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Review Article

Design and Applications of Fucoidan-based Nanocarriers for herbal bio-actives:

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ABSTRACT

Fucoidan is a sulphated marine polysaccharide that comes from brown algae and has a variety of biological properties, such as immunomodulatory, antioxidant, and anticancer properties. Recent developments in nanotechnology have made it possible to create hybrid nanocarriers that combine fucoidan with polymers and herbal bio-actives to increase the effectiveness of medication delivery. The medicinal use of herbal substances like curcumin, quercetin, and Asiatic acid is limited by their low solubility and bioavailability. Hybrid nanocarriers based on fucoidan provide improved stability, controlled release, and targeted delivery. The structural characteristics of fucoidan, hybrid nanocarrier types, drug transport methods, and therapeutic uses are all summarized in this paper. The necessity of clinical translation is further highlighted by the discussion of difficulties and future prospects.

INTRODUCTION

Fucoidan is a fucose-rich sulphated polysaccharide primarily obtained from brown seaweeds such as *Fucus*, *Laminaria*, and *Sargassum*. It exhibits a wide range of biological activities including anticoagulant, antiviral, anticancer, and anti-inflammatory effects. The first extraction of fucoidan was in 1913 from a species of brown algae **[1]** such as Laminaria digitata, Ascophyllum nodosum and Fucus vesiculosus. Fucoidan is a negatively charged and highly hygroscopic polysaccharide **[2].** A high content of fucoidan is mainly found in the leaves of L. digitata, A. nodosum, Macrocystis porifera and F. vesiculosus. Fucoidan is soluble in both water and acid solutions. After the first publication took place in 1913, the number of published articles (studies) on fucoidan has increased significantly, especially in the modern era. The reason behind the increase in studies is that fucoidan has anti-tumour, anti-coagulant and anti-oxidant activities, as well as the importance in terms of regulating the metabolism of glucose and cholesterol **[3].** Also,

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there has been an interest in fucoidan because of its potential to provide protection against liver damage and urinary system failures. It is evident that research on fucoidan is gradually flourishing, as these activities are carried out, and more of its bio-activities and health-related benefits are being discovered as studies continue to accumulate.

Sources Of Fucoidan

Fucoidan is a sulphated polysaccharide which can be found amongst a number of marine sources, including sea cucumbers **[4]** or brown algae **[5].** A great number of algae and invertebrates have been ascertained for their fucoidan contents inclusive of Fucus vesiculosus, Sargassum stenophyllum, Chorda filum, Ascophyllum nodosum, Dictyota menstrual is, Fucus evanescens, Fucus serratus, Fucus distichus, Caulerpa racemosa, Hizikia fusiforme, Padina gymnospora, Kjellmaniella crassifolia, Analipus japonicus and Laminaria hyperborea exhibited in Figure 1. In these sources, different types of fucoidan can be obtained and the methods of extraction employed are different, especially when they are reported in different studies.

Fig. 1. Sources of fucoidan. 1. Fucus vesiculosus, 2. Laminaria digitata, 3. Fucus evanescens, 4. Fucus serratus, 5. Ascophyllum nodosum, 6. Pelvetia canaliculata, 7. Cladosiphon okamuranus, 8. Sargassum fusiforme, 9. Laminaria japonica, 10. Sargassum horneri, 11. Nemacystus decipiens, 12. Padina gymnospora, 13. Laminaria hyperborea.

However, herbal bioactives (phytochemicals) such as curcumin and asiatic acid suffer from:

- Low aqueous solubility
- Poor bioavailability
- Rapid metabolism

Nanotechnology-based delivery systems have emerged as a promising strategy to overcome these limitations. Hybrid nanocarriers combining fucoidan with polymers or lipids provide enhanced targeting and controlled release properties.

Structure And Properties Of Fucoidan

Fucoidan is known as a fucose-enriched and sulphated polysaccharide that is mainly sourced from the extracellular matrix of brown algae. Fucoidan is made up of L-fucose, sulphate groups and one or more small proportions of xylose, mannose, galactose, rhamnose, arabinose, glucose, glucuronic acid and acetyl groups in a variety of brown algae **[6-8].** In a number of studies, researchers have also used galactofucan to represent a kind of fucoidan. Galactofucan is known as a monosaccharide, and the composition of the monosaccharide is galactose accompanied by fucose, similar to rhamnofucan (rhamnose and fucose) and rhamnoalactofucan (rhamnose, galactose and fucose). In addition to the structure of fucoidan, there is also a variation amongst different seaweed types. Nevertheless, fucoidan normally has two types of homos fucose One type (I) encompasses repeated (1→3)-L-fucopyranose, and the other type (II) encompasses alternating and repeated (1→3)- and (1→4)-L-fucopyranose **[9].** Reports based on structures of fucoidan, sourced from different species of brown algae, brought about an improved categorization in terms of structures. By a way of illustration, most of the fucoidans sourced from species belonging to the

Fucales have an alternating linkage of (1→3)-α-L-fucose and (1→4)-α-L-fucose **[10-14].** Structures of Ascophyllum nodosum fucoidan **[15]** and F. vesiculosus fucoidan show a resemblance of one another, the difference is only significant based on sulfate patterns and the presence of glucuronic acid. A number of Fucales species, such as Fucus serratus, Fucus distichus and Pelvetia canaliculate, present similar fucoidan backbone, but show more diversity in the branching and the presence of different monosaccharides **[13,14,16].** However, exceptions do exist, for instance, fucoidans from the Bifurcaria bifucardia and Himanthalia elongate do not follow or ascribe to such a structural feature **[17].** Hence, identifying the structure of fucoidan based on the specie.

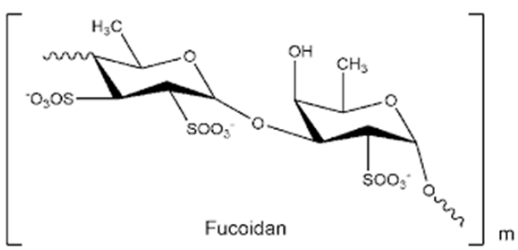

Fig. 2. Chemical Structure of Fucoidan

Another important fact that deserves mentioning is that the structure of fucoidan is also highly dependent on the harvest season. This is based on the Undaria pinnafida fucoidan, which exhibited distinct characteristics and bioactivity, especially when harvested during different seasons **[18,19].** In addition, it should be indicated that the purification method also plays a critical role in the structure of fucoidan. To such an extent that new purification methods have led to the revelation that the fucoidan structure is comprised of multiple fractions **[20].** An investigation reported that the structure of crude fucoidan sourced from A. nodosum showed a predominant repetition of [→(3)-α-L-Fuc(2SO3−) − (1→4)-α-Fuc(2,3diSO3−)-(1)]n **[21].** However, from the same species, a purified fraction comprised of primarily α-(1→3)-fructosyl residues with a sparse linkage of α-(1→4) and was found to be highly branched **[22].** Therefore, the employment of different extraction methods results in distinct structures. For example, a report states that one species produced two distinct fucoidan structures, particularly galactofucan and uronofucoidans **[23].** Hence, it should be emphasized that purification techniques are one of the determining factors towards the structure and the associated bioactivities. **[24,25,26]**

Fucoidan is structurally complex and varies depending on its source. It contains: **[27-31]**

- L-fucose backbone
- Sulfate ester groups
- Variable molecular weight

These sulfate groups provide:

- Negative charge
- Ability to form polyelectrolyte complexes

Fucoidan can interact with positively charged polymers like chitosan, forming stable nanoparticles

Extraction And Production

Source [32-36]

Fucoidan is mainly obtained from brown marine algae (brown seaweeds). Important natural sources include:

- Fucus vesiculosus
- Undaria pinnatifida
- Sargassum species

These seaweeds are rich in sulfated polysaccharides and are widely used for commercial fucoidan production.

Extraction Methods

Fucoidan is extracted from seaweed biomass through several conventional and advanced techniques:

- **Hot Water Extraction** Seaweed powder is treated with hot water to dissolve fucoidan and separate it from other components.
- **Acid Extraction** Mild acidic conditions help improve the release of fucoidan from the algal cell wall.
- **Alkaline Extraction** Alkali treatment is sometimes used to remove impurities and enhance polysaccharide recovery.
- **Enzyme-Assisted Extraction** Specific enzymes break down cell wall materials, increasing extraction efficiency and preserving bioactivity.
- **Microwave-Assisted Extraction** Microwave energy accelerates cell disruption and improves yield while reducing extraction time and solvent usage.

Industrial Applications

Due to its biological and functional properties, fucoidan is increasingly utilized in several industries:

- **Food Industry:** Used as a functional food ingredient and natural stabilizer.
- **Dietary Supplements:** Included in nutraceutical products for health-promoting effects.
- **Cosmetic Industry:** Added to skincare and anti-aging formulations because of its antioxidant and moisturizing properties.
- **Pharmaceutical Research:** Investigated for anticancer, anti-inflammatory, antiviral, and drug-delivery applications.

Extraction Techniques And Potential Impurities

The nature of the chemical components, method of extraction, and interfering substances influence the extraction **[24].** Most polysaccharides are extracted using water, acids, and organic solvents. Solvent extraction is difficult to implement owing to the complex nature of polymers **[37].** The extraction procedure is a critical point in the purification of the target compound. The yield and structural alterations of sulphated polysaccharides are greatly influenced by the appropriate adjustment of parameters such as temperature, time, and pH **[38].** This part of the review addresses the implemented extraction procedures that effectively enhance the purification of sulphated polysaccharides. The source of extraction of the sulphated polysaccharides is marine brown algae rather than marine invertebrates. The molecular weight, sulfation percentage, point of sulfation, and monosaccharide composition are vital to the bioactivity of fucoidan. Therefore, purification should be performed under mild conditions to avoid structural shifts **[38].** The application of an ethanolic system helps remove co-extracting interferences, such as lipids, terpenes, and phenols Chlorophyll pigments are immediately removed using this method. Some researchers perform immersion and washing using acetone or hexane.

Phenols are tightly bound to fucoidans or other polysaccharides during the extraction process. Formaldehyde treatment is a method of preventing cross-contamination by polymerizing phenols, proteins, and nucleic acids, and converting them into insoluble high-molecular-weight components **[38,40,41].** Although it is useful in eradicating interfering modules, it may decrease fucoidan yield by interacting with polysaccharides and precipitating them into complexes **[42].**

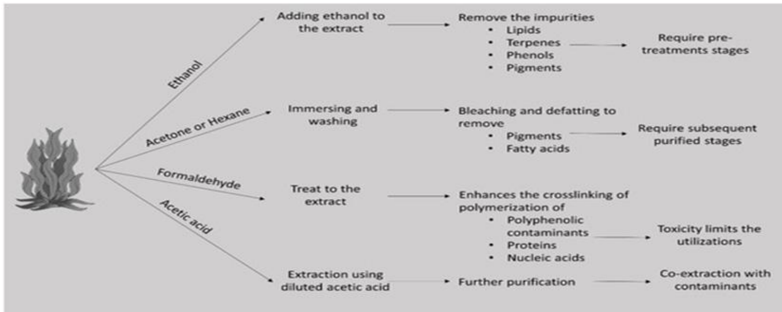

Fig.3 "Effect of Different Solvents and Chemical Treatments on Aloe vera Extract Purification"

Herbal Bioactives In Nanocarrier Systems [43-47]

Herbal bioactives are widely used due to their pharmacological properties but face delivery challenges.

- Anticoagulant and antithrombotic activity.
- Antivirus activity
- Antitumor and immunomodulatory activity
- Antioxidant activity
- Reducing blood lipids
- Anticomplementary activity
- Therapeutic potential in surgery
- Anti-inflammatory
- Gastric protection
- Against hepatopathy
- Against uropathy and renal Pathy

Common Bioactive: [48-53]

- Curcumin → anticancer
- Quercetin → antioxidant
- Asiatic acid → wound healing
- Resveratrol → anti-aging

Nanocarriers improve:

- Stability
- Solubility
- Targeted delivery

Nano formulations significantly enhance the therapeutic efficiency of phytochemicals

Fucoidan-Based Hybrid Nanocarriers [54-61]

Table 1 - Types of Hybrid Systems

Type	Composition	Method	Application

Fucoidan–Chitosan NPs	Polyelectrolyte complex	Ionic gelation	Drug delivery
Fucoidan–Alginate Gel	Polymer blend	$CaCl_2$ crosslinking	Wound healing
Fucoidan–Metal NPs	Green synthesis	Reduction method	Antimicrobial
Fucoidan–Liposomes	Lipid + polysaccharide	Thin film hydration	Targeted therapy

Fucoidan's sulphate groups enable strong interaction with polymers, forming stable nanostructures for drug delivery.

Mechanism Of Drug Delivery [62-68]

Hybrid Nanocarrier Mechanism

Curcumin, a bioactive phytoconstituent obtained from Curcuma longa, is widely known for its anti-inflammatory, antioxidant, and anticancer properties, but its clinical application is restricted due to poor aqueous solubility and low systemic bioavailability. To address these limitations, curcumin is encapsulated within a nanocarrier system, commonly prepared using natural polymers such as fucoidan and chitosan. These polymers form a stable polyelectrolyte complex matrix through electrostatic interaction between negatively charged sulphate groups of fucoidan and positively charged amino groups of chitosan, resulting in enhanced stability and protection of the encapsulated drug. Importantly, fucoidan imparts targeting capability by interacting with selectin receptors that are overexpressed on inflamed and tumor cells, enabling selective accumulation at the diseased site. Upon reaching the target, the nanocarrier binds to these receptors and undergoes receptor-mediated cellular uptake, primarily through endocytosis. Once internalized, the intracellular environment—characterized by acidic pH and enzymatic activity—triggers controlled and sustained release of curcumin from the nanocarrier system. This targeted and stimuli-responsive drug release enhances the therapeutic efficacy of curcumin while minimizing systemic toxicity, ultimately leading to improved anti-inflammatory and anticancer outcomes. Such fucoidan–chitosan based nanocarrier systems have been actively investigated in Indian pharmaceutical research for their potential in advanced herbal drug delivery applications.

Table – 2. Comparison: Fucoidan Vs Other Polymers [69-73]

Property	Fucoidan	Chitosan	Alginate
Charge	Negative	Positive	Negative
Source	Marine	Crustacean	Algae
Bioactivity	High	Moderate	Low
Drug Targeting	Excellent	Good	Moderate
Gel Formation	Moderate	Strong	Strong

Therapeutic Applications

1. Anticancer Activity [74,75,76]

Fucoidan, a sulphated polysaccharide isolated from brown seaweeds such as Sargassum weighted and Turbin aria conoids, has shown significant anticancer potential in various in vitro and in vivo studies conducted in India. It induces apoptosis in cancer cells through activation of caspase-dependent pathways and regulates key signalling mechanisms such as PI3K/Akt and MAPK. Indian studies have reported its effectiveness against breast, colon, and liver cancer cell lines, where it inhibits cell proliferation and metastasis while enhancing immune surveillance.

2. Antioxidant and Anti-inflammatory Effects [77,78,79]

Fucoidan exhibits strong antioxidant activity by scavenging free radicals and reducing oxidative stress. Research from institutions like CSIR-Central Food Technological Research Institute has demonstrated that fucoidan extracted from Indian seaweeds can significantly reduce lipid peroxidation and enhance endogenous antioxidant enzymes such as superoxide dismutase (SOD) and catalase. Additionally, its anti-inflammatory properties are attributed to the inhibition of pro-inflammatory mediators like TNF-α, IL-1β, and COX-2, making it useful in managing chronic inflammatory disorders.

3. Anticoagulant and Cardioprotective Activity [80,81,82]

Fucoidan possesses anticoagulant properties similar to heparin due to its sulphated structure. Studies conducted at Central Marine Fisheries Research Institute have reported that fucoidan from Indian brown algae can inhibit thrombin activity and reduce blood clot formation. This makes it a promising candidate for the prevention and management of cardiovascular diseases such as thrombosis and atherosclerosis, with potentially fewer side effects compared to synthetic anticoagulants.

4. Antidiabetic Potential [83,84]

Fucoidan has shown promising results in controlling blood glucose levels and improving insulin sensitivity. Indian experimental studies indicate that it can inhibit α-amylase and α-glucosidase enzymes, thereby reducing postprandial hyperglycaemia. Additionally, it helps in protecting pancreatic β-cells from oxidative damage, suggesting its therapeutic relevance in diabetes management.

5. Antiviral and Immunomodulatory Activity [85,86]

Fucoidan exhibits broad-spectrum antiviral activity by preventing viral attachment and entry into host cells. Research in India has explored its activity against viruses such as herpes simplex and influenza. It also enhances immune responses by stimulating macrophages, dendritic cells, and natural killer (NK) cells, thereby strengthening host defense mechanisms.

6. Wound Healing and Tissue Regeneration [87,88,89]

Fucoidan plays an important role in wound healing by promoting fibroblast proliferation, collagen synthesis, and angiogenesis. Studies from Central Salt and Marine Chemicals Research Institute have highlighted its potential in accelerating tissue repair and regeneration, particularly in burn and diabetic wounds. Its biocompatibility and ability to form hydrogels make it useful in advanced wound dressing systems. Fucoidan-based nanocarriers show improved therapeutic efficiency due to targeted delivery systems [90,91]

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