Ruhuna. J. Med., 13(01), 2025, pp. 11–28
ISSN (p) ISSN 3084-942X ; ISSN (e) ISSN 3084-9063

Review article

Natural products encapsulated alginate nanoformulations for diabetes mellitus: Preparation, characterisation, properties, and biological activities

De Silva ND[1], Attanayake AP[1]*
[1]*Department of Biochemistry, Faculty of Medicine, University of Ruhuna, Galle, Sri Lanka*
**Correspondence: anojaattanayake@med.ruh.ac.lk*

Abstract. The rising global prevalence of diabetes brings severe complications driven by inflammation and oxidative stress. Alginate is a naturally derived biopolymer revealing good biocompatibility and biodegradability. Alginate has been extensively utilised in pharmaceutical applications. The inclusion of natural products into an alginate/alginate-based matrix is identified as a promising strategy for the development of new effective therapies against diabetes mellitus. This review attempts to summarise the studies reported on the development of natural product-based alginate nanoformulations for the management of diabetes, focusing on its main pathophysiological features such as hyperglycemia, inflammation, and oxidative stress. The electronic databases "Science Direct", "PubMed", and "Google Scholar" were searched to retrieve articles published over the past five years (2019-2024). Herbal extracts and compounds encapsulated alginate-based nanoformulations were documented for their antidiabetic, antioxidant, and anti-inflammatory potentials through either *in vivo* studies or *in vitro* assays. Natural products encapsulated alginate-based nanoformulations have been formulated using various methods and characterised mainly via dynamic light scattering, zeta potential, polydispersity index, scanning electron microscopy, and Fourier transform infrared spectroscopy. Abundantly, inhibitory potentials of α-amylase and α-glucosidase enzymes and inflammatory cytokines have been assessed to evaluate antidiabetic and anti-inflammatory activities of natural product-based nanoformulations, respectively. Most of the studies reported 2,2-diphenyl-1-picrylhydrazyl assay *in vitro* and estimation of malonaldehyde and antioxidant enzymes *in vivo* in the assessment of antioxidant activity of natural products-based alginate nanoformulations. To date, clinical trials have not been reported for natural products-based alginate formulations. The present review frames an overview of natural products encapsulated alginate-based nanoformulations, and their evaluation of antidiabetic, anti-inflammatory, and antioxidant activities.

Keywords. Alginate formulations, Antidiabetic assays, Antioxidant assays, Diabetes mellitus, Inflammation

INTRODUCTION

Diabetes mellitus is a chronic, non-transmissible endocrine disorder that causes substantial challenges in healthcare systems. The global prevalence of diabetes mellitus continues to increase, creating a public health burden. The latest estimates in 2021 showed a global prevalence of around 530 million people with diabetes, according to the IDF Diabetes Atlas (1). As per the projections, the diabetic population will increase to 637 million by 2030 (2). The estimated global diabetes-related health expenditure was 966 billion USD in 2021, and this is expected to reach 1,054 billion USD by 2045 (2). Several classes of oral hypoglycemic agents, such as sulfonylureas, biguanides, meglitinides, dipeptidyl peptidase-IV inhibitors, etc., are used in the management of diabetes. However, they are associated with adverse effects such as weight gain, hypoglycemia, gastrointestinal intolerance, myocardial infarction, and kidney damage (2). This highlights the urgent need for advanced therapies that can provide better glycemic control while minimizing the burden of adverse effects and complications. Herbs have long been utilized to manage diabetes mellitus. Several bioactive extracts and natural bioactive compounds demonstrated antidiabetic efficacy via a variety of molecular mechanisms, including suppressing α-glucosidase activity, controlling glucose absorption in the gut, regulating glucagon-like peptide-1 homeostasis, and inhibiting amylin aggregation, etc. (3). Repeated admin-istration or high doses of medicaments are necessary to achieve therapeutic levels in the

Ruhuna. J. Med., 13(01), 2025, pp. 11–28
ISSN (p) ISSN 3084-942X ; ISSN (e) ISSN 3084-9063

body due to the low solubility of herbal extracts. The foremost problems in the use of herbal medicines in traditional medicine remedies are bitter and astringent taste and the degradation of ingredients under unfavorable conditions while processing and storage (3). Moreover, because of the wide range and pH fluctuation, mucosal barrier, and various enzymes present in the gastrointestinal tract, natural medicines in the form of crude extracts have very low bioavailability and membrane permeability. In this context, the therapeutic utility of these herbal medications is limited. This highlights the significance of developing more appropriate antidiabetic drug leads targeting inflammation and oxidative stress, and studies need to delve into the development of antidiabetic drug leads that are more efficacious, particularly using herbal extracts, and safe while being flexible in their ability to treat a broader patient base.

Recently, alternative approaches have been proposed to improve the efficacy and bioactivity of natural products, such as plant extracts and compounds, using various nanotechnology-based applications. This may lead to limiting the problems associated with the direct use of plant extracts as therapeutic agents (4). Indeed, nano-encapsulation was emphasized as a worthwhile strategy for the protection of phytochemicals in plant extracts since it allows efficient immobilization into various delivery carriers. The nanoformulated drug leads have led to remarkable advancements in drug delivery since nanosized formulations are well-organized to advance the clinical efficacy of curative agent by improving their biopharmaceutical attributes, bioavailability, and target specificity (4). Further, plant derived nanoformulations lead to a reduction in the frequency of dosing and repeated administration due to the sustained release of therapeutic components over a prolonged period. The pronounced advantages of nanotherapeutics signify a positive step forward in improving the therapeutic value of plant extracts, particularly in the management of diabetes mellitus.

Polymeric nanoparticles such as chitosan, wheat gluten, cellulose, alginate, etc., are highlighted for providing innovative opportunities in pharmaceutical applications due to their satisfactory biocompatibility and low toxicity. Among the polymeric nanoparticles, alginate has been used in numerous applications because of its versatility and wide range of physicochemical properties. Alginate is a natural water-soluble polysaccharide that can be extracted from some brown algae cell walls and bacteria. The building blocks of alginate are α-L-guluronic acid and β-D-mannuronic acid. In nature, alginate exists as a salt of alginic acid bound to various metal cations, particularly Na^+. It allows chemical modification for site-specific targeting, the highest mucoadhesive strength, controlled gelation, mechanical strength, surface tailoring, biocompatibility, and modulation of cell affinity. Furthermore, alginate reduces hemolysis when it comes into contact with the blood, showing minimum cytotoxicity (5). However, herbal extracts mediated nanoformulations have regained enormous interest in the management of diabetes.

Several articles have discussed the applications of nanotechnology in the development of antidiabetic drug leads. Although studies have reported on alginate nanoformulations against hyperglycemia, natural products-based alginate nano-formulations on inflammation, oxidative stress, etc., are less explored. Therefore, the present review focuses on a brief account of diabetes mellitus, highlighting the key pathophysiological features of hyper-glycemia, the significance of alginate nanoformulations in the development of antidiabetic drug leads, preparation and characterization of alginate nano-formulations, bioactivity studies, and toxicity evaluation of natural products encapsulated alginate nanoformulations.

OVERVIEW OF DIABETES MELLITUS

Diabetes mellitus is a common and complex metabolic disorder of multiple etiologies with profound acute and chronic consequences, that has increased in prevalence over the past few decades. The heterogeneous etiopathology includes defects in the secretion of insulin, the action of insulin, or both, and disturbance of carbohydrate, protein, and fat metabolism.

Type 2 diabetes mellitus is the most common and major form of diabetes, accounting for more than 90% of all diabetic cases (6). The onset of type 2 diabetes mellitus is preceded by impaired glucose

Ruhuna. J. Med., 13(01), 2025, pp. 11–28
ISSN (p) ISSN 3084-942X ; ISSN (e) ISSN 3084-9063

tolerance due to insulin resistance and deficiency of insulin secretion by pancreatic β-cells. Insulin secretion is decreased, limiting the capacity of the body to maintain physiological glucose levels in the case of cell dysfunction. In contrast, insulin resistance contributes to enhancing the production of glucose in the liver and diminishing the glucose uptake in the muscle, liver, and adipose tissue. Insulin sensitivity can be influenced by factors such as lipids and glucose overloading, inflammation, and oxidative stress. Further, obesity is correlated with oxidative stress as well as the low-grade inflammation of the white adipose tissues. As a consequence, activation of some pro-inflammatory signaling pathways ends up with insulin resistance, impaired glucose tolerance, and ultimately diabetes mellitus (7).

Diabetes mellitus and its complications are complex and multifactorial, with both environmental and genetic components. There are numerous mechanisms underlying hyperglycemia-evoked vascular damage, such as increased production of advanced glycation end products, expression of their receptors, and activation of protein kinase C. Evidence indicates that oxidative stress and inflammation contribute to the onset of insulin resistance, which is a key feature of type 2 diabetes. They activate stress kinases like c-Jun N-terminal kinase and the inhibitor of nuclear factor-kβ kinase and impair insulin signaling. Therefore, it is crucial to translate research findings into therapeutic applications by targeting hyperglycemia and hyperglycemia induced oxidative stress and inflammation.

NANOTECHNOLOGY IN MEDICINE AND PHARMACEUTICAL SCIENCES

Nanotechnology comprises a diverse range of scientific disciplines and is regarded as one of the most promising tools for solving a wide variety of modern-day issues. Advancements in nanotechnology have vital applications in numerous fields, including food, medicine, healthcare, and industrial purposes, while medicine and pharmaceutical applications are gaining more importance because of their distinctive physical and chemical characteristics. Pharmaceutical uses in nanotechnology could revolutionize the purposes and procedures of targeting the management of diseases and their pathogenesis, drug delivery, improving cell-material interactions, etc. (8).

Nanotechnology could refer to any technology functioning within the nanoscale range of approximately 1-100 nm. The term nanotechnology was originally coined in 1974 (9). Nanotechnology has been a modern-day revolution, gaining momentum from the late 19th century and reaching its zenith in the early 20th century. Its profound impact has permeated various fields, including medicine and pharmaceutical sciences. Nanotechnology is identified as a promising area in medicine and pharmaceutical sciences since it is entirely based on its exclusive functional features and characteristics, which can coordinate with the natural system of the human body. Therefore, nanotechnology can create applications that include comprehensive surveillance, manipulation, and defense of biological human systems (9).

Nanomedicine stands out as one of the prominent applications of nanotechnology, which is committed to developing highly targeted medical interventions for disease diagnosis, prevention, and treatment in the present scenario. Thus, an interdisciplinary approach is being adopted to apply the outcomes of nanomedicines as nanomaterials (10). Active compound encapsulated nanodrugs have demonstrated enhanced bioavailability and desirable pharmacokinetic properties, eliminated/reduced side effects, and absorbed their therapeutic potential effectively through scientific investigations. Medication delivery with nanotechnology facilitates precise targeting and entry of drugs into the cell, improves imaging capabilities, enables precise intracellular targeting, and enhances the controlled release of therapeutic agents (10). In recent decades, there has been a spike in nanomedicine research, which is currently being turned into commercialization activities worldwide. Numerous nanomaterials have now become a prolific area of scientific research due to their clinically correlated modulations.

Ruhuna. J. Med., 13(01), 2025, pp. 11–28
ISSN (p) ISSN 3084-942X ; ISSN (e) ISSN 3084-9063

Review article

CLASSES OF NANOMATERIALS USED FOR MEDICAL AND PHARMACEUTICAL DOMAINS

Nanotechnology forms materials of different types at the nanoscale level and can be arranged based on their dimensionality, agglomeration state, morphology, functionalization, and chemical composition (11). These materials are broadly divided into several dimensions depending on the overall shape, as one-dimensional, two-dimensional, or three-dimensional. Nanoparticles are typically classified based on the type of nanomaterials/chemical properties as organic, inorganic, carbon, and composite-based nanomaterials. In addition, the place of origin, pore size, and potential toxicity are also considered in the classification of nanomaterials.

Nanoparticles employ noncovalent interactions to self-assemble and design molecules, enabling the conversion of organic nanoparticles or organic nanomaterials into desired structures such as liposomes, micelles, dendrimers, and polymeric nanoparticles. Some nanoparticles, like micelles and liposomes, are biodegradable, non-toxic, and encompass a hollow core, which is recognized as nanocapsules. The diverse classifications and categories of nanomaterials possess unique applications and uses within the field of medicine. Biodegradable polymers, liposomes, metal nanoparticles, dendrimers, hydrogel nanocomposites, nanorods/nanofilms/nanofibers, and nano-micelles (Figure 1) have been reported in the available literature as nanomaterials that facilitate the utilization and applications in the medical and pharmaceutical domain (12).

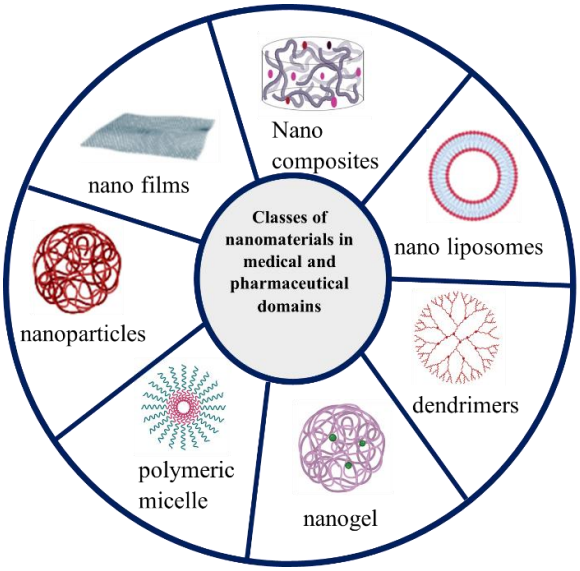


Figure 1. Different classes of nanomaterials in medical and pharmaceutical domains

STRUCTURE OF ALGINATE AND ITS CROSS-LINKING

Alginate is one of the vital naturally occurring biopolysaccharides. The United States Food and Drug Administration has recognized alginate as a safe material for use in food and drug applications (13). Alginate is found abundantly in nature from some brown marine algae, including *Macrocystis pyrifera* L. (Family: Laminariaceae), *Ascophyllum nodosum* L. (Family: Fucaceae), and *Laminaria hyperborea* (gunnerus) Foslie (Family: Laminariaceae) and exists as a matrix polysaccharide. Alginate subsists as an alginic acid salt of various metal cations like $Mg2^{+}$, Na^{+}, $Ba2^{+}$, and $Sr2^{+}$ in nature. The molecular structure of sodium alginate is characterized as an anionic copolymer comprising α-L-guluronic acid units (G-unit) and β-D-mannuronic acid units (M-unit) organized in an irregular block-wise pattern of varying proportions, as homopolymeric (MM and GG) and heteropolymeric blocks (MG and GM) (Figure 2A). They are connected with 1,4-glycosidic linkages (13).

Alginate demonstrates intriguing biopharmaceutical properties such as pH sensitivity, biodegradability, biocompatibility, mucoadhesiveness, lack of toxicity, and absence of immunogenicity. These attributes make an attractive and modified drug delivery system with controlled and sustained release of drugs. The solubility of alginate is affected by the pH of the surrounding medium. It undergoes precipitation when the pH of the medium is lower than the pKa of the alginate, leading to the formation of alginic acid, which is insoluble in water (14). One of the reasons for the versatile use of alginate is its unique capability to bind diverse cations, leading to stable and tailor-made hydrogels compared to other polymers. Advancements in chemical and biochemical techniques enable the enrichment of alginate with new functionalities, such as enhanced hydrophobicity and the ability to bind specific proteins to meet specific requirements. Sulfation and oxidation reactions can be used

Ruhuna. J. Med., 13(01), 2025, pp. 11–28
ISSN (p) ISSN 3084-942X ; ISSN (e) ISSN 3084-9063

to modify the -OH groups, whereas amidation and esterification reactions can be used to modify the -COOH groups in alginate. These chemical modifications can control their differentiation behavior for medicinal and pharmaceutical applications.

One of the key characteristics of alginate is its capability to form an ionic gel when exposed to polyvalent cations. Electrostatic interactions between positively charged various divalent ($Ca2^+$, $Cu2^+$, $Cd2^+$, $Pb2^+$) as well as trivalent ($Al3^+$, $Fe3^+$) metal cations and -COOH groups in alginate molecules are responsible for ion-induced alginate gels. This leads to the polyelectrolyte complex formation (15). Various cations show a diverse affinity for alginate, where calcium is the most frequently utilized for alginate gelation as it is clinically safe and also due to its economical attraction. An exchange of sodium ions from the G-blocks with multivalent cations leads to alginate gelation and the stacking of these G-blocks to form a characteristic “egg-box” structure. The linkage of each chain with many other chains results in the formation of a three-dimensional gel network (15).

Grant et al. (16) first described the egg-box model based on the cross-linking of alginate with divalent cations. However, there were two suggestions for steps involved in calcium ion-induced cross-linking of the alginate (Figure 2B). Fang et al. (17) suggested that the cross-linking process starts with the formation of a mono-complex, followed by an egg-box dimer through cross-linking. It ultimately forms inter-cluster associated multimers, constituting the fully cross-linked form of calcium alginate. Borgogna et al. (18) opposed the idea of mono-complex formation and suggested the tilted egg-box model. This process starts with the interaction of one calcium ion with monomeric G-units from two different alginate chains. This interaction leads to the formation of an egg-box-like structure, namely a tilted egg-box

ALGINATE NANOFORMULATIONS

Alginate has been extensively investigated for various applications particularly in drug delivery in the past decades owing to its versatile properties. Recent advancements in nanotechnology have facilitated the exploitation of nanostructured materials based on alginate, offering entirely novel competence. Thereby, it is not surprising that a wide array of alginate-based nanomaterials with different forms and compositions are formulated via various approaches.

The remarkable properties of alginate facilitate the synthesis of diverse particle designs and alginate-based multiple-unit systems such as nanoparticles, microparticles, and beads. These systems can encapsulate drugs, enzymes, and other compounds by dissolving, entrapping them, or attaching them to the particle matrix (19). Nanosystems are potential tools to expand the choices of drug administration routes and control drug delivery and stability. Alginate particles for encapsulation were first developed in 1980. Since then, much research has been performed on the development of alginate particles, resulting in alginate being one of the most commonly applied materials for the formation of nanoparticles in medicinal and pharmaceutical fields. However, few attempts have been made to formulate plant-origin natural products-based alginate nanoformulations towards managing diabetes, inflammation, and oxidative stress.

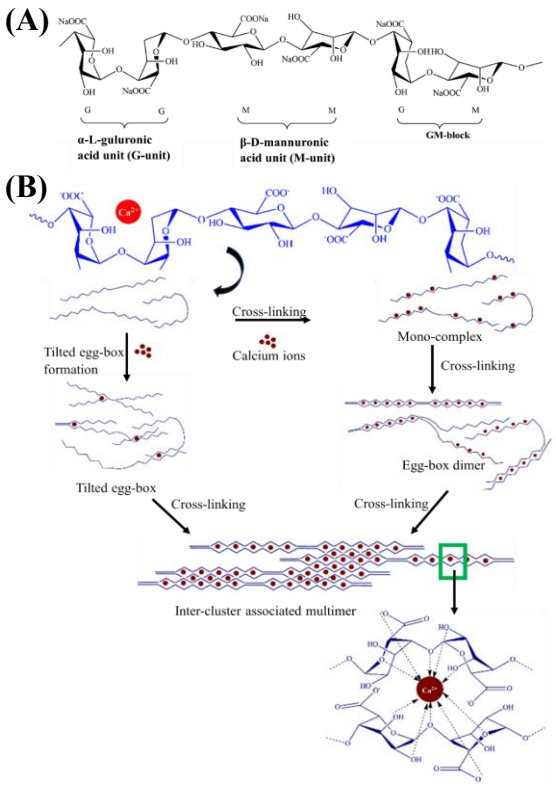


Figure 2. (A) Chemical structure of sodium alginate (B) Schematic diagram showing the steps involved in calcium ion-induced cross-linking of alginate. Source: (Authors)

Ruhuna. J. Med., 13(01), 2025, pp. 11–28
ISSN (p) ISSN 3084-942X ; ISSN (e) ISSN 3084-9063

PREPARATION OF ALGINATE NANOFORMULATIONS

It is important to select appropriate preparation methods based on the requirement in the preparation of alginate based nanoformulations. Alginate can be used as isolated, derivatives/modifications of alginate and combined with other polymers to enhance/achieve its functionality and broaden its applications. Alginate based nanoparticles are obtained in different ways, using single-step or two-step procedures. Ionotropic gelation and polyelectrolyte complexation are widely used methods to formulate alginate nanoparticles (20). Emulsification, solvent evaporation, solvent diffusion, layer-by-layer, electrospinning, spray drying, solvent casting method, doping with inorganic materials, etc. (Figure 3) are the other techniques used for the preparation of alginate nanoparticles (20).

CHARACTERIZATION OF ALGINATE-BASED NANOPARTICLES

Nanomaterials have attracted attention because of their unique physical, chemical, and mechanical properties. After the preparation of the alginate particulate system, consistent characterization is crucial to ensure reliable and reproducible synthesis of nanoparticles. Determination of the mean diameter of particles, polydispersity index (PDI), zeta potential, and shape/morphology are critical to confirm the suitability of nanoparticles for medicinal and pharmaceutical applications. Particle size and shape are among the most influential physical characteristics guiding the behavior of nanoparticles (21). Dynamic light scattering (DLS) is the most common approach to analyzing hydrodynamic particle size, while scanning electron microscopy (SEM) is widely used to evaluate size and morphology of nanoparticles. When the mean diameter of nanoparticles is small, it increases the surface-to-volume ratio of nanoparticles, leading to advanced physiochemical properties and facilitating intracellular access easily and passing through the skin barrier, which is ideal for topical drug delivery (21).A wide range of characterization techniques is available for the determination of chemical properties, including Fourier transform infrared spectroscopy (FTIR), Ultraviolet-visible spectroscopy, and nuclear magnetic resonance spectroscopy. These methods identify structural differences in molecular binding between entities, which can reveal details about the existence of their interactions. Attenuated total reflectance - FTIR, transmittance FTIR, and micro-spectroscopy FTIR are the favored FTIR-based methods for characterization (22). Mechanical properties could be referred to as the mechanical characteristics of a material under various conditions. The mechanical properties of nanomaterials generally consist of strength, hardness, brittleness, and plasticity. To evaluate the mechanical properties of nanoparticles, atomic force microscope techniques and *in situ* transmission electron microscopes can be used. In addition, the mechanical properties of the nanofilms could be evaluated by universal tensile test equipment (23). Apart from the mentioned characterization techniques, nanofilms are subjected to evaluate water content, water solubility, swelling index, and water vapor permeability to develop qualified nanofilms for the application of medicinal and pharmaceutical streams (23).

NANOENCAPSULATION

Nanoencapsulation is a technique used in the field of nanotechnology based on enclosing active substances, such as drugs, vitamins, or other bioactive compounds in liquid, solid, or gaseous states within nanoscale carriers called nanoparticles. Encapsulation allows the development of formulations in which the bioactive compounds are protected, and their release can be controlled to act at a targeted site, for a set period, and at a specific rate. Resistance to the conditions of the gastrointestinal tract and the presence of low viscosity are important features of the ideal matrix for the preservation of bioactive compounds (24). Among the matrix materials

Ruhuna. J. Med., 13(01), 2025, pp. 11–28
ISSN (p) ISSN 3084-942X ; ISSN (e) ISSN 3084-9063

Review article

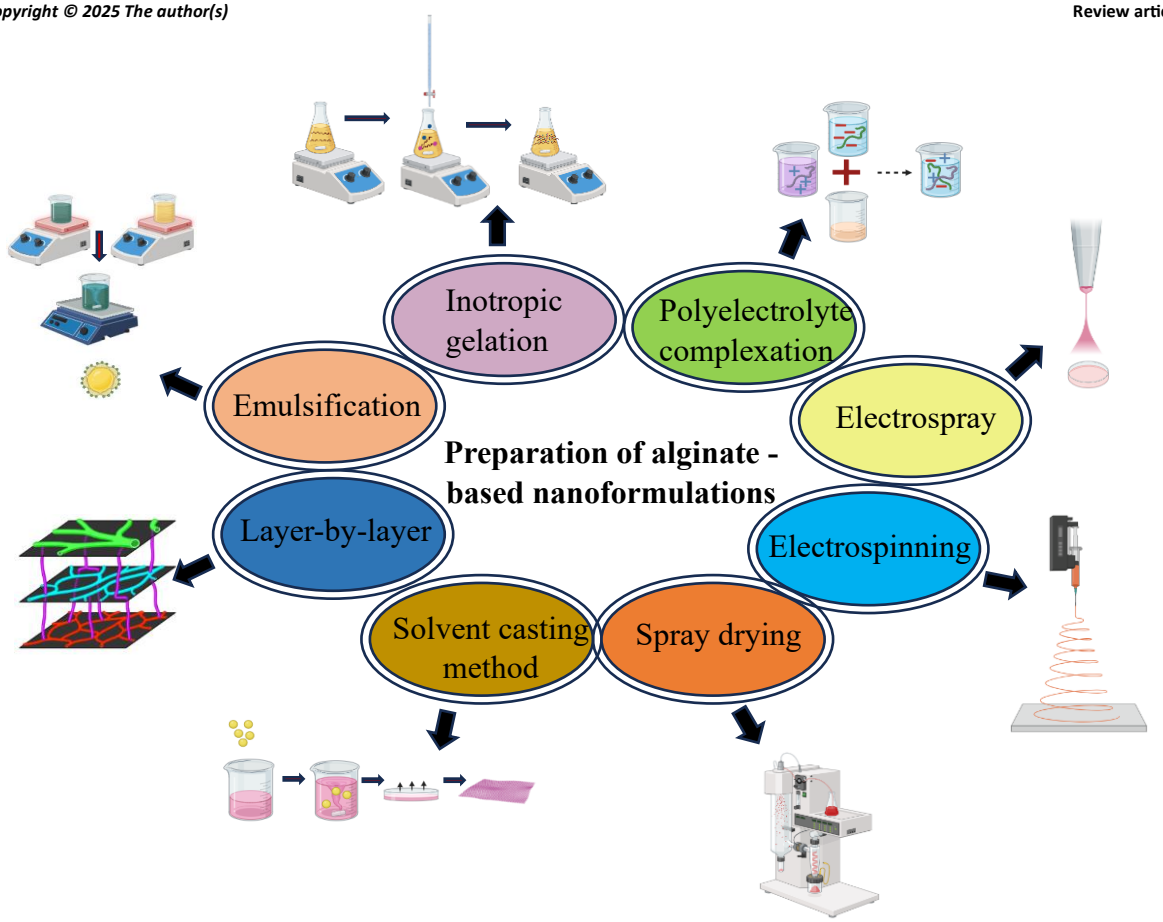


Figure 3. Various preparation methods of alginate based nanoformulations Source: (Authors)

commonly used for encapsulation, one class worth mentioning is represented by polysaccharides, including sodium alginate. Drug encapsulation efficiency (EE%) and drug loading content are two important parameters of nanoencapsulation. Drug EE% reflects the percentage of drugs that are successfully entrapped into drug carriers. It is defined by the concentration of the incorporated material detected in the nanoformulation over the initial concentration used to make the formulation. The amount of drug loaded per unit weight of the nanoparticle is defined as the loading capacity (LC%) and indicates the percentage of the mass of the nanoparticle that is due to the encapsulated drug.

NATURAL PRODUCTS BASED ALGINATE NANOFORMULATIONS FOR DIABETES

Natural products offer a vast reservoir of bioactive compounds with therapeutic potential. Since ancient times, natural sources have served as the foundation for both nourishment and curative remedies. Plants have always been an exemplary source of drugs, with many of the currently available drugs being obtained directly or indirectly from them. The World Health Organization has listed a total of 21,000 plants that are used for medicinal purposes around the world. More than 1200 plants have allegedly been identified as having antidiabetic properties. One-third of them have been the subject of around 460 publications and scientific research to develop plant-based antidiabetic drug leads (2).

Medicinal plants are rich sources of diverse phytoconstituents, such as phenolic acids, flavonoids, terpenoids, saponins, carotenoids, alkaloids, and glycosides, which may possess antidiabetic, anti-inflammatory, and antioxidant properties. Further, the combined action of phytoconstituents leads

Ruhuna. J. Med., 13(01), 2025, pp. 11–28
ISSN (p) ISSN 3084-942X ; ISSN (e) ISSN 3084-9063

to the potentially beneficial properties of each plant matrix. Traditional herbal medicines are believed to ameliorate diabetic syndromes through notable mechanisms such as α-amylase and α-glucosidase inhibition, glucagon-like peptide-1 secretion, and free radical scavenging activity (25). A combination of plant extracts with alginate based nanoformulations would facilitate the mechanisms and offer a smart strategy for the discovery process of new and effective candidates for diabetes, oxidative stress, and inflammation.

Several research studies on natural products-based alginate nanoformulations were conducted to demonstrate their improved bioactivities and drug delivery systems (26, 27). Conscientious efforts are being made by researchers to come up with novel alginate based nanoformulations for vast applications in the medicinal and pharmaceutical field due to the extraordinary advantages of sodium alginate in the development of drug delivery systems.

Scientific studies have been focused on natural products based nanoformulations as drug leads not only to deliver them safely and actively to the targeted site but also to amount of polyphenols and improved their antioxidant capacity, pancreatic α-amylase inhibitory activity, and bile acid binding potential after gastrointestinal digestion (29). Similarly, Noor et al. (30) also carried out a study on alginate based encapsulation of polyphenols of *Piper betel* L. (Family: Piperaceae) leaves to assess the impact of alginate encapsulation on stability, bioavailability, and therapeutic properties of polyphenols. The antioxidant activity in terms of 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging activity, 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radical scavenging activity, metal chelating activity, hydrogen peroxide scavenging activity, and antidiabetic activity in terms of α-amylase and α-glucosidase inhibitory activities of alginate encapsulated *P. betel* leaf extract were studied for 24 months. It was found that the scavenging activity and antidiabetic activity of free *P. betel* leaf extract decreased as the months progressed, enhance their therapeutic efficacy. Bioactive compounds particularly polyphenols have been found to suppress postprandial hyperglycemia by interrupting carbohydrate digestion and retarding glucose absorption through inhibition of intestinal carbohydrate digesting enzymes including α-amylase (EC 3.2. 1.1) and α-glucosidase (EC 3.4.14.5). The encapsulation of polyphenols helps to protect their activity and thereby improves the inhibitory activity of digesting enzymes (Figure 4) (28). Further, the upregulation of glucose transporter-4 (GLUT-4), an increase of insulin secretion, and activation of the 5'adenosine monophosphate-activated protein kinase pathway are highlighted as multiple therapeutic targets of natural products encapsulated alginate formulations in the management of diabetes mellitus and are potentiated with the nanoencapsulation (Figure 4) (28).

Encapsulation of phenolic extracts of *Clitoria ternatea* L. (Family: Fabaceae) was demonstrated by Pasukamonset et al. (29) via the extrusion method of alginate with calcium chloride. The findings revealed that encapsulation of phenolic extracts of *C. ternatea* allowed them to retain a high whereas encapsulated polyphenols were found to be stable for over 24 months, suggesting the potency of nanoencapsulation towards the retention of bioactivity (30).

Further, Parijoto (Medinilla speciosa Blume, Family: Melastomataceae) had strong antioxidant activity, but its usage as an antioxidant agent was restricted because of its' low bioavailability. Therefore, an effort was made by Vifta et al. (31) to prepare parijoto encapsulating alginate nanoparticles using the ionic gelation method. Characterization techniques proved the successful formation and encapsulation of nanoparticles. The results of the ferric ion-reducing antioxidant power (FRAP) assay revealed that antioxidant activity could be enhanced upon encapsulation when compared to the free extract (31). In addition, Wongverawattanakul et al. (32) also developed an alginate formulation

Ruhuna. J. Med., 13(01), 2025, pp. 11–28
ISSN (p) ISSN 3084-942X ; ISSN (e) ISSN 3084-9063

Review article

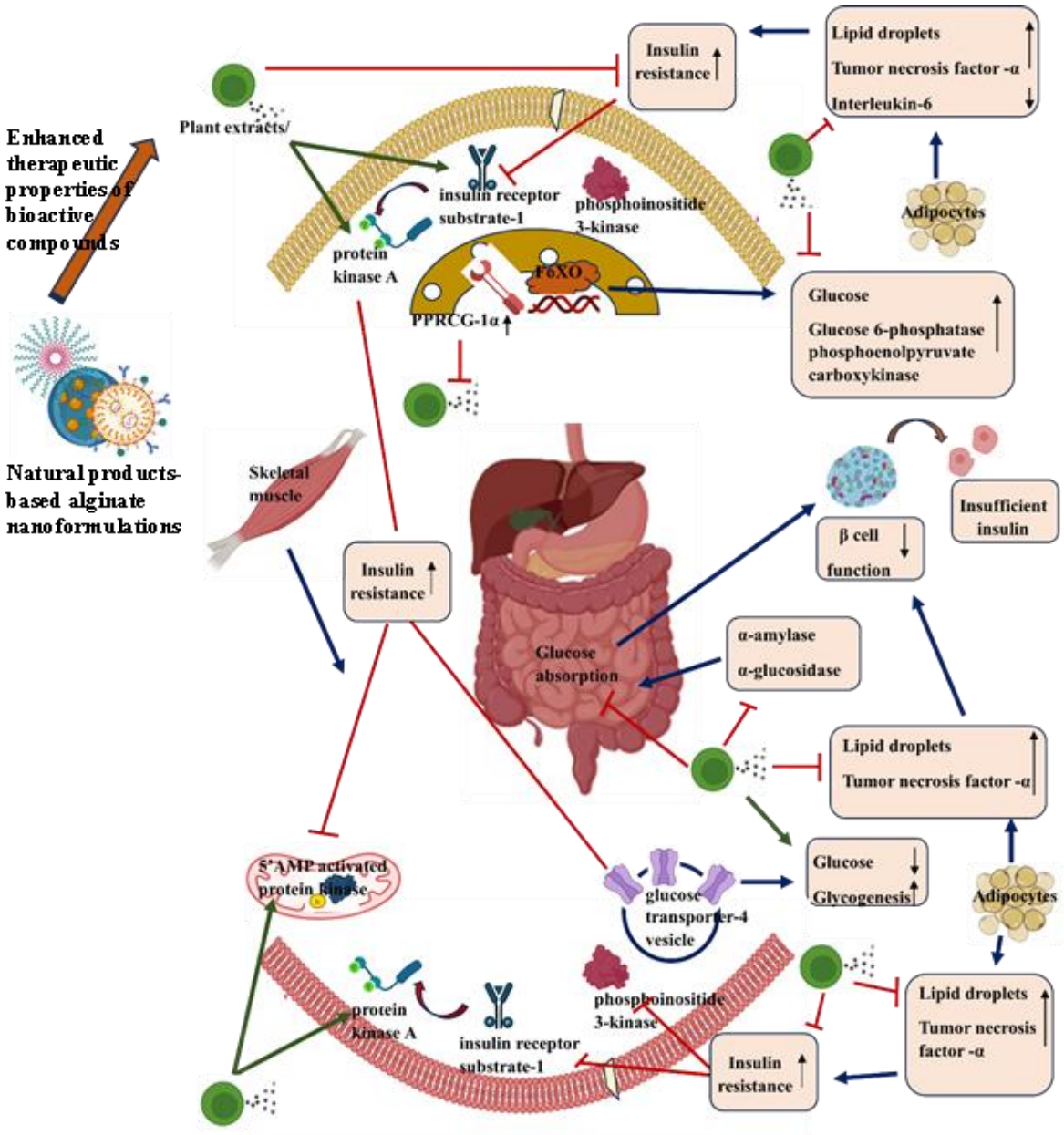


Figure 4. Proposed antidiabetic mechanisms of natural products encapsulated alginate nanoformulations. Source: (Authors)
[FoxO: forkhead box protein O, PEPCK: phosphoenolpyruvate carboxykinase]

encapsulating *Meson chinensis* Benth (Family: Lamiaceae) extract by extrusion technique to assess the stability and antioxidant activity of polyphenols in *M. chinensis* during simulated gastrointestinal digestion. The FRAP assay was conducted to evaluate the antioxidant capacity of the *M. chinensis* encapsulated alginate formulation. It was reported that *M. chinensis* markedly declined the FRAP value, whereas the encapsulation of M. chinensis with alginate significantly increased the FRAP value highlighting the importance of encapsulation. Overall, the findings of the study suggested that encapsulation with alginate improved the bioaccessibility and biological activity of polyphenols in *M. chinensis* (32).

Ruhuna. J. Med., 13(01), 2025, pp. 11–28
ISSN (p) ISSN 3084-942X ; ISSN (e) ISSN 3084-9063

The importance of combining alginate with other polymers/compounds lies in the ability to enhance the properties of the resulting nanoparticles for specific applications, thereby expanding their versatility and biodegradability, possessing enhanced bioactivities, and promoting drug delivery. Alginate-chitosan nanoparticles are capable of working as carriers of the hydrophobic drugs quercetin and rutin and were investigated by Nalini et al. (33) and Surendran and Palei (34), respectively. The results of *in vitro* release were comparable with a study in which quercetin exhibited a sustained release in a pH-dependent pattern (33). The encapsulation of rutin into an alginate-chitosan matrix facilitates the enhancement of the glucose uptake by human hepatoma (HepG2) cells and could significantly enhance the viability of the cells compared to free rutin (34). A scientific study carried out recently on chitosan-coated sodium alginate formulation containing ethanolic leaf extract of *Elaeocarpus tectorius* L. (Family: Elaeocarpaceae) revealed that it could enhance the antidiabetic and antioxidant activities when compared to the free extract (35).

Apart from the broadly described studies, investigations have been carried out todate to demonstrate the potential of natural products alginate based nanoformulations for application in the management of diabe
Studies based on plant derived compounds and extracts encapsulated alginate nanoformulations carried out from 2019 to 2024 are included in Table 1.

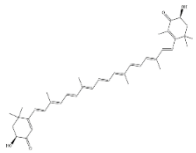
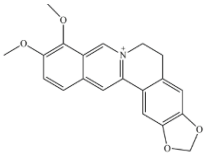
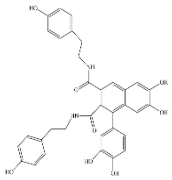
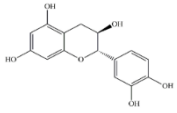
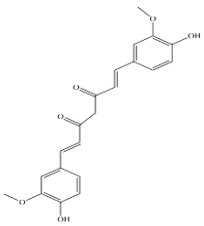
XICITY STUDIES OF ALGINATE FORMULATIONS

Drug toxicity remains a major challenge in the process of drug discovery and may affect various biological processes involving single or multiple target organs. Therefore, toxicity studies are paramount in screening of newly developed drug leads before they are used in clinical trials. Evaluation of toxicity is the determination of potential hazards of the test substance that may likely produce and characterization of its action.

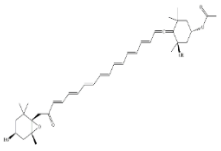
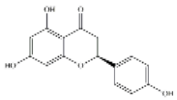
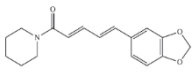
Several scientific reports are available based on toxicity studies of alginate based nanoformulations targeting diabetes mellitus. Maity et al. (58) carried out a study on alginate coated chitosan core-shell nanoparticles for efficient oral delivery of naringenin in diabetic animals and toxicity evaluation was conducted based on biochemical parameters (alanine transaminase (EC: 2.6.1.2), alkaline phosphatase (EC: 3.1.3.1), and aspartate transaminase (EC: 2.6.1.1), and histopathology evaluations. The results of the histopathology and blood parameters revealed that alginate coated chitosan core-shell nanoparticles were free from toxicity (58). Assessment of acute oral toxicity of quercetin loaded alginate/chitosan nanoparticles was conducted by Nalini et al. (33). The *in vivo* toxicity study of the quercetin loaded alginate/chitosan nanoparticles revealed no acute systemic toxicity following its oral administration in rats with median lethal dose greater than 75 mg/kg body weight ensuring an efficient nanocarrier of oral quercetin in the animal model. The biochemical analysis of liver and kidney enzymes revealed that the nanoformulations had no decline in the normal functions of the vital organs, indicative of the biosafety of nanoencapsulated quercetin (33).

Ruhuna. J. Med., 13(01), 2025, pp. 11–28
ISSN (p) ISSN 3084-942X ; ISSN (e) ISSN 3084-9063

Table 1. Plant derived compounds and plant extracts mediated alginate based nanoformulations as antidiabetic, antioxidant, and anti-inflammatory agents/drug leads

Bioactive compound/plant extract	Type of alginate nanoformulation	Characterization techniques	Experimental model/assay	Key findings	Reference/s
Astaxanthin 	Chitosan oligosaccharides/ alginate nanoparticles	Particle size, zeta potential, FTIR, TEM	Antioxidant assays (DPPH assay,	Improved PI – 31.18%	36
			hydroxyl radical scavenging activity)	Improved PI – 37.17%	
Berberine 	Sodium alginate nanoparticles	Particle size, SEM, TEM, AFM, FTIR, DSC	Antioxidant activity (DPPH assay)	Improved DPPH inhibition – 26.63%	37
			Anti-inflammatory activity (membrane stabilization assay)	Improved membrane stabilization – 22.89%	
Berberine	Chitosan/alginate nanogel	DLS, zeta potential, FTIR, TEM, UV-visible spectroscopy, XRD	Reactive oxygen species generation (using 2',7'-dichlorodihydro fluorescein diacetate dye)	Improved of ~ 4.5-fold in green fluorescence	38
Cannabisin A 	Alginate nanoparticles	Particle size, zeta potential, FTIR, XRD, DSC, CD	Antioxidant activity (DPPH assay,	Improved PI – 79.82 %	39
			ABTS assay)	Improved PI – 79.08 %	
Catechine 	Chitosan-alginate nanoparticles	Particle size, zeta potential, FE-SEM, FTIR	Oxidative stress in male Wistar rats (Catalase enzyme assay,	Improved activity – 3.18%	40
			total antioxidant capacity)	Improved activity – 1.42%	
Curcumin 	Chitosan-sodium alginate and polyvinyl alcohol combined nanocomposite	FTIR, FE-SEM, TEM, XRD	Antioxidant activity (DPPH assay),	Improved PI - 85.79%	41
			Anti-inflammatory activity (albumin denaturation method)	Improved PI - 83.59%	
	Gum-Arabic-sodium alginate nanoparticles	ATR-FTIR, XRD, DSC, TEM	Antioxidant activity (DPPH assay),	Improved PI - 85.6% at 200 µg/mL	42

Ruhuna. J. Med., 13(01), 2025, pp. 11–28
ISSN (p) ISSN 3084-942X ; ISSN (e) ISSN 3084-9063

Curcumin	Zein/caseinate-alginate nanoparticles	Mean diameter, zeta potential, PDI, SEM, XRD	Antioxidant activity (DPPH assay, ABTS assay)	Improved scavenging activity – 2.18 ± 0.14 mM – 3.05 ± 0.81 mM	43
Fucoxanthin 	Alginate hydrogel beads	Optical microscope, SEM, FTIR	Oxidative stress (SPG grade KM mice) MDA Catalase SOD activity	 Decreased by 22% Increased activity > 1.5 U/mL Increased activity > 0.6 x 10^3 U/mL	44
Metformin and curcumin	Chitosan/alginate nanoparticles	DLS, SEM, FTIR	Anti-inflammatory activity (nitrite assay in RAW 264.7 macrophage and BV-2 microglial cells) ICR mice (A mouse model of inflammatory pain)	Improved PI - 70% Improved PI - 68%	45
Naringenin 	Zein-sodium alginate complex nanoparticles	Particle size, PDI, zeta potential, TEM, DSC, XRD, FTIR,	Antioxidant activity(DPPH assay, ABTS assay)	Improved scavenging activity by 83.54% 82.68%	46
Piperine 	Hyaluronic acid-sodium alginate based nanomembrane	DLS, PI, FTIR, SEM	Male Swiss albino mice – anti-inflammatory activity (mouse ear edema model)	Reduced inflammation up to 43.6%	47
Aegle marmelos L. (Rutaceae) Aqueous extract	Alginate nanoparticles	DLS, zeta potential, PDI, Sem, FTIR	Antidiabetic activity (α-amylase, α-glucosidase, DPP-IV assay, glucose adsorption) Anti-inflammatory activity (Xanthine oxidase assay, heat-induced hemolysis, hypotonicity-induced hemolysis)	Improved PI-33.99% 64.57% 48.59% Improved adsorption – 60% Improved PI – 14.78% 27.58% 95.80%	48

Ruhuna. J. Med., 13(01), 2025, pp. 11–28
ISSN (p) ISSN 3084-942X ; ISSN (e) ISSN 3084-9063

Ethanol extract (100%)			Antidiabetic activity (DPP-IV assay)	26.66%	
			Anti-inflammatory activity (Xanthine oxidase assay,	Improved PI – 6.5%	
			heat-induced hemolysis,	78.04%	
			hypotonicity-induced hemolysis),	59.40%	
50% ethanol extract			Antidiabetic activity (α-glucosidase,	Improved PI-52.34%	
			DPP-IV assay,	46.86%	
			glucose adsorption)	Improved adsorption – 24.10%	
			Anti-inflammatory (Xanthine oxidase assay,	54.62%	
			heat-induced hemolysis,	93.29%	
			hypotonicity-induced hemolysis)	59.03%	
50% acetone extract			Antidiabetic activity (α-glucosidase,	50.16%	
			DPP-IV assay,	32.34%	
			glucose adsorption)	Improved adsorption – 30.25%	
			Antioxidant activity (ABTS assay)	Improved PI – 50%	
			Anti-inflammatory activity (Xanthine oxidase assay,	68.84%	
			heat-induced hemolysis,	92.68%	
			hypotonicity-induced hemolysis)	94.79%	
Coccinia grandis L. (Cucurbitaceae)	Alginate nanoparticles	DLS, zeta potential, PDI, Sem, FTIR	Antidiabetic activity(α-amylase,	Improved PI - 60.75%	49
			α-glucosidase,	1.91%	
			DPP-IV assay,	30.32%	
			glucose adsorption)	20%	
			Antioxidant activity (ABTS assay)	17.24%	

Ruhuna. J. Med., 13(01), 2025, pp. 11–28
ISSN (p) ISSN 3084-942X ; ISSN (e) ISSN 3084-9063

Ethanol extract (100%)			Antidiabetic activity (α-amylase, glucose adsorption)	26.44% 4.00%	50
50% acetone extract			Antidiabetic activity (α-amylase)	45.50%	49
Convolvulus arvensis L. (Convolvuceae)	Alginate/chitosan nanoparticles	Particle size, zeta potential, PDI, FTIR, TGA	Anti-inflammatory activity (Protein denaturation assay, membrane stabilization assay)	Improved PI – 83.33 % 6.89%	51
n-butanol fraction			(Protein denaturation assay, membrane stabilization assay)	Improved PI – 83.33 % 2.22%	
Fumaria officinalis L. (Papaveraceae)	Alginate hydrogel	Particle size, zeta potential, SEM	Anti-inflammatory activity (in male Wistar rats) (IL-6)	Decreased concentration 43.75%	52
Nigella sativa L. (Ranunclaceae) Oil extract	Alginate microcapsules	Mean size, Optical microscopy, environmental SEM	Antioxidant activity (DPPH)	Preserved activity	53
Panax ginseng C. A. Meyer (Araliaceae), Ginseng extract	Sodium alginate nano hydrogel	Particle size, PDI, Zeta potential, FTIR, SEM, TEM	Antioxidant activity (Wistar rats) MDA Glutathione peroxidase Superoxide dismutase Anti-inflammatory activity (NF-kβ, TNF-α, IL-1β, IL-6)	 0.573 ± 0.163 19.25 ± 4.03 159.75 ± 9.17 14.32 ± 0.59 ng/mL 13.27 ± 1.43 pg/mL 12.60 ± 0.63 pg/mL 4.4 ± 0.64 pg/mL	54
Plantago major L. (Plantaginaceae) Ethanol extract	Sodium alginate hydrogel	SEM, FTIR	Oxidative damage (MDA) Inflammatory cytokines (IL-1α,	Decreased malondialdehyde level < 2μM/mg protein Induced anti-inflammatory effect < 7 pg/ml	55

Ruhuna. J. Med., 13(01), 2025, pp. 11–28
ISSN (p) ISSN 3084-942X ; ISSN (e) ISSN 3084-9063

			IL -1β)	< 0.07 OD/mL	
Spirulina sp., methanol extract of phenolic compound (LEB 18)	Alginate particles	Optical microscopy, DSC	Antioxidant activity (DPPH assay)	Improved activity by 49.37%	56
Viola odorata L. (Family: Violaceae), Ethanol extract from flower	Chitosan-coated alginate microcapsules	DLS, Zeta potential, SEM, FTIR	Antioxidant activity (DPPH assay)	Improved scavenging activity by 20%	57

ABTS: 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid), ATR-FTIR: attenuated total reflectance-Fourier transform spectroscopy, AFM: atomic force microscopy, DPPH: 2,2-diphenyl-1-picrylhydrazyl, DLS: dynamic light scattering, DSC: differential scanning colorimetry, DPP-IV: dipeptidyl peptidase IV, FE-SEM: field emission scanning electron microscopy, FTIR: Fourier transform spectroscopy, HepG2: human hepatoma, IL-6: interleukin-6, IL-1β: interleukin-1β, MDA: malondialdehyde, PI: percentage inhibition, PDI: polydispersity index, RAW 264.7: macrophage cell line from tumor in a male mouse, SOD: superoxide dismutase, SEM: scanning electron microscopy, TNF-α: tumor necrosis factor-α, TEM: transmission electron microscopy, XRD: X-ray diffractometry

CLINICAL TRIALS ON ALGINATE-BASED FORMULATIONS

Clinical trials on alginate-based formulations demonstrated their potential in various biomedical applications. Cell microencapsulation technology was tested in patients with diabetes mellitus by Soon-Shiong et al. (59). Allogeneic islet in alginate microcapsules was injected intraperitoneally and blood glucose levels were estimated for 9 months. The results of this study revealed the safe usage of alginate and its biocompatibility. In addition, Snow et al. (60) conducted randomized, double blind, placebo-controlled dose ranging investigation to assess the impact of immunoprotected (alginate-encapsulated) porcine choroid plexus cells for xenotransplantation in patients with Parkinson's disease. This highlighted the clinical validity of alginate. However, clinical trials have not been reported for natural products-based alginate formulations.

Based on the literature, the experimental studies on natural products encapsulated alginate-based nanoformulations exhibited great promise for the development of antidiabetic drug leads. However, certain limitations may be associated with the experimental studies. Factors such as pH of the alginate solution, changes in ionic strength and composition, temperature variation, and mechanical stress had the potential to alter nanoparticle characteristics and properties. Therefore, attention must be taken to avoid such variations during the preparation of alginate nanoformulations. Reproducibility and stability of nanoformulations represent significant challenges in large-scale production. Batch-to-batch variability can occur due to sensitive parameters such as pH, concentration of cross-linking agent, and ionic strength. Therefore, ensuring formulation consistency is essential for commercial applications as it plays a critical role in maintaining the reproducibility of therapeutic outcomes.

CONCLUSION AND FUTURE PERSPECTIVES

The use of natural products encapsulated alginate nanoformulations as drug leads for the development of antidiabetic therapeutic agents has been increasingly popularized worldwide. The limitations associated with the direct therapeutic use of plant extracts and isolated compounds from plants are overcome by their nanoformulations, which improve compliance and biological activity. The present review reports information on natural products based alginate nanoformulations in the management of diabetes, targeting hyperglycemia, oxidative stress, and inflammation. Natural products

encapsulated alginate nanoformulations have been formulated in different forms of various types, i.e. nanogel, nanoparticles, nanocomposites, hydrogels, and microcapsules. DLS, zeta potential, PDI, SEM, and FTIR were frequently used as characterization techniques to confirm the successful formation and properties of respective nanoformulations. The majority of the synthesized nanoformulations have been evaluated for their antidiabetic, antioxidant, and anti-inflammtory activities using *in vitro* assays. The above-mentioned biological activities of the alginate based nanoformulations were generally superior to those of the corresponding plant extracts and isolated compounds. The natural products encapsulated alginate nanoformulations could improve the antidiabetic, antioxidant, and anti-inflammatory properties of plant extracts and isolated compounds. However, the data from the most recent studies are still inadequate to interpret the vast therapeutic potential of natural products encapsulated alginate nanoformulations. Future research should focus on detailed and long-term *in vitro* and *in vivo* mechanisms of antidiabetic, anti-inflammatory, and antioxidant effects to properly understand their usefulness in clinical applications. Undoubtedly, natural products encapsulated alginate based nanoformulations have opened up new therapeutic options for the development of novel antidiabetic drug leads targeting hyperglycemia, oxidative stress, and inflammation.

Conflict of interests:

The authors declare that they have no conflict of interest

References

1.IDF. International Diabetes Federation Atlas. 2021. 10th edition.
2.Bhavsar D, Kutre S, Shikhare P, et al. Pharmacoinformatics approach for type 2 diabetes mellitus therapeutics using phytocompounds from Costus genus: an in-silico investigation. Journal of Biomolecular Structure and Dynamics 2024:1-17.
3.Rani R, Karmakar P, Singh N, et al. Encapsulation methods in the food industry: mechanisms and applications: Goyal MR, Veena N, Watharkar RB, editors. Advances in Food Process Engineering: Apple Academic Press; 2023; 93-139.
4.Ganesan P, Arulselvan P, Choi DK. Phytobioactive compound-based nano delivery systems for the treatment of type 2 diabetes mellitus–current status. International Journal of Nanomedicine 2017;1097-1111.
5.Severino P, Da Silva CF, Andrade LN, et al. Alginate nanoparticles for drug delivery and targeting. Current Pharmaceutical Design 2019;25(11):1312-1334.
6.Ortiz-Martínez M, González-González M, Martagón AJ, et al. Recent developments in biomarkers for diagnosis and screening of type 2 diabetes mellitus. Current Diabetes Reports 2022;22(3):95-115.
7.Safavi M, Foroumadi A, Abdollahi M. The importance of synthetic drugs for type 2 diabetes drug discovery. Expert Opinion on Drug Discovery 2013;8(11):1339-63.
8.Patra JK, Das G, Fraceto LF, et al. Nano based drug delivery systems: recent developments and future prospects. Journal of Nanobiotechnology 2018;16:1-33.
9.Sahu T, Ratre YK, Chauhan S, et al. Nanotechnology based drug delivery system: Current strategies and emerging therapeutic potential for medical science. Journal of Drug Delivery Science and Technology 2021;63:102487.
10.Malik S, Muhammad K, Waheed Y. Emerging applications of nanotechnology in healthcare and medicine. Molecules 2023;28(18):6624.
11.Saleh TA. Innovation. Nanomaterials: Classification, properties, and environmental toxicities. Environmental Technology and Innovation 2020;20:101067.
12.Haleem A, Javaid M, Singh RP, et al. Applications of Nanotechnology in Medical field. Global Health Journal 2023;7(2):70-77.
13.Kontominas MG. Use of alginates as food packaging materials. Foods 2020;9(10):1440.
14.Severino P, Da Silva CF, Andrade LN, et al. Alginate nanoparticles for drug delivery and targeting. Current Pharmaceutical Design 2019;25(11):1312-1334.
15.Nayak AK, Hasnain MS. Ionotropically gelled alginate particles in sustained drug release: Nayak AK, Hasnain MS, editors, Alginates in Drug Delivery. London: Academic Press, Elsevier; 2020;203-30.
16.Grant GT, Morris ER, Rees DA, et al. Biological interactions between polysaccharides and divalent cations: the egg-box model. FEBS Letters 1973;32(1):195-8
17.Fang Y, Al-Assaf S, Phillips GO, et al. Multiple steps and critical behaviors of the binding of calcium to alginate. The Journal of Physical Chemistry B 2007;111(10):2456-2462.
18.Borgogna M, Skjåk-Bræk G, Paoletti S, et al. On the initial binding of alginate by calcium ions.

Ruhuna. J. Med., 13(01), 2025, pp. 11–28
ISSN (p) ISSN 3084-942X ; ISSN (e) ISSN 3084-9063

The tilted egg-box hypothesis. The Journal of Physical Chemistry B 2013;117(24):7277-7282.
19. Paques JP, Van der Linden E, Van Rijn CJM, et al. Preparation methods of alginate nanoparticles. Advances in Colloid and Interface Science 2014;209:163-71.
20. Venkatesan J, Anil S, Singh SK, et al. Preparations and applications of alginate nanoparticles: Venkatesan J, Anil S, Kim S, editors. Seaweed Polysaccharides: London: Elsevier; 2017;251-268.
21. Mudalige T, Qu H, Van Haute D, et al. Characterization of nanomaterials: Tools and challenges: Rubio AL, Rovira MJF, Sanz MM, Gómez-Mascaraque LG, editors. Nanomaterials for Food Applications. London: Elsevier; 2019; 313-353.
22. Eid MM. Characterization of Nanoparticles by FTIR and FTIR-Microscopy: Mallakpour S, Hussain CM, editors. Handbook of Consumer Nanoproducts. Singapore: Springer; 2022;1-30.
23. Joudeh N, Linke D. Nanoparticle classification, physicochemical properties, characterization, and applications: a comprehensive review for biologists. Journal of Nanobiotechnology, 2022;20(1):262.
24. Jafari S, Jafari SM, Ebrahimi M, et al. A decade overview and prospect of spray drying encapsulation of bioactives from fruit products: Characterization, food application and *in vitro* gastrointestinal digestion. Food Hydrocolloids 2023;134:108068.
25. Alam S, Sarker MMR, Sultana TN, et al. Antidiabetic phytochemicals from medicinal plants: prospective candidates for new drug discovery and development. Frontiers in Endocrinology 2022;13:800714.
26. Jayapal JJ, Dhanaraj S. Exemestane loaded alginate nanoparticles for cancer treatment: formulation and *in vitro* evaluation. International Journal of Biological Macromolecules 2017;105:416-21.
27. Sohail R, Abbas SR. Evaluation of amygdalin-loaded alginate-chitosan nanoparticles as biocompatible drug delivery carriers for anticancerous efficacy. International Journal of Biological Macromolecules 2020;153:36-45.
28. Dewanjee S, Chakraborty P, Mukherjee B, et al. Plant-based antidiabetic nanoformulations: the emerging paradigm for effective therapy. International Journal of Molecular Sciences 2020;21(6):2217.
29. Pasukamonset P, Kwon O, Adisakwattana S. Alginate-based encapsulation of polyphenols from Clitoria ternatea petal flower extract enhances stability and biological activity under simulated gastrointestinal conditions. Food Hydrocolloids 2016;61:772-779.
30. Noor A, Al Murad M, Chitra AJ, et al. Alginate based encapsulation of polyphenols of Piper betel leaves: Development, stability, bio-accessibility and biological activities. Food Bioscience 2022;47:101715..
31. Vifta RL, Nurlaila D, Yanti S. Alginate-based nanoencapsulation on ultrasonic-assisted extraction of Parijoto Fruit (Medinilla Speciosa Blume) and its antioxidant activity. Walisongo Journal of Chemistry 2022;5(2):145-52.
32. Wongverawattanakul C, Suklaew PO, Chusak C, et al. Encapsulation of Mesona chinensis benth extract in alginate beads enhances the stability and antioxidant activity of polyphenols under simulated gastrointestinal digestion. Foods 2022;11(15):2378.
33. Nalini T, Basha SK, Sadiq AMM, et al. Development and characterization of alginate/chitosan nanoparticulate system for hydrophobic drug encapsulation. Journal of Drug Delivery Science and Technology 2019;52:65-72
34. Surendran V, Palei NN. Formulation and characterization of rutin loaded chitosan-alginate nanoparticles: antidiabetic and cytotoxicity studies. Current Drug Delivery 2022;19(3):379-394.
35. Manoharan K, Chitra P, Ragunathan R. Effect of microencapsulation on the antidiabetic and antioxidant activities of Elaeocarpus tectorius (Lour.) Poir. leaf extracts-An *in vitro* study. Research Journal of Pharmacy and Technology 2024;17(1):149-55.
36. Sorasitthiyanukarn FN, Muangnoi C, Rojsitthisak P, et al. Chitosan oligosaccharide/alginate nanoparticles as an effective carrier for astaxanthin with improving stability, *in vitro* oral bioaccessibility, and bioavailability. Food Hydrocolloids 2022;124:107246.
37. Mehra M, Sheorain J, Bakshi J, et al. Sodium alginate polymer nanoformulation as promising carrier for berberine delivery: Synthesis, morphology and in-vitro evaluation. Carbohydrate Polymer Technologies and Applications 2024;7:100408.
38. Singh N, Anand SK, Sharma A, et al. Chitosan/alginate nanogel potentiate berberine uptake and enhance oxidative stress mediated apoptotic cell death in HepG2 cells. International Journal of Biological Macromolecules 2024;257:128717.
39. Xu PW, Yue XJ, Yuan XF, et al. Hemp seed globulin-alginate nanoparticles for encapsulation of Cannabisin A with enhanced colloidal stability and antioxidant activity. International Journal of Biological Macromolecules 2024;256:128380.
40. Mohammadbaghban E, Taravati A, Najafzadehvarzi H, et al. Oral administration of encapsulated catechin in chitosan-alginate nanoparticles improves cognitive function and neurodegeneration in an aluminum chloride-induced rat model of Alzheimer's disease. Physiological Reports 2024;12(13):e16095.

41. Rezagholizade-shirvan A, Najafi MF, Behmadi H, et al. Preparation of nano-composites based on curcumin/chitosan-PVA-alginate to improve stability, antioxidant, antibacterial and anticancer activity of curcumin. Inorganic Chemistry Communications 2022;145:110022.
42. Hassani A, Mahmood S, Enezei HH, et al. Formulation, characterization and biological activity screening of sodium alginate-gum arabic nanoparticles loaded with curcumin. Molecules 2020;25(9):2244.
43. Huang Y, Zhan Y, Luo G, et al. Curcumin encapsulated zein/caseinate-alginate nanoparticles: Release and antioxidant activity under *in vitro* simulated gastrointestinal digestion. Pharmacological Research 2023;6:100463.
44. Li Y, Dou X, Pang J, et al. Improvement of fucoxanthin oral efficacy via vehicles based on gum Arabic, gelatin and alginate hydrogel: Delivery system for oral efficacy enhancement of functional food ingredients. Journal of Functional Foods 2019;63:103573.
45. Wasana PWD, Vajragupta O, Rojsitthisak P, et al. Metformin and curcumin co-encapsulated chitosan/alginate nanoparticles as effective oral carriers against pain-like behaviors in mice. International Journal of Pharmaceutics 2023;640:123037.
46. Wu T, Han W, Han Y, et al. Fabrication and characterization of zein-sodium alginate complex nanoparticles as an effective naringenin delivery system: physicochemical stability, solubility, antioxidant activity. Journal of Molecular Liquids 2023;386:122569.
47. Politi FAS, Carvalho SG, Rodero CF, et al. Piperine-loaded nanoparticles incorporated into hyaluronic acid/sodium alginate-based membranes for the treatment of inflammatory skin diseases. International Journal of Biological Macromolecules 2023;227:736-48.
48. De Silva ND, Attanayake AP, Karunaratne DN, et al. Bael (Aegle marmelos L. Correa) fruit extracts encapsulated alginate nanoparticles as a potential dietary supplement with improved bioactivities. Journal of Food Science 2023;88(12):4942-4961.
49. De Silva ND, Attanayake AP, Karunaratne DN, et al. Synthesis and bioactivity assessment of Coccinia grandis L. extract encapsulated alginate nanoparticles as an antidiabetic drug lead. Journal of Microencapsulation 2024;41(1):1-17.
50. Silva WNDD, Attanayake AP, Arawwawala LDAM, et al. *In vitro* antioxidant activity of alginate nanoparticles encapsulating the aqueous extract of Coccinia grandis L. Turkish Journal of Chemistry 2023;47(4):715-25.
51. Osman EE, Shemis MA, Abdel-Hameed E-SS, et al. Phytoconstituent analysis, anti-inflammatory, antimicrobial and anticancer effects of nano encapsulated Convolvulus arvensis L. extracts. BMC Complementary Medicine and Therapies 2024;24(1):122.
52. Yang X, Mo W, Shi Y, et al. Fumaria officinalis-loaded chitosan nanoparticles dispersed in an alginate hydrogel promote diabetic wounds healing by upregulating VEGF, TGF-β, and b-FGF genes: A preclinical investigation. Heliyon 2023;9(7):e17704.
53. Samak YO, Santhanes D, El-Massik MA, et al. Formulation strategies for achieving high delivery efficiency of thymoquinone-containing Nigella sativa extract to the colon based on oral alginate microcapsules for treatment of inflammatory bowel disease. Journal of Microencapsulation 2019;36(2):204-214.
54. Md S, Abdullah S, Alhakamy NA, et al. Sustained-release ginseng/sodium alginate nano hydrogel formulation, characterization, and *in vivo* assessment to facilitate wound healing. Journal of Drug Delivery Science and Technology 2022;74:103565.
55. Bâldea I, Lung I, Opriş O, et al. Antioxidant, anti-Inflammatory effects and ability to stimulate wound healing of a common-plantain extract in alginate gel formulations. Gels 2023;9(11):901.
56. Machado AR, Silva PM, Vicente AA, et al. Alginate particles for encapsulation of phenolic extract from spirulina sp. LEB-18: physicochemical characterization and assessment of *in vitro* gastrointestinal behavior. Polymers 2022;14(21):4759.
57. Yousefi M, Khanniri E, Shadnoush M, et al. Development, characterization and *in vitro* antioxidant activity of chitosan-coated alginate microcapsules entrapping Viola odorata Linn. extract. International Journal of Biological Macromolecules 2020;163:44-54.
58. Maity S, Mukhopadhyay P, Kundu PP, et al. Alginate coated chitosan core-shell nanoparticles for efficient oral delivery of naringenin in diabetic animals-An *in vitro* and *in vivo* approach. Carbohydrate Polymers 2017;170:124-32.
59. Soon-Shiong P, Heintz RE, Merideth N, et al. Insulin independence in a type 1 diabetic patient after encapsulated islet transplantation. Lancet 1994; 343(8903):950-951.
60. Snow B, Mulroy E, Bok A, et al. A phase IIb, randomised, double-blind, placebo-controlled, dose-ranging investigation of the safety and efficacy of NTCELL®[immunoprotected (alginate-encapsulated) porcine choroid plexus cells for xenotransplantation] in patients with Parkinson's disease. Parkinsonism and Related Disorders 2019;61:88-93