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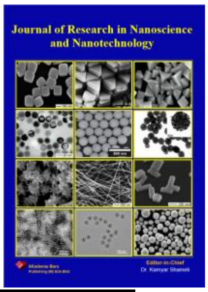

Plant Extract Loaded Sodium Alginate Nanocomposites for Biomedical Applications: A Review

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ABSTRACT

The advancement of clinical medicine established exceptionally in today's era is used to cure many infectious diseases. Unfortunately, the negative aftermath associated with synthetic drugs has caused many to turn their attention towards an alternative, which is natural plant-extract drugs. Plant-based drugs have a vast number of benefits and applications in the biomedical field and are further formulated with nanocomposite hydrogel, namely sodium alginate. Sodium alginate is a biopolymer that is water-soluble, non-toxic, biocompatible, and biodegradable, therefore having a high demand in the medical field. The objective of this review is to highlight the nanotechnology development that is used in the medical field to enhance the therapeutic effects of naturally occurring drugs. This review will discuss the use of sodium alginate nanocomposite to create a nanohybrid drug loaded with plant extracts.

Keywords:
Plant extracts, bioactive compounds, sodium alginate, nanocomposite, biomedical

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1. Introduction

Synthetic drugs are created in the laboratory using man-made chemicals instead of natural ingredients [1]. In 1897, the first synthetic drug, aspirin, was created using salicyclic acid extracted from willow barks [2] . Over the time, synthetic drugs begin to dominate the pharmaceutical industry because of its efficacy in treating complex diseases such as asthma [3], diabetes [4], cancer and heart diseases [5]. Unfortunately, as effective as these drugs can be, they still threaten the human body due to its high toxicity. For example, chemotherapeutic drugs not only inhibit tumor growth, but they also effect the normal cells in the body [6]. Based on the American Cancer Society, anticancer drugs are highly toxic and causes many side effects such as diarrhea, vomiting, tiredness and fatigue. Based on the statistics of the hospital admissions in the U.S.A, about 8% of entrance is due to the side effects of synthetic drugs [7]. Therefore, over the years, scientists are working on using plant extracts to produce drugs because they have a high demand in the biomedical field due to its zero cytotoxicity and no side effects [8]. Based on the World Health Organization (WHO), 70-95% of the world's population depend on herbal medicine for healthcare, which includes the use of plant extracts and the biological active components in the extracts [9-10]. In advanced countries, herbal medicines have a high demand due to several factors such as the effectiveness of herbal medicines and side effects and cost of synthetic drugs [11].

These medicinal plants come from roots, stems, wood, bark, leaves, flowers, fruits, seeds or their extracts [12]. Examples of medicinal plants are *Trachyspermum ammi* (ajwain) [13], *Cuminum cyminum L* (cumin) [14] , *Coriandrum sativum L.* (coriander) [15], *Cinnamomum Zeylanicum* (cinnamon) [16] and many others. Each of these plant extract has its own property and can be used to cure or prevent specific diseases [17]. However, medicinal plants are not highly developed compared to synthetic drugs due to the limitation of knowledge and also clinical experiments. Therefore, many researches are being done to start implementing the use of plant extract in a larger scale in the biomedical field. For example, in a clinical test, it was found that the ginsenosides extracted from ginseng, can help treat anaemia [18].

Herbal medicines are usually available in the form of conventional dosage but recently, many impactful strategies are developed to enhance the therapeutic effects and delivery efficiency of extracts, especially using nanotechnology [19] . The plant extract encapsulation is being developed using nanocomposites to increase biomedical efficiency and applications [20]. The advancement using biopolymers such as sodium alginate and chitosan have extraordinary benefits in the medical field due to their solubility, toxicity, stability, pharmacological activity, and physical and chemical degradation when consumed [21].

2. Plant Extracts

2.1 Properties of Bioactive Compounds in Plant Extracts

Medicinal plants are extracted and processed for herbal and traditional medicine and also for research purposes [5]. The medicinal plant preparation for experimental purposes entails proper and time-consuming plant collecting, professional authentication, suitable drying, and grinding [8]. Extraction of medicinal plants is the separation of active plant materials or secondary metabolites such as alkaloids [22], flavonoids [23] , terpenes, saponins, steroids, and glycosides [24] from inert or inactive material using a suitable solvent and a conventional extraction procedure [25]. Extraction, fractionation, and isolation of the bioactive molecule, is then done [26]. Each of the plant extract has its own phytochemicals that can be used to fight against various diseases [27].

In a report, Shoemaker et al stated that there are over 40,000 plant species on earth that contain a vast number of biological active compounds. When pharmacological screening is done, it was observed that the herbs have contains many therapeutic contributions to the medical field [11]. The main steps to exploit the phytochemicals in a plant extract are extraction [28] , pharmacological screening [29], isolation and characterization of phytochemicals [28], toxicological evaluation and clinical evaluation [25].

Based on clinical experiments, the numerous phytochemicals from medicinal plants are safe and effective to be consumed. Plant extracts are nontoxic, therefore does not cause any side effect to the human body. Plant extracts have various biological properties such as anticancer [30], antimicrobial [31], antioxidant [32], antibacterial [33] and many more as shown in Figure 1 [26]. For example, a study conducted has proven that the bioactive components in an endemic yellow iris plant have antioxidant, antibacterial and DNA protecting properties [27]. Besides that, essential oils of basil, laurel, clove, thyme and rosemary exhibits antibacterial activity against *Listeria monocytogenes (L. monocytogenes)* and other pathogens [34].

Figure 1. Properties of bioactive compounds in medicinal plants

2.2 Biomedical Application of Plant Extracts

Recently, many studies have scientifically proven that medicinal plants such as spices and herbs can be used in the biomedical field due to their wide range of applications. Herbs and spices such as basil [35] , lemon grass [36] , saffron [37] and ginger [18] are being used as effective therapeutic food since decades. These natural extracts have become a dietary choice because of the advantages of the naturally occurring bioactive compounds in the plants [38] . Therefore, in today's era with the help of modern biological and computational science technology, various remarkable advances are being done to produce drugs based on plant extracts [39,40].

Around 60% of the world's population depend on herbal medicine because they have no side effect have naturally curing effect for cardiovascular diseases [41], digestion [20], tumor [42], skin diseases, obesity and many other sicknesses. There are many clinical experiments done to prove that these plant extracts have properties that contains therapeutic effect when consumed or injected with [41]. For instance, in both developed and developing countries, oxidative stress and inflammation are the primary cause of metabolic syndrome and this issue has become a financial burden. Natural plants with anti-inflammation and antioxidant properties such as cinnamon, turmeric [43], and fennels [44] are used as an alternative and economical method to treat this problem. More tests are done to know the correct amount of dosage for the effective curing of metabolic syndrome [38].

Furthermore, curcumin has antioxidant and anti-inflammatory properties which was proven on a study conducted on diabetic rats. Application of curcumin caused an acceleration in wound healing with marked collagen synthesis and fully regenerated epithelial layer [45]. The essential oil from cinnamon has antidiabetic property because a study has shown that it helps decrease the blood glucose level and also improves the lipid profile and the function of pancreas islet β cells [46]. Trans-cinnamaldehyde, one of the bioactive compounds of cinnamon has anticancer property as it can restrain tumor cell growth and enhance tumor cell apoptosis [16]. There are many other clinical tests have been conducted on other herbs to prove their biomedical properties can be applied in the medical field as shown in Table 1.

3. Alginate-Based Biomaterials

3.1 Biopolymers

For years now, vast researches are being done for the high demand of naturally derived products with unique physiochemical properties and a high degree of compatibility for food and drug delivery applications. Among them, biopolymers have attracted an undeniable attention in the medical field [47]. Biopolymers are polymers produced from natural sources either chemically synthesized from a biological material or entirely biosynthesized by living organisms. Biopolymers have significant usage for various medical applications for example occlusion, suturing, covering, fixation, isolation, adhesion, cellular proliferation, controlled drug delivery, contact inhibition, and tissue guide [24]. Biopolymers can be classified differently based on their origin. Biopolymers can be traditionally distinguished into natural, synthetic and microbial biopolymers [49] as shown in Figure 2.

3.2 Sodium Alginate

Among them, alginate, is the most widely known natural polyanionic polymer, Alginates are generally derived from kelp or brown algae and several bacterial strains [24]. Alginate is a linear polysaccharide which is anionic in nature and has a chemical formula of $(C_6H_7NaO_6)_n$ with the average molecular weight of 216.121 g/mol [21].

Table 1. Summary of significant properties plant extracts, medical applications and experimental findings

Medicinal plants	Bioactive compounds	Medicinal uses	Experimental findings	Reference
Ajwain (*Trachyspermum ammi*)	Thymol, oleic acid, linoleic acid, γ-terpinene, o-cymene	Antimicrobial activity	Ajwain seeds are remarkably active against the food-borne pathogenic Gram positive and Gram-negative bacterial strains.	[49]
Basil (*Ocimum Lamiaceae)*	Linalool, rosmarinic acid, cinapic acid, ursolic acid, and eugenol	Metabolic disorders	30g of dried seeds of basil reduces blood glucose level in a Thai patient after 1 month. Ethanolic extracts of basil relieves patients from asthmatic symptoms and enhances vital capacities.	[35]
Coriander (*Coriandrum sativum L.)*	Linalool, phenolic acids, α-pinene, γ-terpinene and camphor	Antimicrobial and antidiabetic activity	Coriander extracts mixed in drinking water decreases *E. Coli* of ileal microflora. Corriander extract showed reduction in the levels of triacylglycerol (TCA) and total cholesterol (TC), which proves it's potential in decreasing lipid in rats blood.	[15, 35]
Ginger (*Zingiber officinale)*	Zerumbone, gingerols, shogaols, and paradols	Anticancer and antiviral activity	Zerumbone reduced the percentage of human myeloid leukemia (HL60) cell viability. The rhizome of ginger proved to have antiviral effect by decreasing Human Respiratory Syncytial Virus (HRSV).	[31,33]
Fenugreek (*Trigonella foenum graecum L.)*	alkaloids, flavonoids, fibers, saponins, steroidal saponins	Antidiabetic activity	0.44-1.74g of aqueous extract of fenugreek reduces blood glucose level. Fenugreek was found to strongly inhibit the growth of two bacteria, (*Staphylococcus aureaus* and *Pseudomonus aeruginosa)* in a petri dish.	[42, 50-51]

Black Cumin *(Nigella sativa L.)*	Thymoquinones, trans-anethole, p-cymene limonene, carvone, α-thujene	Antioxidant and antihypertensive activity	Essential oil of black cumin seed shows an efficient increase of antioxidant agents such as Glutathione-S-transferase (GST), glutathione reductase and GSH-Px against oxidative stress brought by potassium bromate in rats' model. For 1 year, 57 individuals who were given 2 g daily supplements of black cumin showed great improvement in the decrease of heart rate and blood pressure.	[44,52]
Cinnamon *(Cinnamomum Zeylanicum)*	Trans-cinnamaldehyde, eugenol, cinnamyl-acetate, camphor.	Antidiabetic and anticancer activity	. The study also found that when 60 people with type 2 diabetes ingested up to 6g of cinnamon per day for 40 days to 4 months, their serum glucose, triglycerides, low-density lipoprotein cholesterol, and total cholesterol levels were all reduced. An extract of cinnamon and cardamom was used to treat cancer in mice. In tests, the mice that received the therapy had decreased levels of oxidative stress in its' melanoma cells.	[16,46,53]
Turmeric *(Curcuma longa)*	Demethoxy-curcumin curcumin, bis-demethoxy curcumin	Wound healing, and antitumor activity	Turmeric enhances epithelial regeneration, increases fibroblast proliferation and vascular density. Turmeric inhibits cell proliferation and induces apoptosis in human leukemia, prostate cancer, and non-small cell lung line.	[43,54]

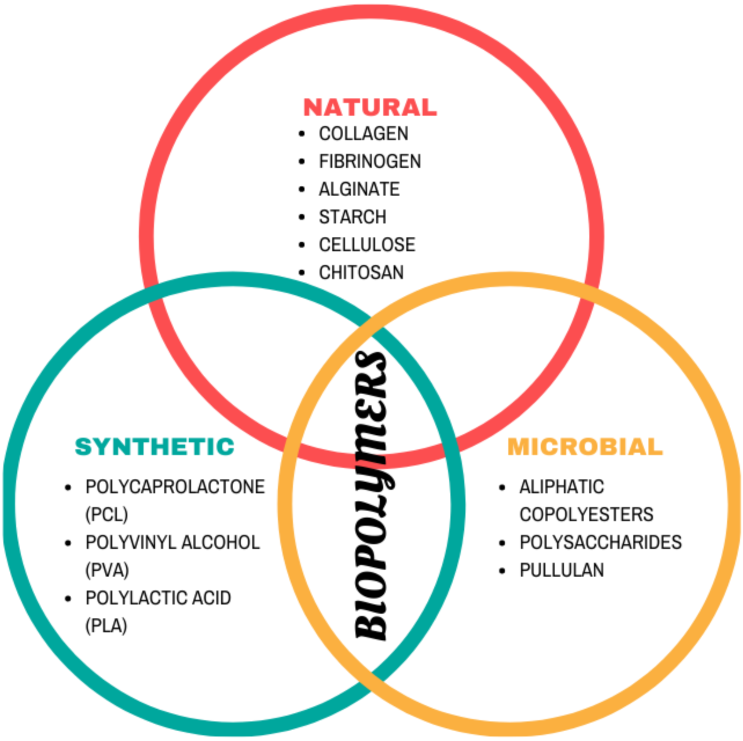

Figure 2. Summary of different types of biodegradable biopolymers

3.3 Molecular Structure of Sodium Alginate

Alginates are unbranched polysaccharides composed of M-blocks and G-blocks as well as blocks of alternating sequences (MG blocks). The M unit is known as β-D-mannuronic acid residue and the G unit is α-L-guluronic acid residues [21]. From Figure 3, it can be observed that the MM block is β-1,4-glycosidic bond and the GG block is α- 1,4 glycosidic bond. The corresponding flexibility of blocks increases in the order of GG < MM < MG or GM. This shows that GG block is the stiffest block and has the most extended chain conformation than the rest. The rigidity of blocks on the other hand, increases in the order of MG < MM < GG [55].

3.4 Properties of Sodium Alginate

Sodium alginate represents alginate's most common salt. The physiochemical properties of alginates are determined based on the compositions and conformation structures of the G and M blocks. It is readily available, environmentally friendly, and has low production cost. This natural biopolymer is a linear, pH-sensitive, water-soluble, non-immunogenic poly-anionic copolymer [21]. Alginates are also biocompatible, biodegradable and is nontoxic which leads to a high demand in the food and medical industries [56]. The biodegradability and biocompatibility properties enable alginates to absorb 200 to 300 times more water that its original weight [57]. The most significant property of alginates is their ability to form ionic gel in the presence of polyvalent cations. A gelation mechanism involves the coordination and chelating structures in an egg-box model. During this process, G units in alginates bind to polyvalent metal ions together with the hydrogen-bonding interaction of these cross-linking agents with oxygen atoms in the G blocks of two adjacent polymer chains [23]. Alginates can form nanogel due to their thickening and film making ability [56].

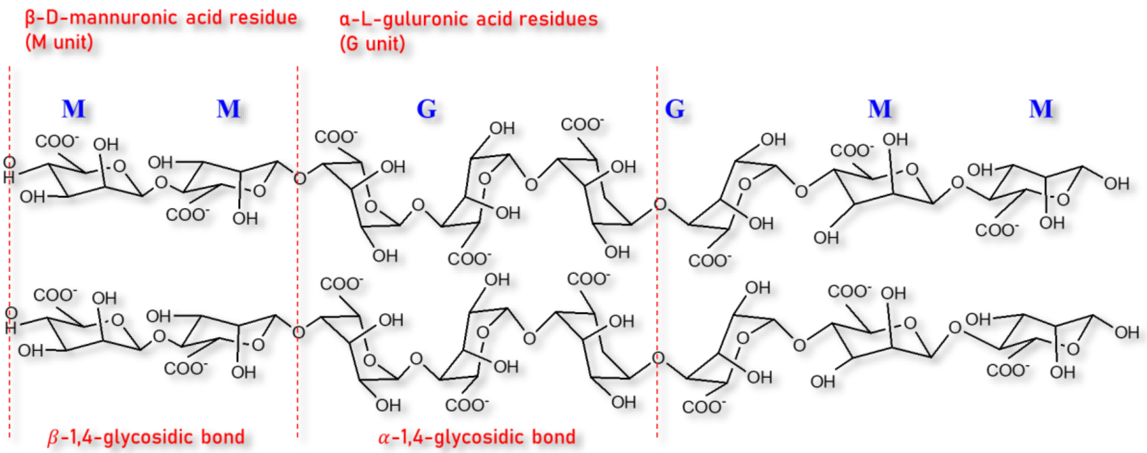

Figure 3. Molecular structures of alginate units, blocks and their linkage

3.5 Biomedical Applications of Sodium Alginate

The novel sodium alginate polysaccharide has a vast application in the biomedical field, for example, in wound healing, gene and drug delivery and tissue engineering [21]. Sodium alginate has an extraordinary advantage in the drug delivery development. For example, alginates have been used as a delivery mechanism for anticancer agents (microcapsules) [24] and ibuprofen [58]. Sodium alginate is also used as a coating element for drugs. Various delivery systems have been developed using alginate biomaterial such as hydrogels, tablets, capsules, liposomes, nanoparticles, beads, microspheres and others [47]. Recently, the drug delivery system is being advanced for the application of sodium alginate biomaterial in the drug encapsulation.

Sodium alginate can also be used in wound dressing and wound healing. Sodium alginate is used in wound dressing and wound healing applications, including the transplantation of OE-MSCs cells [59], multifunctional scaffolds in tissue engineering [60], soft tissue engineering, and bone tissue engineering [61], 3D bioprinting [62], neuro-regenerative applications, mechanical filling in cartilage regeneration [63] in vivo wound healing, treating numerous irregular and chronic wounds, and alkali burns and other types of serious eye injury. Figure 4 shows the application of alginate in the biomedical field.

3.6 Crosslinking of Sodium Alginate

The most significant property of alginates is their ability to form ionic gel in the presence of polyvalent cations [21]. Ions-induced alginate gels are formed mainly by electrostatic interactions between the negatively charged carboxyl groups in alginate molecules and the positively charged cations, leading to the formation of polyelectrolyte complexes [23] .

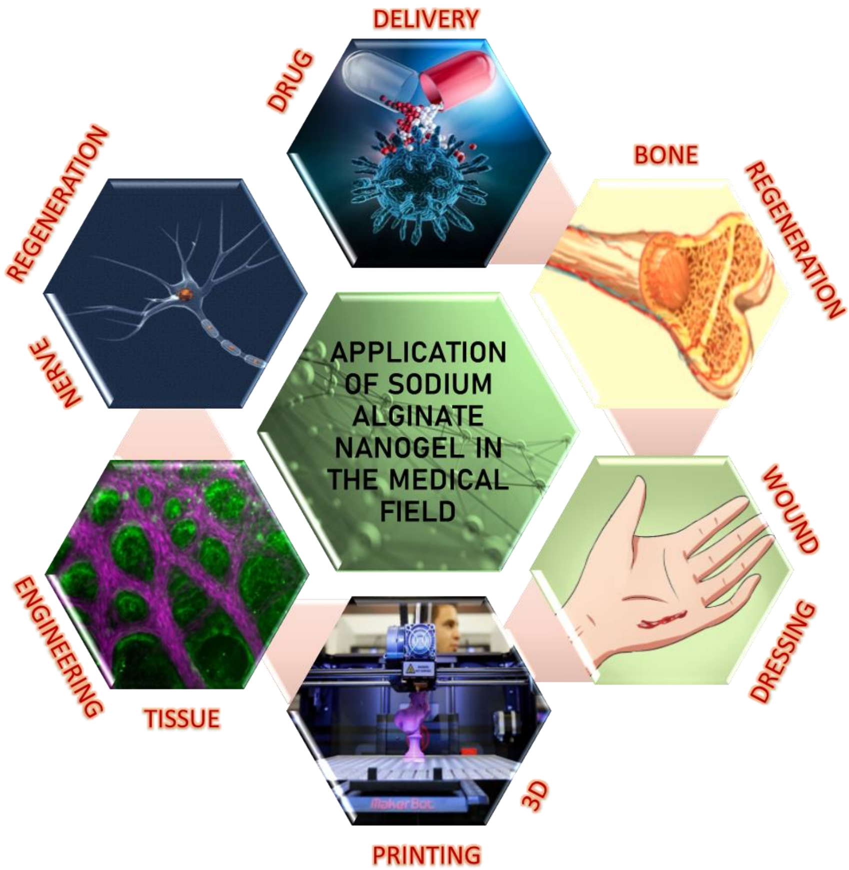

Figure 4. Biomedical application of sodium alginate.

A gelation mechanism involves the coordination and chelating structures in an egg-box model. During this process, G units in alginates bind to polyvalent metal ions together with the hydrogen-bonding interaction of these cross-linking agents with oxygen atoms in the G blocks of two adjacent polymer chains [24]. The binding mode, preparation, characteristics, and applications of different ions-induced alginate gels are summarized in Table 2.

Table 2: Different ion-induced gelation of alginate.

Crosslinking Ions	Binding Mode	Preparation	Characteristics	Application	Reference
$\boldsymbol{H^+}$	Carboxyl Protonation	1) Glucono Delta-Lactone (GDL) is added to turn down the pH value of alginate solution; 2) Proton exchange	In-homogenous because the pH requirement for gel preparation with H^+ ion is hard to be controlled.	No application	[64,65]
$\boldsymbol{Ba^{2+}}$	Egg-box model	External & Internal gelation	Stable in both acidic and neutral pH environment. Ba^{2+} binds to M and G blocks	Drug Delivery	[66,67]

Cu^{2+}	Analogous egg-box model	External & Internal gelation	Affinity to bind with alginate chains is ten times higher than Ca^{2+}. Dense and thick gel layer. Prevents further diffusion of Cu^{2+}in gel.	Printing and dying industry.	[68,69]
Sr^{2+}	Analogous egg-box model	External & Internal gelation	Nontoxic gel with high chemical stability and strong mechanical performance. Binds to G-block of alginate	Wound dressing and tissue scaffold	[67,70]
Zn^{2+}	Analogous egg-box model	External & Internal gelation	Weak and in-homogenous cell. Cause vomiting, diarrhea and other gastrointestinal symptoms if ingested at a high level.	Protect color and chemical degradation	[70,71]
Fe^{2+}	Analogous egg-box model	External & Internal gelation	Unstable gel (easy to oxidize)	Resist organic pollutants	[71,72]
Ca^{2+}	Egg-box model	External & Internal gelation	Easy to prepare, safe and nontoxic gel.	Drug delivery and cosmetics	[70,72]

After looking into the pros and cons of monovalent and divalent ions, it is safe to say that $Ca^{2+}$is the best choice to form crosslink with alginate nanogel. Ca^{2+} the most commonly studied divalent cation that can induce the gelation of alginate and is considered as the most acceptable ion for gelation compared to the rest divalent ions [70]. The binding mechanism between Ca^{2+} and alginate as the pairing of successive G blocks forming a buckle, that creates cavities to hold Ca^{2+}in chelate binding is initially proposed. This structure is known as the egg-box model. The Ca^{2+} coordinates with six oxygen atoms of two neighboring G units and one to three oxygen atoms of water molecule to form a stable egg-box structure [71]. It has been accepted that Ca-alginate gelation undergoes three distinct and successive steps, starting with the interaction of $Ca^{2+}$with a single G unit to form mono-complexes in a tilted egg-box structure, followed by the pairing of the mono-complexes to form egg-box dimers, and then lateral association of the egg-box dimers to generate multicomplexes [73]. The binding structure of Ca^{2+} to alginate is shown in Figure 5. When calcium ions are induced to the gel, electrostatic interactions occur between the positively charged calcium ion and the negatively charged carboxylate ion in alginate.

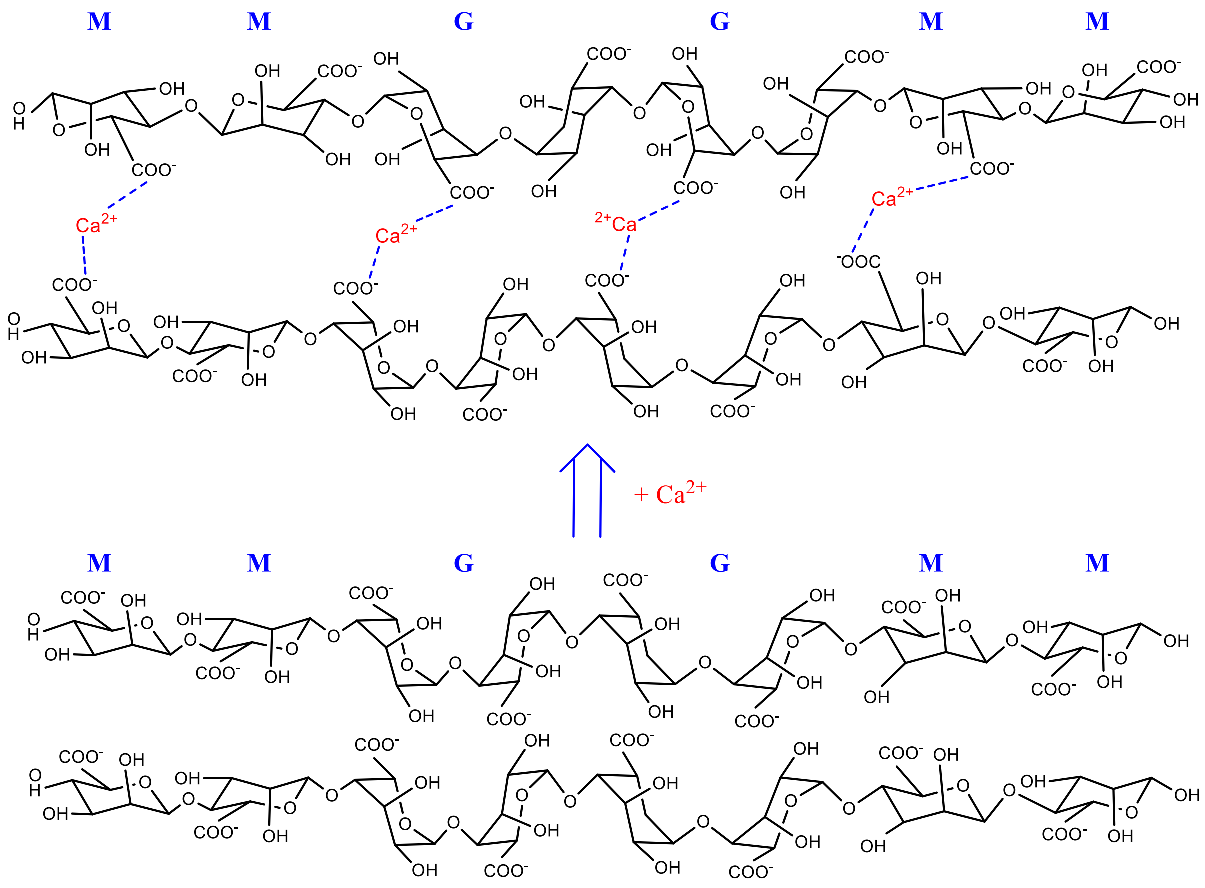

Figure 5. The binding structure of Ca^{2+} to alginate

Pharmaceutical applications of Calcium alginate nanogels have been explored for tissue regeneration, wound healing, drug delivery, glucose sensing, thickening and stabilizing agents and more [73]. Alginates crosslinked with Ca^{2+} plays a significant role in drug delivery and is highly demanded due to its biodegradability, biocompatibility and zero cytotoxicity. Oral dosage forms are currently the most frequent use of alginate in pharmaceutical applications. Controlled release drug delivery systems are designed to give a reproducible and kinetically predictable release of drug substance [74].

3.7 Alginate based nanocomposites with magnetic properties

Magnetic nanoparticles (MNPs) are currently attracting a lot of attention from scientists because of their potential applications in many fields including physics, medicine, biology, and materials science [75]. Advances in the utilization of magnetic particles for biomedical applications are dependent on synthesis methods that allow for more precise control of structural properties such as size, size distribution, phases, and so on [76]. Examples of MNPs are iron, nickel, cobalt, chromium, manganese and gadolinium [77]. Eight different forms of iron oxide (Fe_3O_4) are commonly known in nature. Among them are the main ones known as magnetite (Fe_3O_4), maghemite (γ-Fe_2O_3) and hematite (α-Fe_2O_3) [78]. These three forms show unique magnetic properties and they have different polymorphic forms and undergo temperature induced phase transition. Magnetite and maghemite are ideal materials for industrial and biomedical applications. Both have reusable advantage over other Fe_3O_4 due to their unique magnetic, catalytic and biochemical properties.

Furthermore, magnetic properties and particle surface characteristics are critical qualities that must be managed. MNPs have few properties which makes them suitable in the medical field such as good biodegradability, small in size which means it has a higher surface area to absorb biomaterials, and of course it's magnetic ability. Iron oxide nanoparticles can be detected by MRI scan, which is highly useful for doctors to observe and monitor drug target and delivery in a body [79]. The depth of tissue penetration is influenced by size and shape of MNPs. When compared to bigger MNPs, spherical MNPs lesser than 10 nm exhibit the best penetration and retention. The size and form of SPIONs are important for cancer treatment [80]. To address specific biomedical difficulties, the shape and particle size must be correctly determined. The particle size should be small enough to pass through capillaries and large enough to be adjusted using magneto-mechanical actuation in transdermal drug delivery (TDD) via intravenous injection [81].

MNPs, particularly iron oxide nanoparticles, have long been explored and employed in a variety of applications, including hyperthermia, targeted magnetic drug delivery, magnetic resonance imaging, data storage, environmental cleanup, photocatalysts, and sensors [82]. MNPs is highly preferred in drug transportation because it is small in size and has a larger surface area, combined with their magnetic properties for targeted drug delivery. MNPs is also efficient because it has the potential to carry a big amount of drug dose to the targeted cell [83]. This causes high concentration of therapeutic effect to cell while avoiding toxicity. MNPs have been used as carriers of anticancer [84], anti-inflammatory [85], antibiotic [86] and antifungal agents [87].

The surface modification using inorganic and organic polymeric materials would represent an efficient strategy to utilize the diagnostic and therapeutic potentials of Fe_3O_4 NPs in various human. Fe_3O_4 NPs obtained from different methods needs a surface modification to achieve biocompatibility and longstanding stability especially in biological field. These days, dextran [88], chitosan [89], alginate [90], polyethylene glycol (PEG), and polyvinyl alcohol (PVA) [91] are the most commonly used polymers for the surface modification of MNPs. The properties and applications of certain natural polymers are listed in Table 3.

Table 3: Properties and applications of important natural polymers used to ensure stabilization of Fe_3O_4 NPs.

Natural Polymer	Source /Production	Characteristics	Applications	References
Alginate	Anionic polymer obtained from brown algae (natural polysaccharide)	Biocompatible. Rich in carboxylic group. Non-toxic. Addition of divalent cations result in mild gelation leads to biomedical application	Delivery of low molecular weight drugs and proteins. Wound dressing. Tissue and bone regeneration. Transplantation of stem cells	[90],[92]
Chitosan	Extracted from shellfish	Biocompatible and	Hyperthermia	[89]

	(natural polysaccharide)	biodegradable. Low allergenicity. Non-toxic. Ability to react with biomolecules such as DNA .and antibodies	tissue engineering gene delivery	
Dextran	Produced by lactic acid bacteria ((Natural polymer	Biocompatible biodegradable Optimum-polar interactions Low cost simple alternation	In vivo cancer drug carriers MRI contrast agents	[88]
Polyethylene glycol (PEG)	Synthetic polymer	Hydrophilic emulsifier good biocompatibility and biodegradable non-toxic	prolong blood circulation time improve drug efficacy	[93]
Polyvinyl alcohol (PVA)	Synthetic polymer	Water solubility good biocompatibility and biodegradable film formation	Drug delivery ocular films	[91,94]

In this paper, we are mainly focusing on using alginate biopolymer. Natural polymer composites are in the spotlight as green adsorbents, and alginate appears to be a promising contender due to its high adsorption capacity. Synthesized iron oxide nanoparticles are incorporated into the crosslinked alginate film solution, thus producing a composite hydrogel that has magnetic properties [92]. Alginates can encapsulate iron oxide nanoparticles due to its capacity to create stable hydrogels, which can improve the adsorption qualities and provide the gel with magnetic traits for improved mechanical response [90]. The molecular structure of iron oxide nanoparticles when undergo surface modification using crosslinked alginate is shown in Figure 6. Fe^{3+} from Fe_3O_4 NPs attaches itself to the carboxyl (-COOH) and hydroxyl (OH^-) group of alginates through van der wall forces.

3.8 Alginate based nanocomposites as a carrier for plant extract

In recent times, patients prefer plant-based drugs because it is more biocompatible, biodegradable, non-toxic and has no side effects. Unfortunately, the use of many extracts are limited due to the need of repeated administrations or high doses because of low hydrophilicity and intrinsic dissolution rates, or physical and chemical instability [95]. Other limits are low absorption, poor pharmacokinetics and bioavailability, scarce

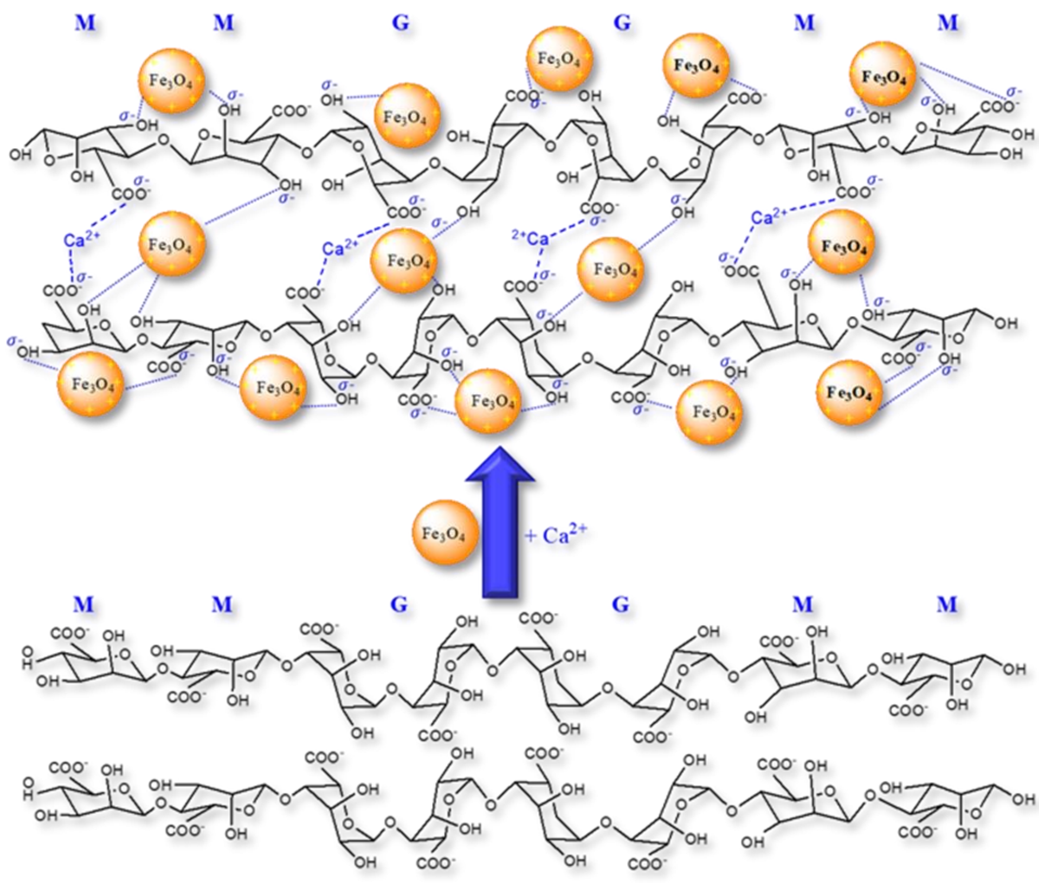

Figure 6. The binding structure of crosslinked alginate with iron oxide nanoparticles

biodistribution, first pass metabolism, trivial penetration and accumulation in the organs of the body. In the case of essential oils, the high volatility and instability are further limitations. Plant extract drugs are not as efficient when it functions independently. Thus, nanocomposites are used in the production of drug delivery system that can offer an advanced approach to optimized the therapeutic efficacy of extracts and essential oils [96]. A successful drug carrier system should have optimal drug loading and release properties, a long shelf life, and exert a much higher therapeutic efficacy as well as lower side effects.

This paper has discussed the advantages of alginate biopolymers in medical field and also the encapsulation of this hydrogel with magnetic nanocomposites to increase drug target and delivery efficiency. When plant extracts are loaded into nanocarriers, the carriers such as alginate nanocomposite help the encapsulation of bioactive compounds of plant extracts, representing a feasible and efficient approach to modulate drug release, increase the physical stability of the active substances, protect them from the interactions with the environment, decrease their volatility, enhance their bioactivity, reduce toxicity, and improve patient compliance and convenience [96].

For example, this can be used in cancer treatment because the drug can be easily monitored through MRI scan and can be sent to targeted cancer cells without effecting normal cells through an external magnetic field [97]. A summarized figure of the working principle of these nanocomposite plant-based drugs in drug delivery for cancer treatment is shown in Figure 7.

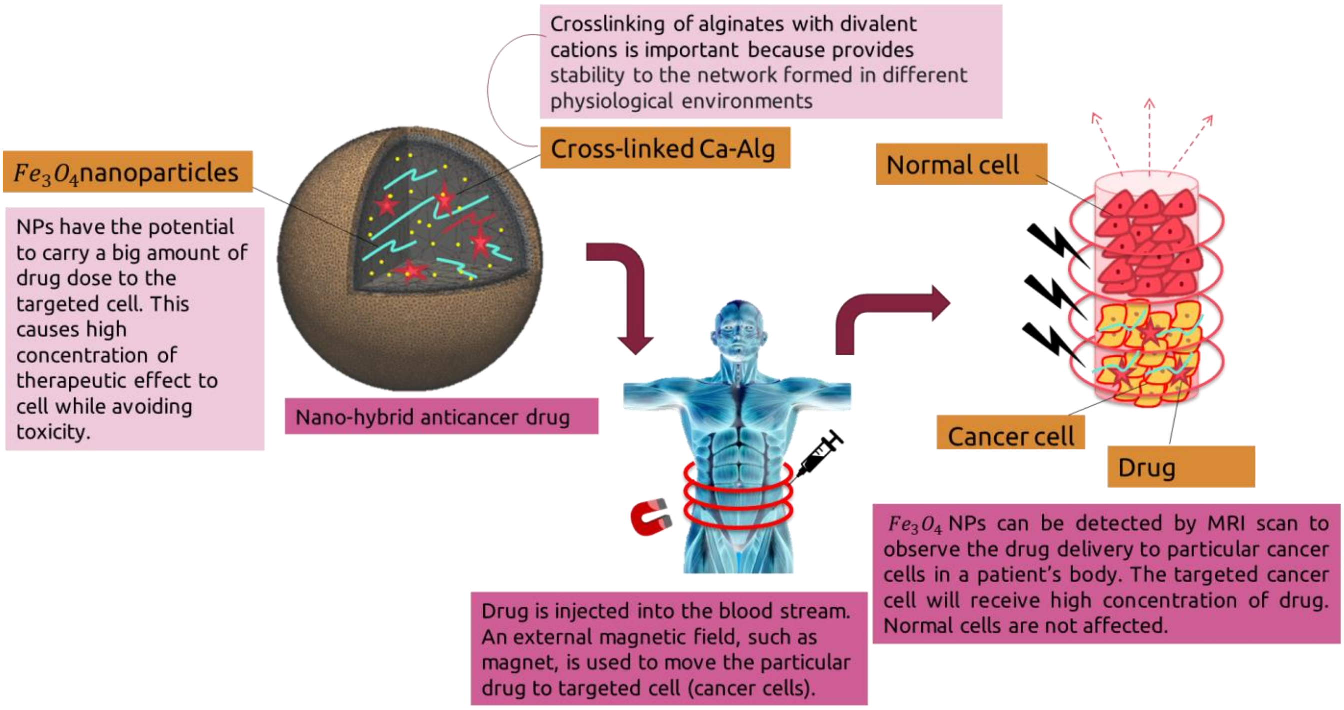

Figure 7. Working principle of these nanocomposite plant-based drugs in drug delivery for cancer treatment

4. Conclusion

In this paper, the advantages and biomedical applications of using plant extracts as an alternative of clinical drugs is discussed and it can be concluded that the phytochemicals in natural extracts indeed have properties such as antibacterial, antifungal, antidiabetes, antimicrobial, anticancer and other diseases. The extracts can be a substitute for clinical drugs to help treat or inhibit certain diseases. There are many clinical trials that have been successfully done to prove these theories but more research and tests are needed to check the efficiency and dosage of extract. Moreover, biopolymers such as alginate crosslinked with calcium ions also have a vast application in the biomedical field such as bone, nerve and tissue regeneration, 3D printing, and also drug delivery system. Furthermore, the applications of iron oxide nanoparticles especially it's magnetic property has also been highlighted here. This is to create a alginate based nanocomposite with magnetic properties that can help in biomedical field especially to increase and develop the drug delivery system. This biopolymer nanocomposite together with plant extracts can altogether be loaded in a drug to produce a nanohybrid drug that is highly efficient and non-toxic to the human body. Therefore, it can be concluded that alginate bases nanocomposite can be used as a carrier for plant extract to help increase its biomedical efficiency.

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