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Encapsulation of bioactive compounds in foods for diabetics - sources, encapsulation technologies, market trends and future perspectives – A systematic review

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ABSTRACT

Diabetes is a metabolic disorder characterized by hyperglycemia and is a disease with an increasing prevalence. Hyperglycemia triggers abnormalities in the metabolism of carbohydrates, proteins, fats, and can cause complications. This disease is caused by poor lifestyles, such as food consumption patterns and lack of physical activity, and what is more potential is genetics. In this regard, efforts are being made to increase self-awareness on food intake and developing functional food which can be done by the food industry. Many studies have been conducted to find bioactive compounds from natural ingredients that can prevent and treat diabetes. The effectiveness of bioactive compounds in preventing and treating diabetes is influenced by how these compounds reach their target. Nanotechnology can be a solution in the process of encapsulating anti-diabetic bioactive compounds into processed foods with the aim of stabilizing the function of these compounds in the processed food matrix, up to their absorption in the body. In this context, innovations are needed to develop a commercially viable and efficient delivery system, while industrial applications also need to be scaled up following scientific validation at the laboratory level. In addition, ethical, safety, and regulatory aspects should also be considered during the development of a delivery system for bioactive compounds. In these perspectives, this review highlights nanoencapsulation of anti-diabetic compounds in food, nanodelivery systems, market trends in bioactive-based anti-diabetic food products, and future perspectives.

1. Introduction

Diabetes mellitus (DM) perceived as a prevalent non-communicable disease (NCD), with cases expected to rise to 700 million by 2045 (Saeedi et al., 2019; Yanai, 2020). Identified by symptoms including excessive urination, increased appetite, constant thirst, and high blood glucose level, DM is often linked to obesity, a condition categorized by fat accumulation that affects health (Asgharnezhad et al., 2019; Glovaci et al., 2019; Kuwelker et al., 2021; World Health Organization, 2021; Xin et al., 2022). The global prevalence of obesity has significantly risen with about 1.9 billion adults over the age of 18 being overweight in 2016; of which more than 650 millions of them were obese. The surge in

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obesity, in which a primary contributor to DM, along with dietary consumption factors, highlights the growing concern about DM (World Health Organization, 2021). Therefore, the development of food with natural anti-diabetic effects has gained significant interest from researchers, industry players and food manufacturers.

The impact of food particularly on public health is apparent, not only fulfilling nutritional needs but also playing a crucial role in disease prevention and improving overall well-being. Functional foods, which offer health benefits beyond essential nutrition, are growing at an average annual rate of 8.5 % globally (Bogue et al., 2017). This is owing to its ability to influence bodily functions beyond basic nutrition, such as improving health, and mitigate NCD including DM and cardiovascular disease (Domínguez Díaz et al., 2020; Granato et al., 2020). As the consumer awareness grows, functional foods are becoming more widely available across multiple food categories, driven by their potential to prevent chronic diseases and boost the immune system (Baker et al., 2022).

Recent studies have highlighted the efficacy of various bioactive compounds in diabetes management, particularly focusing on compounds such as peptides, protein hydrolysates, phenolic acids, and polysaccharides. Yakubu (2023) conducted *in vivo* studies on bitter gourd seed protein hydrolysate, demonstrating its anti-diabetic properties. Similarly, Zhou et al. (2023) discovered an α-amylase inhibitory peptide originated from quinoa protein hydrolysate, indicating its potential for diabetes remedy. Gao et al. (2023) investigated the role of glucuronic acid metabolites of phenolic acids on glucose metabolism, providing insights into new therapeutic targets. Meanwhile, Tang et al. (2023) highlighted the application of marine fucosyl-polysaccharides in controlling blood glucose levels and mitigating hyperglycemic complications. These studies illustrate the promising potential of natural bioactive compounds in managing diabetes, which can be effectively incorporated into various food products.

Today, functional foods have emerged as a major focus in novel food product development as they are playing a significant role in the global health industry. The development of functional food products requires complex methodologies, distinct from those used for regular food products. This is to ensure the stability of functional ingredients within the food matrix and preserve the bioactive components through processing, storage, digestion, and absorption (Villaño et al., 2016).

Several methods and formulations have been explored to encapsulate anti-diabetic bioactive compounds into food matrices, improving the stability and gastrointestinal bioavailability. Due to the significant variability, identifying the most efficient approach to maintain stability and enhance the bioavailability of anti-diabetic compound in food systems is challenging. In theory, nanoencapsulation allows for the production of bioactive compounds in both powder and liquid forms through the utilization of various technologies including high-pressure homogenization, ultrasonication, thin layer hydration, spray drying, electrospinning, electrospraying and nanoprecipitation to encapsulated anti-diabetic compounds (de Melo et al., 2021; de Souza Simões et al., 2017; Dundar et al., 2023; Gonçalves et al., 2023; Hadidi et al., 2021; Mahalakshmi et al., 2020; Mousavi et al., 2021). Additionally, the use of nanocarriers can improve the thermal stability of these drugs with nano droplet size and large surface nanoemulsions providing resistance to droplet aggregation and creaming resulting in efficient digestion and high in bioavailability (Liu et al., 2021; Liu et al., 2019). Within this framework, this review focuses on recent developments in the nanoencapsulation of anti-diabetic compounds in different food products. It discusses nanodelivery systems, current market trends in bioactive-based anti-diabetic food products, and future directions. The objective is to provide researchers and the food industry with insights that could enhance the development of anti-diabetic food products through nanoencapsulation technology.

2. Bioactive compounds with anti-diabetic effects

Over the years, numerous types of anti-diabetic compounds, both synthetic and naturally derived have been discovered through research. In Type 2 diabetes (T2D), the failure of pancreatic beta cells, which primarily produce insulin, is crucial in the disease progression (Tsalamandris et al., 2019). These cells are stressed by genetic predisposition, obesity and insulin resistance and prolonged high glucose and fatty acid exposure leads to their dysfunction, and eventual failure. As beta cells become less efficient, blood sugar will increase, exacerbating T2D symptoms such as hyperglycemia (Tsalamandris et al., 2019). Understanding this complex mechanism is crucial to develop treatment protocol, that preserve beta cell function and improve patient outcomes (Fig. 1).

According to Donath & Shoelson (2011), high levels of glucose and fatty acids stress pancreatic islets and adipose tissue, triggering the release of cytokines like interleukin-1β (IL-1β) and tumor necrosis factor (TNF), while reducing IL-1 receptor antagonist production by β-cells. This leads to immune cell recruitment and inflammation in these tissues, further exacerbating systemic inflammation in Type 2 diabetes, as depicted in Fig. 2 and Fig. 3.

A key method to prevent hyperglycemia is by inhibiting enzymes like α-amylase and α-glucosidase that manage blood sugar levels. Drugs such as acarbose, saxagliptin, and vildagliptin have been effective in inhibiting these enzymes (Wang et al., 2021). However, due to concerns over side effects from synthetic anti-diabetic drugs, there is increasing interest in using natural inhibitors from sources like animals, plants, fungi, algae, plants, as safer alternatives (Yuesheng Dong et al., 2022). Natural α-glucosidase inhibitors are generally preferred for their safety. Fig. 4 illustrates the function of the nanoencapsulated and encapsulated anti-diabetic compounds.

Naturally derived anti-diabetic compounds are categorized according to their chemical structure including protein hydrolysates and peptides, polysaccharides and phenolic acids. Thus, understanding the biological and physiological pathways involved in hyperglycemia is crucial, as these compounds able to target specific metabolic pathway to exert the anti-diabetic effect (Fig. 5). Table 1 lists various bioactive compounds with anti-diabetic properties from previous research, and the next section discusses the primary compounds with anti-diabetic effects.

2.1. Protein hydrolysates and peptides

Protein hydrolysates and peptides, extracted through enzymatic treatment or fermentation (Fig. 6), have been shown to effectively manage hyperglycemia in both *in vitro* and *in vivo* mode (Table 2). These compounds also offer additional health benefits, such as antihypertensive, antimicrobial, antioxidant, and hypoglycemic effects, primarily by inhibiting enzymes like α-glucosidase and α-amylase to lower blood glucose levels (Table 3) (Kehinde & Sharma, 2020; Peighambardoust et al., 2021). Typically, enzymatic hydrolysis is commonly used to activate these peptides, while subcritical water hydrolysis is promoted as an eco-friendly alternative for producing these anti-diabetic agents (Toldrá et al., 2018; Ulug et al., 2021).

Protein hydrolysates and bioactive peptides can be derived from diverse natural protein-rich entities such as microbes (fungi and algae), plants, animals, and even insects (Kehinde & Sharma, 2020). Research indicates that peptides from both fresh and fermented milk can inhibit α-glucosidase and α-amylase, which in turn reduces plasma glucose levels in alloxan-induced albino rats (El-Sayed et al., 2016; Shukla et al., 2022). El-Sayed et al. (2016) observed that diabetic rats fed with milk protein hydrolysate experienced significant reductions in plasma glucose, total lipids, triglycerides, cholesterol, LDL-C (low-density lipoprotein cholesterol), and VLDC-C (very low-density cholesterol), highlighting milk protein hydrolysate's potential as a dual-action anti-diabetic and cholesterol-managing compounds.

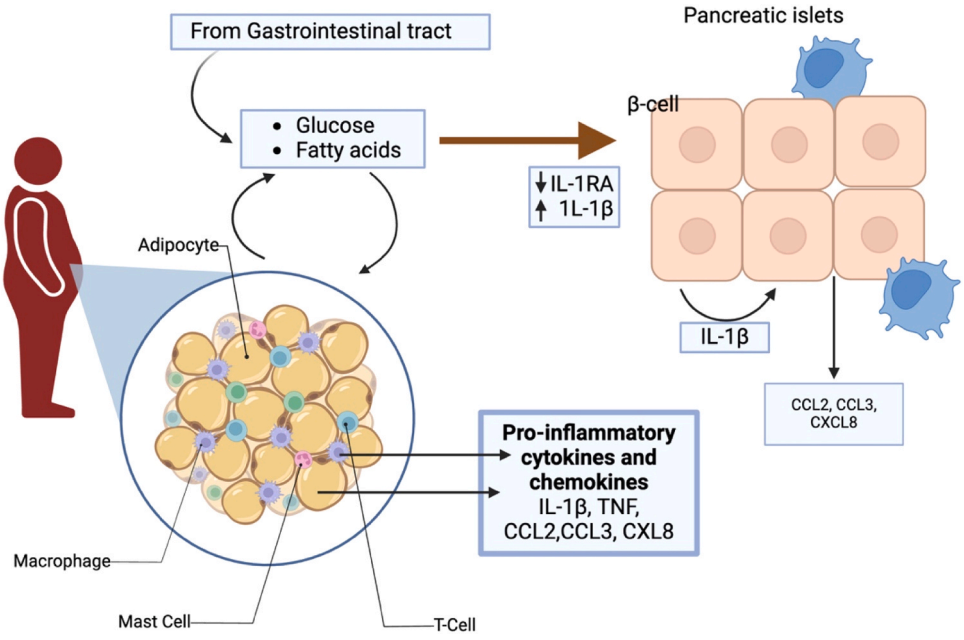

Fig. 1. Type 2 diabetes occurrence. In Type 2 diabetes, inflammation develops due to elevated levels of nutrients like glucose and free fatty acids, causing stress on pancreatic islets and insulin-sensitive tissues such as adipose tissue, liver, and muscle. This stress triggers the local production and release of cytokines and chemokines, such as interleukin-1β (IL-1β), tumor necrosis factor (TNF), CC-chemokine ligand 2 (CCL2), CCL3, and CXC-chemokine ligand 8 (CXCL8). Additionally, there's a reduction in the production of IL-1 receptor antagonist (IL-1RA) by β-cells, leading to recruitment of immune cells and tissue inflammation. The cytokines and chemokines released from adipose tissues also contribute to inflammation in other organs, including the pancreatic islets.

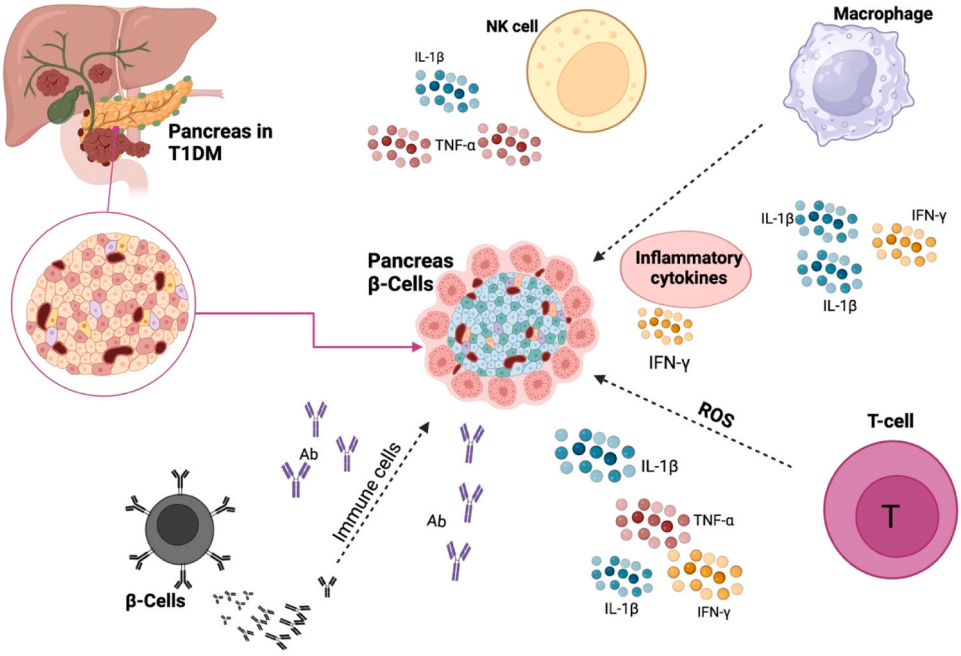

Fig. 2. The continuous loop of inflammation in different affected organs in Type 2 diabetes.

A study found that black cricket protein hydrolysates inhibited primary diabetes-related enzymes α-amylase and α-glucosidase by 55 % and 17 %, respectively (de Matos et al., 2022). Also, dry-cured pork loin hydrolysates yielded peptides with a sequence of APPPPAEV and VATPPPPPPK with strong dipeptidyl peptidase IV inhibitory activity, suggesting their potential in Type 2 diabetes management (Lafarga & Hayes, 2017). Additionally, bovine lung hydrolysates treated with alcalase under high temperature and pressure exerted in a significant inhibition of dipeptidyl peptidase IV and prolyl endopeptidase, demonstrating their efficacy as anti-diabetic agents (IC_{50} values of 1.43 ± 0.06 and 3.62 ± 0.07 mg/mL, respectively) (Lafarga & Hayes, 2017).

Huang et al. (2022) discovered that fermented shrimp shell consumption improves glucose uptake and insulin resistance, particularly in TNF-α-stimulated FL83B hepatocytes, suggesting the presence of hypoglycemic peptides. In diabetic rats, a high dosage of this fermented product reduced glucose-6-phosphatase activity over seven weeks. Meanwhile, plant proteins like lupin bean flavourzyme hydrolysates also exhibit α-glucosidase and α-amylase inhibitory activities, with effects

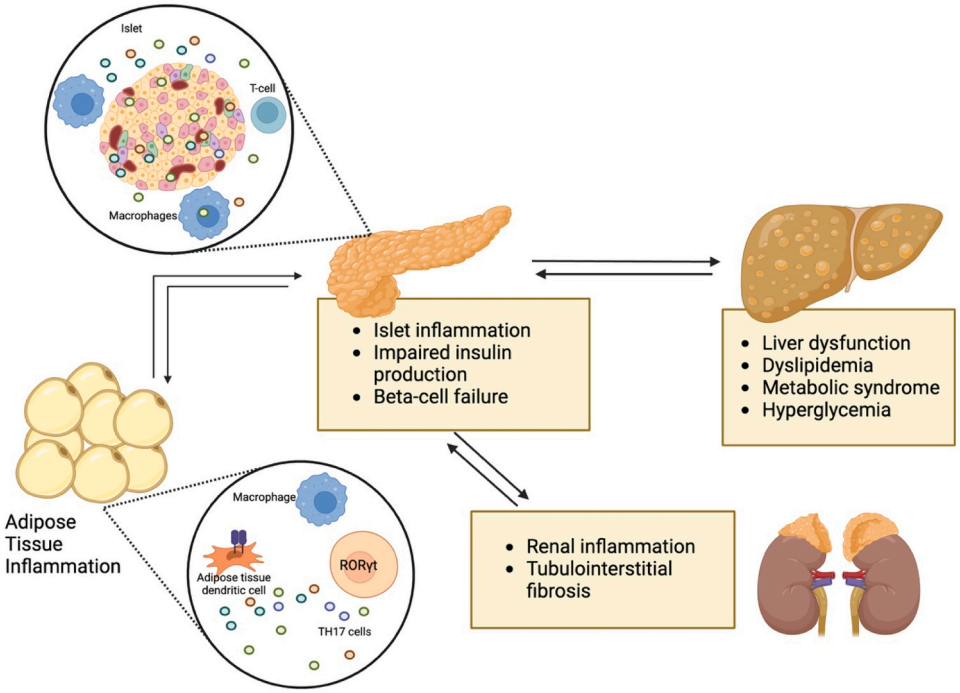

Fig. 3. Type 2 diabetes multiple organ impairment due to inflammation.

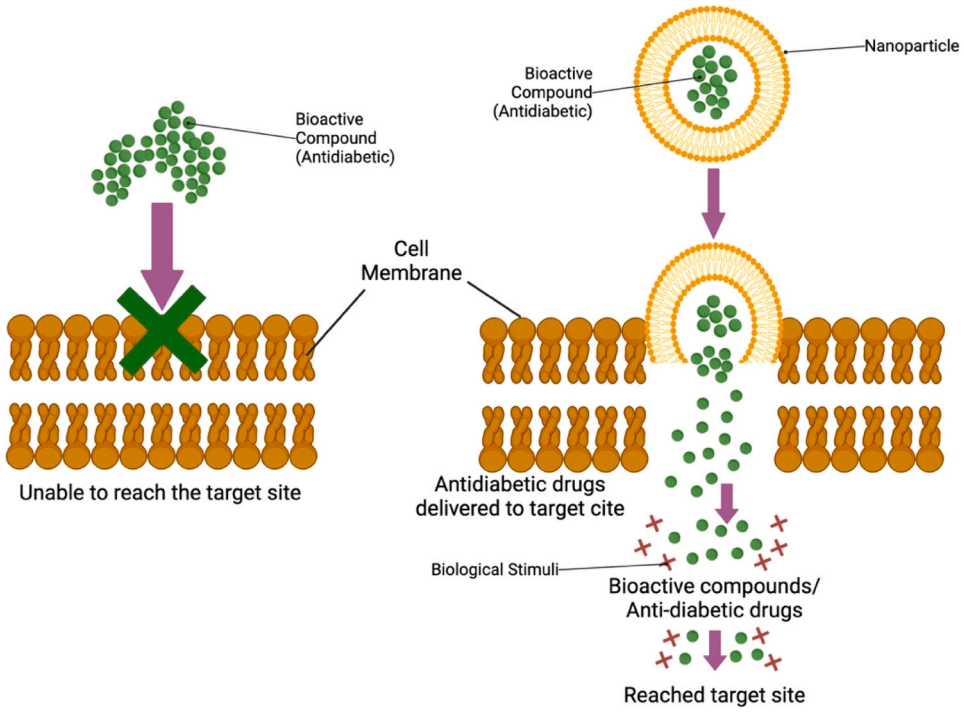

Fig. 4. General mechanism of nanoparticle delivery of bioactive compounds.

enhanced by sonication (Fadimu et al., 2022).

2.2. Polysaccharides

Polysaccharides from sources like fungi and plants have been shown to prevent hyperglycemia. Previously, acidic polysaccharides from mushrooms like *Auricularia judae* and *Tremella fuciformis* can reduce glucose transport in in Caco-2 cells during an *in vitro* digestion model (Orqueda et al., 2022). Also, a study found that polysaccharides from the brown macroalgae *Sargassum fusiforme*, extracted at pH 7 and precipitated with 40 % ethanol, effectively inhibit α-glucosidase with IC50 values of 0.304 mg/mL, suggesting their good potential as α-glucosidase inhibitors (Zheng et al., 2022).

Recently, there was a study that highlights the potential of selenium-polysaccharide blend as a source of organic selenium in food supplements due to their good stability and strong biological activities. They

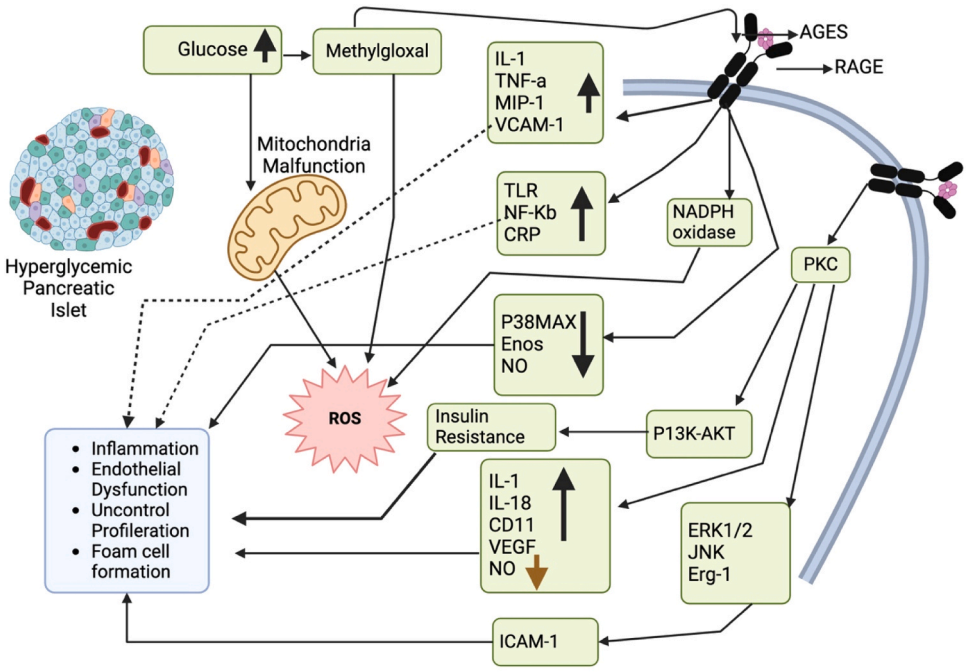

Fig. 5. Pathways illustrating the interplay between diabetes, oxidative stress, inflammation, and advanced glycation end products (AGEs) in metabolic disorders.

have discovered that the selenized polysaccharides from *Ribes nigrum* L. exhibited a significant effect against α-amylase and α-glucosidase activity (Zhao et al., 2021). The results from the conducted *in vivo* studies also revealed that polysaccharides from *Ziziphus mistol* and *Lycium barbarum* showed hypoglycemic activity by improving the transport of glucose through cell membrane (Orqueda et al., 2022; W. Zhou et al., 2022). These polysaccharides exhibit inhibitory properties on α-amylase and α-glucosidase by hydrophobic interactions and hydrogen bonds forming polysaccharide-enzyme complexes. Additionally, when modified using nitric acid-sodium selenite method, they contribute available selenium for the synthesis of antioxidant glutathione peroxidase (Zhao et al., 2021). Therefore, this finding enhances the possibility of using polysaccharides from natural sources as anti-diabetic agents for the prevention or treatment of DM.

2.3. Phenolic acids

Phenolic acids, primarily obtained from plants, have been identified for their ability to manage or treat diabetes by improving insulin sensitivity and reducing the prevalence of Type 2 diabetes (Godos et al., 2021). Research has highlighted that tea polyphenols (TPs), particularly from green, black, and oolong teas, are potent α-glucosidase inhibitors. For instance, green tea showed a significant inhibitory effect with an IC50 value of 2.33 μg/mL, while oolong tea, having the lowest IC50 value, demonstrated the highest inhibitory potential (Yang & Kong, 2016).

Furthermore, polyphenols from unripe apples, such as tannic acid and chlorogenic acid, also capable to exert hypoglycemic activity by inhibiting α-amylase, with tannic acid showing the highest binding constant (Sun et al., 2019). Additionally, sweet potato leaf phenolic acids have shown hypoglycemic activities by inhibiting α-glucosidase and α-amylase, with di-caffeoylquinic acids constituting the major component (60.3 %) of these phenolic acids in sweet potato leaves (Luo et al., 2021). This inhibition mechanism involves phenolic acid compounds binding to surface amino acid residues on the enzymes, changing their conformation, distorting the active site, and reducing enzyme activity. This mechanism of action is well demonstrated in studies observing the capability of epicatechin gallate (ECG) to bind with α-amylase and α-glucosidase, forming an ECG-enzyme complex and effectively demonstrating an anti-diabetic effect (Wu et al., 2019).

3. Methodology

3.1. Eligibility criteria, article search strategy, and dataset development

In this study, we used Population, Intervention, Comparators, Outcomes (PICO) design that following inclusion criteria: (1) emphasis on bioactive compounds with anti-diabetic effect; (2) pertains to studies that utilize encapsulation methodology; (3) focus on hypoglycemic effect of bioactive compounds through encapsulation techniques; (4) articles consistently written in English and published after being peer-reviewed. Accordingly, a raw dataset was constructed and extracted after careful evaluation of articles that reported encapsulated bioactive compounds with anti-diabetic effects. The articles were carefully chosen and selected by following Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines. The published articles were extracted into Mendeley references manager (https://www.mendeley.com/ (31 January 2023)) with criteria as follows: (1) name of author; (2) publication year; (3) type of bioactive compound; (4) type of encapsulation method used; (5) and results. Initially, 556 results were obtained through a search of Science Direct (https://www.sciencedirect.com/ (31 January 2024)). However, 444 studies were excluded because they were not related to the bioactive compounds with anti-diabetic effect. Then, 91 studies were excluded from the remaining 112 studies, because the eligibility criteria were not met. After this process, 21 articles finally remained for systematic review. The algorithm search key for published articles was set for 2015–2022 using the MESH terms (“antidiabetic”) AND (“encapsulation”) AND (“bioactive”) AND (“hypoglycemic”). The articles that met the criteria were selected according to PRISMA method (Page et al., 2021). (Fig. 7; Table 4).

4. Encapsulation technologies for improving efficacy of bioactive compounds

Developing functional foods enriched or fortified with high-purity bioactive compounds presents various challenges, particularly due to the degradation of these compounds during manufacturing, storage, and digestion, which impacts their ability to reach target cells effectively.

Table 1
Various type of bioactive compounds with anti-diabetic property.

Type of bioactive compound	Source	Anti-diabetic effect / mechanism	Main Findings	References
Hydrolysate /peptide	Milk proteins	Inhibiting alpha-glucosidase and dipeptidyl peptidase IV (DPP-IV) enzymes	Improved postprandial glycemia control and insulin secretion in individuals with T2D.	Patil et al. (2015)
	Casein-based protein hydrolysate	Insulinotropic effect -The casein-based protein hydrolysate demonstrated an insulinotropic effect, stimulating postprandial insulin secretion, which improved insulin sensitivity in patients with gestational diabetes mellitus (GDM) and resulted in better glucose control.	• 8.5 g of PH supplement twice daily did not increase plasma insulin or C-peptide levels in GDM patients, but it did lead to a small decrease in average daily glucose levels, suggesting an increase in insulin sensitivity. • The study highlighted the potential of PH as an adjunct therapy for managing GDM.	Saleh et al. (2018)
	Lupinus mutabilis protein hydrolysate	Peptide with the sequence MMPDAQPR, showing dual ACE inhibitor and DPP-IV inhibitor properties.	• Specific peptide fraction (F IV) with lower molecular weight exhibited significant antioxidant activity, ACE inhibition, and DPP-IV inhibition. • The compound responsible for the anti-diabetic activity was identified as a peptide with the sequence MMPDAQPR, showing dual ACE inhibitor and DPP-IV inhibitor properties.	Chirinos et al. (2022)
	Tilapia skin gelatin hydrolysate	The novel bioactive peptide GPXGPPGPGP was screened and found to exhibit DPP-IV inhibitory activity.	The identified peptide GPXGPPGPGP demonstrates significant inhibitory activity against DPP-IV, suggesting its role in diabetes management	Liu et al. (2022)
	Earthworm (*Perionyx excavatus*) protein hydrolysate	α-amylase inhibitory activity (α-AIA) and α-glucosidase inhibitory activity (α-GIA).	A peptide fraction of the hydrolysate exhibited higher α-AIA than Acarbose and similar α-GIA to voglibose, suggesting its potential as an α-amylase and α-glucosidase inhibitor.	Bui et al. (2023)
Polysaccharides	Mycelium polysaccharides from *Coprinus comatus*	• CMP was identified as comatin, which demonstrated a hypoglycemic effect in diabetic rats. • The specific mechanism involved in the anti-diabetic action of CMP included the suppression of reactive oxygen species (ROS) and NLRP3 inflammasome activation.	• The study found that CMP treatment effectively improved insulin resistance, energy metabolism, and kidney function in streptozotocin-induced diabetic nephropathy mice. • Specifically, CMP modulated the PI3K/Akt and Wnt-1/β-catenin signaling pathways, reducing oxidative stress and chronic inflammation in the kidneys.	Gao et al. (2021)
	Pumpkin polysaccharides.	Activating specific signaling pathways such as the PI3K/Akt pathway.	Pumpkin acid hydrolyzed polysaccharide was found to exhibit complex cell signal transduction and related gene and protein interactions, leading to a slow but significant reduction in blood sugar levels.	Wu et al. (2021)
	Dendrobium officinale polysaccharides	Regulation of PI3K/Akt-mediated glycogen synthesis and glucose metabolism	Attenuation of Type 2 diabetes mellitus by Dendrobium officinale polysaccharides through the identified mechanism.	Li et al. (2021)
	Plantago ciliata Desf. leaves and seeds	• Inhibiting myeloperoxidase, NADPH oxidase, α-amylase, and α-glucosidase activities. • The mechanism of action involved delaying the digestion process by preventing the cleavage of carbohydrates into simple sugars, thus prolonging their stay in the jejunum.	The compound responsible for the anti-diabetic activity was identified as S-PSPC, which demonstrated inhibitory effects on α-amylase and α-glucosidase enzymes	Addoun et al. (2021)
	Undaria pinnatifida polysaccharides	Modulation of the IRS/PI3K/AKT signaling pathway, leading to enhanced insulin sensitivity and glucose uptake.	The study found that UPP administration significantly reversed the increase in water intake and decrease in body weight in T2DM rats, improved kidney function, and reduced adipose tissue accumulation.	Li et al. (2021)
	Brasenia schreberi	Polysaccharide BSP-U100 was identified as the compound responsible for the anti-diabetic effects, promoting the PI3K/Akt signaling pathway of insulin and increasing glycogen synthesis in the liver and muscles.	• The results indicated that BSP-U100 had a more positive impact on T2DM mice compared to BSP-1a, potentially due to its polyphenol content. • *Brasenia schreberi,* particularly BSP-U100, show promising anti-diabetic effects through the activation of the PI3K/Akt pathway and improved glycogen synthesis, highlighting their potential as a natural treatment for Type 2 diabetes.	Liu et al. (2022)
	Dendrobium officinale compound (DOCP)	DOCP upregulated the expression of key genes involved in glucose metabolism, such as Glut2, Gck, Pklr, and Insr, in the liver. Moreover, DOCP induced the upregulation of Pdx-1 and Ins1, and the downregulation of Caspase-3 in the pancreas of diabetic mice.	The study concluded that DOCP can alleviate Type 2 diabetes and its complications in mice through multiple mechanisms, including the modulation of gene expression related to glucose metabolism and pancreatic function.	Li et al. (2023)
	Marine Fucosyl-Polysaccharides	Fucoidan protects against high-level glucose-induced oxidative damage through the Ca2+-dependent ERK signaling pathway.	Beneficial effects in ameliorating diabetic nephropathy and retinopathy, reducing	Tang et al. (2023)

(*continued on next page*)

Table 1 (*continued*)

Type of bioactive compound	Source	Anti-diabetic effect / mechanism	Main Findings	References
			inflammation, and improving endothelial barrier function.	
Phenolic acid	Glucuronic acid metabolites	• Glucuronic acid structure in CA4G and FA4G binds to the PH domain of AKT, activating AKT and downstream signaling pathways involved in glucose metabolism. • The carbonyl group in the glucuronic acid structure interacts with the key Arg-25 site in the AKT PH domain.	Activation of AKT by targeting the PH domain improves glucose metabolism, suggesting that glucuronic acid metabolites are key active substances in enhancing glucose metabolism.	Gao et al. (2023)
	Mongolian oak cups enriched in ellagic acid, kaempferol, and their derivatives	• Compound Responsible: Ellagic acid, kaempferol, and their derivatives. • Specific Mechanism: – Antioxidant activity of the extract may enhance pancreatic β-cells viability. – Inhibition of α-glucosidase and α-amylase enzymes.	• Significant hypoglycemic effects observed in alloxan-induced diabetic rats. • Improved pancreatic β-cells viability and potential management of Type 2 diabetes through enzyme inhibition.	Yin et al. (2018)

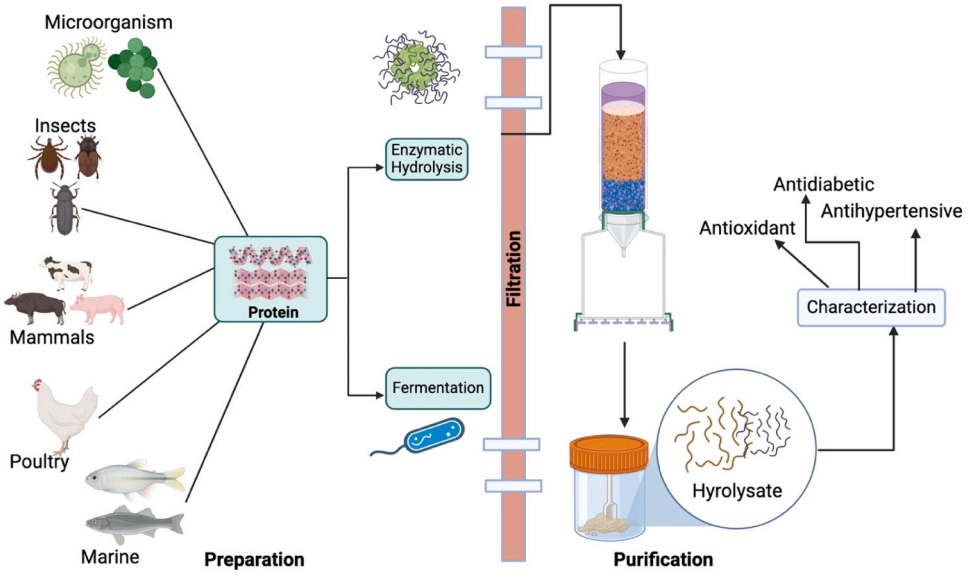

Fig. 6. The production of protein hydrolysate as bioactive compound.

Table 2
An overview of the effect of various protein hydrolysates and peptides on insulin resistance and/or Type-2 diabetes mellitus.

Source	Experimental Model/ Condition	Experimental trial	Main outcomes	References
Milk protein hydrolysate	*in vivo* alloxan-induced albino rats	Oral administration of milk protein hydrolysate (800 mg/kg BW/day) for 6 weeks	Reduction in plasma glucose level	El-Sayed et al. (2016)
Fermented camel milk peptides	*in vitro*	α-glucosidase and α-amylase inhibition assay	Inhibition of α-glucosidase and α-amylase were 59.62 % and 80.75 %, respectively	Shukla et al. (2022)
Black cricket protein hydrolysates	*in vitro*	α-glucosidase and α-amylase inhibition assay	Protein hydrolysates were able to inhibit up to 55 % and 17 % of the α-amylase and α-glucosidase activities, respectively	de Matos et al. (2022)
Peptides from dry-cured pork loin	*in vitro*	Dipeptyl peptidase IV inhibition assay	Peptides inhibited the activity of dipeptyl peptidase IV	Keska et al. (2022)
Protein hydrolysates from bovine lung	*in vitro*	Dipeptyl peptidase IV and prolyl endopeptidase inhibition assay	Protein hydrolysates inhibited the activity of dipeptyl peptidase IV and prolyl endopeptidase	Lafarga & Hayes (2017)
Peptides from fermented shrimp shell	*in vitro* and *in vivo* using TNF-α-stimulated FL83B hepatocytes and diabetic rats	Glucose uptake, insulin resistant, and glucose-6-phosphatase inhibition assay	Peptides improved glucose uptake and insulin resistance of TNF-α-stimulated FL83B hepatocytes and downregulated the activity of glucose-6-phosphatase	Huang et al. (2022)
Sonicated lupin beans protein hydrolysate	*in vitro*	α-glucosidase and α-amylase inhibition assay	Sonicated protein hydrolysate exhibited α-glucosidase and α-amylase inhibition	Fadimu et al. (2022)
Acidic mushroom polysaccharides	*in vitro* digestion/Caco-2 cells model	Glucose transport study	Acidic polysaccharides reduced the amount of transported glucose by 34.2 % and 38.7 %, respectively.	Tu et al. (2023)

Table 3
Previous studies on different protein hydrolysate compounds with anti-diabetic effects.

Source	Anti-diabetic effect / mechanism	Main Findings	References
Gluten hydrolysate	Formation of thiol peroxyl radicals that deoxygenated thiol groups in the gluten peptides to form SS bonds.	• The study found that the post-treatments influenced the molecular weight distribution, surface hydrophobicity, and free sulfhydryl group content of the peptides. • Specifically, the medium molecular weight fraction (10–100 kDa) exhibited the highest inhibitory activity towards α-glucosidase and α-amylase enzymes, with inhibitory percentages of 31.44 % and 13.85 %, respectively.	Mousavi et al. (2023)
Telfairia occidentalis Hook f. seed protein hydrolysate	Improving β-cell function, enhancing insulin sensitivity, and regulating glucose metabolism.	Treatment with peptide hydrolysate significantly decreased fasting serum glucose levels in diabetic rats compared to untreated controls, with comparable efficacy to glibenclamide.	Olasehinde et al. (2023)
Sacha inci meal protein hydrolysate	Inhibition of DPP-IV and α-amylase enzymes,	• The main findings revealed that the hydrolysates exhibited significant inhibitory effects on DPP-IV and α-amylase enzymes, with the highest inhibition rates observed for SPr and Sal hydrolysates. • Specifically, SPr and Sal showed concentration-dependent inhibition of DPP-IV, with IC50 values of 1.007 mg/mL and 2.130 mg/mL, respectively.	Shu et al. (2023)
Bromelain bitter gourd seed protein hydrolysate	Enhancing insulin sensitivity, promoting glucose uptake, and regulating glycogen synthesis.	The compound responsible for the anti-diabetic activity was identified as a peptide with a molecular weight $\leq$ 25 kDa.	Yakubu et al. (2033)
Quinoa protein hydrolysate	Amino acids associated with α-amylase inhibition were determined, including LGGGN, KLPGF, MMFPH and ELS.	The peptide MMFPH was identified as a potent α-amylase inhibitor, highlighting its potential as a natural anti-diabetic agent.	Zhou et al. (2023)

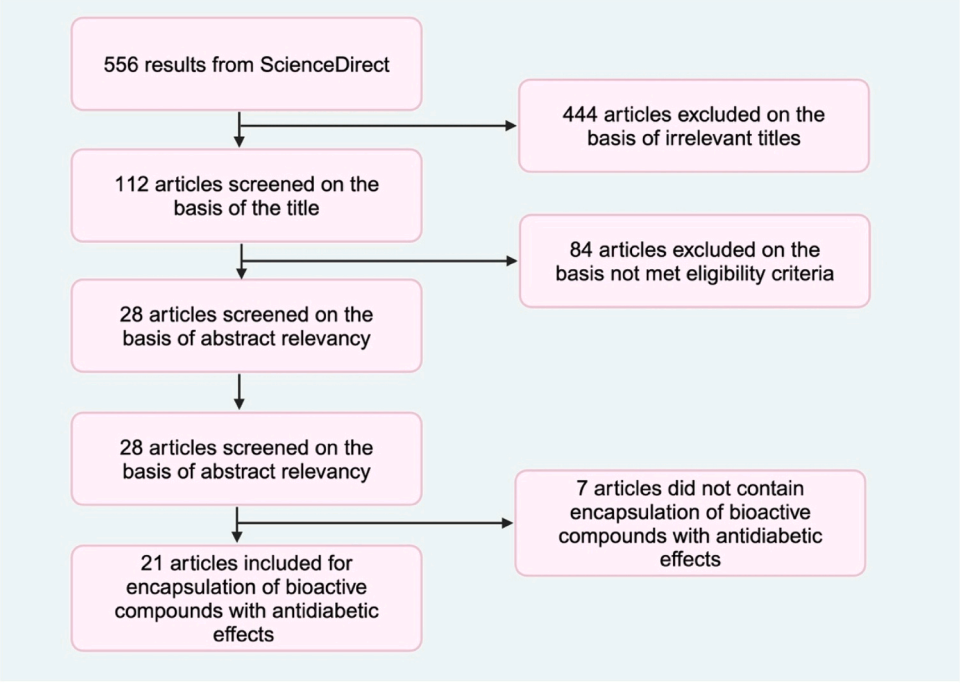

Fig. 7. Diagram flow of article selection for encapsulation of bioactive compounds with anti-diabetic effects using PRISMA method.

Several factors including molecular structure, interactions with gastrointestinal pathway, the food matrix, and the reactivity of nutraceuticals influence the bioavailability of these compounds (Dima et al., 2020). These interactions with other food elements can affect their absorption, distribution, metabolism, and excretion, ultimately impacting their overall bioavailability. To effectively incorporate these compounds into functional foods for managing Type 2 diabetes, it is crucial to address these interactions to maximize the health benefits. On the other hand, direct fortification with pure bioactive compounds often raises concerns regarding the sensory profile and consumer overall acceptance. This is due to the potential changes in taste and aroma, such as increased bitterness and unpleasant odors (Delfanian & Sahari, 2020).

Therefore, to address these challenges, initiatives have been instigated to develop food products with anti-diabetic effects, primarily focusing on encapsulating bioactive compounds within nanodelivery systems. These systems utilize specialized coating materials to maintain the stability and bioavailability of the compounds, improving their effectiveness at reaching targeted sites within the human body (Maqsoudlou et al., 2020). Consuming such foods can significantly benefit patients with DM. The advances in nanotechnology suggest that nanoencapsulation is more effective in delivering these compounds than microencapsulation (Rossi et al., 2021). Table 5 summarizes the various encapsulation technologies from previous studies. Fig. 8 illustrates a method for encapsulating bioactive compounds, specifically using extrusion combined with vibrational technology. The optimal particle size for effective delivery to the target site is less than 1 μm (Jafari et al., 2021).

In the encapsulation process demonstrated in Fig. 9, vibrational

Table 4
Overview of 21 studies included in this systematic review.

Payload/compound	Encapsulation techniques	Anti-diabetic effects/mechanism	Reference
Bioactive molecules from *Stevia rebaudiana* leaf extract (SRLE)	Chitosan nanoparticles (CNPs)	Serum levels of enzymes (SGOT, SGPT, ALP), lipid peroxidation, and antioxidants (CAT, GSH, SOD) were closer to normal levels in the SRLE CNP-treated group compared to the diabetic control group. SRLE CNP-treated diabetic rats showed significant improvements in fasting blood glucose levels and enzyme levels compared to the diabetic control group.	Perumal et al. (2016)
PEGylated Exendin-4 (Ex4)	Poly (Lactic-co-Glycolic Acid) (PLGA) microspheres	Sustained release of active PEG-Ex4 from the microsphere resulted in an increased AUC (2.4-fold vs. Ex-4) compared with native peptide. Ex4 loaded PLGA microspheres normalized blood glucose levels to 100 mg/dL and maintained normoglycemia for ~5 d.	Lim et al. (2015)
Glycyrrhizin and metformin	Ionotropic gelation method with biocompatible polymers chitosan and gum Arabic.	The nanoparticles loaded with glycyrrhizin and metformin demonstrated significant anti-hyperglycemic effects in diabetic rats. Both compounds induced a dose-dependent increase in body weight and a decrease in blood glucose levels, glycosylated hemoglobin (HbA1c), and lipid profiles compared to the diabetic control group	Rani et al. (2017)
Selenium	Chitosan-stabilized selenium nanoparticles (CTS-SeNPs)	– CTS-SeNPs at a dose of 2.0 mg Se/kg bw exhibited higher anti-diabetic activity than other doses of CTS-SeNPs and other selenium compounds with the same selenium content. – CTS-SeNPs, particularly those with middle selenium content, could be a promising candidate for the treatment of diabetes, showing comparable effects to glibenclamide, an anti-diabetic drug	Zeng et al. 2018
Mulberry leaf and Pueraria Lobata extracts (MPE) Rutin and puerarin (marker components in MPE)	MPE-loaded SeNPs (Selenium-layered nanoparticles) Prepared through a solvent diffusion/in situ reduction technique	– MPE-SeNPs showed good physiological stability and slow drug release. – Enhanced hypoglycemic effect observed in normal rats with MPE-SeNPs – Optimal dose compatibility of MPE-SeNPs with M/P ratio of 1:2 for best hypoglycemic effect.	Deng et al. (2019)
Betanin	Nanoliposomes using the thin layer hydrating method.	Betanin-loaded nanoliposomes were more effective than free betanin in regulating hyperglycemia, hyperlipidemia, and oxidative stress in streptozotocin-induced diabetic rat.	Amjadi et al. (2019)
Date palm (*Phoenix dactylifera* L.) seeds oil	Poly(ethyl acrylate-co-methyl Methacrylate-co-trimethylammoniethyl methacrylate chloride) (Eudragit RS100-based nanocapsules	– *In vitro* inhibition activity against α-amylase and α-glucosidase enzymes – α-amylase inhibition: DS oil-loaded NPs showed dose-dependent inhibition better than acarbose – α-glucosidase inhibition: DS oil-loaded NPs exhibited inhibitory activity related to the presence of oleic acid in DS oil – DS oil-loaded NPs exhibited better inhibition of α-amylase and α-glucosidase compared to unencapsulated oil and acarbose.	Lammari et al. (2020)
Rutin (3',4',5,7-tetrahydroxy-flavone-3-rutinoside)	Nanophytosomes	– Rutin-loaded nanophytosomes were more effective than free rutin in controlling hyperglycemia, regulating liver marker enzymes, and improving antioxidant defenses in diabetic rats.	Amjadi et al. (2021)
Insulin and insulin glargine	Zwitterionic polymer nanoparticles of diverse morphologies (spherical, cylindrical, and platelet-like)	– Insulin- and insulin glargine-loaded nanoparticles of diverse morphologies demonstrated up to 2.6-fold and 1.7-fold increase in pharmacological availability, respectively, compared to free insulin and insulin glargine. – Laser scanning confocal microscopy imaging showed significant intracellular uptake of insulin in vascular smooth muscle cells and fibroblasts treated with FITC-insulin-loaded nanoparticles of various morphologies.	Elsabahy et al. (2021)
Palmatine, berberine, and palmatoside from *Tinospora cordifolia* extract	Whey protein based electrosprayed nanospheres	– Molecular docking studies on target proteins such as Glucokinase, Aldose reductase, Fructose-1,6-bisphosphate, AMP, and GFAT provide insights into the interaction of bioactive compounds with these targets. – Compounds like palmatine, berberine, and palmatoside showed promising binding energies, indicating their potential as anti-diabetic agents.	Jain et al. (2021)
Dehydrocostus lactone costunolide	Poly (ethyl acrylate-co-methyl methacrylate-co-trimethylammo- niethyl methacrylate chloride) PMMA-based nanoparticles.	– The nanoparticles demonstrated anti-inflammatory activity by reducing metalloprotease MMP-9 enzyme activity and RNA expression of inflammatory cytokines. – The nanoparticles exhibited a strong anti-diabetic effect with IC50 values against α-amylase and α-glucosidase.	Lammari et al. (2021)
Repaglinide (REP)	Cubosomes – Myrj 59-stabilized cubosomal dispersion and in-situ gel forms.	– Cubosomal forms exhibited cubic nanostructures entrapping high amounts of REP with sustained release properties. – The REP-loaded cubosomes and cubosomal gel exhibited superior long-acting in-vivo traits over IV REP solution in terms of anti-diabetic efficacy.	Mansour et al. (2021)
Tremella fuciformis polysaccharides (TPs)	Spray drying- to prepare TPs microcapsules using maltodextrin (MD) and whey protein (WP) as carriers.	– TPs microcapsules containing MD with lower DE values and higher concentration showed lower water adsorption and caking strength.	Niu et al. (2021)

(*continued on next page*)

Table 4 (*continued*)

Payload/compound	Encapsulation techniques	Anti-diabetic effects/mechanism	Reference
		– They were found to reduce food and water intake, levels of sugar and insulin in blood, and elevate contents of liver and skeletal muscle glycogen. The mechanism study confirmed that TPs microcapsules could ameliorate insulin resistance by increasing glucose uptake and improving glycogen synthesis	
Exenatide (EXE)	Polylactide-co-glycoside (PLGA) nanoparticles (NPs)	– The carrier system significantly improved pharmacological availability, with the EXE-PLGA NPs @YCWPs showing a 1.9 times higher efficacy compared to EXE-PLGA NPs alone. – This enhanced hypoglycemic effect highlights the potential of the carrier system for improving diabetes management and patient outcomes by providing a sustained and effective oral delivery strategy for therapeutic peptides like EXE.	Ren et al. (2021)
Tyrosol, from olive pomace	– Free Phenolic Compounds: Not specified – Encapsulated Phenolic Compounds: Encapsulation in gelatinized potato starch matrix using microwave heating, lyophilization technique	– The IC50 values for α-amylase inhibition ranged from 72.28 to 559.57 μg/mL. – Encapsulation improved the antioxidant and anti-diabetic activities of phenolic compounds. – Encapsulation of phenolic compounds from olive pomace in a gelatinized potato starch matrix using microwave heating showed improved antioxidant and anti-diabetic activities	Sylla et al. (2021)
Repaglinide (REP)	Solid lipid nanoparticles (SLNs)	– The intranasal administration of these SLNs demonstrated sustained drug release and superior anti-diabetic effects in diabetic rats, as evidenced by the highest values of drug activity, percentage of mean reduction. – The intranasal administration of REP-loaded SLNs in the form of an *in situ* gel shown to be a promising approach for diabetes treatment.	Elkarray et al. (2022)
Fomes fomentarius Selenium (Se) polysaccharide	Solid lipid nanoparticles (SLNs)	– Encapsulation with SLN improved the anti-inflammatory effect of PS and PS-Se, enhancing absorption and controlling release. – *F. fomentarius* PS reduces blood glucose levels, and selenium conjugation with the PS enhances its antihyperglycemic effect. Also, SLN-PS and SLN-PS-Se treatment have more hyperglycemic effects than free PS and PS-Se.	Keshavarza-Rezaei et al. (2022)
Mangiferin (MGF)	N-succinyl chitosan-alginate grafted nanoparticles	– Comprehensive MGF encapsulation efficiency of 88 % – Significant hypoglycemic and hypolipidemic responses in diabetic rats. – MGF loaded nanoparticles demonstrated significant hypoglycemic effects in diabetic rats. – Blood glucose levels were lowered from 300 mg/dL to approximately 90 mg/dL after administration of NSC-MGF nanoconjugate. – This reduction in blood glucose levels indicates the potential of MGF in improving glucose metabolism and insulin sensitivity.	Wang et al. (2022)
Teucrium polium (TP)	Polyethylene oxide/sodium alginate nanofibers by electrospinning	– TPF (*Teucrium polium*-loaded nanofibers) released in an ultra-fast manner in 120 seconds suitable for sublingual administration. – Increased expression of insulin and proteins in the glucose-sensing mechanism in beta cells due to TPF.	Polat et al. (2023)
Insulin (INS)	Nanoparticles (acetylated cashew gum (ACG) and chitosan by the polyelectrolyte complexation method)	– The nanoparticles reduced blood glucose levels by 51 % of baseline levels after 12 hours in diabetic rats without inducing signs of toxicity or death. – Cytotoxicity assays on HT-29 cell lines indicated the biocompatibility of ACG and nanoparticles. – Biochemical and hematological profiles were not clinically modified, and histological studies showed no signs of toxicity, indicating the potential of the nanostructured system for oral insulin release.	Vasconcelos et al. (2023)
Apigenin	Casein nanoparticle (apigenin-casein nanoparticles (AP-Cas-NPs)	– The study demonstrates that AP-Cas-NPs effectively reduce fasting blood glucose levels in diabetic mice, with a significant decline rate compared to the control groups. Additionally, AP-Cas-NPs show potential in improving body weight and weight gain in diabetic mice.	Wang et al. (2024)

frequency is important for extrusion. By regulating vibrational frequencies, the laminar jet is sorted precisely, ensuring uniform spherical capsules and consistent capsule sizes and shapes. This emphasizes the importance of vibrational frequency in optimizing encapsulation. On the other hand, Fig. 10 shows various technological approaches from preparation to drying of powdered nanoparticles, with a detailed discussion on these technologies and their application in encapsulating anti-diabetic bioactive compounds to follow in subsequent sections.

4.1. High pressure homogenization

Nanocarriers are produced through either high energy (top-down) or low energy (bottom-up) processes. In food formulations, top-down methods such as High Pressure Homogenization (HPH) are commonly used due to their high throughput capabilities, making them suitable for industrial-scale applications (Sahani & Sharma, 2021). HPH can operate at pressures 10–15 times higher than conventional methods, typically ranging from 100 to 400 MPa. When pressures exceed 400 MPa, the process is referred to as Ultra-High-Pressure Homogenization (UHPH). UHPH systems require meticulously designed equipment to achieve high

Table 5
Encapsulation technologies from previous research in encapsulating bioactive compounds.

Payload/ compound	Encapsulation techniques	Parameters	Anti-diabetic effects	Encapsulation advantages	Reference
Mulberry leaf and *Pueraria Lobata* extracts (MPE) Rutin and puerarin (marker components in MPE)	MPE-loaded SeNPs (Selenium-layered nanoparticles) Method: Solvent diffusion/in situ reduction	– Particle size: 120 nm – Entrapment efficiency (EE): 89.38 % for rutin, 90.59 % for puerari	– MPE can inhibit α-glucosidase, stimulate insulin excretion, modulate intestinal microflora, enhance glucose utilization, and activate islet β cells – Selenium (Se) as a hypoglycemic cofactor with antioxidant and curative effects against DM.	– MPE-SeNPs showed good physiological stability and slow drug release – Enhanced hypoglycemic effect observed in normal rats with MPE-SeNPs	Deng et al. (2019)
Betanin	Nanoliposomes using the thin layer hydrating method. Method: Ultrasonication	– Particle size: 36 nm – zeta potential −19 mV – Loading capacity of 26 %	Betanin-loaded nanoliposomes were more effective than free betanin in regulating hyperglycemia, hyperlipidemia, and oxidative stress in streptozotocin-induced diabetic rats	– Betanin-loaded nanoliposomes exhibited a relatively good sustained release profile in simulated gastric and intestinal fluids. – The encapsulation provided a slow-release profile in simulated digestion fluids.	Amjadi et al. (2019)
Date palm (*Phoenix dactylifera* L.) seeds oil	Poly(ethyl acrylate-co-methyl Methacrylate-co-trimethylammoniethyl methacrylate chloride) (Eudragit RS100-based nanocapsules Method: nanoprecipitation	– Particle size: 207 nm – Zeta potential: +59 mV – Encapsulation efficiency: 97 %	DS oil-loaded NPs exhibited better inhibition of α-amylase and α-glucosidase compared to unencapsulated oil and acarbose.	– Enhanced stability and protection of Date palm seeds oil – Controlled and sustained release for targeted delivery – Improved bioavailability and efficacy of bioactive compounds – Preservation of bioactive components – Enhanced anti-diabetic activity through enzyme inhibition	Lammari et al. (2020)
Teucrium Polium (TP)	Polyethylene oxide/ sodium alginate nanofibers Method: Electrospinning	NM	TPF showed increased expression of insulin and proteins in beta cells, enhancing the anti-diabetic effects.	TPF (*Teucrium polium*-loaded nanofibers) released in an ultra-fast manner in 120 seconds suitable for sublingual administration.	Polat et al. (2023)

NM= Not Mentioned

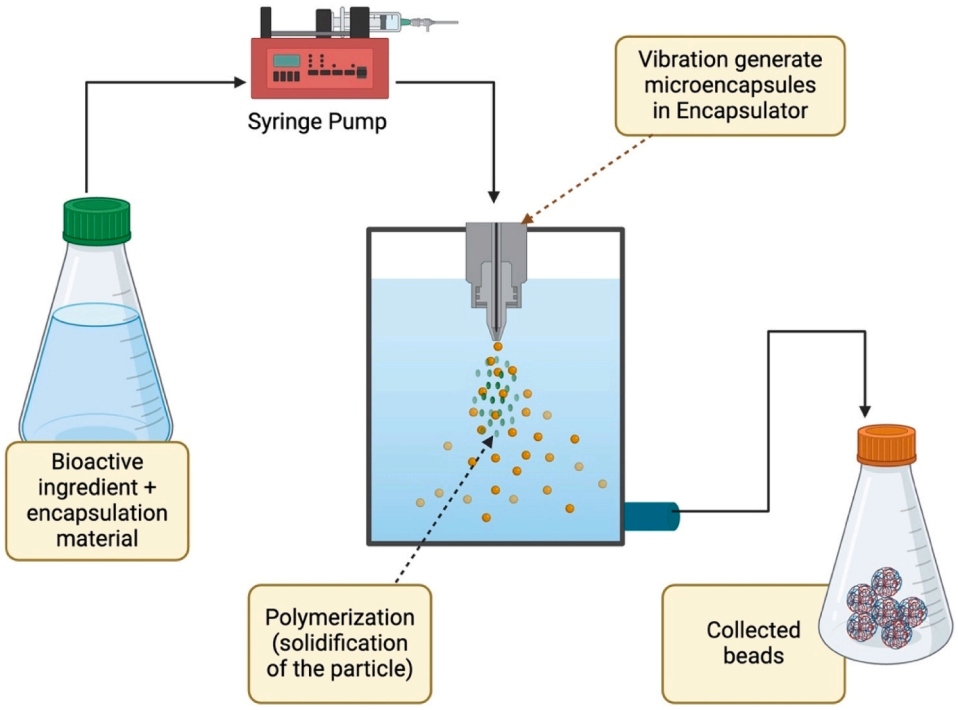

Fig. 8. Encapsulation process of bioactive compound.

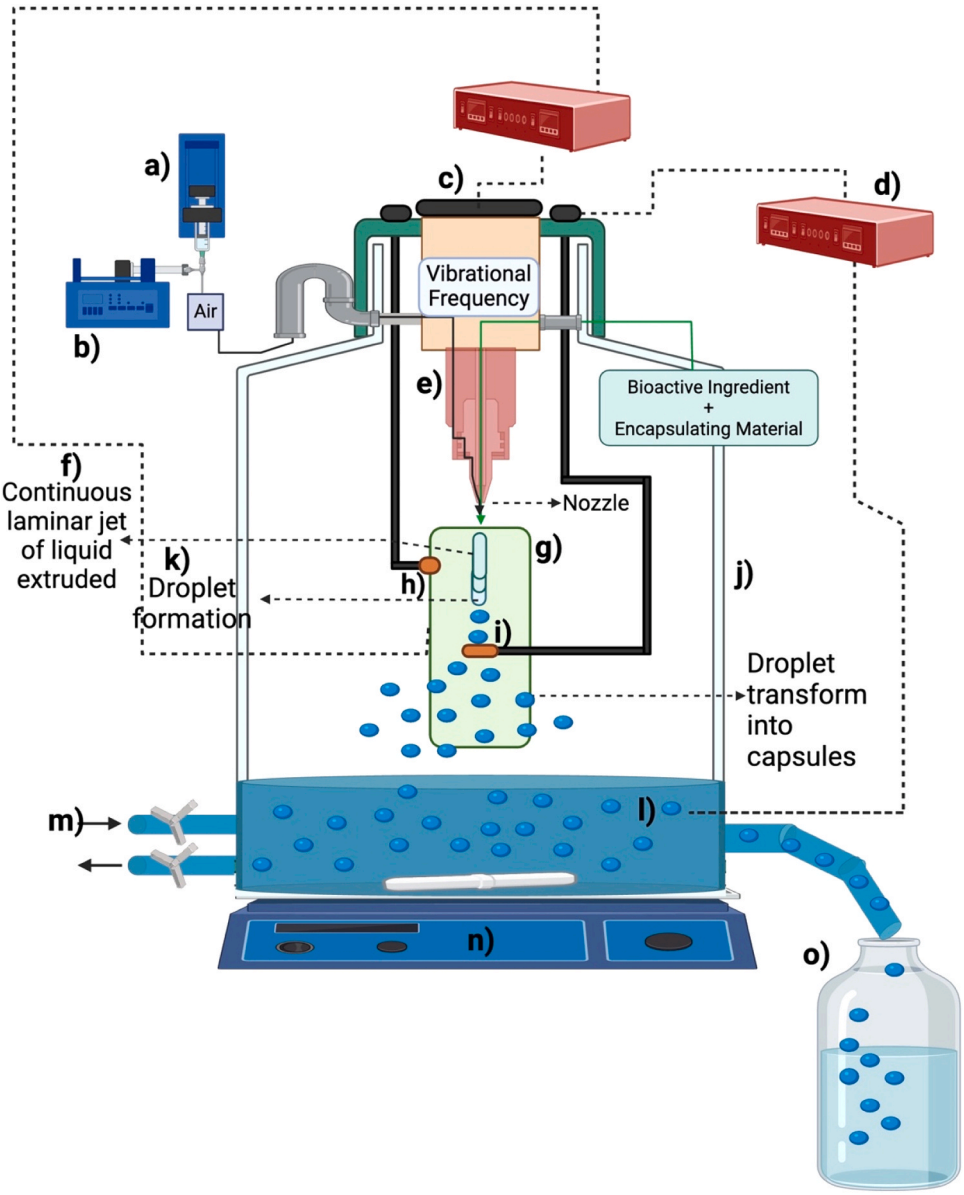

Fig. 9. Encapsulation through vibrational frequency application. a) Syringe pump; b) pressure regulator system; c) vibrational frequency control mechanism; d) electrostatic charge generator; e) vibrating nozzle; f) liquid extruded; g)stroboscopic light; h) bypass mechanism; i)electrode; j) reaction vessel; k) droplet formation – dispersed; l) gelling bath; m) flow of in/out of gelling material for continuous operation; n) magnetic stirrer; o) end product collection.

levels of pressure and stability. Furthermore, HPH techniques reduce the need for surfactants when creating nanoemulsions for essential oils (Qi et al., 2022; Shi et al., 2022).

HPH utilizes high shear and cavitation to disrupt droplets, reducing particle size and creating nanoemulsions with droplets ranging from 20 to 200 nm, allowing for efficient dispersion in the aqueous phase (Hidajat et al., 2020). This technology is promising for producing stable, small-sized nanoemulsions infused with anti-diabetic compounds for integration into food matrices. For instance, HPH was used to produce a stable nanoemulsion of Sichuan pepper essential oil, noted for its good antimicrobial activity and stability in terms of water solubility, pH, and storage (Shi et al., 2022). Additionally, UHPH has also proven to be effective in developing nanoemulsions that incorporate anti-diabetic compounds. A study applying UHPH to egg yolk granules demonstrated structural changes and microstructure alterations without affecting the overall composition or protein profile, highlighting its potential in food technology (Gaillard et al., 2022).

4.2. Ultrasonication

Ultrasonication (top-down nanoencapsulation technique), employs mechanical devices to transform larger droplets into nano-sized particles, ensuring even distribution. This method, operating at ultrasound frequencies above 20 kHz and intensities over 1 W/cm2, creates turbulence that collapses cavities and starts emulsification (Ruan et al., 2022). The process fragments large droplets into smaller ones, typically needs up to 550 W for 2–15 minutes (Abral et al., 2019; Azmi et al., 2022; Yang et al., 2022). Studies show that ultrasonication is able to enhance the stability of nanoemulsions and nanoparticles, indicated by improved polydispersity and Zeta potential values (Azmi et al., 2022). Additionally, it is effective in producing and sterilizing nanocoatings (Diao et al., 2020). Conversely, bottom-up sonication like thin layer hydration is used in initial preparation stages, incorporating various preparation methods for nanocarriers.

Previously, a study utilized thin layer hydration to prepare pomegranate peel extract loaded nanophytosomes, assessing their bio-

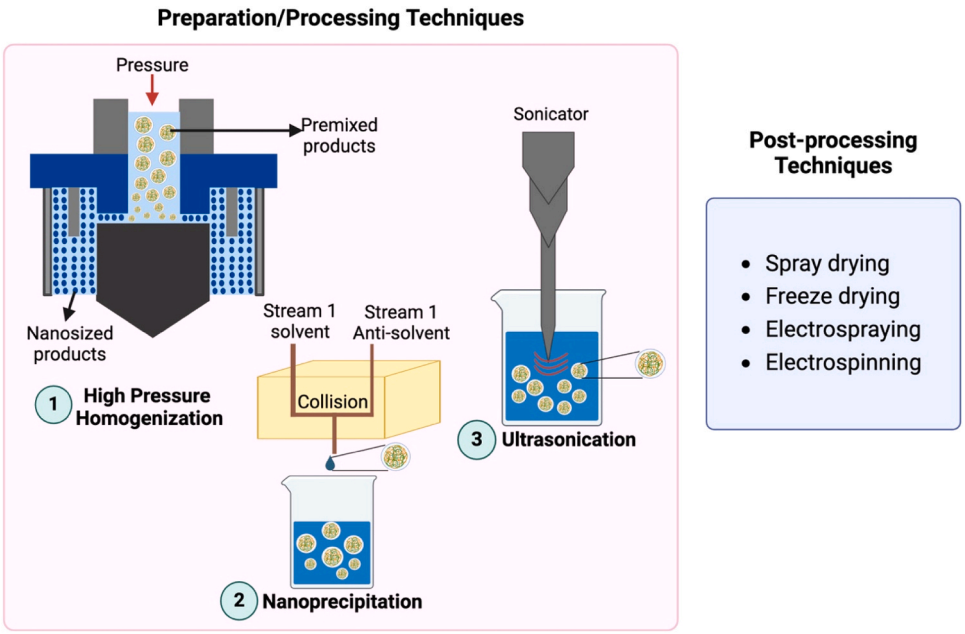

Fig. 10. Overview of nanoencapsulation technologies for the fabrication of bioactive-loaded nanoparticles.

accessibility and storage stability. The extract was formed into a thin film via rotary evaporation, then hydrated and homogenized at 7500 rpm for 10 minutes, followed by ultrasonic homogenization to reduce particle size (Dundar et al., 2023). This process improved the water solubility and bioaccessibility of the bioactive compounds, enhancing their bioavailability and stability in anti-diabetic applications. Additionally, another study explored ultrasound-assisted techniques for preparing nanocarriers loaded with food bioactives (Koshani & Jafari, 2019). The findings demonstrated that this method significantly enhanced the bioavailability of lipophilic bioactives, underscoring the importance of particle size in the efficacy of food bioactive compounds like chitosan sodium alginate nanocomplex containing crocin, and polysaccharide glycosylated protein. This technique is considered effective for encapsulating various bioactive compounds, including those with anti-diabetic properties, into food matrices.

4.3. Nanoprecipitation

Rapid nanoprecipitation is an efficient method for producing solute nanoparticles with high encapsulation efficiency, relying on key factors such as mixing techniques, saturation points, and stabilization. Flash nanoprecipitation (FNP) is a specific approach under this method, which has been shown to optimize nanoparticle formation effectively, especially in making progesterone nanoparticles with enhanced stability and high drug loading (Saad & Prud'Homme, 2016). This method is promising for producing stable, size-regulated nanoparticles suitable for various applications, including the encapsulation of anti-diabetic compounds in functional foods to manage T2D. Moreover, nanoprecipitation is considered environmentally friendly for creating bioactive-loaded nanocarriers (Han et al., 2022; Wang et al., 2022). The process involves phases including saturation, nucleation, and growth by condensation and coagulation, leading to the formation of nanoparticles or polymer aggregates (Rivas et al., 2017).

Generally, nanoprecipitation is a straightforward, rapid, and reproducible method scalable for industrial production of both hydrophobic and hydrophilic compounds. Han et al. (2022) successfully produced nanoscale catechin/β-cyclodextrin complexes using ethanol as a precipitant, enhancing catechin's antioxidant and storage stability through controlled release, with post-processing involving freeze-drying. The preparation utilized dark conditions, magnetic stirring, and a syringe pump for precise mixing, with centrifugation and freeze-drying to collect the nanoparticles. Similarly, Wang et al. (2022) used FNP to produce lutein-soy protein isolate nanoparticles, a quick and continuous process yielding highly stable nanoparticles sized 80–122 nm. This involved mixing solvent streams of soy protein isolate and lutein with anti-solvent streams of phosphate buffer saline at pH 7.4 in a multi-inlet vortex mixer, enhancing bioavailability up to 94 % with subsequent freeze-drying.

4.4. Spray and freeze drying

Spray and freeze drying are predominant post-processing methods used in bioactive-loaded nanocarrier fabrication. Spray drying is favored for its rapid process that minimizes thermal degradation, enhances the stability of bioactive compounds in food products, and facilitates scaling up (Jafari et al., 2021). It uses high temperatures to quickly convert liquid nanoemulsions into nanopowders, suitable for coating bioactive ingredients, although it may reduce yield and require adjustments to control particle sizes (Jafari et al., 2021).

In spray drying, the liquid material is atomized in a chamber where it contacts hot, dry air, causing rapid evaporation and formation of dry particles at temperatures between 70 °C and 90 °C, without exceeding the inlet air temperature of 150 °C to 200 °C. This method ensures the safe drying of heat-sensitive materials and is effective for protein-based nanocarriers, which are resistant to heat degradation and quickly stabilize (Akbarbaglu et al., 2021). Nanopowder recovery is enhanced by electrostatic force (Arpagaus et al., 2018; Del Gaudio et al., 2017). Thus, spray drying is well-suited for encapsulating heat-sensitive and anti-diabetic compounds on a commercial scale. Alternatively, freeze drying is another technique for creating nanopowder. This method involves a rapid freezing stage at temperatures below −40 °C to preserve the physical and chemical properties of the material, followed by an annealing phase where the product is kept at subfreezing temperatures until crystallization occurs in a vacuum. The final drying step involves sublimation, leaving behind dry particles (do Vale Morais et al., 2016). Although freeze-drying is commonly used in the pharmaceutical industry to encapsulate heat-sensitive drugs, it has drawbacks such as lengthy processing times and high investment and operational costs.

4.5. Electrospraying and electrospinning

Electrohydrodynamic atomization, also regarded as electrospray, is one of the promising methods for encapsulating bioactive components with potential for large-scale applications. This technique employs external electrodynamic forces to produce micro and nano-sized liquid particles, using high molecular weight polymers and suspensions. Electrospray functions by electrically creating droplets from a material to form a powder, with nozzles, high-voltage power supplies, syringe pumps, and chambers as key components influencing atomization (Cetinkaya et al., 2021). It minimizes solvent evaporation in a chamber, yielding nanoparticles with fine surface morphology. According to Niu et al. (2020), electrospray excels in preserving heat-sensitive bioactives since it operates at ambient temperatures, unlike higher temperatures used in spray drying. Commonly utilized in active food packaging to immobilize proteins and enzymes, electrospray is noted for its high encapsulation efficiency, stability enhancement, extended shelf life, and improved release efficiency. Additionally, it effectively regulates enzyme release and reduces degradation and off-flavor production (Tomadoni et al., 2022).

Meanwhile, electrospinning utilizes external electrodynamic forces to develop sub-micron or nanofibers. These fibers are noted for their high porosity and surface area, which enhance the stability and bioavailability of encapsulated bioactive compounds and aid in controlling their release (Ceylan et al., 2021). Similar to electrospraying, the efficacy of electrospinning relies on factors including the polymer concentration, viscosity, molecular weight of the solution, voltage magnitude, distance from the tip-to-collector, and flow rate (Hadad & Goli, 2019). The process starts by applying an electric current to the material containing the bioactive compound, forming nanodroplets at the needle tip that require optimization for controlled size and properties.

5. Influence of particle composition on delivery system formulation

Encapsulation represents an important implementation especially in the nanotechnologies application within the various spectrum in the food industry (Table 6). Nanomaterial plays a crucial role in augmenting the biological functionality, solubility, and bioavailability of encapsulants, owing to their wide surface area per unit mass and reduced particle size (Nile et al., 2020). Nevertheless, the primary consideration according to technical and economic aspects, the wall material should fulfill certain criteria such as resilience, inertness during processing and storage, generally recognized as safe (GRAS) certified and a biobased nature. Furthermore, the delivery system should also maintain stability and exhibit robust rheological properties to suit its desired application in the food system (Gómez-Mascaraque et al., 2022). As shown earlier in Fig. 4, the release mechanism of the nanoencapsulated and encapsulated bioactive compounds demonstrates this effectiveness. The carrier materials used for encapsulation can be majorly classified as lipid based, polysaccharide based, and protein based which is discussed below in detail.

5.1. Lipid-based delivery systems

Lipid-based delivery systems, including fatty acids, phospholipids, waxes, and fats, are excellent for encapsulation due to their amphiphilic nature, which reduces surface tension between phases. However, to enhance their physicochemical stability, lipids are often conjugated with proteins or polysaccharides (Gómez-Mascaraque et al., 2022). Fig. 11 illustrates the absorption mechanism of lipid-nano carriers enhancing the bioavailability. Conjugated systems improve encapsulation by combining the physicochemical properties of their components, as shown earlier in Table 5 which lists various encapsulation technologies from previous studies.

Lipid-based nanocarriers have been reported to effectively maintain the targeted release and increase the bioaccessibility of carotenoids (like lycopene, lutein, and β-carotene) in the gastrointestinal system by preventing crystallization (Rostamabadi et al., 2021). They also enhance the bioavailability of phenolic compounds (Faridi Esfanjani et al., 2018). Previously, a study integrating β-carotene-loaded liposomes stabilized with xanthan and guar gums into yogurt showed that β-carotene was well-preserved over 95 days, with 88.3–95.9 % retention after three months, attributed to the slow peroxidation of the phospholipid membrane and hindered diffusion of oxidants (Toniazzo et al., 2014). Additionally, the color of β-carotene remained stable, as confirmed by instrumental colorimetry (Toniazzo et al., 2014). Liposomes have also been used to encapsulate curry leaf and clove oils, improving their antibacterial activity and chemical stability (Ajeeshkumar et al., 2021). Curcumin loaded in liposomes exhibited a slower release and higher retention under various conditions, indicating the protective effect of the liposome structure (Jin et al., 2016). Lipid-based delivery systems, including nanoemulsions, nanoliposomes, solid lipid nanoparticles, and nanostructured lipid carriers, are discussed in the next section, with Table 7 and Fig. 12 summarizing the lipid-based delivery of anti-diabetic bioactives from prior studies.

5.1.1. Nanoemulsions

Nanoemulsions refer to the colloidal particulate delivery system in which an internal phase is dispersed through an external continuous phase. These could be single emulsion either oil in water (O/W) or water in oil (W/O) or double emulsion: water in oil in water (W/O/W) or oil in water in oil (O/W/O) (Dib et al., 2023). Several essential oil based nanoemulsions have been developed which have applications in the food industry. However, the rapid release of bioactive components is its major limitation.

5.1.2. Nanoliposomes

Nanoliposomes are spherical amphiphilic lipid vesicles containing an aqueous internal cavity (Zarrabi et al., 2020). According to Qi et al. (2022) nanoliposomes considered to be one of the effective delivery system for catechin due to its ability to reduced toxicity, and controlled released of active compounds. Fortification of dairy products (cream and cheese) has been done by introducing nanoliposomes loaded with vitamin D (Mohammadi et al., 2015). Some of the drawbacks associated with liposomes include low loading space for the encapsulant, lack of stability in response to low pH and digestive enzymes (Akhavan et al., 2018).

5.1.3. Solid lipid nanoparticles (SLNs)

SLNs are modified O/W nanoemulsions in which liquid lipid is replaced by solid lipid. The substitution forms a crystalline structure which impedes the mobility of bioactive components resulting in its controlled release (da Silva Santos et al., 2019). The loss of bioactive components via expulsion during storage and low free space for entrapment of payload phase are two of its major limitations. Table 8 depicts recent successful attempt in utilizing SLNs as the encapsulation technique for bioactive compound delivery.

5.1.4. Nanostructured lipid carriers (NLCs)

In order to overcome the limitations of SLNs, NLCs were formulated. NLCs are modified SLN structures wherein less ordered crystalline solids and liquid lipids coexist in concentration corresponding to 70–95 % and 0.1–30 % respectively. NLCs offer higher capacity of bioactive retention and enhanced physical stability (Luo et al., 2020).

5.2. Polysaccharide-based delivery systems

Polysaccharides, consist of functional groups including amino, hydroxyl, and carboxyl, facilitate robust interactions with bioactive compounds. Their simple, linear, or branched structures assist the creation of nanostructures, classified into polyelectrolytes (with a surface charge)

Table 6
Nanodelivery systems used for encapsulation of active compounds in food applications.

Nanodelivery System and Wall Material	Encapsulated Compound and Technique	Size and Efficiency	Food Application and Purpose	Key Findings	References
Nanocomplex (Pectin/ Lysozyme)	β-lactose, Self-assembled	81.2 nm, >96 %	Oral delivery in food matrix	Enhanced thermal stability (endothermic peak at 170 °C), spherical morphology, efficient cellular uptake by HCT-116 cancer cells (*in vitro*)	Da Silva et al. (2019)
Nanoemulsion (Medium chain triglyceride, Phospholipon R)	Curcumin, High pressure homogenization	149.6 nm, NM	Beverages	High stability and bioavailability, curcumin remained solubilized, improved antioxidant activity, suitable for functional drinks (*in vitro*)	Goncalves et al. (2023)
Solid lipid nanoparticles (Beewax, Phospholipon R, Tween 80)	Curcumin, Micro-emulsification	181.1 nm, NM	NM	Stable formulation, high encapsulation efficiency, suitable for functional beverages (*in vitro*)	Goncalves et al. (2023)
Nanostructured lipid carriers (Beewax, Phospholipon R, Tween 80)	Curcumin, High speed homogenization, ultrasonication	133.2 nm, NM	NM	Enhanced stability and bioavailability of curcumin, high encapsulation efficiency, improved antioxidant activity (*in vitro*)	Goncalves et al. (2023)
Nanophytosome (Phosphatidylcholine)	Pomegranate peel extract (PPE), Thin layer hydration	144–166.7 nm, 93–96 %	Nutraceuticals, food ingredients	Spherical structures, improved bioaccessibility (60 % in intestinal medium, *in vitro*), enhanced storage stability	Dundar et al. (2023)
Nanocapsule (Maltodextrin, Colloidal silicon dioxide)	*B. forficata* extract, Spray drying	179 nm, 62.73 %	Functional ingredient in food and pharmaceutics	Thermal stability up to 400 °C, spherical shapes, high bioaccessibility (64.17 % and 79.06 % in gastric and duodenal phases, *in vitro*).	De Souza et al. (2022)
Nanoparticles (β-Glucan from oats)	Catechin, NM	200 nm, 89.9 %	Functional food fortification	Ellipsoidal shape, controlled release, reduced antioxidant activity after digestion (*in vitro*).	Da Silva et al. (2023)
Nanoparticles (Polylactic-co-glycolic acid)	*Asparagus stipularis* extract, Solvent emulsification-evaporation	260 nm, 83 %	Dietary supplement in food and pharmaceutical industry	Spherical shape, smooth exterior, suitable for dietary supplements.	Shah et al. (2022)
Nanoemulsion (Maltodextrin, WPI)	Pomegranate peel extract (PPE), Emulsification	157.82 nm, 89.6 %	Food preservatives	Shielded antioxidant activity, extended shelf life of oils (24 days, *in vitro*).	Adouni et al. (2022)
Nanoparticles (Tapioca starch)	Catechin, Epicatechin, Proanthocyanidin, NM	100 nm, NM	Food dietary supplement	Lower IC50 values for DPPH activity, controlled release, improved bioavailability (*in vitro*).	Rashid et al. (2022)
Nanoparticles (Pectin from *Akebia trifoliata*)	Curcumin, Coating	230 nm, 89.65 %	Sustained release in food matrix and pharmaceutics	Spherical shape, higher DPPH activity (91.3 %), improved bioaccessibility (51.21 %, *in vitro*).	Lian et al. (2022)
Microcapsules (Pectin, Sodium alginate)	Carvacrol, Homogenization, spray drying	2.58 μm, 82.79 %	Food industry stabilizer	Spherical shape at 100 °C and 130 °C, higher DPPH activity (17.95 mgGA/ g), optimal antimicrobial activity (MIC 0.25 mg/mL).	Cai et al. (2020)
Nanoparticles (β-lactoglobulin)	Anthocyanin (AC), Desolvation, ultrasonication	351.85 nm, 77 %	Food and beverage colorant	Square morphology, high stability (thermal peak at 100 °C), high scavenging activity (82.5 %, *in vitro*).	Sun et al. (2020)
Nanocapsule (Chitosan)	Phenolics from golden apple, red grape, Solvent displacement	25 nm (APP), 24 nm (GPP), 75 %	Health supplement, preservative	Spherical shape, increased antioxidant activity compared to unencapsulated counterparts (*in vitro*).	Salah et al. (2020)
Nanocomplex (Pea protein isolate, Beet pectin)	Curcumin, NM	470 nm, 75 %	Functional food and nutraceutical formulations	High thermal stability (71.09 °C), photostability (38.6 % retention after 90 minutes UV), quick release in acidic medium (32 % in 30 minutes, *in vitro*).	Ahmed et al. (2020)
Nanofibril (Silk fibroin)	AC from black rice, Ultrasonication	200 nm, NM	Natural colorant, food ingredient	Improved heat resistance, enhanced peptide protection during heat treatment (*in vitro*).	Guo et al. (2020)
Nanofibres (Chitosan-gelatin)	Stigmasterol, Electrospinning	217 nm (25:75 ratio), 87 %	Food fortification	Bead-free fibers, controlled release in small intestine (46 %).	Mousavi et al. (2021)
Nanoparticles (Zein)	β-carotene, Electrospraying	599 nm (1:100 ratio), 81 %	Food enrichment	Quasi-spherical shape, fast release (66 % bioaccessibility in intestinal condition, *in vitro*).	Mahalakshmi et al. (2020)
Nanoparticles (Pectin-lysozyme)	AC from blackberry, NM	198.5 nm, 73 %	Food colorant	High thermal stability (degradation onset at 169 °C), smooth shape, high retention rate during digestion.	Rosales et al. (2021)
Nanocomplex (Chitosan, Pea protein isolate)	Hyssop essential oil (HEO), Nanoprecipitation	216.4 nm, NM	Food/fruit preservation	Spherical shape, higher antioxidant (66.5 % DPPH) and antifungal (97.8 % on day 8) activity compared to unencapsulated.	Hadidi et al. (2021)

(*continued on next page*)

Table 6 (*continued*)

Nanodelivery System and Wall Material	Encapsulated Compound and Technique	Size and Efficiency	Food Application and Purpose	Key Findings	References
Nanofibres (Zein)	Cinnamic aldehyde (CA), Needleless electrospinning	383 nm, 99.52 %	Shelf-life extension, aroma retention	Bead-free morphology, improved thermal stability (weight loss at 253 °C), controlled release (21 % in 6 hours).	Karim et al. (2021)
Nanoemulsion (Zein peptide hydrolyzed by flavorzyme)	Lutein, Spontaneous emulsification	~360 nm, NM	Nutrient fortification	Spherical shape, higher bioavailability of lutein in SLN particles (*in vivo*).	Liu et al. (2021)
Nanocapsule (Zein)	Vitamin D3, Nanoprecipitation	<200 nm, 97.21 %	Food fortification	Spherical shape, molecular dispersion, high release rate (81.3 % in duodenum stage, *in vitro*).	de Melo et al. (2021)

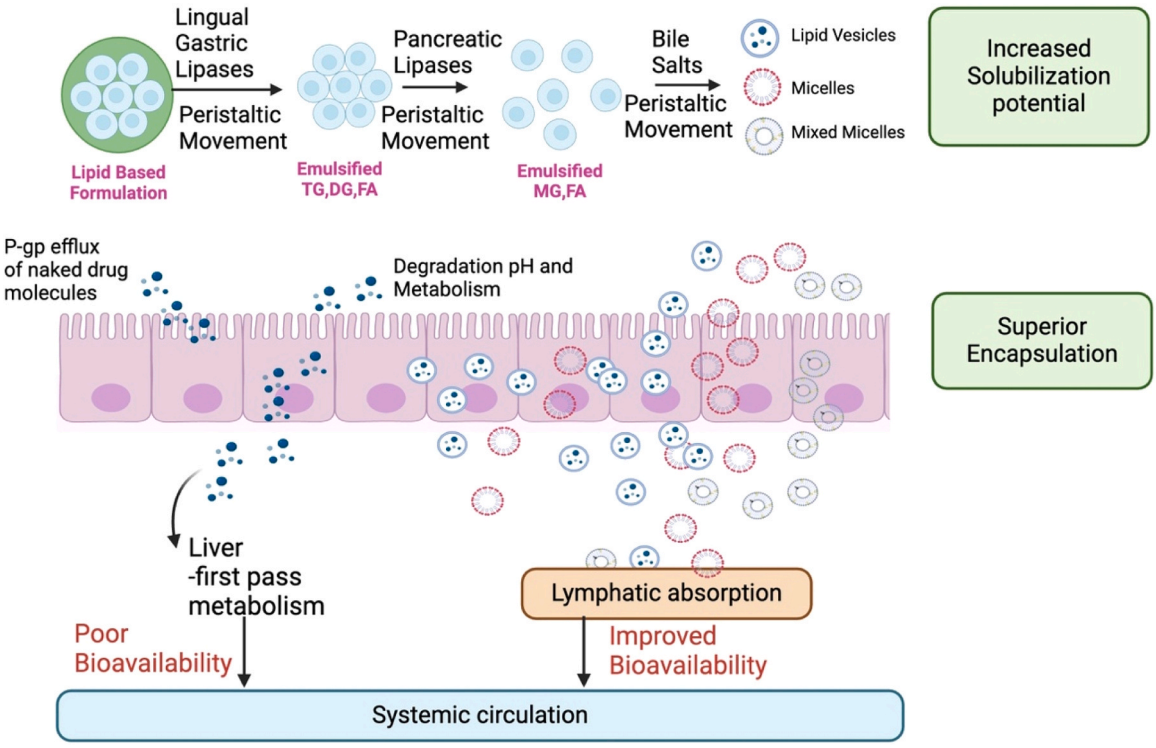

Fig. 11. Lipid-nanocarriers absorption mechanism. P-gp= P-glycoprotein.

and non-polyelectrolytes (without surface charge). Table 9 illustrates their use in anti-diabetic compound delivery, with chitosan, alginate, and various plant gums as key materials in polysaccharide-based nanoscale systems (Richa & Roy Choudhury, 2020). Fig. 13 demonstrates polysaccharide drug delivery mechanism of action.

Richa & Roy Choudhury (2020) compared the entrapment efficiency of curcumin in nanoemulsions stabilized by polysaccharides (fucoidan, guar gum, levan, sodium alginate, and carrageenan) with those stabilized by the synthetic emulsifier Tween 20. They found that polysaccharide-stabilized nanoemulsions had particle sizes ranging from 35.77 nm to 580 nm, with fucoidan achieving the smallest size and highest stability. The nanoemulsion with Tween 20 and guar gum exhibited a negative surface charge. Most nanoemulsions showed high encapsulation efficiencies above 61 %, except for the alginate-stabilized version using olive oil. Rheological analysis confirmed that all nanoemulsions behaved as Newtonian liquids, suitable for the food industry. FTIR studies indicated that polysaccharides preserved curcumin's functional integrity, while synthetic emulsifiers reduced its bioactivity. Overall, polysaccharides proved to be more effective stabilizers for curcumin nanoemulsions compared to synthetic emulsifiers.

Several proteins can result in allergic reactions due to their inability to be digested in the stomach and duodenum (Zhang et al., 2020). In contrast, polysaccharides are easily digestible, non-toxic, biocompatible, and stable across various pH levels and temperatures (Feng et al., 2017). For instance, corn fiber gum stabilized nanoemulsions loaded with lutein were highly stable, exhibits strong electrostatic repulsion that prevented droplet flocculation, maintaining good encapsulation efficiency (86–88 %) and lutein bioavailability. The emulsions demonstrated robust physical stability, with a slight increase in mean diameter size (from 162 nm to 172 nm) after 7 days of storage, and a slower rate of lutein degradation under varying storage temperatures (25 °C and 55 °C) compared to the control (Dong et al., 2021).

Furthermore, inulin, a water-soluble polysaccharide, is used in oil-in-water (O/W) nanoemulsions to protect sensitive bioactive components through the thickening of the mixture and reducing droplet movement, thereby preventing coalescence and enhancing stability (Feng et al., 2017). Carrageenan combined with chitosan, zein, and whey protein were used to encapsulate ascorbic acid, piperine, and curcumin, respectively, improving both encapsulation efficiency and physicochemical stability (Dong et al., 2021). Additionally, Ma et al. (2022) developed a carboxymethylated corn fiber gum (CMFG)/chitosan delivery system that achieved a high encapsulation efficiency of 93.85 %

Table 7
Lipid based-delivery of encapsulated anti-diabetic bioactive compounds from previous studies.

Bioactive compounds	Compound released	Main Findings	Reference
Quercetin	– Encapsulation in a multiple nanoemulsion significantly increased the *in vitro* permeability of quercetin. – The apparent permeability (Papp) of quercetin in cells treated with the HBP-loaded multiple nanoemulsion was 19.1 $\times 10^{-6}$ cm/s, higher than that of free HBP extract. – The multiple nanoemulsion improved the permeability of encapsulated quercetin *in vitro*, suggesting enhanced bioavailability potential.	– Quercetin, encapsulated in the multiple nanoemulsion, showed increased permeability in wt-MDCK monolayers, indicating its potential for improved bioavailability and potential anti-diabetic effects.	Bridi et al. (2023)
Nigella sativa nanoemulsion loaded with Pioglitazone	– Optimized PGZ-loaded nanoemulsion exhibited a particle size of 167.1 nm and *in vitro* release of 89.5 %. – Drug release followed the Korsmeyer–Peppas mechanism.	The formulation showed stability over 3 months at different storage temperatures. *In vivo* investigation demonstrated a significant reduction in blood glucose levels, enhanced by the presence of *Nigella sativa* oil (NSO).	Shehata et al. (2022)
Terminalia catappa Linn fruit extract.	– The aqueous extract of Terminalia catappa fruit showed high α-amylase inhibition, with complete inhibition observed at 0.8 mg/mL dosage. – Different phenolic profiles were obtained, with the aqueous extract exhibiting high phenolic compound content and effective α-amylase inhibition. – The extract displayed potent antioxidant activity, with the ability to scavenge ABTS radicals and inhibit DPPH radicals at low dosages.	– Phenolic compounds form stable complexes with α-amylase, leading to enzyme inhibition. – The high concentration of phenolic compounds in the extract intensifies interactions with the enzyme, resulting in competitive and non-competitive inhibition. – Complete α-amylase inhibition at higher dosages may lead to undigested starch in the intestinal microflora, causing discomfort.	Uchida et al. (2023)
Pelargonidin-3-O-glucoside (P3G) using pectin-chitosan-nanoliposomes.	– CH-P3G-NL and P-CH-P3G-NL showed significantly higher α-amylase inhibition activity compared to P3G-NL. – α-amylase inhibition activities were 59.78 % (P3G-NL), 47.37 % (CH-P3G-NL), and 33.49 % (P-CH-P3G-NL). – α-glucosidase inhibition activity: 66.33 % (P3G-NL), 36.82 % (CH-P3G-NL), and 42.14 % (P-CH-P3G-NL).	– Functionalized nanoliposomes, particularly P-CH-P3G-NL, showed enhanced free radical scavenging capacity post-SGF digestion. – Anti-diabetic potential of digested nanoliposomes was significantly higher than non-digested samples.	Shishir et al. (2020)
Lipoid S75-biopeptides nanoliposome composite	– BLS75-CM showed higher stability in terms of particle size, pdi, and zeta potential compared to BLS75-DHM. – BLS75-DHM exhibited higher EE and efficacy with greater residual ACE-inhibitory activity.	– The study demonstrated the potential of lipoid S75-biopeptides nanoliposome composite for anti-diabetic applications. – The comparison between conventional and direct heating methods highlighted differences in stability and efficacy of the nanoliposomes	Auwal et al. (2018)

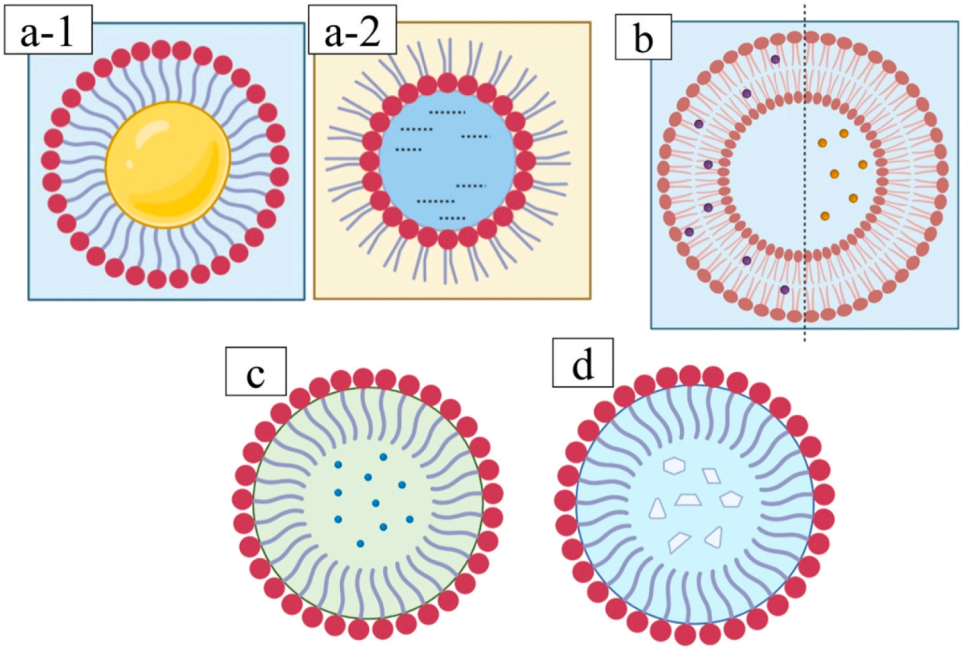

Fig. 12. Lipid-based delivery systems (a) Nanoemulsion – (a-1) oil in water (O/W), (a-2) water in oil (W/O), (b) Nanoliposomes, (c) Solid lipid nanoparticles (SLNs) and (d) Nanostructured lipid carriers (NLCs).

for curcumin, maintaining 57.57 % of curcumin after 120 minutes of UV exposure compared to a rapid degradation in free curcumin, which retained only 34 % after 30 minutes. This encapsulation showed an enhanced curcumin's bioaccessibility, with encapsulated forms showing bioavailability of 58 % and 74.94 % at different CMFG:chitosan ratios, compared to only 17.35 % for free curcumin.

Furthermore, proteins and polysaccharides can form effective blends through electrostatic interactions and hydrogen bonding, ideal for

Table 8
Solid lipid nanoparticle (SLNs) application in various encapsulation of bioactive compounds.

Encapsulated bioactive Compounds	Mechanism of anti-diabetic action through SLN	Main findings	Reference
Berberine loaded solid lipid nanoparticles (BBR-SLNs)	– BBR-SLNs may enhance the anti-diabetic action of berberine through improved bioavailability and targeted delivery. – Berberine activates AMP-activated protein kinase (AMPK), promoting glucose metabolism and insulin sensitivity. – Berberine inhibits hepatic gluconeogenesis and promotes glucagon-like peptide-1 secretion.	– BBR-SLNs at 100 mg/kg dosage demonstrated superior effects compared to an equivalent dose of free BBR in improving glucose tolerance and insulin sensitivity in db/db mice. – BBR-SLNs increased pancreatic islet numbers, potentially facilitating islet regeneration. – The carrier materials, including lecithin and tripalmitin, did not exhibit toxic side effects. – BBR-SLNs showed enhanced bioavailability of BBR in plasma, indicating improved absorption.	Xue et al. (2013)
SLN of Myricitrin	– Myricitrin SLN improved glucose uptake in skeletal muscle by enhancing Glut-4 gene expression and mobilization to the plasma membrane. – Enhanced glycogen content in muscle cells suggests improved glucose metabolism and insulin sensitivity. – Myricitrin SLN may act during hyperinsulinemia and prediabetes stages to prevent or delay the development of Type 2 diabetes mellitus.	– SLN of Myricitrin at doses of 1, 3, and 10 mg/kg increased plasma insulin levels significantly compared to the diabetic group. – Treatment with Myricitrin SLN improved β-cell function index, skeletal muscle glycogen content, and Glut-4 gene expression in skeletal muscle and C2C12 cells. – Myricitrin SLN reduced pancreatic cell apoptosis and increased islet diameter in diabetic animals. – SLN of Myricitrin showed antioxidant effects by enhancing antioxidant defense and reducing oxidative stress in both *in vivo* and *in vitro* studies.	Ahangarpour et al. (2018)
SLN of Quercetin	– Significant inhibitory activity against α-amylase and α-glucosidase enzymes. – SLN2 exhibited higher inhibitory action compared to quercetin alone. – Quercetin, a flavonoid compound, was identified as the key component responsible for the anti-diabetic effect. – The mechanism of anti-diabetic action involved the inhibition of α-amylase and α-glucosidase enzymes, leading to reduced blood glucose levels.	– Quercetin-loaded SLN2 demonstrated 75.329 % inhibition of α-amylase and 58.9542 % inhibition of α-glucosidase. – Quercetin alone exhibited 59.384 % inhibition of α-amylase and 45.938 % inhibition of α-glucosidase. – The study utilized *in vitro* enzyme and substrate reaction methods to assess anti-diabetic effects.	Ain et al. (2022)
Glyburide loaded glyceryl monostearate SLNs	– Glb-SLNs containing 0.34 mg of equivalent drug in 10 mg/kg dose showed comparable blood glucose-lowering effect to 1 mg of pure drug. – Enhanced glucose uptake was observed in rats L6 myotubes compared to metformin.	– Glb-SLNs demonstrated improved anti-diabetic activity compared to pure glyburide. – The specific compound responsible for the anti-diabetic effect was glyburide, which showed enhanced glucose uptake and comparable blood glucose-lowering effects to the pure drug.	Olga et al. (2015)

Table 9
Polysaccharide-based delivery system of compounds with anti-diabetic effect.

Polysaccharide	Compound	Barrier	Size (nm)	Mechanism	Reference
Chitosan/Pectin	Insulin	Chemical	240–420	pH trigger	Anda-Flores et al. (2021)
Pectinate/chitosan	Cucurmin	Mucoadhesive	218.1	Mucoadhesiveness	Sabra et al. (2019)
Succinyl Chitosan/Alginate	Quercetin	Chemical	90	pH trigger	Wang et al. (2022)
Chitosan-modified	Cucurmin	Chemical	281	Epithelium	Tavano et al. (2014)

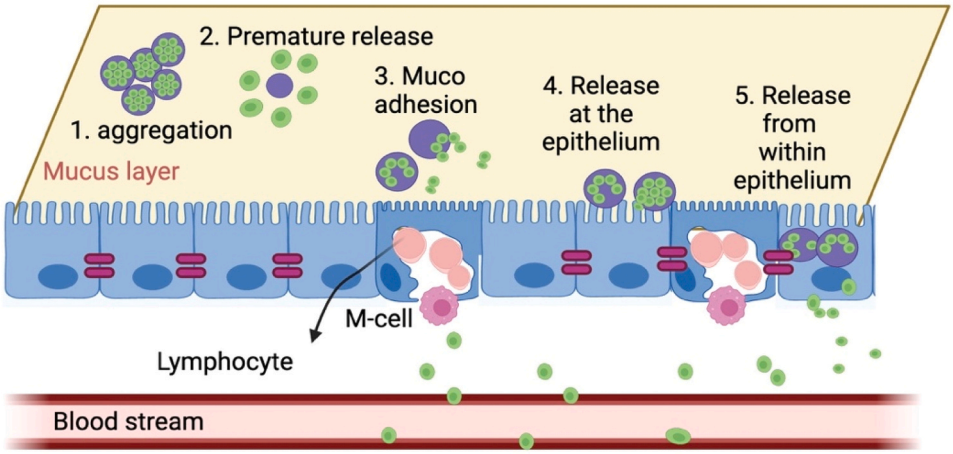

Fig. 13. Mechanism of polysaccharide-based system in drug delivery.

encapsulating bioactive ingredients with high efficiency and controlled release in targeted site (Ubeyitogullari et al., 2022). For instance, wheat and corn starch aerogels have reduced phytosterol crystallinity, enhancing water solubility. The encapsulation of phytosterol into wheat starch aerogel notably improved its bioaccessibility (27.7 %) compared to a crude mixture (1.4 %). This innovative method facilitates the incorporation of water-insoluble bioactives, making it particularly suitable for developing functional foods with anti-diabetic properties (Ubeyitogullari et al., 2022).

Salvia hispanica mucilage alginate complex, evaluated as an encapsulation matrix for chia seed oil, achieved 82.92 % efficiency using a 2 % polymer concentration and 20 minutes cross-linking time, effectively preventing oil deterioration across varying conditions (Us-Medina et al., 2017). Additionally, *Alyssum homolocarpum* seed gum nanoparticles encapsulated D-limonene with 93.24 % efficiency in an O/W nanoemulsion, making it suitable as a flavoring agent. However, entrapment efficiency declined with increased D-limonene concentrations due to insufficient surfactant to stabilize the flavor droplets. Thermogravimetric analysis confirmed the encapsulated D-limonene's thermostability up to 230 °C, with the encapsulating material degrading only above 240 °C, thus preserve the flavor integrity in thermally processed foods (Khoshakhlagh et al., 2017).

In addition, β-carotene emulsions, stabilized by a blend of whey protein isolate and gum Arabic, demonstrated high encapsulation efficiency over 90 %, indicating a delivery system that effectively preserves bioactive compounds compared to direct mixing (Falsafi et al., 2022). Additionally, pectin, commonly used for its emulsifying and color protection properties in food, enhances the bioavailability of bioactives, such as vitamin C and anthocyanins, through nanoencapsulation. For example, vitamin C in a pectin/bovine serum albumin nanohydrogel retained 73.95 % effectiveness after 10 weeks, while a pectin/chitosan nanocomplex protected bilberry anthocyanin against stomach acid, releasing 26 % in gastric juices and 56 % in the intestine, showcasing improved absorption and stability (Peng et al., 2016; Zhao et al., 2020). Hence, polysaccharide-based delivery systems show promise as biomaterials to be applied in the effort of encapsulating anti-diabetic compounds, either independently or in combination with other delivery systems, due to their successful physicochemical characterization for encapsulating bioactive compounds.

5.3. Protein-based delivery systems

Proteins are effective encapsulation materials for bioactive compounds due to their solubility, biodegradability, and emulsifying properties. Their ability to form hydrophobic, pi-pi, hydrogen, and disulfide bonds makes them suitable for encapsulation (Benedé et al., 2015). Fig. 14 and Fig. 15 illustrate the mechanism of protein-based delivery systems. Despite their benefits, proteins, such as plant-based (gliadin, zein, pea protein) and animal-based (whey casein, albumin, gelatin), face challenges like high cost and low cold-water solubility. But, their diverse functional groups on the encapsulation surface allow them to transport both hydrophobic and hydrophilic payloads (Fathi et al., 2018).

Soy protein aggregates enhance stability and UV protection for anti-diabetic bioactives such as vitamin D3, while soy protein-based nanoemulsions improve the bioaccessibility and retention of catechin. Additionally, soy protein isolates enhance the water solubility and bioaccessibility of substances like curcumin, resveratrol, and Coenzyme Q10. The high encapsulation efficiency and durability of lycopene in soy protein-alginate beads demonstrate the efficacy of protein-based carriers for anti-diabetic compounds (Gomes & Sobral, 2022; Lee et al., 2016; Tang, 2019). Furthermore, human and bovine serum albumin are

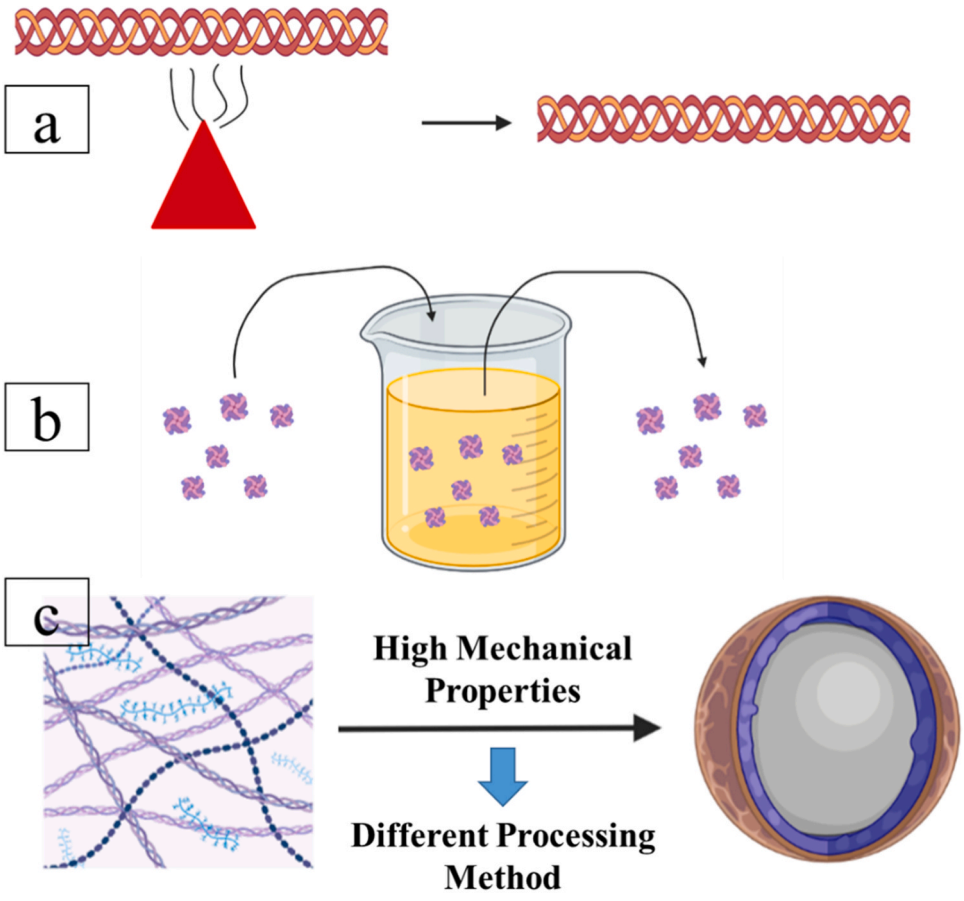

Fig. 14. Physico-chemical properties of protein delivery system (a) high temperature stability, (b) acid resistance and (c) mechanical strength.

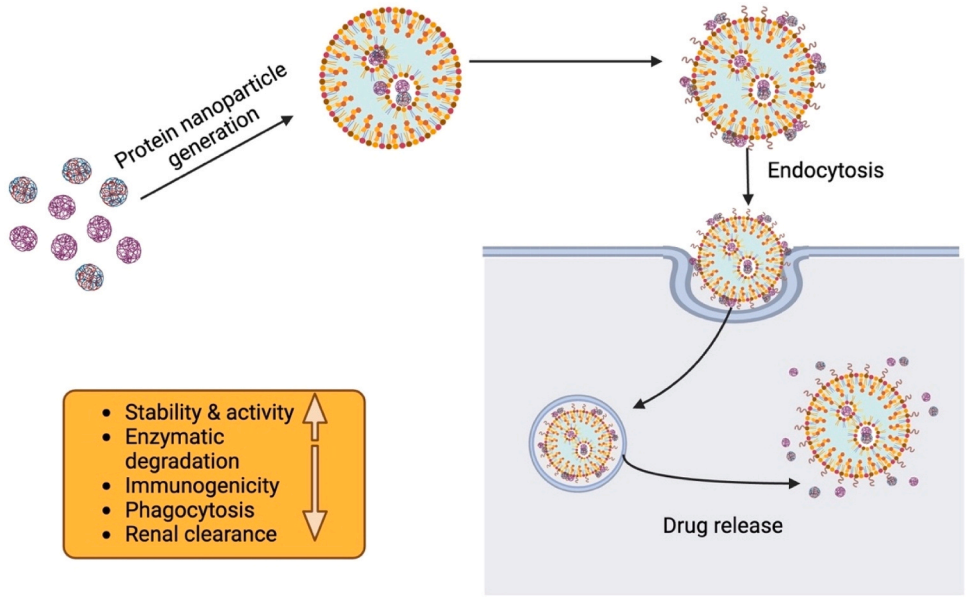

Fig. 15. Mechanism of protein-based delivery system.

widely used to encapsulate bioactive compounds such as catechins and curcumin, owing to their biodegradability, non-toxicity, and non-immunogenicity, making them suitable for delivering anti-diabetic agents (Visentini et al., 2023).

A study on biopolymers combining pectin and whey protein concentrate for encapsulating orange peel oil highlights pH as a critical factor influencing particle size, shape, and encapsulation efficiency (Ghasemi et al., 2017). It was observed that, the most stable nanoparticles (182 nm) were created at pH 6, below the isoelectric point of whey protein, whereas larger particles (185 nm and 360 nm) created at pH 9 and below. Optimal encapsulation efficiency (88 %) was achieved at pH 3, despite particle size growth at higher pH levels, highlighting the need for precise pH optimization for successful encapsulation. Proteins such as collagen, casein, β-lactoglobulin, and silk fibroin, known for their unique properties such as temperature stability, acid resistance, and mechanical strength, are also ideal for bioactive delivery (Ma & Jing, 2020). Lactoferrin, extensively studied for its encapsulation capabilities and revealed to successfully enhances the stability and bioavailability of nutrients such as iron and gambogic acid. This shows that they are more stable and bioavailable in iron-fortified food and demonstrating controlled release in digestive simulations (Liu et al., 2019).

Recent studies have focused on using plant-based proteins as carriers for encapsulating lipophilic bioactive compounds (Gomes & Sobral, 2022). Curcumin encapsulated in pea protein showed a 98.6 % encapsulation efficiency and 72 % bioavailability, while resveratrol in pea protein nanoparticles enhanced water solubility and chemical stability compared to its free form. Protein-based nanocarriers are promising for overcoming the physical and chemical limitations of bioactive compounds in food and therapeutic applications, crucial for producing anti-diabetic enriched foods. They ensure the prolonged release of bioactives, enhancing stability, and minimizing off-flavors, beneficial for managing DM. Table 10 outlines encapsulation strategies using protein-based carriers in food systems, highlighting the effectiveness of this carriers in delivering health benefits, particularly to Type 2 diabetes patients.

Table 10
Protein-based delivery system application in anti-diabetic bioactive compounds encapsulation.

Payload	Particle size of encapsulate	Main Findings	Reference
Tinospora cordifolia extract	187 nm	Enhanced prolonged release of the bioactive, with an encapsulation efficiency of around 91 %, and improved anti-diabetic efficacy.	Jain et al. (2021)
Blackcurrant concentrate soy isoflavones	15–271 μm ~54–60 nm	– Anticancer characteristics of the formulation – Improved the bioactive's stability, antioxidant activity, and bioaccessibility.	Falsafi et al. (2022)
Panax notoginseng saponins	50–60 nm	Reduced bitterness and increased stability in simulated GI media.	Zhou et al. (2021)
Propolis extract	100–242 nm	Highly stable in GI conditions and allows for controlled digestion.	Falsafi et al. (2022)

6. Application of encapsulated bioactive compounds in food products

Encapsulation has attained significant importance in the food industry by safeguarding active material (nutraceutical, vitamins, minerals, flavors, colors, enzymes, chemical leavening agents, antioxidants, and flavors) from extreme environmental conditions and thus maintains its viability and enhances its stability. Additionally, it also become one of the favored methods in bioactive compound encapsulation. There are four major applications of encapsulation in food industry as discussed below.

6.1. Protection of bioactive compound

Protein encapsulation acts as a barrier to protect the bioactive compounds from oxygen, light, pH, heat, moisture, and other extreme conditions, maintaining their bioactivity during processing and storage (de Souza Simões et al., 2017). This method is crucial as antioxidants and vitamins, which are susceptible to bioactivity loss, become more bioavailable when encapsulated. For example, encapsulating vitamins and introducing them into omega-3 fortified cheese has been shown to

delay lipid oxidation over a 90-day storage period at 4 °C (Chawda et al., 2017).

Encapsulation enhances stability by suppressing chemical changes that normally occur during storage, preventing the formation of harmful compounds. For instance, protein encapsulation can effectively inhibit the oxidation of sensitive compounds, ensuring their long-term stability and efficacy. It has been found to be effective especially for probiotics, known for boosting immune and digestive health. Encapsulation supports the survival and activity of microorganisms in the gut. For example, yogurt with encapsulated *L. acidophilus* has shown greater stability compared to yogurt with non-encapsulated cultures (Dias et al., 2017).

The use of nano-biopolymer for encapsulation significantly improves the stability of sensitive bioactive compounds, safeguarding them from degradation. For examples, anthocyanin encapsulated in nano-biopolymers remained stable against thermal degradation (Arroyo-Maya & McClements, 2015). Similarly, nano-spray drying has been effective for encapsulating folic acid in whey protein concentrate, retaining 60 % of its content for 45 days, compared to just 1 % in non-encapsulated form after 15 days (Pérez-Masiá et al., 2015). Furthermore, encapsulated folic acid remained completely stable in dry and dark conditions for 60 days (Pérez-Masiá et al., 2015). Similarly, encapsulation technique such as cross-linked nanosponges have shown remarkable results in enhancing the stability of bioactive compounds. The encapsulation of curcumin in cross-linked nanosponges (cyclodextrin and pyromellitic dianhydride) showed no photodegradation over 10 hours, unlike non-encapsulated curcumin, which degraded by about 48 % in the same timeframe (Pushpalatha et al., 2018). This highlights the capability of encapsulation to prolong the efficacy and stability of bioactive compounds such as curcumin, known for its anti-diabetic and anti-inflammatory properties.

Gum-based nanocarriers are crucial for encapsulating anti-diabetic compounds, ensuring the protection and delivery of bioactive food components. Encapsulation able to maintain the flavour and organoleptic properties of foods such as milk and yogurt by preventing the evaporation of volatile bioactive compound during processing or storage (Taheri & Jafari, 2019). Meanwhile, Tavares et al. (2021) highlighted various encapsulation methods that enhance the stability and antioxidant activity of garlic's alliin, in which emphasizing the importance of adjusting factors such as type of material, wall composition, and final desired properties such as size and release rate are vital for an effective encapsulation. Additionally, Silva et al. (2015) studied the oxidative stability of annatto seed oil, rich in geranylgeraniol, revealed that encapsulated oil showed less oxidation compared to free oil. This exhibited the effectiveness of methods particularly spray and freeze drying in protecting bioactive components. The important for encapsulation is further proved by studies revealed the rapid degradation of non-encapsulated anti-diabetic compounds such as flavonoids and vitamin C under intestinal conditions (Bao et al., 2019). Evidently, encapsulation not only shields bioactive compounds, but also improve food functionality and the performance of the delivery system, increasing the efficacy and bioavailability of anti-diabetic compounds in food applications.

6.2. Controlled delivery

The techno-functional prowess of proteins in delivering bioactive food components to the human body and within the food matrix is characterized by controlled release (Boostani & Jafari, 2021). Earlier, *in vitro* gastrointestinal study by González et al. (2019) focused on encapsulated olive leaf extract in sodium alginate, revealing a controlled release of oleuropein, the predominant polyphenol in olive leaves. The results revealed that the encapsulation positively influenced oleuropein's bioavailability and bioaccessibility, with a gradual release during digestion reaching 58 % after 120 minutes. This resulted, in the bioavailability of oleuropein in encapsulated extract was 20 %, while it remained undetected in the non-encapsulated counterpart due to unrestricted degradation during digestion.

Encapsulation enhances bioactive functionality and timed release in various applications, such as using microstructure gels for controlled iron release in mineral delivery systems (Onwulata, 2013). For instance, *Thymus daensis* in an essential oil-based nanoemulsion shows stronger antibacterial activity than its pure form, demonstrating the advantages of controlled release. Additionally, microencapsulated bioactive compounds in chewing gums exhibit prolonged flavor release, reduced chewiness, and enhanced cooling sensation, as studied by Chawda et al. (2017). Employing encapsulation also maintained 80 % of sour cherries anthocyanin's bioactivity during simulated gastric digestion, ensuring controlled release in the gut (Oancea et al., 2018). Moreover, orange oil encapsulated in electrospun gelatin nanofibers showed an initial rapid release followed by a sustained release over 72 hours (Tavassoli-Kafrani et al., 2018) prompted the addressing of the industrial challenges of using bioactive components by enhancing stability and reducing off-flavors. For example, Reishi medicinal mushroom extract encapsulated with *L. acidophilus* in calcium alginate beads showed a reduction in phenol release by 24.9 %, due to hydrophobic interactions between the wall material and the extract (Mirmazloum et al., 2021). Effective encapsulation systems are characterized by their high loading capacity, efficiency, and the ability to prolong the release of compounds, crucial for the encapsulation of anti-diabetic compounds.

6.3. Taste masking/enhancing organoleptic profile

The rise of commercial and tailored foods enriched with bioactive compounds often leads to bitterness, reducing consumer acceptability. Conventionally, the debittering approach is through the addition of salt and sugar, which, while effective, compromises healthiness and increases consumer rejection due to growing health awareness. Consequently, encapsulation has emerged as a preferable industry technique for debittering (Fig. 16). This method not only masks bitterness but also controls the release of bioactive compounds, modifying undesirable sensory qualities like metallic astringency (Jiménez-Colmenero, 2013; Sun-Waterhouse & Wadhwa, 2013). Thus, encapsulation enhances the overall acceptability of functional foods by ensuring the undesirable tastes are not perceived by consumers.

Vitamins, minerals, and polyphenols are known for their disease mitigation owing to their scavenging properties but their bitter or astringent taste limits their integration in food. Encapsulation reduces the bitterness, improves flavor, and makes them more palatable (Đorđević et al., 2014). Bitterness often results from hydrophobic amino acids produced during proteolytic hydrolysis, with its intensity linked to the spatial arrangement of the peptide's binding and stimulating units. Encapsulation masks the bitterness by limiting the exposure of these amino acids and reducing the concentration that activates bitter taste receptors (Liu et al., 2022).

In addition, the encapsulation techniques were also employed to overcome bitterness in other bioactive compounds relevant to anti-diabetic applications. For example, spray drying was used to mask the bitter taste of whey protein hydrolysate (WPH), resulting in a significantly lower taste dilution assay (TDA) score for encapsulated WPH (TDA = 4) compared to non-encapsulated WPH (TDA = 32) (Yang et al., 2012). Liposome-encapsulated enzymes demonstrated progress in controlling proteolysis during cheese manufacturing, reducing the formation of bitter peptides (Nedović et al., 2013).

Encapsulation techniques are increasingly utilized for reducing the particle size of encapsulated WPH, enhancing food qualities like texture, aroma, and appearance (Yang et al., 2012). Caballero et al. (2022) observed that encapsulated dry phenolic extract of lemon waste and hesperidin has improve orange juice acceptability by mitigating polyphenol bitterness, crucial for adding anti-diabetic compounds to foods. Similarly, encapsulation enabled the stabilization of volatile bioactive lipids like eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)

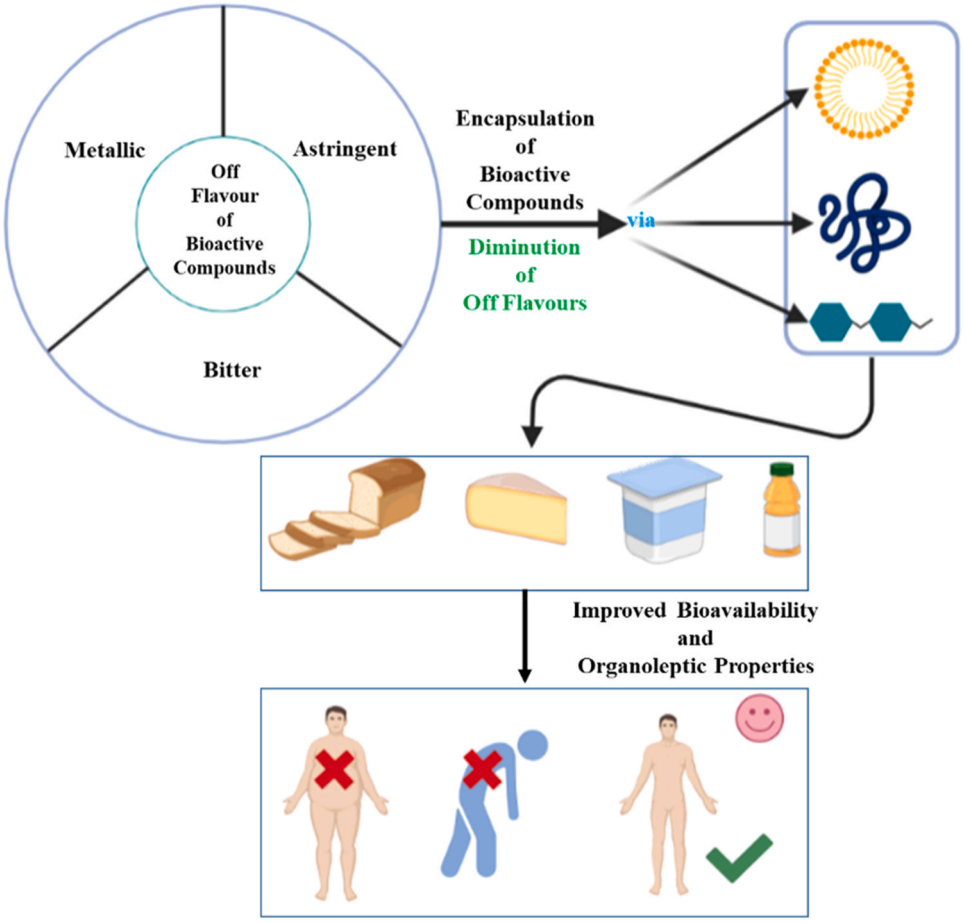

Fig. 16. Nanotechnology – a strategy for improved bio-availability and organoleptic bioactive compounds.

in nanoemulsions, preserving over 60 % retention and enhancing stability and bioavailability for potential therapeutic uses (Ma & Jing, 2020).

Milk proteins, particularly casein-derived, possessed anti-diabetic effect but face challenges like bitterness and poor stability that limit their food application. A study was conducted revealed to be able to tackle these issues by encapsulating casein peptides in electrospun nanofibers using pullulan as the wall material, aiming to mask the bitterness and enhance stability under stomach environment for targeted release. Physicochemical analysis showed these nanofibers were smooth and uniform, and milk fortified with them able to maintain its organoleptic properties (Rajanna et al., 2022).

Furthermore, quercetin, a plant-derived flavonoid known for its anti-diabetic properties, faces limitations in food use due to its bitterness. Hot melt extrusion microencapsulation, using excipients like carnauba wax and zein, effectively reduced this bitterness, as evidenced by electronic tongue evaluations showing a significant taste-masking effect with encapsulated quercetin compared to non-encapsulated forms (Khor et al., 2017). Similarly, cinnamon extract, another potent anti-diabetic agent, also presents palatability challenges due to its strong flavor and astringency. Complex coacervation encapsulation has proven successful in masking these undesirable traits, significantly enhancing the sensory appeal in food products, with trained panelists noting reduced astringency in encapsulated forms compared to non-encapsulated cinnamon (Brito de Souza et al., 2020). This encapsulation also enhances cinnamon's functional benefits, as demonstrated by a study showing a 7.45 % reduction in fasting glucose levels over two months with the consumption of its spray-dried water extract (Anderson et al., 2016).

Based on the previous studies depicted in Table 6, a comparative analysis of various nanodelivery systems reveals the most suitable options for incorporating antidiabetic compounds into food products. Among these, the nanophytosome (Phosphatidylcholine) and nanostructured lipid carriers (Beewax, Phospholipon R, Tween 80) emerge as the most effective. The nanophytosome system, with particle sizes ranging from 144 to 166.7 nm and encapsulation efficiencies of 93–96 %, offers excellent bioaccessibility and enhanced storage stability, making it highly suitable for nutraceuticals and food ingredients aimed at managing diabetes. In comparison, nanostructured lipid carriers, with a smaller size of 133.2 nm and similarly high encapsulation efficiency, provide enhanced stability and bioavailability. This is crucial for functional foods and beverages that require both long shelf-life and high efficacy of the active compounds. These systems ensure that bioactive compounds remain stable during processing and storage and are effectively released and absorbed in the body, thereby enhancing their therapeutic potential in managing diabetes. Therefore, considering both size and encapsulation efficiency, nanophytosome and nanostructured lipid carriers stand out as the best nanodelivery systems for encapsulating bioactive compounds for diabetics.

7. Market trends in bioactive-based anti-diabetic food products

According to the diabetic food research report by the Business Research Company, the global relevant market is growing at a compound annual growth rate (CAGR) of 5.2 %, valued at 10.63 billion USD in 2022, and is expected to reach 12.91 billion USD by 2025 with a CAGR of 5.0 %, driven by rising diabetes cases among children and youth (The Research Business Company, 2022). In 2021, the Centers for Disease Control and Prevention (CDC) reported that approximately 8.5 % of the U.S. adult population was diagnosed with diabetes mellitus (DM) (CDC, 2021). Factors such as a sedentary lifestyle and stress are

Table 11
Various commercial product from multiple companies with anti-diabetic prevention initiatives.

Company	Examples of products	Anti-diabetic prevention	Reference
Nestlé S.A.	Nescafé Protect Proslim,	Low-sugar and low-carb products that help regulate blood sugar levels and support digestive health	Nestle (2021)
The coca cola company	Coca-cola life	Reduced-sugar and natural-sweetened beverages that may help lower calorie intake, but still contain some sugar and calories	The CocaCola Company (2014)
	Coca-cola zero sugar		
	Honest kids		The CocaCola Company (2019)
Unilever PLC	Lipton green tea	Low-sugar, low-fat, and high-fiber products that may help reduce the risk of diabetes and obesity	Unilever (2018)
	Breyers delight		Unilever (2017)
Pepsi.Co, Inc	Quaker oat	Natural, whole-grain, and high-protein products that may help improve blood sugar control and satiety	Fraser (2022)
Mars, Inc	Dove dark chocolate	Lower-sugar and lower-calorie products that may help satisfy cravings, but still contain some sugar and fat	Marc (2022)
Kellog Company	Special K	Whole-grain, high-fiber, and low-sugar products that may help lower blood sugar levels and cholesterol	Kellog (2022)
	All-Bran		Kellogs (2018)
	Kashi		Kellogs (2018)
Cadbury	Cadbury	Reduced-sugar products that may help reduce sugar intake, but still contain some artificial sweeteners and calories	Wood (2018)

anticipated to increase DM prevalence, fueling the relevant market growth. Major players in this market include Nestlé, Hill Pharmaceutical, Unilever, Kellogg's, The Coca-Cola Company, Mars Incorporated, PepsiCo, Hersheys, and Tyson Foods (Table 11) (Report Market Analysis, 2022).

The diabetic food market is segmented by product type, end consumers, distribution channel, and region. Dairy products, particularly cheese and yogurt, accounted for the largest revenue share, approximately 25 % in 2021, with companies like Chobani expanding their offerings to include 'Zero Sugar' yogurts sweetened with natural, non-GMO sugar alternatives that are lactose-free and less than 70 calories (Report Market Analysis, 2022). The global market for functional foods and beverages is projected to reach USD 356.3 billion by 2025, growing annually at about 7 %. Major beverage companies like Sprite, Pepsi, and Coke are diversifying into functional beverages and protein shakes to dominate the market. This surge in functional food development has led companies to heavily invest in R&D, aiming to produce novel foods from natural sources with improved biological and sensory properties to combat diseases like diabetes. Several impact innovations include FlavoPlusTM by Riddet Institute, a patented ingredient that stabilizes high concentrations of flavonoids in food and the use of grape anthocyanins and black tea flavonoids in kefir, carbonated drinks, and bakery products (de Oliveira et al., 2022).

The demand for functional foods is increasing, particularly in the development of anti-diabetic beverages using ingredients like isomaltulose and sucralose, highlighted for their metabolic benefits (Ahmad et al., 2020). The discovery for low-glycemic, low-calorie sweeteners such as allulose, inulin, stevia, and monk fruit is increasing, aiming to substitute sugar in foods including confectionery and desserts (Clemens, 2017). Additionally, functional pasta enriched with soy isoflavone has shown benefits for cardiovascular health in individuals with T2DM. other than that, research on alcohol-free beer, which is rich in phenolic acids, flavonoids, and vitamins, revealed that modifying its carbohydrate content with isomaltulose and maltodextrin can improve insulin resistance T2DM diabetes by promoting beneficial gut bacteria (Mateo-Gallego et al., 2021). Another study found that beverages with isomaltulose enhanced hydration more effectively than those with sucrose, demonstrating a delayed increase in postprandial blood glucose (Amano et al., 2021). These multifaceted innovations highlight the growing interest in formulating functional foods and beverages with anti-diabetic benefits.

Market trends show an increasing interest in bioactive-based anti-diabetic foods, particularly herbal, vegetable, and fruit-based beverages. For instance, nutritive and low-calorie powdered drink developed from tannins of sorghum underwent a comparative assessment of antioxidant activity and total phenol content. The findings exhibited higher antioxidant activity and total phenol content 75 μmol TE/g and 6.05 GAE/g, respectively. On the other hand, tannin free powdered mix exhibited lower antioxidant activity (15.2 μmol TE/g) and total phenol content (4.4 GAE/g). The results indicate the potential of introducing the tannin fortified powdered drink mix into the market to ensure health benefits (Queiroz et al., 2018). Medicinal plants like *Azadirachta indica*, *Matricaria chamomilla*, and *Camellia sinensis*, as well as various fruits and vegetables, have demonstrated anti-diabetic properties in previous research (Gayathry & John, 2021). These plants are used in Ayurvedic and traditional Chinese medicine and are potential candidates for functional beverages to treat or prevent diabetes. Similarly, seaweeds, integral to diets in coastal Asian communities, exhibit anti-diabetic effects due to their rich content of carotenoids, polyphenols, and other bioactive compounds. For instance, methanolic extracts of P. arborescens inhibited α-glucosidase and α-amylase with IC50 values of 0.23 mg/mL and 0.26 mg/mL, respectively. *S. ringgoldium* extracts showed stronger inhibition, with IC50 values of 0.12 mg/mL for α-glucosidase and 0.18 mg/mL for α-amylase in which highlighted their potential in diabetes management (Lee & Jeon, 2013; Sharifuddin et al., 2015). These findings support further *in vitro*, *in vivo*, and clinical studies to validate these foods hypoglycemic properties. Additionally, marine algae, with their abundant bioactive components, are being incorporated into various snacks and fermented foods, enhancing their nutritional and health benefits (Nova et al., 2020). Briefly, functional food-based interventions and lifestyle changes, alongside therapeutics, are effective in managing diabetes. Foods low in carbohydrates and sugar regulate blood glucose levels (Data Reports, 2022). In this context, the other possible reasons for the concerned market expansion include rising disposable income, proliferation of hypermarkets, supermarkets and increasing geriatric population (IMARC, 2022). Products with a low glycemic index or enriched with functional bioactive compounds appeal to both individuals managing diabetes and health-conscious consumers, promoting a healthier, sustainable future.

8. Future perspective and conclusions

The utilization of nanoencapsulation for bioactive compounds represents a significant advancement, in which improving the shelf life and

thermal stability of food products. The choice of encapsulation technique should align with the properties of the bioactive components to maximize loading efficiency and select the most effective delivery system—whether its protein, lipid, polysaccharide, or a conjugated system. Ultimately, the goal of encapsulation is to achieve high loading efficiency, ensuring the preservation of bioactivity within the food matrix for consumer benefit.

The integration of nanotechnology has significantly advanced the development of smart foods with bioactive substances, serving to the needs of individuals with DM and health-conscious consumers. Despite this advancement, challenges remain in transforming scientific discoveries into marketable products. Addressing this challenge requires scaling up production once nanoencapsulated bioactive substances are validated in the laboratory. On the other hand, further *in vivo* studies are crucial to understand how biomaterials interact with bioactive compounds, their release profiles, and behavior in the gastrointestinal tract. In addition, a detailed and comprehensive approach is essential, focusing on ethical, safety, and regulatory considerations in the development of delivery systems for bioactive compounds.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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