLP-1 class drugs in Parkinson's disease. Front. Neurol. 15. https://doi.org/10.3389/fneur.2024.1462240.
Machindra, M. G., Sanjay, P. P., Swati, K., & Nandkumar, P. S. (n.d.). Review OnTargeted Drug Delivery System and Its Carriers as Drug Targeted to A Specific Organ.
Magadani, R., Ndinteh, D. T., Roux, S., Nangah, L. P., Atangwho, I. J., Uti, D. E., Alum, E. U., & Egba, S. I. (n.d.). Cytotoxic effects of Lecaniodiscus Cupanioides (Planch.) extract and triterpenoids-derived gold nanoparticles on MCF-7 breast cancer cell lines. http://Www.Eurekaselect.Com. Retrieved February 18, 2025, from https://www.eurekaselect.com/article/146149.
Magro, B.S., Dias, D.P.M., 2024. Brown and beige adipose tissue: new therapeutic targets for metabolic disorders. Health Sciences Review 10, 100148. https://doi.org/10.1016/j.hsr.2024.100148.

Maliszewska, K., Kretowski, A., 2021. Brown adipose tissue and its role in insulin and glucose homeostasis. Int. J. Mol. Sci. 22 (4), 1530. https://doi.org/10.3390/ijms22041530.
Mall, J., Naseem, N., Haider, Md F., Rahman, M.A., Khan, S., Siddiqui, S.N., 2024. Nanostructured lipid carriers as a drug delivery system: a comprehensive review with therapeutic applications. Intelligent Pharmacy. https://doi.org/10.1016/j.ipha.2024.09.005.
Mann, V., Sundaresan, A., Shishodia, S., 2024. Overnutrition and lipotoxicity: impaired efferocytosis and chronic inflammation as precursors to multifaceted disease pathogenesis. Biology 13 (4). https://doi.org/10.3390/biology13040241.
Mehta, M., Bui, T.A., Yang, X., Aksoy, Y., Goldys, E.M., Deng, W., 2023. Lipid-Based nanoparticles for Drug/Gene delivery: an overview of the production techniques and difficulties encountered in their industrial development. ACS Mater. Au 3 (6), 600–619. https://doi.org/10.1021/acsmaterialsau.3c00032.
Michałowska, J., Miller-Kasprzak, E., Bogdański, P., 2021. Incretin hormones in obesity and related cardiometabolic disorders: the clinical perspective. Nutrients 13 (2), 2. https://doi.org/10.3390/nu13020351.
Mima, A., 2016. Incretin-Based therapy for prevention of diabetic vascular complications. J. Diabetes Res. 2016, 1379274. https://doi.org/10.1155/2016/1379274.
Mima, A., Gotoda, H., Lee, R., Murakami, A., Akai, R., Lee, S., 2023a. Effects of incretin-based therapeutic agents including tirzepatide on renal outcomes in patients with type 2 diabetes: a systemic review and meta-analysis. Metabolism Open 17, 100236. https://doi.org/10.1016/j.metop.2023.100236.
Mima, A., Hiraoka-Yamomoto, J., Li, Q., Kitada, M., Li, C., Geraldes, P., Matsumoto, M., Mizutani, K., Park, K., Cahill, C., Nishikawa, S.-I., Rask-Madsen, C., King, G.L., 2012. Protective effects of GLP-1 on glomerular endothelium and its inhibition by PKCβ activation in diabetes. Diabetes 61 (11), 2967–2979. https://doi.org/10.2337/db11-1824.
Mima, A., Nomura, A., Fujii, T., 2023b. Current findings on the efficacy of incretin-based drugs for diabetic kidney disease: a narrative review. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie 165, 115032. https://doi.org/10.1016/j.biopha.2023.115032.
Min, S.H., 2024. Mechanisms of Glucagon receptor agonism and GLP-1/Glucagon/GIP receptor triple agonism for treatment of diabetes and obesity. The Journal of Korean Diabetes 25 (2), 82–88. https://doi.org/10.4093/jkd.2024.25.2.82.
Mısırlıoğlu, P.E., 2025. Energy restriction drives adipose tissue remodeling and thermogenic adaptation. Discov. Med. 2 (1), 295. https://doi.org/10.1007/s44337-025-00535-y.
Morin, S., Segafredo, G., Piccolis, M., Das, A., Das, M., Loffredi, N., Larbi, A., Mwamelo, K., Villanueva, E., Nobre, S., Burrone, E., 2023. Expanding access to biotherapeutics in low-income and middle-income countries through public health non-exclusive voluntary intellectual property licensing: considerations, requirements, and opportunities. Lancet Global Health 11 (1), e145–e154. https://doi.org/10.1016/S2214-109X(22)00460-0.
Mu, W., Cheng, X., Liu, Y., Lv, Q., Liu, G., Zhang, J., Li, X., 2019. Potential Nexus of non-alcoholic fatty liver disease and type 2 diabetes mellitus: insulin resistance between hepatic and peripheral tissues. Front. Pharmacol. 9. https://doi.org/10.3389/fphar.2018.01566.
Mukherjee, S., Diéguez, C., Fernø, J., López, M., 2023. Obesity wars: hypothalamic sEVs a new hope. Trends Mol. Med. 29 (8), 622–634. https://doi.org/10.1016/j.molmed.2023.04.006.
Muzurović, E.M., Volčanšek, Š., Tomšić, K.Z., Janež, A., Mikhailidis, D.P., Rizzo, M., Mantzoros, C.S., 2022. Glucagon-Like Peptide-1 receptor agonists and dual glucose-dependent insulinotropic Polypeptide/Glucagon-Like Peptide-1 receptor agonists in the treatment of Obesity/Metabolic syndrome, Prediabetes/Diabetes and non-alcoholic fatty liver Disease—Current evidence. J. Cardiovasc. Pharmacol. Therapeut. 27, 10742484221146371. https://doi.org/10.1177/10742484221146371.
Nauck, M.A., Müller, T.D., 2023. Incretin hormones and type 2 diabetes. Diabetologia 66 (10), 1780–1795. https://doi.org/10.1007/s00125-023-05956-x.
Ndara, F.N., Nuuyoma, V., 2023. Patients' lived experiences of self-injectable diabetes treatment: a phenomenological study. Health SA Gesondheid 28, 2359. https://doi.org/10.4102/hsag.v28i0.2359.
Negash, Z., Tadiwos, A., Urgessa, E.M., Gebretekle, G.B., Abebe, E., Fentie, A.M., 2023. Insulin injection practice and health related quality of life among individuals with diabetes at Tikur Anbessa Specialized Hospital, Ethiopia: a cross-sectional study. Health Qual. Life Outcome 21 (1), 38. https://doi.org/10.1186/s12955-023-02123-z.
Negroiu, C.E., Tudoraşcu, I., Bezna, C.M., Godeanu, S., Diaconu, M., Danoiu, R., Danoiu, S., 2024. Beyond the cold: activating brown adipose tissue as an approach to combat obesity. J. Clin. Med. 13 (7), 7. https://doi.org/10.3390/jcm13071973.
Neto, A., Fernandes, A., Barateiro, A., 2023. The complex relationship between obesity and neurodegenerative diseases: an updated review. Front. Cell. Neurosci. 17. https://doi.org/10.3389/fncel.2023.1294420.
Newsome, P.N., Ambery, P., 2023. Incretins (GLP-1 receptor agonists and dual/triple agonists) and the liver. J. Hepatol. 79 (6), 1557–1565. https://doi.org/10.1016/j.jhep.2023.07.033.
Nicze, M., Borówka, M., Dec, A., Niemiec, A., Bułdak, Ł., Okopień, B., 2024. The Current and promising oral delivery methods for Protein- and peptide-based drugs. Int. J. Mol. Sci. 25 (2), 815. https://doi.org/10.3390/ijms25020815.
Nogueiras, R., 2021. Mechanisms IN ENDOCRINOLOGY: the gut–brain axis: regulating energy balance independent of food intake. Eur. J. Endocrinol. 185 (3), R75–R91. https://doi.org/10.1530/EJE-21-0277.
Novikoff, A., Müller, T.D., 2023. The molecular pharmacology of glucagon agonists in diabetes and obesity. Peptides 165, 171003. https://doi.org/10.1016/j.peptides.2023.171003.
Oteng, A.-B., Liu, L., Cui, Y., Gavrilova, O., Lu, H., Chen, M., Weinstein, L.S., Campbell, J.E., Lewis, J.E., Gribble, F.M., Reimann, F., Wess, J., 2024. Activation of G_s signaling in mouse enteroendocrine K cells greatly improves obesity- and diabetes-related metabolic deficits. J. Clin. Investig. 134 (24). https://doi.org/10.1172/JCI182325.
Padín-González, E., Lancaster, P., Bottini, M., Gasco, P., Tran, L., Fadeel, B., Wilkins, T., Monopoli, M.P., 2022. Understanding the role and impact of Poly (Ethylene Glycol) (PEG) on nanoparticle formulation: implications for COVID-19 vaccines. Front. Bioeng. Biotechnol. 10, 882363. https://doi.org/10.3389/fbioe.2022.882363.
Palani, A., Nawrocki, A.R., Orvieto, F., Bianchi, E., Mandić, E., Pessi, A., Huang, C., Deng, Q., Toussaint, N., Walsh, E., Reddy, V., Ashley, E., He, H., Mumick, S., Hawes, B., Marsh, D., Erion, M., Nargund, R., Carrington, P.E., 2022. Discovery of MK-1462: GLP-1 and glucagon receptor dual agonist for the treatment of obesity and diabetes. ACS Med. Chem. Lett. 13 (8), 1248–1254. https://doi.org/10.1021/acsmedchemlett.2c00217.
Peng, M., Fang, F., Wang, B., 2025. Nanoparticle technologies for liver targeting and their applications in liver diseases. Front. Bioeng. Biotechnol. 13, 1661872. https://doi.org/10.3389/fbioe.2025.1661872.
Peri, R.V., Anchan, H., Jonnalagadda, K., Varghese, R., Gupta, P., 2025. Designing GLP-1 delivery: structural perspectives and formulation approaches for optimized therapy. Nutr. Diabetes 15, 53. https://doi.org/10.1038/s41387-025-00397-4.
Pinto, S.F.T., Santos, H.A., Sarmento, B.F.C.C., 2024. New insights into nanomedicines for oral delivery of glucagon-like peptide-1 analogs. WIREs Nanomed. Nanobiotechnol. 16 (2), e1952. https://doi.org/10.1002/wnan.1952.
Pise, P., 2024. A review on nanoparticle-loaded hydrogels for extended drug release. Asian Journal of Pharmacy and Technology 55–58. https://doi.org/10.52711/2231-5713.2024.00011.
Pixner, T., Stummer, N., Schneider, A.M., Lukas, A., Gramlinger, K., Julian, V., Thivel, D., Mörwald, K., Mangge, H., Dalus, C., Aigner, E., Furthner, D., Weghuber, D., Maruszczak, K., 2023. The relationship between glucose and the liver-alpha cell axis – a systematic review. Front. Endocrinol. 13. https://doi.org/10.3389/fendo.2022.1061682.
Pondman, K., Le Gac, S., Kishore, U., 2023. Nanoparticle-induced immune response: health risk versus treatment opportunity? Immunobiology 228 (2), 152317. https://doi.org/10.1016/j.imbio.2022.152317.
Poudwal, S., Misra, A., Shende, P., 2021. Role of lipid nanocarriers for enhancing oral absorption and bioavailability of insulin and GLP-1 receptor agonists. J. Drug Target. 29 (8), 834–847. https://doi.org/10.1080/1061186X.2021.1894434.
Psaltis, J.P., Marathe, J.A., Nguyen, M.T., Le, R., Bursill, C.A., Marathe, C.S., Nelson, A.J., Psaltis, P.J., 2025. Incretin-based therapies for the management of cardiometabolic disease in the clinic: past, present, and future. Med. Res. Rev. 45 (1), 29–65. https://doi.org/10.1002/med.22070.

Puri, A., Mohite, P., Maitra, S., Subramaniyan, V., Kumarasamy, V., Uti, D.E., Sayed, A.A., El-Demerdash, F.M., Algahtani, M., El-kott, A.F., Shati, A.A., Albaik, M., Abdel-Daim, M.M., Atangwho, I.J., 2024. From nature to nanotechnology: the interplay of traditional medicine, green chemistry, and biogenic metallic phytonanoparticles in modern healthcare innovation and sustainability. Biomed. Pharmacother. 170, 116083. https://doi.org/10.1016/j.biopha.2023.116083.

Quesada-Vázquez, S., Eseberri, I., Les, F., Pérez-Matute, P., Herranz-López, M., Atgié, C., Lopez-Yus, M., Aranaz, P., Oteo, J.A., Escoté, X., Lorente-Cebrian, S., Roche, E., Courtois, A., López, V., Portillo, M.P., Milagro, F.I., Carpéné, C., 2024. Polyphenols and metabolism: from present knowledge to future challenges. J. Physiol. Biochem. 80 (3), 603–625. https://doi.org/10.1007/s13105-024-01046-7.

Razavi, M., Wei, Y.-Y., Rao, X.-Q., Zhong, J.-X., 2022. DPP-4 inhibitors and GLP-1RAs: cardiovascular safety and benefits. Milit. Med. Res. 9 (1), 45. https://doi.org/10.1186/s40779-022-00410-2.

Razavi, S., Janfaza, S., Tasnim, N., Gibson, D. L., & Hoorfar, M. (n.d.). Nanomaterial-based encapsulation for controlled gastrointestinal delivery of viable probiotic bacteria. Nanoscale Adv., 3(10), 2699–2709. https://doi.org/10.1039/d0na00952k.

Razzaq, S., Fatima, I., Moafian, Z., Rahdar, A., Fathi-karkan, S., Kharaba, Z., Shirzad, M., Khan, A., Pandey, S., 2025. Nanomedicine innovations in colon and rectal cancer: advances in targeted drug and gene delivery systems. Med. Oncol. 42 (4), 113. https://doi.org/10.1007/s12032-025-02670-z.

Reddy, T.K., Villavaso, C.D., Pulapaka, A.V., Ferdinand, K.C., 2024. Achieving equitable access to incretin-based therapies in cardiovascular care. Am. Heart J.: Cardiol. Res. Pract. 46, 100455. https://doi.org/10.1016/j.ahjo.2024.100455.

Reed, J., Bain, S.C., Kanamarlapudi, V., 2024. The regulation of metabolic homeostasis by incretins and the metabolic hormones produced by pancreatic islets. Diabetes Metab. Syndr. Obes. 17, 2419–2456. https://doi.org/10.2147/DMSO.S415934.

Ren, X., Chen, D., Wang, Y., Li, H., Zhang, Y., Chen, H., Li, X., Huo, M., 2022. Nanozymes-recent development and biomedical applications. J. Nanobiotechnol. 20 (1), 92. https://doi.org/10.1186/s12951-022-01295-y.

Roh, E., Choi, K.M., 2023. Hormonal gut–brain signaling for the treatment of obesity. Int. J. Mol. Sci. 24 (4), 4. https://doi.org/10.3390/ijms24043384.

Rus, I., Tertis, M., Cristea, C., Sandulescu, R., 2021. Modern analytical techniques for drug delivery systems characterization. Curr. Anal. Chem. 17 (8), 1064–1073. https://doi.org/10.2174/1573411016999200612100927.

Ruud, J., Steculorum, S.M., Brüning, J.C., 2017. Neuronal control of peripheral insulin sensitivity and glucose metabolism. Nat. Commun. 8 (1), 15259. https://doi.org/10.1038/ncomms15259.

Saini, K., Sharma, S., Khan, Y., 2023. DPP-4 inhibitors for treating T2DM - hype or hope? An analysis based on the current literature. Front. Mol. Biosci. 10, 1130625. https://doi.org/10.3389/fmolb.2023.1130625.

Sakers, A., De Siqueira, M.K., Seale, P., Villanueva, C.J., 2022. Adipose-tissue plasticity in health and disease. Cell 185 (3), 419–446. https://doi.org/10.1016/j.cell.2021.12.016.

Santhanakrishnan, K. R., Koilpillai, J., & Narayanasamy, D. (n.d.). PEGylation in pharmaceutical development: current status and emerging trends in macromolecular and immunotherapeutic drugs. Cureus, 16(8), e66669. https://doi.org/10.7759/cureus.66669.

Sargazi, S., Barani, M., Zargari, F., Arshad, R., Sharma, R.K., 2024. Preparation of pH-Responsive vesicular doxorubicin: evidence from In-Vitro and In-Silico evaluations. Current Applied Sciences 2 (1), 31–48. https://doi.org/10.22034/cas.2022.346726.1024.

Scheel, A.K., Espelage, L., Chadt, A., 2022. Many ways to Rome: exercise, cold exposure and Diet—Do they all affect BAT activation and WAT browning in the same manner? Int. J. Mol. Sci. 23 (9), 4759. https://doi.org/10.3390/ijms23094759.

Semwal, P., Painuli, S., Abu-Izneid, T., Rauf, A., Sharma, A., Daştan, S.D., Kumar, M., Alshehri, M.M., Taheri, Y., Das, R., Mitra, S., Emran, T.B., Sharifi-Rad, J., Calina, D., Cho, W.C., 2022. Diosgenin: an updated pharmacological review and therapeutic perspectives. Oxid. Med. Cell. Longev. 2022, 1035441. https://doi.org/10.1155/2022/1035441.

Sharmah, B., Borthakur, A., Manna, P., 2024. PLGA-Based drug delivery systems: a promising carrier for antidiabetic drug delivery. Adv. Therapeut. 7 (6), 2300424. https://doi.org/10.1002/adtp.202300424.

Shepard, B.D., Ecelbarger, C.M., 2021. Sodium glucose transporter, type 2 (SGLT2) inhibitors (SGLT2i) and glucagon-like peptide 1-Receptor agonists: newer therapies in whole-body glucose stabilization. Seminars in Nephrology, Obesity and the Kidney 41 (4), 331–348. https://doi.org/10.1016/j.semnephrol.2021.06.005.

Shrestha, B., Tang, L., Romero, G., 2019. Nanoparticles-Mediated combination therapies for cancer treatment. Adv. Therapeut. 2 (11), 1900076. https://doi.org/10.1002/adtp.201900076.

Siddeeque, N., Hussein, M.H., Abdelmaksoud, A., Bishop, J., Attia, A.S., Elshazli, R.M., Fawzy, M.S., Toraih, E.A., 2024. Neuroprotective effects of GLP-1 receptor agonists in neurodegenerative disorders: a large-scale Propensity-Matched cohort study. Int. Immunopharmacol. 143, 113537. https://doi.org/10.1016/j.intimp.2024.113537.

Simberg, D., Barenholz, Y., Roffler, S. R., Landfester, K., Kabanov, A. V., & Moghimi, S. M. (n.d.). PEGylation technology: addressing concerns, moving forward. Drug Deliv., 32(1), 2494775. https://doi.org/10.1080/10717544.2025.2494775.

Solis-Herrera, C., Kane, M.P., Triplitt, C., 2024. Current understanding of Sodium N-(8-[2-Hydroxylbenzoyl] Amino) Caprylate (SNAC) as an absorption enhancer: the oral semaglutide experience. Clin. Diabetes : A Publication of the American Diabetes Association 42 (1), 74–86. https://doi.org/10.2337/cd22-0118.

Spezani, R., Mandarim-de-Lacerda, C.A., 2022. The current significance and prospects for the use of dual receptor agonism GLP-1/Glucagon. Life Sci. 288, 120188. https://doi.org/10.1016/j.lfs.2021.120188.

Stefanakis, K., Upadhyay, J., Ramirez-Cisneros, A., Patel, N., Sahai, A., Mantzoros, C.S., 2024. Leptin physiology and pathophysiology in energy homeostasis, immune function, neuroendocrine regulation and bone health. Metabolism 161, 156056. https://doi.org/10.1016/j.metabol.2024.156056.

Sun, R., Chen, Y., Pei, Y., Wang, W., Zhu, Z., Zheng, Z., Yang, L., Sun, L., 2024. The drug release of PLGA-based nanoparticles and their application in treatment of gastrointestinal cancers. Heliyon 10 (18), e38165. https://doi.org/10.1016/j.heliyon.2024.e38165.

Sun, X., Sui, W., Mu, Z., Xie, S., Deng, J., Li, S., Seki, T., Wu, J., Jing, X., He, X., Wang, Y., Li, X., Yang, Y., Huang, P., Ge, M., Cao, Y., 2023. Mirabegron displays anticancer effects by globally browning adipose tissues. Nat. Commun. 14, 7610. https://doi.org/10.1038/s41467-023-43350-8.

Tamayo-Trujillo, R., Ruiz-Pozo, V.A., Cadena-Ullauri, S., Guevara-Ramírez, P., Paz-Cruz, E., Zambrano-Villacres, R., Simancas-Racines, D., Zambrano, A.K., 2024. Molecular mechanisms of semaglutide and liraglutide as a therapeutic option for obesity. Front. Nutr. 11. https://doi.org/10.3389/fnut.2024.1398059.

Tasdemiroglu, Y., Gourdie, R.G., He, J.-Q., 2022. In vivo degradation forms, anti-degradation strategies, and clinical applications of therapeutic peptides in non-infectious chronic diseases. Eur. J. Pharmacol. 932, 175192. https://doi.org/10.1016/j.ejphar.2022.175192.

Tasyurek, M.H., Altunbas, H.A., Canatan, H., Griffith, T.S., Sanlioglu, S., 2014. GLP-1-mediated gene therapy approaches for diabetes treatment. Expert Rev. Mol. Med. 16, e7. https://doi.org/10.1017/erm.2014.7.

Tattoli, I., Mathew, A.R., Verrienti, A., Pallotta, L., Severi, C., Andreola, F., Cavallucci, V., Giorgi, M., Massimi, M., Bencini, L., Fidaleo, M., 2024. The interplay between liver and adipose tissue in the onset of liver diseases: exploring the role of vitamin deficiency. Cells 13 (19), 1631. https://doi.org/10.3390/cells13191631.

Thomas, M.K., Nikooienejad, A., Bray, R., Cui, X., Wilson, J., Duffin, K., Milicevic, Z., Haupt, A., Robins, D.A., 2021. Dual GIP and GLP-1 receptor agonist tirzepatide improves beta-cell function and insulin sensitivity in type 2 diabetes. J. Clin. Endocrinol. Metab. 106 (2), 388–396. https://doi.org/10.1210/clinem/dgaa863.

Thursby, E., Juge, N., 2017. Introduction to the human gut microbiota. Biochem. J. 474 (11), 1823–1836. https://doi.org/10.1042/BCJ20160510.

Trucillo, P., 2024. Biomaterials for drug delivery and human applications. Materials 17 (2), 456. https://doi.org/10.3390/ma17020456.

Truong, X.T., Lee, D.H., 2025. Hepatic insulin resistance and steatosis in Metabolic dysfunction-associated steatotic liver disease: new insights into mechanisms and clinical implications. Diabetes & Metabolism Journal 49 (5), 964–986. https://doi.org/10.4093/dmj.2025.0644.

Türeli, N.G., Türeli, A.E., 2020. Upscaling and GMP Production of Pharmaceutical Drug Delivery Systems, pp. 215–229. https://doi.org/10.1016/B978-0-12-817870-6.00011-0.

Uti, D.E., Alum, E.U., Atangwho, I.J., Ugwu, O.P.-C., Egbung, G.E., Aja, P.M., 2025a. Lipid-based nano-carriers for the delivery of anti-obesity natural compounds: advances in targeted delivery and precision therapeutics. J. Nanobiotechnol. 23, 336. https://doi.org/10.1186/s12951-025-03412-z.

Uti, D.E., Atangwho, I.J., Omang, W.A., Alum, E.U., Obeten, U.N., Udeozor, P.A., Agada, S.A., Bawa, I., Ogbu, C.O., 2025b. Cytokines as key players in obesity low grade inflammation and related complications. Obesity Medicine 54, 100585. https://doi.org/10.1016/j.obmed.2025.100585.

Varney, M.J., Benovic, J.L., 2024. The role of G protein–coupled receptors and receptor kinases in pancreatic β-Cell function and diabetes. Pharmacol. Rev. 76 (2), 267–299. https://doi.org/10.1124/pharmrev.123.001015.
Vignesh, A., Menaka, C., Amal, T.C., Selvakumar, S., Vasanth, K., 2025. Exploring the dual impact of nanoparticles on human well-being: a comprehensive review of risks and benefits. Nanotechnology 8, 100223. https://doi.org/10.1016/j.nxnano.2025.100223.
Wang, B., Hu, S., Teng, Y., Chen, J., Wang, H., Xu, Y., Wang, K., Xu, J., Cheng, Y., Gao, X., 2024. Current advance of nanotechnology in diagnosis and treatment for malignant tumors. Signal Transduct. Targeted Ther. 9 (1), 1–65. https://doi.org/10.1038/s41392-024-01889-y.
Wang, J., Yao, M., Zou, J., Ding, W., Sun, M., Zhuge, Y., Gao, F., 2023. pH-Sensitive nanoparticles for colonic delivery Anti-miR-301a in mouse models of inflammatory bowel diseases. Nanomaterials 13 (20), 20. https://doi.org/10.3390/nano13202797.
Wang, L., Wang, N., Zhang, W., Cheng, X., Yan, Z., Shao, G., Wang, X., Wang, R., Fu, C., 2022. Therapeutic peptides: current applications and future directions. Signal Transduct. Targeted Ther. 7 (1), 1–27. https://doi.org/10.1038/s41392-022-00904-4.
Wang, S., Liu, R., Fu, Y., Kao, W.J., 2020. Release mechanisms and applications of drug delivery systems for extended-release. Expert Opin. Drug Deliv. 17 (9), 1289–1304. https://doi.org/10.1080/17425247.2020.1788541.
Wang, X.-Q., Zhang, Q., 2012. pH-sensitive polymeric nanoparticles to improve oral bioavailability of peptide/protein drugs and poorly water-soluble drugs. Eur. J. Pharm. Biopharm. 82 (2), 219–229. https://doi.org/10.1016/j.ejpb.2012.07.014.
Wang, Y., Mo, Y., Sun, Y., Li, J., An, Y., Feng, N., Liu, Y., 2024. Intestinal nanoparticle delivery and cellular response: a review of the bidirectional nanoparticle-cell interplay in mucosa based on physiochemical properties. J. Nanobiotechnol. 22 (1), 669. https://doi.org/10.1186/s12951-024-02930-6.
Wen, X., Zhang, B., Wu, B., Xiao, H., Li, Z., Li, R., Xu, X., Li, T., 2022. Signaling pathways in obesity: mechanisms and therapeutic interventions. Signal Transduct. Targeted Ther. 7 (1), 1–31. https://doi.org/10.1038/s41392-022-01149-x.
Wendt, A., Eliasson, L., 2022. Pancreatic alpha cells and glucagon secretion: novel functions and targets in glucose homeostasis. Curr. Opin. Pharmacol. 63, 102199. https://doi.org/10.1016/j.coph.2022.102199.
Wu, H., Ballantyne, C.M., 2020. Metabolic inflammation and insulin resistance in obesity. Circ. Res. 126 (11), 1549–1564. https://doi.org/10.1161/CIRCRESAHA.119.315896.
Wu, L.-P., Wang, D., Li, Z., 2020. Grand challenges in nanomedicine. Mater. Sci. Eng. C 106, 110302. https://doi.org/10.1016/j.msec.2019.110302.
Xie, L., Wang, H., Hu, J., Liu, Z., Hu, F., 2024. The role of novel adipokines and adipose-derived extracellular vesicles (ADEVs): connections and interactions in liver diseases. Biochem. Pharmacol. 222, 116104. https://doi.org/10.1016/j.bcp.2024.116104.
Xie, Y., Zhou, Q., He, Q., Wang, X., Wang, J., 2023. Opportunities and challenges of incretin-based hypoglycemic agents treating type 2 diabetes mellitus from the perspective of physiological disposition. Acta Pharm. Sin. B 13 (6), 2383–2402. https://doi.org/10.1016/j.apsb.2022.11.008.
Xu, J., Zhao, M., Vrosgou, A., Yu, N.C.W., Liu, C., Zhang, H., Ding, C., Roth, N.W., Pan, Y., Liu, L., Wang, Y., Wang, Y., Bettger, J.P., 2021. Barriers to medication adherence in a rural-urban dual economy: a multi-stakeholder qualitative study. BMC Health Serv. Res. 21 (1), 799. https://doi.org/10.1186/s12913-021-06789-3.
Xu, L., Wang, X., Liu, Y., Yang, G., Falconer, R.J., Zhao, C.-X., 2022. Lipid nanoparticles for drug delivery. Advanced NanoBiomed Research 2 (2), 2100109. https://doi.org/10.1002/anbr.202100109.
Xu, Y., De Keersmaecker, H., Braeckmans, K., De Smedt, S., Cani, P.D., Préat, V., Beloqui, A., 2020. Targeted nanoparticles towards increased L cell stimulation as a strategy to improve oral peptide delivery in incretin-based diabetes treatment. Biomaterials 255, 120209. https://doi.org/10.1016/j.biomaterials.2020.120209.
Yabut, J.M., Drucker, D.J., 2023. Glucagon-like Peptide-1 receptor-based therapeutics for Metabolic Liver disease. Endocr. Rev. 44 (1), 14–32. https://doi.org/10.1210/endrev/bnac018.
Yang, X., Qiu, K., Jiang, Y., Huang, Y., Zhang, Y., Liao, Y., 2024. Metabolic crosstalk between liver and brain: from diseases to mechanisms. Int. J. Mol. Sci. 25 (14), 7621. https://doi.org/10.3390/ijms25147621.
Yao, X., Dani, V., Dani, C., 2020. Human pluripotent stem cells: a relevant model to identify pathways governing thermogenic adipocyte generation. Front. Endocrinol. 10. https://doi.org/10.3389/fendo.2019.00932.
Yao, Y., Zhou, Y., Liu, L., Xu, Y., Chen, Q., Wang, Y., Wu, S., Deng, Y., Zhang, J., Shao, A., 2020. Nanoparticle-Based drug delivery in cancer therapy and its role in overcoming drug resistance. Front. Mol. Biosci. 7, 193. https://doi.org/10.3389/fmolb.2020.00193.
Yu, M., Benjamin, M.M., Srinivasan, S., Morin, E.E., Shishatskaya, E.I., Schwendeman, S.P., Schwendeman, A., 2018. Battle of GLP-1 delivery technologies. Adv. Drug Deliv. Rev. 130, 113–130. https://doi.org/10.1016/j.addr.2018.07.009.
Zeigerer, A., Sekar, R., Kleinert, M., Nason, S., Habegger, K.M., Müller, T.D., 2021. Glucagon's metabolic action in health and disease. Compr. Physiol. 11 (2), 1759–1783. https://doi.org/10.1002/cphy.c200013.
Zhaisanbayeva, B.A., Mun, E.A., Ulmanova, L., Zhunissova, Z., Umbayev, B., Olzhayev, F., Vorobjev, I.A., Hortelano, G., Khutoryanskiy, V.V., 2024. *In vitro* and *in vivo* toxicity of thiolated and PEGylated organosilica nanoparticles. Int. J. Pharm. 652, 123852. https://doi.org/10.1016/j.ijpharm.2024.123852.
Zhang, J., Zheng, Y., Martens, L., Pfeiffer, A.F.H., 2023. The regulation and secretion of glucagon in response to nutrient composition: unraveling their intricate mechanisms. Nutrients 15 (18), 18. https://doi.org/10.3390/nu15183913.
Zhang, Q., Delessa, C.T., Augustin, R., Bakhti, M., Colldén, G., Drucker, D.J., Feuchtinger, A., Caceres, C.G., Grandl, G., Harger, A., Herzig, S., Hofmann, S., Holleman, C.L., Jastroch, M., Keipert, S., Kleinert, M., Knerr, P.J., Kulaj, K., Legutko, B., et al., 2021. The glucose-dependent insulinotropic polypeptide (GIP) regulates body weight and food intake via CNS-GIPR signaling. Cell Metab. 33 (4), 833–844.e5. https://doi.org/10.1016/j.cmet.2021.01.015.
Zhang, Q., Wang, Z., Shen, S., Wang, J., Cao, J., Deng, Y., Meng, H., Ma, L., 2024. Integrating enzyme-nanoparticles bring new prospects for the diagnosis and treatment of immune dysregulation in periodontitis. Front. Cell. Infect. Microbiol. 14. https://doi.org/10.3389/fcimb.2024.1494651.
Zhang, W., Mehta, A., Tong, Z., Esser, L., Voelcker, N.H., 2021. Development of polymeric nanoparticles for blood–brain barrier Transfer—Strategies and challenges. Adv. Sci. 8 (10), 2003937. https://doi.org/10.1002/advs.202003937.
Zhang, Y., Guo, P., Ma, Z., Lu, P., Kebebe, D., Liu, Z., 2021. Combination of cell-penetrating peptides with nanomaterials for the potential therapeutics of central nervous system disorders: a review. J. Nanobiotechnol. 19 (1), 255. https://doi.org/10.1186/s12951-021-01002-3.
Zhou, Y., Peng, Z., Seven, E.S., Leblanc, R.M., 2018. Crossing the blood-brain barrier with nanoparticles. J. Contr. Release 270, 290–303. https://doi.org/10.1016/j.jconrel.2017.12.015.
Zhu, T., Chen, X., Jiang, S., 2023. Progress and obstacles in transplantation of brown adipose tissue or engineered cells with thermogenic potential for metabolic benefits. Front. Endocrinol. 14. https://doi.org/10.3389/fendo.2023.1191278.
Zhu, X., Tang, Q., Zhou, X., Momeni, M.R., 2024. Antibiotic resistance and nanotechnology: a narrative review. Microb. Pathog. 193, 106741. https://doi.org/10.1016/j.micpath.2024.106741.
Ziebarth, J., da Silva, L.M., Lorenzett, A.K.P., Figueiredo, I.D., Carlstrom, P.F., Cardoso, F.N., de Freitas, A.L.F., Baviera, A.M., Mainardes, R.M., 2024. Oral delivery of liraglutide-loaded Zein/Eudragit-Chitosan nanoparticles provides pharmacokinetic and glycemic outcomes comparable to its subcutaneous injection in rats. Pharmaceutics 16 (5), 634. https://doi.org/10.3390/pharmaceutics16050634.