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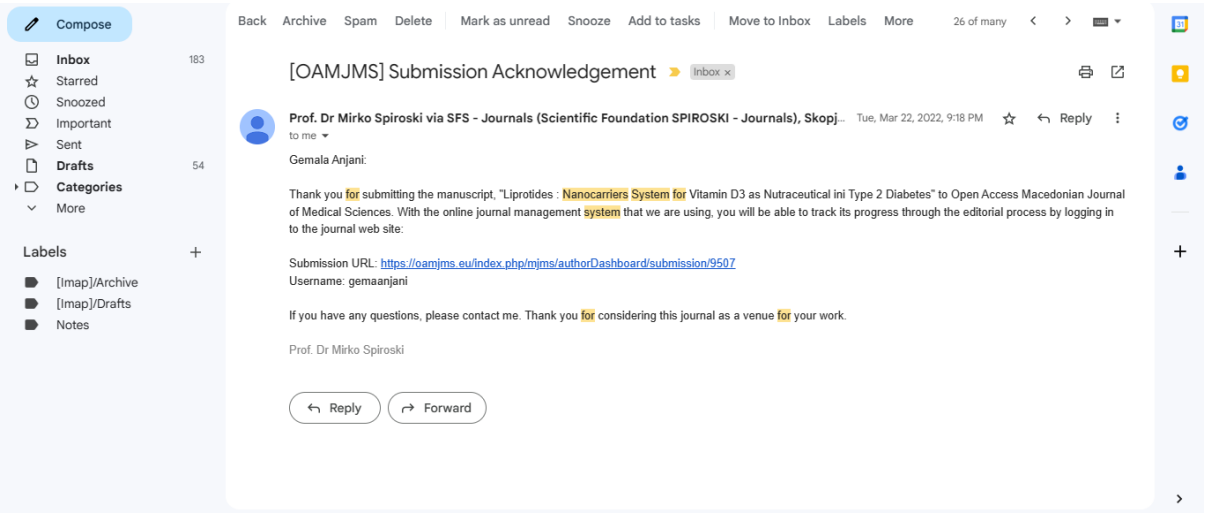

Artikel Awal

Liprotides : Nanocarriers System for Vitamin D3 as Nutraceutical ini Type 2 Diabetes

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Abstract

Incidence of diabetes are common among population around the world. Diabetes may lead to other complication and increasing morbidity and mortality. Many ways have been done to treat and prevent the development of diabetes. In addition of conventional pharmacotherapy, therapeutic therapy shown good opportunity to maintain and improve diabetic conditions. Vitamin D3 is known as nutraceutical and has good opportunity to develop the medication of type 2 diabetes. In another way, vitamin D3 naturally easy to damage by environmental condition. To overcome this weakness, researcher around the world have developed the method for protecting unstable compound as vitamin D3 with encapsulation. Liprotide is one of the various materials which can be used for encapsulation. Combination of lipid and protein molecules is expected to be a carrier and protector of vitamin D3 in gastrointestinal system. Here we review the research advances of liprotide as nanocarriers and vitamin D3 as nutraceuticals to discuss in applied on type 2 diabetes.

Keyword : Liprotides, Vitamin D, Diabetes Mellitus, Encapsulation

Introduction

Diabetes is a major worldwide health problem that increasing every year. Data from International Diabetes Federation (IDF) in 2019 show 9,3% world population aged 20-79 years old had diabetes. Indonesia get 1st ranks country with diabetes in Southeast Asia with 10,7 million diabetic people [1]. The Indonesian Basic Health Research (RISKERDAS) in 2018 showed the prevalence of diabetes in Indonesia was 2% in the population aged >15years [2]. Increasing number of diabetes influenced by vitamin D deficiency. Vitamin D is known has positive effect in diabetes, but the prevalence of vitamin D deficiency shows the large number. Many countries around the world report the incidence of vitamin D deficiency. United Stated and Europe show 5,9% and 13% population has vitamin D deficiency [3]. In Indonesia 45,1% children aged 1-18 years and 82% productive age woman have vitamin D deficiency [4].

Vitamin D has significant role in diabetes to maintain blood glucose tolerance [5], decrease insulin resistance [6], and as a gene transcription factor [7]. These fat-soluble vitamins can be obtained from food intake and formed by the body but have low bioavailability. Food sources of vitamin D is not much and the vitamin D content in foodstuffs is low [8]. The nature of vitamin D is easily to damage by heat, light, oxidation, and acid. That thing made the bioavailability of consumed vitamin D is low [9,10]. One of the methods to maintain vitamin D bioavailability is encapsulation. The method has function as a carrier and protector agent of vitamin D in gastrointestinal tract.

There are various many ways in application of encapsulation method, one of which is using liprotides. Liprotides is a component that composed from complex molecule of lipid and proteins. This biomolecule has potential effect as a nanocarrier of nutrients as vitamin D. The structure of Liprotide consist of a core and a shell. Core structure of liprotide system composed by lipid molecule and the shell structure composed by protein molecules that partially denatured [11]. There is various biomolecules types of

lipid and protein to form liprotide system, but combination form of oleic acid and α-Lactalbumin (OA-α-La) and oleic acid and β-Lactoglobulin (OA-β-Lg) show high encapsulation efficiency [12]. Protein molecule of α-Lactalbumin binding vitamin D through hydrogen bonds, hydrophobic bonds, and van der Walls bonds [13]. β-Lactoglobulin molecules bind to fatty acid molecules through hydrogen and van der Walls bonds [14]. Oleic acid as lipid molecules can bind the vitamin D through hydrophobic bonds and bind lipid molecules through hydrogen and van der Walls bonds [15].

Characteristics of Gastrointestinal in Diabetes

Diabetes mellitus (DM) is a chronic disease characterized by disturbances in carbohydrate, fat and protein metabolism. Common symptoms of this disease are polydipsia, polyuria, polyphagia, and weight loss. This disease involves the endocrine hormones of the pancreas (insulin and glucagon) and is associated with impaired physiological function of insulin. There are two types of DM disease based on endogenous insulin secretion, Insulin Dependent Diabetes Mellitus (IDDM) or commonly known as type 1 diabetes mellitus (T1DM) and Non-Insulin Dependent Diabetes Mellitus (NIDDM), commonly known as type 2 diabetes mellitus (T2DM) [16]. In worldwide, 90-95% of diabetics people have T2DM. The increasing prevalence of T2DM going rapidly influenced by sedentary lifestyle such as low physical activity, high intake of fast food and sweet sugar beverage, and low intake of fruits and vegetables [1]. Overweight, obesity or central obesity, and hyperglycemia in pregnancy are factors that influence the incidence of insulin resistance in people with T2DM [17].

The condition of diabetes affects various physiological functions of the body, including the digestive tract. Some problems in the digestive tract that are often found in patients with diabetes are a longer gastric emptying time to the accompanying diarrhea problem. The physiological functions of digestive tract, starts from the esophagus to the anus will changes in a person with diabetes. Vital function of the digestive tract to maintain life will be disrupted. The condition of diabetes will affect the ability of the gastrointestinal organs both directly and indirectly. Obstacles in the process of swallowing, movement of organs, breakdown and absorption of nutrients, to the process of removing residual waste will affect long-term health. Various digestive problems such as gastro-esophageal reflux (GERD), nausea, vomiting, bloating, diarrhea to constipation can accompany diabetic patients that will worsen the condition if not treated immediately [18]. By reducing the burden of the stomach and mild method of giving oral therapy, diabetics person will be easier to carry out consumption therapy. In addition, proper and efficient administration of nutraceuticals will reduce unwanted signs and symptoms in undergoing therapy.

Vehicles for Delivery Nanocarriers System

Liprotides are complex molecules composed from fat (lipid) molecules and protein molecules. Protein have a role as a shell while fat as a core. The core-shell structure formed from the lipotide complex can be used for encapsulate other molecules. The primary function of the protein coat is to increase the solubility of fatty acids. This ability makes liprotides potential to carry hydrophobic molecules in a hydrophilic environment. Another function of the protein coat is to carry and deliver fatty acids to target cells or hydrophobic surfaces. Liprotides can stabilize small aliphatic molecules such as retinol and tocopherols by inserting the molecules into the fatty acid core [19].

Liprotides can protect tocopherols better than tocopherol-binding proteins such as beta lactoglobulin and protein transfer α-tocopherol. Liprotides can be used to stabilize and deliver a wide variety of hydrophobic small molecules with potential health benefits [14]. In general, liprotides can increase the stability and solubility of molecules to be able to form complexes [20]. Liprotides can easily deliver the carried compound into the membrane target, but can decrease the stability of the complex matrix under various conditions. Liprotides consisting of α-lactalbumin and oleic acid can dissolve vitamin D, increasing vitamin D stability against UV rays by 9 times, and increase the stability of vitamin D at 37^0C up to 1,000 times [20]. α -lactalbumin can interact strongly with monolayer oleic acid by diffusion and absorption on the surface, incorporation with films, and protein-lipid complexes between molecules by hydrophobic interactions [21]. Liprotides are able to release vitamin D by transferring vitamin D to phospholipid vesicles. Vitamin D encapsulated by liprotides using α-lactalbumin-oleic acid and β-lactoglobulin can increase the availability of vitamin D in clear beverage products with neutral pH [20].

α-lactalbumin

α-lactalbumin is one of the whey proteins in cow's milk than can be a good candidate for vitamin encapsulation. α-lactalbumin is able to bind hydrophobic ligands such as retinol and hydrophobic peptides. Bio macro-molecules such as proteins have potential opportunity for vitamin encapsulation. Based on research conducted by Delevari et al α-lactalbumin has one binding site for vitamin D3 [13]. When hydrophobic interactions formed, the conformation of the protein was changes and the hydrophobic surface of α-lactalbumin increases. The secondary structure of α-lactalbumin is changed in the presence of vitamin D3. α-lactalbumin is a small globular protein with 123 amino acids and molecular mass of 14.2 kDa. α-lactalbumin is the predominant protein in human milk. In cow's milk, the concentration of α-lactalbumin is 1-1.5 g/L (3.4% total protein). The natural structure of bovine α-lactalbumin consists of a large helical domain and a small beta layer domain, both of them are connected by a loop. α-lactalbumin has a hydrophobic site and made α-lactalbumin to have one binding site to bind other compounds, like vitamin D3 [13]. Solubility of α-lactalbumin can be affected by certain condition of pH, temperature, and ionic state [22]. α-lactalbumin is relatively resistant to protease digestive enzymes (pepsin and trypsin) because of the globular and dense structure [23]. Whey protein isolate contains 17% of α-lactalbumin and α-lactalbumin contains 48 mg of tryptophan and 48 mg of cysteine per gram of protein [24]. Tryptophan in α-lactalbumin can increase the tryptophan levels in the blood that can help synthesis and increase the availability of serotonin in the brain. α-lactalbumin also accelerate wound healing [25], for recovery from various types of sports [26].

β-lactoglobulin

β-lactoglobulin is a component that found in milk whey and soluble in salt solutions. β-lactoglobulin belongs to the lipocalin protein group [27] and has been shown to bind various hydrophobic molecules like fatty acids [28], retinol, and vitamin D [29]. β-lactoglobulin can bind fatty acids such as oleic acid and linoleic acid. The research

showed that the complex of β-lactoglobulin and oleic acid could increase the tertiary structure. β-lactoglobulins has more binding sites for oleic acid more than linoleic acid that interacting with van der Waals bonds and hydrogen bonds [14]. Encapsulation of vitamin D_3 with β-lactoglobulin with lysozyme modification could increasing the bioavailability, resistance to pH, and solubility [30]. β-lactoglobulin has 162 amino acid residues and molecular weight 18.4 kDa. β-lactoglobulin is the main component of whey protein in milk that can freeze and denature when milk was boils. After denaturation, β-lactoglobulin forms a film layer on the milk surface. It happen because β-lactoglobulin protein molecule can form a transparent gel when heated for a long time at low pH and low ionic strength [30]. β-lactoglobulin is known as an allergen, the manufacturers need to prove the presence or absence of β-lactoglobulin content to ensure that the labeling meets the requirements. Food testing laboratories can use enzyme immunosorbent assay methods to identify and measure β-lactoglobulin in food products. Polymerization of β-lactoglobulin by microbial transglutaminase reduces its allergenicity in children and adults with immunoglobulin E (IgE)-mediated cow's milk allergy [31].

Oleic Acid

Oleic acid is an unsaturated fatty acid that is easily obtained and can be extracted from several different sources, one of which is olive oil. Apart from olive oil (55-80%), these fatty acids are also contained in industrial waste from palm oil, sunflower oil, rapeseed oil, and grape seed oil. The availability of oleic acid in nature is very abundant and is commonly used in the manufacture of surfactants, soaps, plasticizers, and food and drug emulsifiers [32]. This acid is composed of 18 C atoms with one double bond between the 9th and 10th C atoms. The oleic acid structure has two functional groups, alkenes and carboxylic acids. Presence of alkenes with Z isomer, the bond between oleic acid molecules becomes stronger and made oleic acid is in liquid phase at room temperature. In polar solvents, oleic acid forms a bilayer structure [32]. Oleic acid, as part of liposomes, has limitations in its use due to the tendency to break down and causing release. One method to increase its stability is by coating with protein to form a complex called a lipotide [33].

Vitamin D3 as Nutraceutical in Diabetes

Vitamin D is a non-essential fat-soluble vitamin that has a huge and important role in calcium homeostasis [34,35]. Structurally, vitamin D is a derivative of steroid compounds in the body [36]. Vitamin D can be obtained from food intake and supplementation. It can be activated through exposure to sunlight in the form of vitamin D3. However, the prevalence of vitamin D deficiency worldwide is still high [1]. Vitamin D supplementation can be a solution to sufficient vitamin D requirement, but it still does not cover a wide population. Vitamin D fortification is an alternative to reduce vitamin D deficiency that has potential affect to cover a wider population and potentially increase vitamin D intake. The form of vitamin D used for fortification is vitamin D2 or vitamin D3 [37]. Fortification of the active form of vitamin D (vitamin D3) is considered efficient in the supplying requirement of vitamin D. Addition of vitamin D3 to food has shown an improvement of blood glucose and insulin status in diabetes mellitus [38]. Vitamin D deficiency has been associated with decreasing of insulin release, increasing of insulin resistance and type 2 diabetes mellitus. Vitamin D deficiency

causes dysregulation of glucose metabolism by interfering with glucose-stimulated insulin secretion in the hyperglycemic phase [39]. Vitamin D intake has an effect on insulin resistance and positively correlated with insulin secretion in patients with type 2 diabetes mellitus. Supplementation of orally high-dose cholecalciferol (10,000 IU per day for 4 weeks) as a replacement dose showed an increase insulin sensitivity of 37% in subjects with fasting blood glucose disorder [40]. Study in diabetic wistar rats was proven that fortification of vitamin D3 in foodstuffs can significantly reduce blood sugar levels [38]. This thing was happened because increasing of serum vitamin D concentration has a positive effect on insulin homeostasis [41].

Systemic inflammation is one of the causes of type 2 diabetes mellitus (T2DM) and insulin resistance occurs in it. Vitamin D has an anti-inflammatory effect and it is useful to overcome the inflammation. In the metabolic process, vitamin D3 plays a role in preventing and improving the status of diabetes mellitus. Vitamin D can provide benefits for several disease prevention, such as in multiple sclerosis, cancer, bacterial infections [42], and diabetes [40]. Vitamin D is maintaining glucose tolerance through insulin secretion and sensitivity [5]. Vitamin D3 has function in insulin synthesis and secretion by modulating the intracellular calcium homeostatic system. Vitamin D is protective against insulin resistance because it has anti-inflammatory effects. Pancreatic beta cells have a specific receptor for 1,25(OH)2D that regulates insulin secretion. Vitamin D also stimulate insulin receptor expression and trigger insulin response to glucose. In other way, vitamin D provide sufficient intracellular cytosolic calcium for insulin secretion through regulation of calcium flux in cell membrane [6]. The metabolism can be concluded that vitamin D has a positive effect on insulin resistance [43].

Future Perspective

Design and development of nanoparticle-based nutraceuticals therapy as an alternative treatment for degenerative diseases has shown good results. Vitamin D is known have a positive effect to improving diabetes status and used for the alternative therapies for diabetic patients. However, there are many obstacles, both in terms of absorption and bioavailability of Vitamin D. The nano-encapsulation method has a chance to increase the bioavailability of vitamin D. Nutraceuticals therapy using vitamin D3 encapsulated with liprotide could be a new alternative in oral therapy of diabetes type 2.

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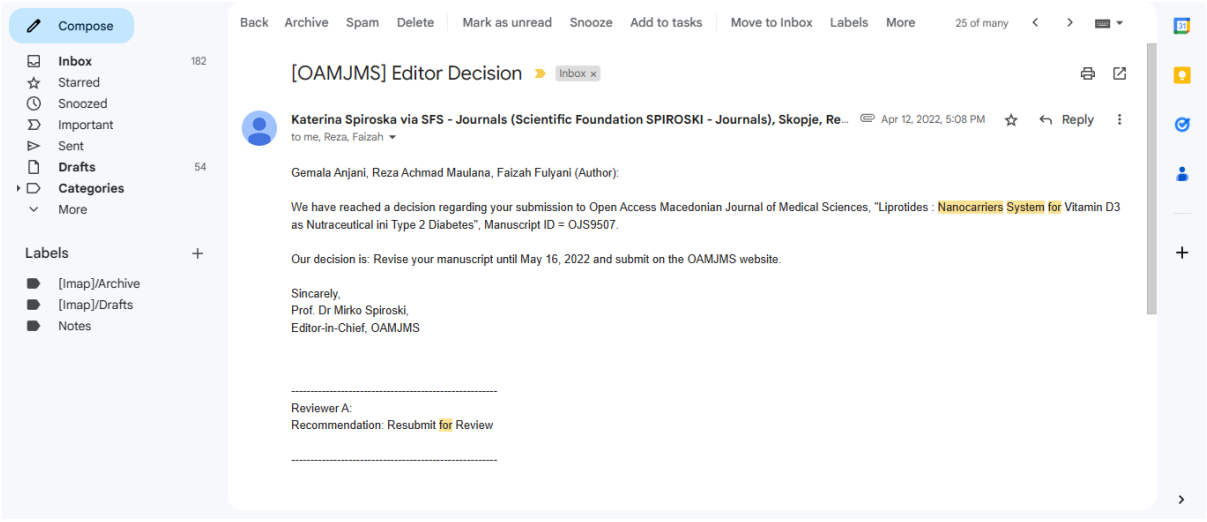
Hasil Review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Artikel Revisi

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Nanocarriers System for Vitamin D as Nutraceutical in Type 2 Diabetes Mellitus:

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Abstract

Incidences of diabetes are common among populations around the world. Diabetes may lead to other complications and increased morbidity and mortality. Many ways have been done to treat and prevent the development of diabetes. In addition to conventional pharmacotherapy, therapeutic therapy has shown good opportunities to maintain and improve diabetic conditions. Vitamin D is known as a nutraceutical and has a good opportunity to develop the medication for type 2 diabetes. The application of nanocarriers as a delivery system increases the bioavailability of vitamins, escalate cellular delivery, and optimizes the vitamin effect. By utilizing nanotechnology-based dietary supplements, the problem of vitamin administration, vitamin stability, absorption, and bioavailability will be resolved. In this review, we would try to compare the most relevant aspect of nanocarrier for vitamin D as a nutraceutical in type 2 diabetes.

Keywords: Nanocarriers, Vitamin D, Diabetes Mellitus, Encapsulation

Introduction

Diabetes is a major worldwide health problem that increasing every year. Data from International Diabetes Federation (IDF) in 2019 show that 9,3% world population aged 20-79 years old had diabetes. Indonesia gets 1st rank country with diabetes in Southeast Asia with 10,7 million diabetic people(1). The Indonesian Basic Health Research (RISKERDAS) in 2018 showed the prevalence of diabetes in Indonesia was 2% in the population aged >15years(2). The increasing number of diabetes is influenced by vitamin D deficiency. Patients with type 2 diabetes mellitus (T2DM) show lower levels of vitamin D compared with normal people(3). Vitamin D is known to have a positive effect on diabetes, but the prevalence of vitamin D deficiency shows a large number. Many countries around the world report the incidence of vitamin D deficiency. The United States and Europe show that 5,9% and 13% population have vitamin D deficiency(4). In Indonesia, 45,1% of children aged 1-18 years and 82% of productive-age women have vitamin D deficiency(5).

Vitamin D has a significant role in diabetes to maintain blood glucose tolerance(6), decrease insulin resistance(7), and as a gene transcription factor(8). This fat-soluble vitamin can be obtained from food intake and formed by the body but have low bioavailability. Food sources of vitamin D are not much and the vitamin D content in foodstuffs is low(9). The nature of vitamin D is easy to damage by heat, light, oxidation, and acid. That thing made the bioavailability of consumed vitamin D low(10,11). To overcome this issue, the application of nanotechnology-based dietary supplements

could be applicated. Vitamin D encapsulation would maintain vitamin bioavailability. The encapsulation method has two functions, as a carrier and protector agent of vitamin D in the gastrointestinal tract.

The application of nanocarrier technology has provided many breakthroughs for the development of medicine around the world. When compared with the conventional method, the application of nanocarrier provides more advantages(12). Nanocarrier involved in drug and vitamin delivery show an increase in water solubility of water-insoluble substances, protecting against degradation from the environmental condition, and inactivation(13). The application of nanotechnology as a nanocarrier system must pay attention to many aspects. The nature and action of the carrier should be investigated when planning to apply as drug-delivery or vitamin delivery (14–16). The most important thing is the biocompatibility system of the nanocarrier. The system must be safe, non-toxic, and not trigger an immune reaction in the human body(17–19). The objective of this review is to highlight the recent update on the development of nanocarrier for vitamin D and the opportunity to be nutraceuticals in T2DM.

Diabetes Mellitus

Glucose is a product of carbohydrate metabolism. Blood glucose is a very important part of maintaining the body's physiological functions as a source of energy. Blood glucose levels rise after meals and are usually low in the morning and before meals. Blood glucose levels are maintained to maintain balance in the body. Blood glucose levels are regulated by the pancreas gland. When blood glucose levels drop, the pancreas releases glucagon, a hormone that targets liver cells, which are glycogen stores. With the help of the hormone glucagon, glycogen is converted into glucose in the liver (the process of glycogenolysis) and glucose is released into the bloodstream. In conditions of high blood glucose levels, the hormone insulin is released from the pancreas. The hormone insulin increases the transport of glucose from the circulation to the muscles and liver. In the liver, glucose is converted to glycogen (the process of glycogenesis). In normal conditions, the homeostasis of the blood glucose in circulation will be balanced, but it not going well in diabetes. In a diabetic person, the blood regulation will be disturbed and causing many defects in the body due to the complications.

Diabetes mellitus (DM) is a chronic disease characterized by disturbances in carbohydrate, fat, and protein metabolism. Common symptoms of this disease are polydipsia, polyuria, polyphagia, and weight loss. This disease involves the endocrine hormones of the pancreas (insulin and glucagon) and is associated with the impaired physiological function of insulin. There are two types of DM disease based on endogenous insulin secretion, Insulin Dependent Diabetes Mellitus (IDDM) or commonly known as type 1 diabetes mellitus (T1DM), and Non-Insulin Dependent Diabetes Mellitus (NIDDM), commonly known as type 2 diabetes mellitus (T2DM)(20). Worldwide, 90-95% of diabetics people have T2DM. The increasing prevalence of T2DM going rapidly influenced by sedentary lifestyles such as low physical activity, high intake of fast food and sweet sugar beverage, and low intake of fruits and vegetables(1,21). Overweight, obesity or central obesity, and hyperglycemia in

pregnancy are factors that influence the incidence of insulin resistance in people with T2DM(22).

Diabetes mellitus is a metabolic disease with the characteristic of insufficient insulin production or ineffective insulin physiological performance. Insulin is a key of the body to deliver blood glucose from circulation to the cell's target(1). T2DM is a metabolic disorder with the characteristic of insulin resistance, impaired insulin secretion, and increased glucose production. T2DM is preceded by abnormal sugar homeostases like impaired fasting glucose or impaired glucose tolerance(23). Insulin resistance (IR) is considered one of the mechanisms that developed T2DM. IR disrupts the glucose intake from blood circulation and is involved with the over-production of hepatic glucose(24). To lead to T2DM, the IR condition usually occurs over a long time. Due to the IR condition, the human body will compensate for homeostasis in the form of producing large amounts of insulin hormone. The long-term condition of insulin overproduction would lead to pancreatic beta-cell dysfunction due to systemic inflammation. The pancreatic beta-cell dysfunction is associated with beta-cell death(25).

The condition of diabetes affects various physiological functions of the body, including the digestive tract. Some problems in the digestive tract that are often found in patients with diabetes are a longer gastric emptying time to the accompanying diarrhea problem. The physiological functions of the digestive tract, starting from the esophagus to the anus will change in a person with diabetes. A vital function of the digestive tract to maintain life will be disrupted. The condition of diabetes will affect the ability of the gastrointestinal organs both directly and indirectly. Obstacles in the process of swallowing, movement of organs, breakdown and absorption of nutrients, to the process of removing residual waste will affect long-term health. Various digestive problems such as gastroesophageal reflux (GERD), nausea, vomiting, bloating, diarrhea to constipation can accompany diabetic patients which will worsen the condition if not treated immediately(26). By reducing the burden on the stomach and mild methods of giving oral therapy, diabetics person will be easier to carry out consumption therapy. In addition, proper and efficient administration of nutraceuticals will reduce unwanted signs and symptoms in undergoing therapy.

Vitamin D as Nutraceutical in Diabetes

Vitamin D is a non-essential fat-soluble vitamin that has a huge and important role in calcium homeostasis(27). Structurally, vitamin D is a derivative of steroid compounds in the body(28). Vitamin D can be obtained from food intake and supplementation. It can be activated through exposure to sunlight in the form of vitamin D3. The nature of vitamin D is easy to damage by heat, light, oxidation, and acid. That thing made the bioavailability of consumed vitamin D low(10,11). However, the prevalence of vitamin D deficiency worldwide is still high(1). Vitamin D supplementation can be a solution to sufficient vitamin D requirements, but it still does not cover a wide population. Vitamin D fortification is an alternative to reduce vitamin D deficiency that has the potential effect to cover a wider population and potentially increase vitamin D intake. The form of vitamin D used for fortification is vitamin D2 or vitamin D3(29). Fortification of the active form of vitamin D (vitamin D3) is considered efficient in the supplying

requirement of vitamin D. Addition of vitamin D3 to food has shown an improvement in blood glucose and insulin status in diabetes mellitus(30). Vitamin D deficiency has been associated with decreasing insulin release, increasing insulin resistance, and type 2 diabetes mellitus. Vitamin D deficiency causes dysregulation of glucose metabolism by interfering with glucose-stimulated insulin secretion in the hyperglycemic phase(20). Vitamin D intake affects insulin resistance and is positively correlated with insulin secretion in patients with type 2 diabetes mellitus. Supplementation of orally high-dose cholecalciferol (10,000 IU per day for 4 weeks) as a replacement dose showed an increased insulin sensitivity of 37% in subjects with fasting blood glucose disorder(31). A study in diabetic Wistar rats has proven that fortification of vitamin D3 in foodstuffs can significantly reduce blood sugar levels(32). This thing happened because increasing serum vitamin D concentration has a positive effect on insulin homeostasis(33).

Systemic inflammation is one of the causes of type 2 diabetes mellitus (T2DM) and insulin resistance occurs in it. Vitamin D has an anti-inflammatory effect and it is useful to overcome inflammation. In the metabolic process, vitamin D3 plays a role in preventing and improving the status of diabetes mellitus. Vitamin D can provide benefits for several disease prevention, such as multiple sclerosis, cancer, bacterial infections(34), and diabetes(35). Vitamin D is maintaining glucose tolerance through insulin secretion and sensitivity(6). Vitamin D3 has a function in insulin synthesis and secretion by modulating the intracellular calcium homeostatic system. Vitamin D is protective against insulin resistance because it has anti-inflammatory effects. Pancreatic beta cells have a specific receptor for 1,25(OH)2D that regulates insulin secretion. Vitamin D also stimulates insulin receptor expression and triggers insulin response to glucose. In another way, vitamin D provides sufficient intracellular cytosolic calcium for insulin secretion through the regulation of calcium flux in the cell membrane(7). The metabolism can be concluded that vitamin D has a positive effect on insulin resistance(36).

Nanocarriers System

In simple terms, a nanocarrier is a nanoparticle that can be used as a transporter for therapeutic compounds or other compounds to their targets(37). The size of a nanocarrier compound has a diameter between 1-100 nanometers (nm)(38). In the application of nanocarriers for therapeutic substances, the nanoparticle size must be less than 200 nm because the microcapillaries in the human body are 200 nm(39). Nanocarrier in the therapeutic provides good biocompatibility as a safe medium for transporting the substance. The nanocarrier is inactive generally so it is regarded as a safe medium. The application of nanocarriers for drug transport shows that in circulation, nanocarriers have a long-term period and sustained release of drugs overcome the endosome-lysosome mechanism(40). The modification of the nanoparticle would affect the physicochemical properties of the nanocarriers like the surface, composition, as well as its shape, which can enhance their activity with decreased secondary effects(41). There are several unique features of the nanocarriers that have been known including Enhanced biodistribution and pharmacokinetics, enhanced stability, enhanced solubility, reduction in toxicity, and sustained-targeted drug delivery(42,43).

Encapsulation is a strategy that can be used to increase the bioavailability of a substance component. Encapsulation technology is carried out by packing solid, liquid, and gaseous materials in small closed capsules with a release that has been designed at a controlled rate within a certain period, through a trigger mechanism in the form of certain environmental factors such as temperature, enzymes, pH, or fermentation(44). The encapsulation technology coating a bioactive material is referred to as the core material or internal phase. The coating material is called the capsule or carrier material. Encapsulation not only helps protect the core material from damaging environmental conditions but also allows the passage of small amounts of material through the capsule walls. The interior (core side) of a nanocarrier system can be filled with nutraceutical or drug molecules. Nanocarriers such as polymer nanocarriers, nanocapsules, dendrimers, etc. can encapsulate the drug efficiently in its perforated cavity(45,46). The hydrophobic nature of the inner cavity (core side) of the nanocarrier system makes it possible to incorporate more hydrophobic molecules into the nanocarrier through hydrophobic interactions or hydrogen bonding. This encapsulation can also occur through physical interactions. The release of the molecule occurs through neutralization of the pH-prone or hydrolysis, thiolysis, and the mechanism of thermolysis(47). The materials that have the opportunity as a nanocarrier for vitamin D have been researched. Solid lipid, liposome, micelles, and liprotides are materials that have been observed for vitamin D encapsulation. Previous studies showing the application of using nanocarriers as encapsulation materials for vitamin D are shown in table 1.

Solid Lipid

The development of solid lipid as a nanocarrier has been used and developed a decade before the 2000s. At the time, the solid lipid nanocarriers are used as a suitable carrier for hydrophobic drugs(37). The special characteristic of solid lipid as nanocarriers make it have a big opportunity as a delivery system for parenteral and oral delivery. The usual major component of solid lipid as nanocarrier are triglycerides and saturated fatty acid as neutral solid lipid, for lipophilic emulsifiers polar phospholipid is used. Neutral lipids such as monoglycerides and diglycerides are naturally more polar than triglycerides and have different surface activities(48). The variety of lipid properties is affected by the fatty acid composition(49). In general, a lipid with long-chain saturated fatty acid is used as the components structure of nanocarrier. The unsaturated fatty acid and medium-chain fatty acid would be liquid lipids in the formulation of the nanocarrier(50,51).

The solid lipid nanocarriers are prepared through the dispersion of melted solid lipids in water and stabilized by way of giving emulsifiers through micro-emulsification or excessive pressure homogenization(52,53). The common materials for the preparation of solid lipid nanocarriers are usually formed from solid lipids like free fatty acid; steroid or waxes; and triglycerides(54). Based on the production circumstance and composition, the encapsulated molecules may be included in the matrix, shell, or core of the stable lipid. Nowadays the solid lipid nanocarrier may be used to comprise ionic and hydrophilic anticancer drug materials at the side of the lipophilic drug. The polymer-lipid nanocarrier was explored to be an effective material for drug delivery from oral intervention(55). The new generation of lipid-based nanocarrier was created

to develop drawbacks of the previous generation of the lipid nanocarrier. This new generation nanocarrier could be used for oral administration, parenteral intervention, and drug delivery through topical administration. Further development of lipid nanocarrier shows the opportunity as genes and nucleic delivery, controlled release of active agents(53), and targeted carrier of antitumor materials agent(56,57).

Liposome

Liposomes are bilayer vesicles formed from cholesterol and phospholipids and have a liquid core located between the layers of the lipid bilayer. Assembled using distinctive features of the self-company of phospholipids, liposomes can be defined as synthetic, small, spherical vesicles which can be each biodegradable and biocompatible. Phospholipids are amphipathic debris with a hydrophobic extension composed of two fatty acid sequences with several carbon atoms from 10 to 24, and a polar head that guarantees their hydrophilic characteristics. The desire for phospholipids is due to their bivalent shape since the formed bilayer can without problems modify its fluidity and influence the release ratio of the engulfed drug(58). liposomes are characterized by using their particular structure, defined by way of the bilayer structure of lipids. aside from phospholipids, cholesterol is another constituent that can be considered to obtain liposomes, because it guarantees more desirable stability of these structures(59,60).

Liposomes are widely used as drug carrier systems or other substances because they are compatible with a variety of bioactive peptides(61). This is due to the structure in which the liquid core is suitable for hydrophilic peptides and the interior of the bilayer is compatible with hydrophobic substances. Moreover, liposomes have a shape resembling a cell membrane, which helps protect polypeptides from enzymatic degradation and oxidation. Liposomes also have many other advantages; easy to prepare, absorbed directly through lymphocyte tissue, non-toxic, biodegradable, and non-immunogenic (62). Previous studies have proven the effectiveness of liposomes as encapsulation materials where the antioxidant capacity of genistein is more optimal by using liposomes than caseinate (63). Two methods possibly can integrate medicinal drugs or materials into liposomes: passive and active carrier techniques. The passive envelopment strategy means that the bioactive molecules are entrapped in nanocarrier for the duration of their assembly, in case of the active loading, the therapeutic materials are packed into the intact liposomes(64).

Micelles

Micelles are colloidal particles with nanosized diameters, and spherical shapes and have a non-polar nature interior with a polar outer surface(12). This system was introduced in 1913 as colloidal aggregates from detergent in a water mixture(37). The amphiphilic molecules formed from the hydrophobic tail that faces the center and the hydrophilic head on the surface. This type of nanocarrier could carry bioactive molecules agents either inside the hydrophobic side or sure covalently to the surface of micelles(65). The big gain of the micelles is composed in the truth that they may be designed and synthetic to hold fats-soluble medicinal drugs or materials right away. Simply above their threshold attention, micelles are built due to the self-aggregation of the amphiphiles in aqueous situations, consequently engulfing passively the fat-

soluble bioactive compound partitioning into the hydrophobic medium of the micelle core(66–68). The capabilities of micelles also are altered by utilizing the encompassing situations. as an instance, blood consists of particular compounds that could affect the potential chemical gradient created among monomeric fractions within the micelles and the surrounding aqueous section, therefore increasing the critical micelle awareness. As a result, the solid micelles in saline answer can also show to have a negative balance in the blood and purpose them to disperse and discharge the carried capsules earlier(69,70).

Liprotide

Liprotides are complex molecules composed of fat (lipid) molecules and protein molecules. Protein has a role as a shell while fat is a core. The core-shell structure formed from the liprotides complex can be used to encapsulate other molecules. The primary function of the protein coat is to increase the solubility of fatty acids. This ability makes liprotides the potential to carry hydrophobic molecules in a hydrophilic environment. Another function of the protein coat is to carry and deliver fatty acids to target cells or hydrophobic surfaces. Liprotides can stabilize small aliphatic molecules such as retinol and tocopherols by inserting the molecules into the fatty acid core(71). Liprotides can protect tocopherols better than tocopherol-binding proteins such as beta-lactoglobulin and protein transfer α-tocopherol. Liprotides can be used to stabilize and deliver a wide variety of hydrophobic small molecules with potential health benefits(72). In general, liprotides can increase the stability and solubility of molecules to be able to form complexes. Liprotides can easily deliver the carried compound into the membrane target but can decrease the stability of the complex matrix under various conditions. Liprotides consisting of α-lactalbumin and oleic acid can dissolve vitamin D, increasing vitamin D stability against UV rays by 9 times, and increasing the stability of vitamin D at 37^0C up to 1,000 times(72,73). α -lactalbumin can interact strongly with monolayer oleic acid by diffusion and absorption on the surface, incorporation with films, and protein-lipid complexes between molecules by hydrophobic interactions(74). Liprotides can release vitamin D by transferring vitamin D to phospholipid vesicles. Vitamin D encapsulated by liprotides using α-lactalbumin-oleic acid and β-lactoglobulin can increase the availability of vitamin D in clear beverage products with neutral pH(75). Many compounds can be used to form a liprotides system, but there is a specific component that has been developed to form a liprotides system such as α -lactalbumin, β-lactoglobulin, and oleic acid.

α -lactalbumin

α-lactalbumin is one of the whey proteins in cow's milk than can be a good candidate for vitamin encapsulation. α-lactalbumin can bind hydrophobic ligands such as retinol and hydrophobic peptides. Bio macro-molecules such as proteins have a potential opportunity for vitamin encapsulation. Based on research conducted by Delevari et al α-lactalbumin has one binding site for vitamin D3(76). When hydrophobic interactions form, the conformation of the protein changes, and the hydrophobic surface of α-lactalbumin increases. The secondary structure of α-lactalbumin is changed in the presence of vitamin D3. α-lactalbumin is a small globular protein with 123 amino acids and a molecular mass of 14.2 kDa. α-lactalbumin is the predominant protein in human

milk. In cow's milk, the concentration of α-lactalbumin is 1-1.5 g/L (3.4% total protein). The natural structure of bovine α-lactalbumin consists of a large helical domain and a small beta layer domain, both of them are connected by a loop. α-lactalbumin has a hydrophobic site and made α-lactalbumin has one binding site to bind other compounds, like vitamin D3(76). The solubility of α-lactalbumin can be affected by certain conditions of pH, temperature, and ionic state(77). α-lactalbumin is relatively resistant to protease digestive enzymes (pepsin and trypsin) because of its globular and dense structure(78). Whey protein isolate contains 17% of α-lactalbumin and α-lactalbumin contains 48 mg of tryptophan and 48 mg of cysteine per gram of protein(79). Tryptophan in α-lactalbumin can increase the tryptophan levels in the blood which can help synthesize and increase the availability of serotonin in the brain. α-lactalbumin also accelerates wound healing(80), for recovery from various types of sports(81).

β-lactoglobulin

β-lactoglobulin is a component is found in milk whey and soluble in salt solutions. β-lactoglobulin belongs to the lipocalin protein group(82) and has been shown to bind various hydrophobic molecules like fatty acids(83), retinol, and vitamin D(84). β-lactoglobulin can bind fatty acids such as oleic acid and linoleic acid. The research showed that the complex of β-lactoglobulin and oleic acid could increase the tertiary structure. β-lactoglobulins have more binding sites for oleic acid than linoleic acid which interacts with van der Waals bonds and hydrogen bonds(85). Encapsulation of vitamin D_3 with β-lactoglobulin with lysozyme modification could increase the bioavailability, resistance to pH, and solubility(86). β-lactoglobulin has 162 amino acid residues and a molecular weight of 18.4 kDa. β-lactoglobulin is the main component of whey protein in milk that can freeze and denature when milk boils. After denaturation, β-lactoglobulin forms a film layer on the milk surface. It happens because β-lactoglobulin protein molecules can form a transparent gel when heated for a long time at low pH and low ionic strength(86). β-lactoglobulin is known as an allergen, the manufacturers need to prove the presence or absence of β-lactoglobulin content to ensure that the labeling meets the requirements. Food testing laboratories can use enzyme immunosorbent assay methods to identify and measure β-lactoglobulin in food products. Polymerization of β-lactoglobulin by microbial transglutaminase reduces its allergenicity in children and adults with immunoglobulin E (IgE)-mediated cow's milk allergy(87).

Oleic acid

Oleic acid is an unsaturated fatty acid that is easily obtained and can be extracted from several different sources, one of which is olive oil. Apart from olive oil (55-80%), these fatty acids are also contained in industrial waste from palm oil, sunflower oil, rapeseed oil, and grape seed oil. The availability of oleic acid in nature is very abundant and is commonly used in the manufacture of surfactants, soaps, plasticizers, and food and drug emulsifiers(88). This acid is composed of 18 C atoms with one double bond between the 9th and 10th C atoms. The oleic acid structure has two functional groups, alkenes, and carboxylic acids. Presence of alkenes with Z isomer, the bond between oleic acid molecules becomes stronger and made oleic acid in the

liquid phase at room temperature. In polar solvents, oleic acid forms a bilayer structure(88). As part of liposomes, Oleic acid has limitations in its use due to the tendency to break down and cause release. One method to increase its stability is by coating it with protein to form a complex called lipotides(89).

Delivery Mechanism

The human digestive system is a complex system that aims to digest food into nutrients. During the digestion process, food will mix with enzymes. Enzymes function as catalysts in biological processes that can provide speed, specification, and control of reactions in the body by increasing the rate of chemical reactions by 108 to 1011 times faster(90). Each enzyme has maximum activity at a certain temperature. When the temperature increases, the enzyme activity also increases until the optimum temperature is reached. After passing the optimum temperature, the enzyme activity decreased(91). In addition to enzymes, stomach acids contribute to the breakdown of food into nutrients. However, the acidic pH of the stomach can affect the stability of vitamin D, because the vitamin is not stable in acidic conditions(10).

Encapsulation of vitamin D with nanocarrier could be the new perspective of nutraceutical therapy in type 2 diabetes. The nanocarriers system has a potential opportunity as a transporter of vitamin D. The system can carry and protect vitamin D from the gastrointestinal tract until absorbed into blood circulation. After vitamin D encapsulated with a nanocarrier system has been consumed by oral administration, the system would protect the vitamin in the gastric environment. The gastric environment is acidic and contains a variety of digestive enzymes such as pepsin and gastric acid. The shell of the nanocarriers system that forms from organic properties will be affected by the gastric environment but the vitamin is still safe in the core of the system. After passing through the gastric, the system will enter the intestine. The intestine system will be affected by an intestine enzymes such as trypsin, chymotrypsin, and pancreatic fluid. Due to the environmental condition in the intestine, vitamin D will be released from the system. Vitamin D that is protected by the nanocarrier system still has a good condition after passing through the gastrointestinal system and is ready to be absorbed in the intestinal with good bioavailability.

Future Perspectives

One of the challenges in the medical field today is the use of nutraceutical therapy that returns to its natural state. The application of nanotechnology in the development of the world of health is an important point in the treatment of a disease. Currently, there have been many studies related to the application of nanotechnology which is used as a delivery agent and protector of substances and vitamins. The design and development of nanoparticle-based nutraceutical therapy as an alternative treatment for degenerative diseases has shown good results. Vitamin D is known to have a positive effect on improving diabetes status and is used for alternative therapies for diabetic patients. However, there are many obstacles, both in terms of absorption and bioavailability of Vitamin D. The nano-encapsulation method has a chance to increase the bioavailability of vitamin D. Nutraceuticals therapy using vitamin D3 encapsulated with nanocarrier could be a new alternative for oral therapy of diabetes type 2.

Conclusion

Recently, nanotechnology has been developed as the approach for vitamin delivery agents. The nanocarrier technology brings the development in vitamin delivery. Exploration of nanocarrier systems in the application of supplemental vitamin administration shows a better prospect than direct administration of vitamins. There are many challenges to producing an economical nanocarrier system with good quality. The application and manufacture of standardized nanocarrier systems will have a very potent impact on the application of vitamin delivery in the body. In the future, the application of nanocarriers in various fields including vitamin delivery in the body will continue to grow. The encapsulation of vitamin D provides another point of view in the implementation of therapy in patients with type 2 diabetes mellitus. The use of encapsulation of vitamin D with nanocarrier is expected to help treat type 2 diabetes patients to improve their quality of life.

Tabel.1 Previous studies of nanocarriers application for vitamin D

	Nanocarriers System	Nature of nanocarriers	Previous Research
Vitamin D	Solid Lipid	A colloidal carrier that has good stability naturally degrades and is easy to modify(40).	A combination of vitamin d loaded with solid lipid nanocarriers combined with anti-cancer materials improves the effectivity therapy in breast cancers(92).
			The system of vitamin D and nanoparticles determined the increasing systemic absorption and prolonged presence of the bioactive materials in the blood plasma(93,94).
	Liposome	A phospholipid bilayer nanocarriers that has low toxicity naturally degrades and is biocompatible (41,42).	Anti-aging agents that directly apply to the skin using liposomes with vitamin D3 loaded(95).
			The stability of liposomes as nanocarriers is affected by vitamin D3(96).
	Micelles	The colloidal aggregate of the molecules with amphiphilic nature has good biostability and dynamic system (52,97).	The micelles have a role as a protective agent in vitamin D encapsulation with the intervention of UV-light with deterioration induced(98).
			The bioavailability of vitamin D diminished to 37% in micelles with chitosan use(99).
	Liprotide	Complex molecules are composed of fat (lipid) molecules and protein molecules. Potential to carry hydrophobic molecules in a hydrophilic environment (71,72).	Vitamin D can be encapsulated and stabilized for the enrichment of clear beverages(72).
			Optimal formulation of the liprotide as a nanocarrier(73).

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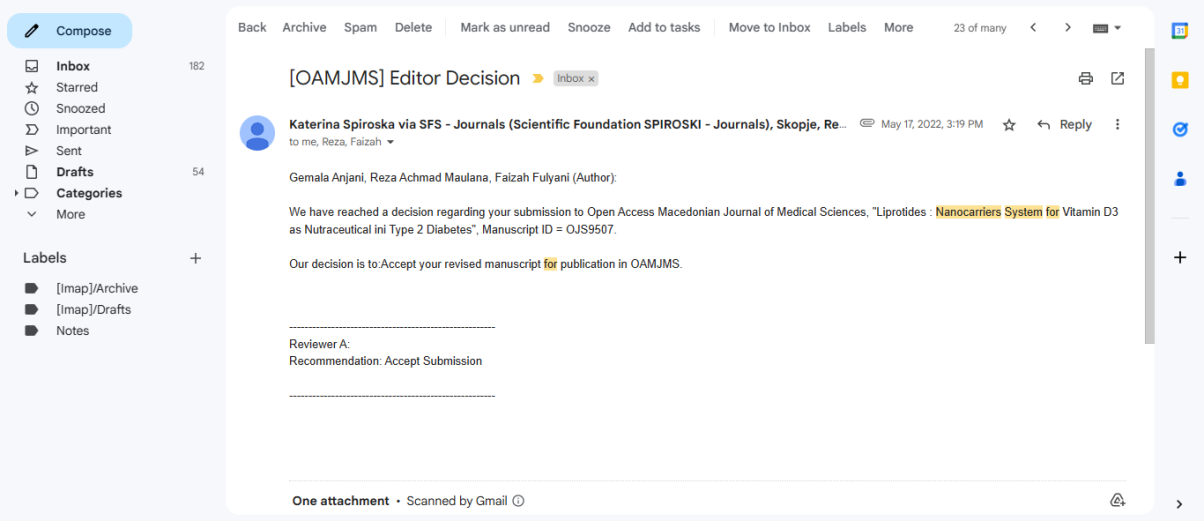

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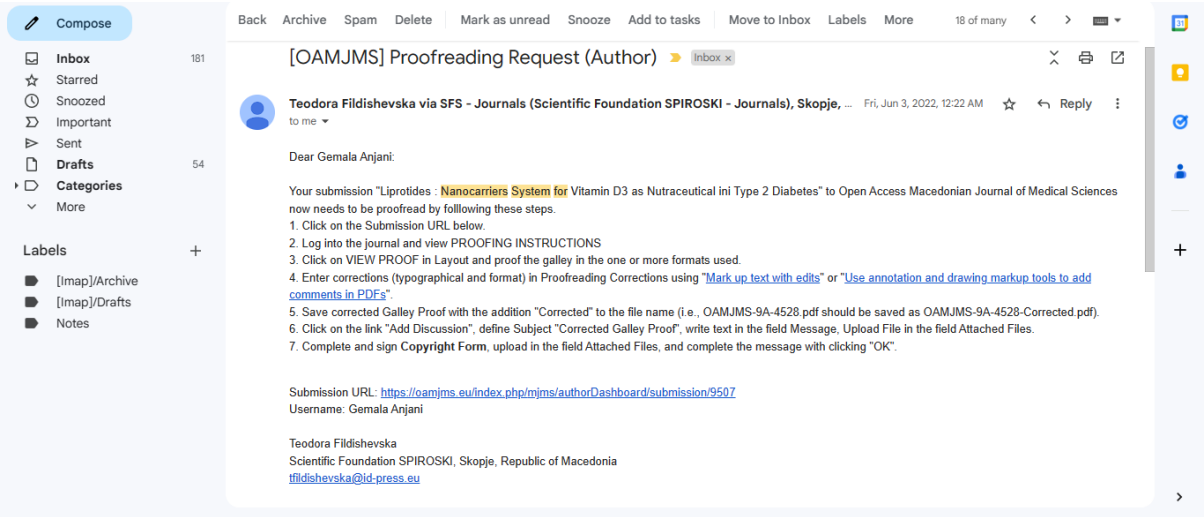

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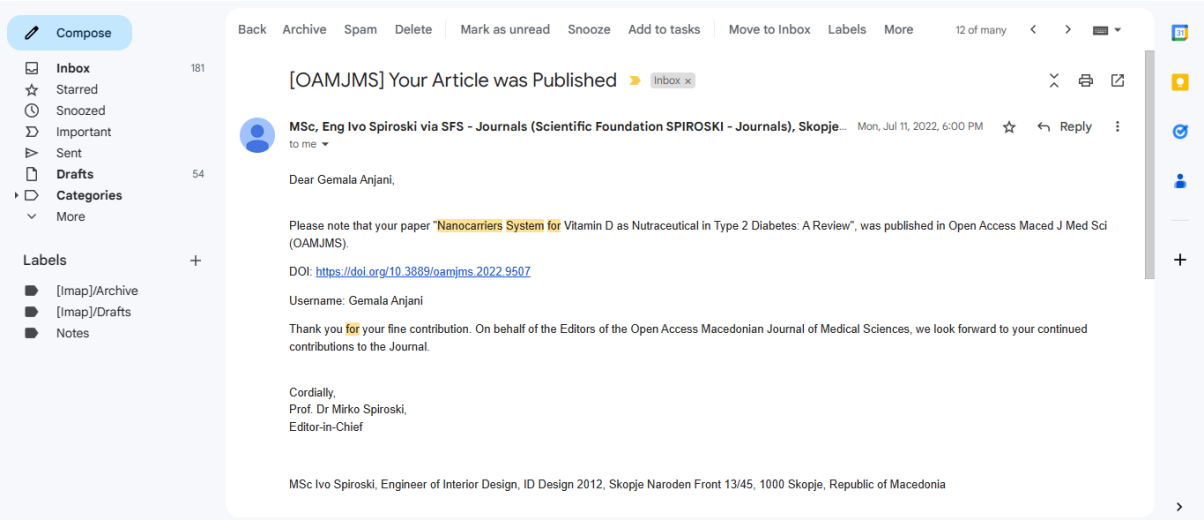

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Nanocarriers System for Vitamin D as Nutraceutical in Type 2 Diabetes: A Review

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Abstract

Incidences of diabetes are common among populations around the world. Diabetes may lead to other complications and increased morbidity and mortality. Many ways have been done to treat and prevent the development of diabetes. In addition to conventional pharmacotherapy, therapeutic therapy has shown good opportunities to maintain and improve diabetic conditions. Vitamin D is known as a nutraceutical and has a good opportunity to develop the medication for type 2 diabetes. The application of nanocarriers as a delivery system increases the bioavailability of vitamins, escalates cellular delivery, and optimizes the vitamin effect. By utilizing nanotechnology-based dietary supplements, the problem of vitamin administration, vitamin stability, absorption, and bioavailability will be resolved. In this review, we would try to compare the most relevant aspect of nanocarrier for Vitamin D as a nutraceutical in type 2 diabetes.

Introduction

Diabetes is a major worldwide health problem that increasing every year. Data from International Diabetes Federation (IDF) in 2019 show that 9,3% world population aged 20–79 years old had diabetes. Indonesia gets 1st rank country with diabetes in Southeast Asia with 10,7 million diabetic people [1]. The Indonesian Basic Health Research (RISKERDAS) in 2018 showed that the prevalence of diabetes in Indonesia was 2% in the population aged >15 years [2]. The increasing number of diabetes is influenced by Vitamin D deficiency. Patients with type 2 diabetes mellitus (T2DM) show lower levels of Vitamin D compared with normal people [3]. Vitamin D is known to have a positive effect on diabetes, but the prevalence of Vitamin D deficiency shows a large number. Many countries around the world report the incidence of Vitamin D deficiency. The United States and Europe show that 5,9% and 13% population have Vitamin D deficiency [4]. In Indonesia, 45.1% of children aged 1–18 years and 82% of productive age women have Vitamin D deficiency [5].

Vitamin D has a significant role in diabetes to maintain blood glucose tolerance [6], decrease insulin resistance [7], and as a gene transcription factor [8]. This fat-soluble vitamin can be obtained from food intake and formed by the body but has low bioavailability. Food sources of Vitamin D are not much and the Vitamin D content in foodstuffs is low [9]. The nature of Vitamin D is easy to damage by heat, light, oxidation, and acid. That thing made the bioavailability of consumed Vitamin D low [10], [11]. To overcome this issue, the application of nanotechnology-based dietary supplements could be applicated. Vitamin D encapsulation would maintain vitamin bioavailability. The encapsulation method has two functions, as a carrier and protector agent of Vitamin D in the gastrointestinal tract.

The application of nanocarrier technology has provided many breakthroughs for the development of medicine around the world. When compared with the conventional method, the application of nanocarrier provides more advantages [12]. Nanocarrier involved in drug and vitamin delivery shows an increase in water solubility of water-insoluble substances, protecting against degradation from the environmental condition, and inactivation [13]. The application of nanotechnology as a nanocarrier system must pay attention to many aspects. The nature and action of the carrier should be investigated when planning to apply as drug delivery or vitamin delivery [14], [15], [16]. The most important

thing is the biocompatibility system of the nanocarrier. The system must be safe, non-toxic, and not trigger an immune reaction in the human body [17], [18], [19]. The objective of this review is to highlight the recent update on the development of nanocarrier for Vitamin D and the opportunity to be nutraceuticals in T2DM.

Diabetes Mellitus

Glucose is a product of carbohydrate metabolism. Blood glucose is a very important part of maintaining the body's physiological functions as a source of energy. Blood glucose levels rise after meals and are usually low in the morning and before meals. Blood glucose levels are maintained to maintain balance in the body. Blood glucose levels are regulated by the pancreas gland. When blood glucose levels drop, the pancreas releases glucagon, a hormone that targets liver cells, which are glycogen stores. With the help of the hormone glucagon, glycogen is converted into glucose in the liver (the process of glycogenolysis) and glucose is released into the bloodstream. In conditions of high blood glucose levels, the hormone insulin is released from the pancreas. The hormone insulin increases the transport of glucose from the circulation to the muscles and liver. In the liver, glucose is converted to glycogen (the process of glycogenesis). In normal conditions, the homeostasis of the blood glucose in circulation will be balanced, but it not going well in diabetes. In a diabetic person, the blood regulation will be disturbed and causing many defects in the body due to the complications.

Diabetes mellitus (DM) is a chronic disease characterized by disturbances in carbohydrate, fat, and protein metabolism. Common symptoms of this disease are polydipsia, polyuria, polyphagia, and weight loss. This disease involves the endocrine hormones of the pancreas (insulin and glucagon) and is associated with the impaired physiological function of insulin. There are two types of DM disease based on endogenous insulin secretion, Insulin-Dependent Diabetes Mellitus (IDDM) or commonly known as type 1 diabetes mellitus (T1DM), and Non-Insulin-Dependent Diabetes Mellitus (NIDDM), commonly known as type 2 diabetes mellitus (T2DM) (20). Worldwide, 90–95% of diabetics people have T2DM. The increasing prevalence of T2DM going rapidly influenced by sedentary lifestyles such as low physical activity, high intake of fast food and sweet sugar beverage, and low intake of fruits and vegetables [1], [20], [21]. Overweight, obesity or central obesity, and hyperglycemia in pregnancy are factors that influence the incidence of insulin resistance in people with T2DM [22].

Diabetes mellitus is a metabolic disease with the characteristic of insufficient insulin production or ineffective insulin physiological performance. Insulin is a key of the body to deliver blood glucose from circulation to the cell's target [1]. T2DM is a metabolic disorder with the characteristic of insulin resistance, impaired insulin secretion, and increased glucose production. T2DM is preceded by abnormal sugar homeostases such as impaired fasting glucose or impaired glucose tolerance [23]. Insulin resistance (IR) is considered one of the mechanisms that developed T2DM. IR disrupts the glucose intake from blood circulation and is involved with the over-production of hepatic glucose [24]. To lead to T2DM, the IR condition usually occurs over a long time. Due to the IR condition, the human body will compensate for homeostasis in the form of producing large amounts of insulin hormone. The long-term condition of insulin overproduction would lead to pancreatic beta-cell dysfunction due to systemic inflammation. The pancreatic beta-cell dysfunction is associated with beta-cell death [25].

The condition of diabetes affects various physiological functions of the body, including the digestive tract. Some problems in the digestive tract that is often found in patients with diabetes are a longer gastric emptying time to the accompanying diarrhea problem. The physiological functions of the digestive tract, starting from the esophagus to the anus, will change in a person with diabetes. A vital function of the digestive tract to maintain life will be disrupted. The condition of diabetes will affect the ability of the gastrointestinal organs both directly and indirectly. Obstacles in the process of swallowing, movement of organs, breakdown, and absorption of nutrients, to the process of removing residual waste, will affect long-term health. Various digestive problems such as gastroesophageal reflux (GERD), nausea, vomiting, bloating, and diarrhea to constipation can accompany diabetic patients which will worsen the condition if not treated immediately [26]. By reducing the burden on the stomach and mild methods of giving oral therapy, diabetics person will be easier to carry out consumption therapy. In addition, proper and efficient administration of nutraceuticals will reduce unwanted signs and symptoms in undergoing therapy.

Vitamin D as Nutraceutical in Diabetes

Vitamin D is a non-essential fat-soluble vitamin that has a huge and important role in calcium homeostasis [27]. Structurally, Vitamin D is a derivative of steroid compounds in the body [28]. Vitamin D can be obtained from food intake and supplementation. It can be activated through exposure to sunlight in the form of Vitamin D3. The nature of Vitamin D is easy to damage by heat, light, oxidation, and acid. That thing made the bioavailability of consumed Vitamin D low [10], [11]. However, the prevalence of Vitamin D deficiency worldwide is still high [1]. Vitamin D supplementation can

be a solution to sufficient Vitamin D requirements, but it still does not cover a wide population. Vitamin D fortification is an alternative to reduce Vitamin D deficiency that has the potential effect to cover a wider population and potentially increase Vitamin D intake. The form of Vitamin D used for fortification is Vitamin D2 or Vitamin D3 [29]. Fortification of the active form of Vitamin D (Vitamin D3) is considered efficient in the supplying requirement of Vitamin D. Addition of Vitamin D3 to food has shown an improvement in blood glucose and insulin status in diabetes mellitus [30]. Vitamin D deficiency has been associated with decreasing insulin release, increasing insulin resistance, and type 2 diabetes mellitus. Vitamin D deficiency causes dysregulation of glucose metabolism by interfering with glucose-stimulated insulin secretion in the hyperglycemic phase [20]. Vitamin D intake affects insulin resistance and is positively correlated with insulin secretion in patients with type 2 diabetes mellitus. Supplementation of orally high-dose cholecalciferol (10,000 IU per day for 4 weeks) as a replacement dose showed an increased insulin sensitivity of 37% in subjects with fasting blood glucose disorder [31]. A study in diabetic Wistar rats has proven that fortification of Vitamin D3 in foodstuffs can significantly reduce blood sugar levels [32]. This thing happened because increasing serum Vitamin D concentration has a positive effect on insulin homeostasis [33].

Systemic inflammation is one of the causes of type 2 diabetes mellitus (T2DM) and insulin resistance occurs in it. Vitamin D has an anti-inflammatory effect and it is useful to overcome inflammation. In the metabolic process, Vitamin D3 plays a role in preventing and improving the status of diabetes mellitus. Vitamin D can provide benefits for several disease prevention, such as multiple sclerosis, cancer, bacterial infections [34], and diabetes [35]. Vitamin D is maintaining glucose tolerance through insulin secretion and sensitivity [6]. Vitamin D3 has a function in insulin synthesis and secretion by modulating the intracellular calcium homeostatic system. Vitamin D is protective against insulin resistance because it has anti-inflammatory effects. Pancreatic beta cells have a specific receptor for 1,25(OH)2D that regulates insulin secretion. Vitamin D also stimulates insulin receptor expression and triggers insulin response to glucose. In another way, Vitamin D provides sufficient intracellular cytosolic calcium for insulin secretion through the regulation of calcium flux in the cell membrane [7]. The metabolism can be concluded that Vitamin D has a positive effect on insulin resistance [36].

Nanocarriers System

In simple terms, a nanocarrier is a nanoparticle that can be used as a transporter for therapeutic compounds or other compounds to their targets [37]. The size of a nanocarrier compound has a diameter between 1 and 100 nanometers (nm) [38]. In the application of nanocarriers for therapeutic substances, the nanoparticle size must be <200 nm because the microcapillaries in the human body are 200 nm [39]. Nanocarrier in the therapeutic provides good biocompatibility as a safe medium for transporting the substance. The nanocarrier is inactive generally so it is regarded as a safe medium. The application of nanocarriers for drug transport shows that in circulation, nanocarriers have a long-term period and sustained release of drugs overcome the endosome-lysosome mechanism [40]. The modification of the nanoparticle would affect the physicochemical properties of the nanocarriers such as the surface, composition, as well as its shape, which can enhance their activity with decreased secondary effects [41]. There are several unique features of the nanocarriers that have been known including enhanced biodistribution and pharmacokinetics, enhanced stability, enhanced solubility, reduction in toxicity, and sustained-targeted drug delivery [42], [43].

Encapsulation is a strategy that can be used to increase the bioavailability of a substance component. Encapsulation technology is carried out by packing solid, liquid, and gaseous materials in small closed capsules with a release that has been designed at a controlled rate within a certain period, through a trigger mechanism in the form of certain environmental factors such as temperature, enzymes, pH, or fermentation [44]. The encapsulation technology coating a bioactive material is referred to as the core material or internal phase. The coating material is called the capsule or carrier material. Encapsulation not only helps protect the core material from damaging environmental conditions but also allows the passage of small amounts of material through the capsule walls. The interior (core side) of a nanocarrier system can be filled with nutraceutical or drug molecules. Nanocarriers such as polymer nanocarriers, nanocapsules, and dendrimers can encapsulate the drug efficiently in its perforated cavity [45], [46]. The hydrophobic nature of the inner cavity (core side) of the nanocarrier system makes it possible to incorporate more hydrophobic molecules into the nanocarrier through hydrophobic interactions or hydrogen bonding. This encapsulation can also occur through physical interactions. The release of the molecule occurs through neutralization of the pH-prone or hydrolysis, thiolysis, and the mechanism of thermolysis [47]. The materials that have the opportunity as a nanocarrier for Vitamin D have been researched. Solid lipid, liposome, micelles, and liprotides are materials that have been observed for Vitamin D encapsulation. The previous studies showing the application of using nanocarriers as encapsulation materials for Vitamin D are shown in Table 1.

Table 1: Previous studies of nanocarriers application for Vitamin D

	Nanocarriers system	Nature of nanocarriers	Previous research
Vitamin D	Solid Lipid	A colloidal carrier that has good stability naturally degrades and is easy to modify [40].	A combination of vitamin d loaded with solid lipid nanocarriers combined with anti-cancer materials improves the effectivity therapy in breast cancers [92]. The system of vitamin D and nanoparticles determined the increasing systemic absorption and prolonged presence of the bioactive materials in the blood plasma [93], [94].
	Liposome	A phospholipid bilayer nanocarriers that has low toxicity naturally degrades and is biocompatible [41], [42].	Anti-aging agents that directly apply to the skin using liposomes with vitamin D3 loaded [95]. The stability of liposomes as nanocarriers is affected by vitamin D3 [96].
	Micelles	The colloidal aggregate of the molecules with amphiphilic nature has good biostability and dynamic system [52], [97].	The micelles have a role as a protective agent in vitamin D encapsulation with the intervention of UV-light with deterioration induced [98]. The bioavailability of vitamin D diminished to 37% in micelles with chitosan use [99].
	Liprotide	Complex molecules are composed of fat (lipid) molecules and protein molecules. Potential to carry hydrophobic molecules in a hydrophilic environment [71], [72].	Vitamin D can be encapsulated and stabilized for the enrichment of clear beverages [72]. Optimal formulation of the liprotide as a nanocarrier [73].

Solid Lipid

The development of solid lipid as a nanocarrier has been used and developed a decade before the 2000s. At the time, the solid lipid nanocarriers are used as a suitable carrier for hydrophobic drugs [37]. The special characteristic of solid lipid as nanocarriers makes it have a big opportunity as a delivery system for parenteral and oral delivery. The usual major component of solid lipid as nanocarrier is triglycerides and saturated fatty acid as neutral solid lipid, for lipophilic emulsifiers, polar phospholipid is used. Neutral lipids such as monoglycerides and diglycerides are naturally more polar than triglycerides and have different surface activities [48]. The variety of lipid properties is affected by the fatty acid composition [49]. In general, a lipid with long-chain saturated fatty acid is used as the components structure of nanocarrier. The unsaturated fatty acid and medium-chain fatty acid would be liquid lipids in the formulation of the nanocarrier [50], [51].

The solid lipid nanocarriers are prepared through the dispersion of melted solid lipids in water and stabilized by the way of giving emulsifiers through microemulsification or excessive pressure homogenization [52], [53]. The common materials for the preparation of solid lipid nanocarriers are usually formed from solid lipids such as free fatty acid; steroid or waxes; and triglycerides [54]. Based on the production circumstance and composition, the encapsulated molecules may be included in the matrix, shell, or core of the stable lipid. Nowadays, the solid lipid nanocarrier may be used to comprise ionic and hydrophilic anticancer drug materials at the side of the lipophilic drug. The polymer-lipid nanocarrier was explored to be an effective material for drug delivery from oral intervention [55]. The new generation of lipid-based nanocarrier was created to develop drawbacks of the previous generation of the lipid nanocarrier. This new-generation nanocarrier could be used for oral administration, parenteral intervention, and drug delivery through topical administration. Further development of lipid nanocarrier shows the opportunity as genes and nucleic delivery, controlled release of active agents [53], and targeted carrier of antitumor materials agent [56], [57].

Liposome

Liposomes are bilayer vesicles formed from cholesterol and phospholipids and have a liquid core located between the layers of the lipid bilayer. Assembled using distinctive features of the self-company of phospholipids, liposomes can be defined as synthetic, small, spherical vesicles which can be each biodegradable and biocompatible. Phospholipids are amphipathic debris with a hydrophobic extension composed of two fatty acid sequences with several carbon atoms from 10 to 24, and a polar head that guarantees their hydrophilic characteristics. The desire for phospholipids is due to their bivalent shape since the formed bilayer can without problems modify its fluidity and influence the release ratio of the engulfed drug [58]. Liposomes are characterized using their particular structure, defined by way of the bilayer structure of lipids. Aside from phospholipids, cholesterol is another constituent that can be considered to obtain liposomes, because it guarantees more desirable stability of these structures [59], [60].

Liposomes are widely used as drug carrier systems or other substances because they are compatible with a variety of bioactive peptides [61]. This is due to the structure in which the liquid core is suitable for hydrophilic peptides and the interior of the bilayer is compatible with hydrophobic substances. Moreover, liposomes have a shape resembling a cell membrane, which helps protect polypeptides from enzymatic degradation and oxidation. Liposomes also have many other advantages; easy to prepare, absorbed directly through lymphocyte tissue, non-toxic, biodegradable, and non-immunogenic [62]. The previous studies have proven the effectiveness of liposomes as encapsulation materials where the antioxidant capacity of genistein is more optimal using liposomes than caseinate [63]. Two methods possibly can integrate medicinal drugs or materials into liposomes: Passive and active carrier techniques. The passive envelopment strategy means that the bioactive molecules are entrapped in nanocarrier for the duration of their assembly, in case of the active loading, the therapeutic materials are packed into the intact liposomes [64].

Micelles

Micelles are colloidal particles with nanosized diameters and spherical shapes and have a non-polar nature interior with a polar outer surface [12]. This system was introduced in 1913 as colloidal aggregates from detergent in a water mixture [37]. The amphiphilic molecules formed from the hydrophobic tail that faces the center and the hydrophilic head on the surface. This type of nanocarrier could carry bioactive molecules agents either inside the hydrophobic side or sure covalently to the surface of micelles [65]. The big gain of the micelles is composed in the truth that they may be designed and synthetic to hold fat-soluble medicinal drugs or materials right away. Simply above their threshold attention, micelles are built due to the self-aggregation of the amphiphiles in aqueous situations, consequently engulfing passively the fat-soluble bioactive compound partitioning into the hydrophobic medium of the micelle core [66], [67], [68]. The capabilities of micelles also are altered by utilizing the encompassing situations. As an instance, blood consists of particular compounds that could affect the potential chemical gradient created among monomeric fractions within the micelles and the surrounding aqueous section, therefore increasing the critical micelle awareness. As a result, the solid micelles in saline answer can also show to have a negative balance in the blood and purpose them to disperse and discharge the carried capsules earlier [69], [70].

Liprotide

Liprotides are complex molecules composed of fat (lipid) molecules and protein molecules. Protein has a role as a shell while fat is a core. The core-shell structure formed from the liprotides complex can be used to encapsulate other molecules. The primary function of the protein coat is to increase the solubility of fatty acids. This ability makes liprotides the potential to carry hydrophobic molecules in a hydrophilic environment. Another function of the protein coat is to carry and deliver fatty acids to target cells or hydrophobic surfaces. Liprotides can stabilize small aliphatic molecules such as retinol and tocopherols by inserting the molecules into the fatty acid core [71]. Liprotides can protect tocopherols better than tocopherol-binding proteins such as beta-lactoglobulin and protein transfer α-tocopherol. Liprotides can be used to stabilize and deliver a wide variety of hydrophobic small molecules with potential health benefits [72]. In general, liprotides can increase the stability and solubility of molecules to be able to form complexes. Liprotides can easily deliver the carried compound into the membrane target but can decrease the stability of the complex matrix under various conditions. Liprotides consisting of α-lactalbumin and oleic acid can dissolve Vitamin D, increasing Vitamin D stability against UV rays by 9 times, and increasing the stability of Vitamin D at 37°C up to 1000 times [72], [73]. α-lactalbumin can interact strongly with monolayer oleic acid by diffusion and absorption on the surface, incorporation with films, and protein-lipid complexes between molecules by hydrophobic interactions [74]. Liprotides can release Vitamin D by transferring Vitamin D to phospholipid vesicles. Vitamin D encapsulated by liprotides using α-lactalbumin-oleic acid and β-lactoglobulin can increase the availability of Vitamin D in clear beverage products with neutral pH [75]. Many compounds can be used to form a liprotides system, but there is a specific component that has been developed to form a liprotides system such as α -lactalbumin, β-lactoglobulin, and oleic acid.

α-Lactalbumin

α-lactalbumin is one of the whey proteins in cow's milk than can be a good candidate for vitamin encapsulation. α-lactalbumin can bind hydrophobic ligands such as retinol and hydrophobic peptides. Bio macromolecules such as proteins have a potential opportunity for vitamin encapsulation. Based on research conducted by Delavari ***et al.***, α-lactalbumin has one binding site for Vitamin D3 [76]. When hydrophobic interactions form, the conformation of the protein changes, and the hydrophobic surface of α-lactalbumin increases. The secondary structure of α-lactalbumin is changed in the presence of Vitamin D3. α-lactalbumin is a small globular protein with 123 amino acids and a molecular mass of 14.2 kDa. α-lactalbumin is the predominant protein in human milk. In cow's milk, the concentration of α-lactalbumin is 1–1.5 g/L (3.4% total protein). The natural structure of bovine α-lactalbumin consists of a large helical domain and a small beta layer domain, both of them are connected by a loop. α-lactalbumin has a hydrophobic site and made α-lactalbumin has one binding site to bind other compounds, like Vitamin D3 [76]. The solubility of α-lactalbumin can be affected by certain conditions of pH, temperature, and ionic state [77]. α-lactalbumin is relatively resistant to protease digestive enzymes (pepsin and trypsin) because of its globular and dense structure [78]. Whey protein isolate contains 17% of α-lactalbumin and α-lactalbumin contains 48 mg of tryptophan and 48 mg of cysteine per gram of protein [79]. Tryptophan in α-lactalbumin can increase the tryptophan levels in the blood which can help synthesize and increase the availability of serotonin in the brain. α-lactalbumin also accelerates wound healing [80], for recovery from various types of sports [81].

β-Lactoglobulin

β-lactoglobulin is a component is found in milk whey and soluble in salt solutions. β-lactoglobulin belongs to the lipocalin protein group [82] and has been shown to bind various hydrophobic molecules such as fatty acids [83], retinol, and Vitamin D [84]. β-lactoglobulin can bind fatty acids such as oleic acid and linoleic acid. The research showed that the complex of β-lactoglobulin and oleic acid could increase the tertiary structure. β-lactoglobulins have more binding sites for oleic acid than linoleic acid which interacts with van der Waals bonds and hydrogen bonds [85]. Encapsulation of Vitamin D_3 with β-lactoglobulin with lysozyme modification could increase the bioavailability, resistance to pH, and solubility [86]. β-lactoglobulin has 162 amino acid residues and a molecular weight of 18.4 kDa. β-lactoglobulin is the main component of whey protein in milk that can freeze and denature when milk boils. After denaturation, β-lactoglobulin forms a film layer on the milk surface. It happens because β-lactoglobulin protein molecules can form a transparent gel when heated for a long time at low pH and low ionic strength [86]. β-lactoglobulin is known as an allergen, the manufacturers need to prove the presence or absence of β-lactoglobulin content to ensure that the labeling meets the requirements. Food testing laboratories can use enzyme immunosorbent assay methods to identify and measure β-lactoglobulin in food products. Polymerization of β-lactoglobulin by microbial transglutaminase reduces its allergenicity in children and adults with immunoglobulin E (IgE)-mediated cow's milk allergy [87].

Oleic Acid

Oleic acid is an unsaturated fatty acid that is easily obtained and can be extracted from several different sources, one of which is olive oil. Apart from olive oil (55–80%), these fatty acids are also contained in industrial waste from palm oil, sunflower oil, rapeseed oil, and grape seed oil. The availability of oleic acid in nature is very abundant and is commonly used in the manufacture of surfactants, soaps, plasticizers, and food and drug emulsifiers [88]. This acid is composed of 18°C atoms with one double bond between the 9^{th} and 10^{th} C atoms. The oleic acid structure has two functional groups, alkenes, and carboxylic acids. The presence of alkenes with Z isomer, the bond between oleic acid molecules becomes stronger and made oleic acid in the liquid phase at room temperature. In polar solvents, oleic acid forms a bilayer structure [88]. As part of liposomes, oleic acid has limitations in its use due to the tendency to break down and cause release. One method to increase its stability is by coating it with protein to form a complex called liprotides [89].

Delivery Mechanism

The human digestive system is a complex system that aims to digest food into nutrients. During the digestion process, food will mix with enzymes. Enzymes function as catalysts in biological processes that can provide speed, specification, and control of reactions in the body by increasing the rate of chemical reactions by 108–1011 times faster [90]. Each enzyme has maximum activity at a certain temperature. When the temperature increases, the enzyme activity also increases until the optimum temperature is reached. After passing the optimum temperature, the enzyme activity decreased [91]. In addition to enzymes, stomach acids contribute to the breakdown of food into nutrients. However, the acidic pH of the stomach can affect the stability of Vitamin D, because the vitamin is not stable in acidic conditions [10].

Encapsulation of Vitamin D with nanocarrier could be the new perspective of nutraceutical therapy in type 2 diabetes. The nanocarriers system has a potential opportunity as a transporter of Vitamin D. The system can carry and protect Vitamin D from the gastrointestinal tract until absorbed into blood circulation. After Vitamin D encapsulated with a nanocarrier system has been consumed by oral administration, the system would protect the vitamin in the gastric environment. The gastric environment is acidic and contains a variety of digestive enzymes such as pepsin and gastric acid. The shell of the nanocarriers system that forms from organic properties will be affected by the gastric environment but the vitamin is still safe in the core of the system. After passing through the gastric, the system will enter the intestine. The intestine system will be affected by an intestine enzyme such as trypsin, chymotrypsin, and pancreatic fluid. Due to the environmental condition in the intestine, Vitamin D will be released from the system. Vitamin D that is protected by the nanocarrier system still has a good condition after passing through the gastrointestinal system and is ready to be absorbed in the intestinal with good bioavailability.

Future Perspectives

One of the challenges in the medical field today is the use of nutraceutical therapy that returns to its natural state. The application of nanotechnology in the development of the world of health is an important point in the treatment of a disease. At present, there have been many studies related to the application of nanotechnology which is used as a delivery agent and protector of substances and vitamins. The design and development of nanoparticle-based nutraceutical therapy as an alternative treatment for degenerative

diseases has shown good results. Vitamin D is known to have a positive effect on improving diabetes status and is used for alternative therapies for diabetic patients. However, there are many obstacles, both in terms of absorption and bioavailability of Vitamin D. The nanoencapsulation method has a chance to increase the bioavailability of Vitamin D. Nutraceuticals therapy using Vitamin D3 encapsulated with nanocarrier could be a new alternative for oral therapy of diabetes type 2.

Conclusion

Recently, nanotechnology has been developed as the approach for vitamin delivery agents. The nanocarrier technology brings the development in vitamin delivery. Exploration of nanocarrier systems in the application of supplemental vitamin administration shows a better prospect than direct administration of vitamins. There are many challenges to producing an economical nanocarrier system with good quality. The application and manufacture of standardized nanocarrier systems will have a very potent impact on the application of vitamin delivery in the body. In the future, the application of nanocarriers in various fields including vitamin delivery in the body will continue to grow. The encapsulation of Vitamin D provides another point of view in the implementation of therapy in patients with type 2 diabetes mellitus. The use of encapsulation of Vitamin D with nanocarrier is expected to help treat type 2 diabetes patients to improve their quality of life.

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