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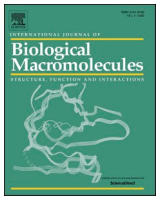

Review

Biological activity of algal derived carrageenan: A comprehensive review in light of human health and disease

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ABSTRACT

Carrageenans are a family of natural linear sulfated polysaccharides derived from red seaweeds and used as a common food additive. Carrageenan's properties, impact on health, and aesthetic benefits have all been studied for a long time; however, the mechanisms are still unclear. In pharmaceutical aspects, carrageenan displayed potential antioxidant and immunomodulatory properties in both in vivo and in vitro action. It also contributes to potential disease-preventive activities through dynamic modulation of important intracellular signaling pathways, regulation of ROS buildup, and preservation of major cell survival and death processes which leads to potential drug development. Furthermore, the chemical synthesis of the current bioactive medicine with confirmational rearrangement may increase availability and bioactivity needs diligent examination. In this review, we give an up-to-date overview of recent research on Carrageenan with reference to health and therapeutic advantages. In addition, we have focused on structural conformation and its primary strategic deployment in disease prevention, as well as the mechanistic investigation of how it functions to combat various disease-preventive employed for future therapeutic interventions. This review may get new insights into the possible novel role of carrageenan and open up a novel disease-preventive mechanism and enhance human health.

1. Introduction

Human health is a major concern in the developing world because of poor eating habits. In the contemporary environment, global population growth, along with changes in lifestyle and eating habits, has emerged as a critical component of illness occurrence. Cancer, diabetes, inflammations, neurological illnesses like Alzheimer's and Parkinson's, as well as organisms linked to diseases like viral and bacterial infections, pose a serious threat to human existence [1–5]. Chemotherapy and other cancer-treatment drugs have negative effects, particularly in terms of drug tolerance. Furthermore, due to traditional pharmacological treatments, bacteria are developing resistance to pharmaceuticals [6]. In this case, looking for new medications from natural sources may be able to remedy the problem [7–14].

Marine and freshwater habitats are rich in algal biodiversity which is the chief contributor of bioactive metabolites [15–24]. Seaweeds, for example, are found in both fresh and seawater, and they serve an important role in maintaining the biodiversity and ecology of aquatic habitats [25,26]. Particularly, marine algae are one of the most potent sources of novel bioactive chemicals (e.g., peptides, amino acids, lipids, fatty acids, sterols, polysaccharides, carbohydrates, polyphenols, photosynthetic pigments, vitamins, and minerals) with biologically intriguing properties such as antioxidant, anticancer, antibacterial, antifungal, antidiabetic, and anti-inflammatory properties [27–33]. Secondary metabolites found in seaweeds include peptides, proteins, phlorotannins, terpenoids, sterols, fucoidans, mannitol, and glycolipids. They mostly have antiviral, antibacterial, antifungal, antidiabetic, anticancer, anti-inflammatory, anticoagulant, antioxidant, neuroprotective, and hepatoprotective properties [34–37]. However, Carrageenan as an elicitor of induced secondary metabolites and can be used as the disease preventive activities [34–37].

Carrageenans are linear sulphated polysaccharides derived from red seaweed of *families* such as Gigartinaceae, Hypneaceae, Solieriaceae, Phyllophoraceae, and Furcellariaceae [38–40]. They have little nutritional value, and are used in food preparation for their gelling, thickening, emulsifying qualities and stabilizing agents in a broad range of commercial applications including foods [38–41]. In recent, these polymers have been more important in medical, pharmaceutical, and biotechnological research, due to their biocompatibility, high molecular weight, high viscosity, and gelling capacity. Carrageenans, for example,

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have been utilized to improve the formulation of medications and the controlled release of drugs, they have become one of the most important biomaterials in the pharmaceutical sector [42–44]. Antioxidant [45,46], antiviral [47,48], antibacterial [49], antihyperlipidemic [50], anticoagulant [51], anticancer [52,53], and immunomodulatory [52,53] effects of carrageenans have also been studied. In addition, carrageenan appears to have biological properties, according to growing research [46–48,51–56]. It also enables fresh investigation into the creation of fresh drugs to treat fatal illnesses. In the modern era of drug discovery, drug synergism focuses on preclinical and clinical applications, pharmacodynamics, pharmacokinetics, and better drug delivery technologies to produce next-generation modified therapeutics for disease prevention. Hence considering the potential role of carrageenan and its disease inhibition activity, in this review, we focus on a mechanistic overview of the regulatory pathways of carrageenan in various disease preventions. Once we understand the likely molecular key players involved, the utilization of carrageenan will open up new possibilities in disease prevention and will be connected to therapy for numerous disorders. Carrageenan could be used as a medicinal medication in the near future, despite its many uses as well as its less toxicity. These findings represent that carrageenan modulates the anti-effective role in different diseases of human (Fig. 1).

2. Chemical structure and properties of carrageenan

Chondrus, *Gigartina*, and numerous *Eucheuma* species in the red algae family Rhodophyceae contain carrageenan, a highly sulfated polymer [57]. Carrageenan is a sulfated polygalactan that contains 15 to 40 % ester-sulfate and has a relative molecular mass of >100 kDa. It is made up of α-1,3 and β-1,4-glycosidic linkages that connect alternating 3-linked β-D- galactose and 4- linked α- D- galactose or 4- linked 3,6-anhydro-α-D-galactose residues, forming the disaccharide repeating unit of carrageenans. Carrageenan is divided into several forms, including λ, κ, ι, ε, μ and all of which include 22 to 35 % sulphate groups. The solubility of the substance in potassium chloride was used to classify them. The number and position of ester sulphate groups, as well as the quantity of 3.6-AG, are the key variables that determine the qualities of carrageenan type. These designations refer to generic changes in the composition and degree of sulfation at certain sites in the polymer, rather than specific chemical structures. Lower solubility temperature and gel strength are associated with higher quantities of ester sulphate. The ester sulphate percentage of kappa type carrageenan is about 25 to 30 %, and the 3,6-AG concentration is about 28 to 35 %. The ester sulphate level of iota type carrageenan is about 28 % to 30 %, and the 3,6-AG concentration is about 25 % to 30 %. The ester sulphate content of lambda type carrageenan ranges from 32 to 39 %, with no 3,6-AG concentration [58–62]. According to their structural characteristics, sulfation patterns, and the presence or absence of 3,6-anhydro bridges in α-linked galactose residues, they are divided into several types denoted by Greek letters (iota, kappa, lambda, or mu). Iota and kappa carrageenans contain equal amounts of galactose and 3,6 anhydrogalactose, whereas lambda-carrageenans are made of galactose units. One sulphate group is present in kappa carrageenan, two sulphate groups are present in iota carrageenan at axial positions, and nearly three equatorial sulphates are present in lambda carrageenan. The majority of natural carrageenans are blends of various hybrid types, such as κ/ι hybrids, κ/μ hybrids, or κ/ι,-hybrids, which frequently form cyclized derivatives. There are varying amounts of their biological precursors, mu- and nu-carrageenans, in kappa- and iota carrageenans [63]. Molecular structures of different carrageenan types have potential therapeutic effects (Fig. 2).

Carrageenans' chemical reactivity is mostly due to their strongly anionic half-ester sulphate groups, which are equivalent to inorganic sulphate In the presence of potassium or calcium ions, kappa- and iota-carrageenans produce gels, whereas ʎ-carrageenan does not [64]. The rheological properties of carrageenans play a big role in their functionality in different applications. Carrageenans are highly viscous aqueous solutions, because they are linear, water-soluble polymers [65]. Viscosity rises exponentially in proportion to concentration, and falls in proportion to temperature. Carrageenans are vulnerable to acid-catalyzed hydrolysis, which can depolymerize them. This can quickly lead to full loss of functioning at high temperatures and low pH [66].

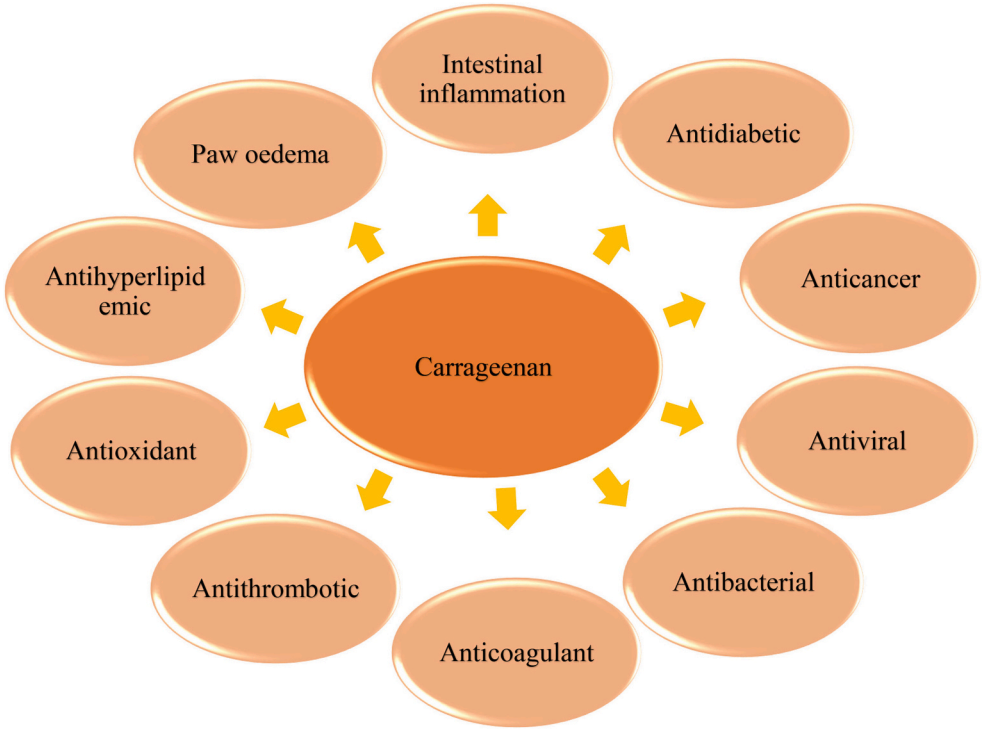

Fig. 1. Biological activity of carrageenan and its anti-effective role in different diseases of human.

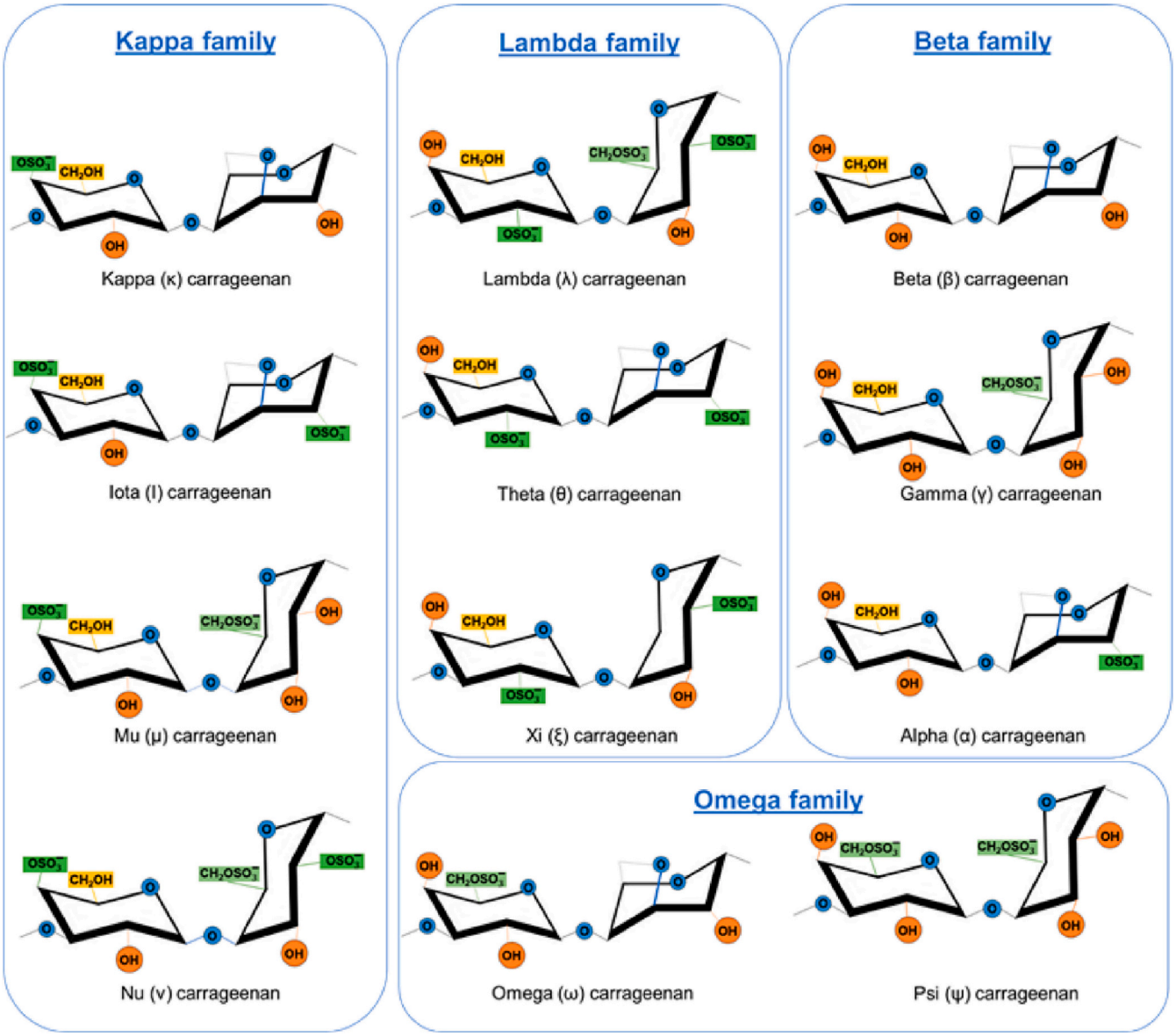

Fig. 2. Molecular structure of different types of carrageenan with potential therapeutic effects adopted from [67] are Basic carrageenan forms: iota (ι), kappa (κ), lambda (λ), mu (μ), nu (ν), theta (Θ), xi (ξ), alpha (α), beta (β), gamma (γ), omega (ω), and psi (Ψ).

3. Carrageenan: the blessing for natural and biological activity

Sulphated polysaccharides from marine algae have all been reported as potent antioxidant, anticancer, anticoagulant, antithrombotic, antiviral, antibacterial, and immunomodulatory properties [28]. Carrageenans, for example, are hydrophilic colloids (water-soluble gums) that appear as matrix material in a variety of red seaweeds (Rhodophyta), where they perform a structural function similar to cellulose in land plants [68]. Carrageenans have strong anionic half-ester sulphate groups that are comparable to inorganic sulphate in terms of their chemical reactivity. Because the free acid is unstable, commercial carrageenans are sold as sodium potassium and calcium salts, or as a combination of these. The physical properties of carrageenans are determined by the related cations and the conformation of the sugar units in the polymer chain [69]. The rheological properties of carrageenans play a big role in their functionality in different applications. Viscosity is affected by concentration, temperature, the presence of other solutes, and the kind and molecular weight of carrageenan. Concentration increases the viscosity nearly tenfold [70]. The kappa or kappa/lambda-carrageenan from *Chondrus crispus* was employed in the majority of toxicological research that used an identified form of carrageenan and an identifiable seaweed species [69]. Carrageenan is used extensively in experimental medicine to test anti-inflammatory medicines [40].

In general, carrageenan's bioactive qualities are critical for the creation of new medicinal medicines with high efficacy and safety [41]. We are at a critical juncture in the development and research of new therapeutic agents derived from seaweed, because it has been demonstrated in all of the studies reviewed that carrageenans can act as bioactive agents on their own or can improve their bioactive capacity by binding to drugs or transforming or modifying their chemical structure [71]. This transformation or alteration of the original sulfated polysaccharides into new ones allows for the development of improved bioactive characteristics that can help treat or prevent diseases [72]. In this regard, carrageenan is getting much attentions, due to its strong disease inhibitory activity [41]. The disease preventive activities of carrageenan to different diseases are given below.

3.1. Antioxidant activity of carrageenan

Marine red algae have been demonstrated to be a rich source of

natural antioxidants with a variety of positive effects in humans [73]. Recent research has revealed that carrageenan also possesses high antioxidant activity, which is linked to its sulphate group concentration [74,75]. Carrageenan extracted successively with water, acid, and alkali from *Mastocarpus stellatus*, and it generated polysaccharides with the highest degree of sulfation and molecular weight, as well as the best in vitro antioxidant potential [55]. The antioxidant activity of a multilayer coating made of kappa-carrageenan loaded with quercetin was demonstrated [76]. Both native carrageenan from *Kappaphycus alvarezii* and commercial carrageenan (Sigma-Aldrich) had strong overall antioxidant activity and hydroxyl radical scavenging ability, as well as NO and DPPH radical scavenging capacity [77]. Numerous studies have shown increased activity of antioxidant enzymes such as catalase and superoxide of carrageenans [78]. For example, κ-carrageenan oligosaccharides from *Kappaphycus striatus*, as well as their over sulfated, acetylated, and phosphorylated derivatives, have antioxidant action in in vitro systems [54]. In addition, λ-carrageenan from *Chondracanthus acicularis* and *G. pistillata*, κ-carrageenan from *K. alvarezii*, and ι-carrageenan from *Eucheuma denticulatum* (Sigma-Aldrich) displayed the most potential hydroxyl radical activity with an IC_{50} value of 0.281 ± 0.072 μg/mL. Even, ι-carrageenan inhibited hydroxyl radials more effectively than λ-carrageenan (EC_{50} = 0.357 ± 0.120 μg/mL) and κ-carrageenan (EC_{50} = 0.335 ± 0.016 μg/mL) [75].

High molecular carrageenans have demonstrated antioxidant capabilities in a variety of tests, including hydroxyl radical scavenging, reducing capacity, and DPPH radical scavenging [79]. It was observed that different forms of carrageenans can be placed in the following order based on their activity as κ > ι > λ [80]. ι-Carrageenan from *Solieria filiformis* with a molecular weight of 210.9 kDa and a significant degree of sulfation (1.08) scavenged DPPH radicals with an IC_{50} of 1.77 μg/mL, and had a 38.39 % iron-chelating capacity [81]. Antioxidant activity of κ-carrageenans with average molecular weights of 209.0, 15.08, 5.82, and 3.25 Da was represented in EC_{50} values for a superoxide anion of 8.13, 6.66, 3.22, and 2.65 mg/mL, respectively, and for hydroxyl radicals of 0.110, 0.062, 0.049, and 0.014 mg/mL [46]. These findings show that κ-carrageenans with lower molecular weight have stronger antioxidant action which can be used as a natural antioxidant.

3.2. Intricate role of carrageenans as anticancer agents via regulation of apoptosis

Free radicals and reactive oxygen species (ROS) are known to hasten the onset of cancer. Because of their poor specificity and widespread biodistribution, synthetic chemopreventive medications frequently produce a slew of negative side effects in the tumor's surroundings and other body organs [82]. Carrageenans have been identified as powerful chemopreventive agents as it modulates cellular proliferation, modulate the cell cycle, and induction of apoptosis [83].

Induction of apoptosis is the main marker in cancer treatment. Carrageenans triggers apoptosis in different cancer cell lines are displayed (Fig. 3).

The red alga *Porphyra yezoensis* can induce cancer cell death via apoptosis in a dose-dependent manner in in vitro cancer cell lines without exhibiting cytotoxicity towards the normal cells. Moreover, carrageenans, hetero-fucans, dieckol and iodine can induce cancer cell death via apoptosis in a dose-dependent manner in in vitro cancer cell lines without exhibiting cytotoxicity towards the normal cells [77]. Several studies also reported that carrageenans show antiproliferative

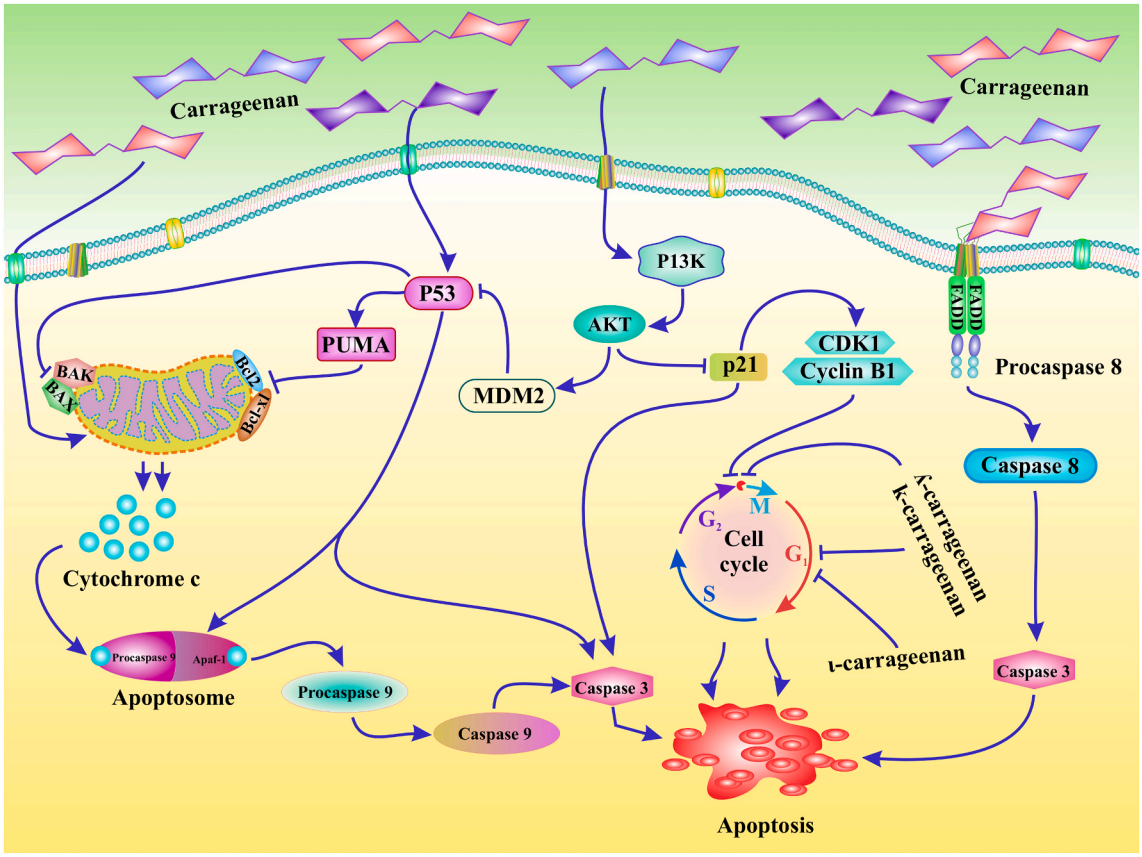

Fig. 3. Carrageenans triggers apoptosis and prevents cancer. Carrageenans downregulate the expression of anti-apoptotic protein Bcl-xl, Bcl-2. Carrageenans supports the intrinsic apoptosis via regulating the cytosolic release of cytochrome C. It induces the expression of caspase 9 and caspase 3 to induce apoptotic cell death. Carrageenans induce apoptosis through modulation of caspase 3 activity via death receptor mediated apoptotic cell death in several cancer cell lines. In addition to this, it also blocks the cell cycle which resulted apoptosis in different cancer cells.

action in cancer cell lines in vitro, as well as tumor growth inhibitory activity in mice [45,53,75]. They also exhibit antimetastatic effect by preventing cancer cells from interacting with the basement membrane, inhibiting tumor cell growth and adherence to diverse substrates, but their exact methods of action are yet unknown. Carrageenans from *Kappaphycus alvarezii* reduced the growth of liver, colon, breast, and osteosarcoma cell lines [77]. Yamamoto et al. [84] found that oral administration of numerous seaweeds reduced the incidence of carcinogenesis in vivo significantly. In male rats, the effects of carrageenan on colonic carcinogenesis were evaluated [85]. There were no treatment-related changes in clinical symptoms or body weights. Carrageenan does not have any promoting activity for colorectal carcinogenesis at the greatest dietary intake of 5.0 % for colorectal carcinogenesis under the current experimental settings, according to histopathological analysis [85].

Carrageenans have been shown to have specific cytotoxic effects on cancer cells in various studies. Such investigations have demonstrated that doses of 250–2500 μg/mL of both ʎ-carrageenan and k-carrageenan inhibited human cervical cancer cells by not only halting the cell cycle at particular stages, but also by delaying the time of it [57]. The G2/M phase of the cell cycle was delayed by k-carrageenan, while the G1 and G2/M phases were both delayed by ʎ-carrageenan. However, on the human hepatoma cell line, k-selenocarrageenan (i.e., k-carrageenan containing selenium) is anti-proliferative. In the S phase, it stops the cell cycle [86]. In vitro and in vivo experiments, however, showed that native ι-carrageenan exhibited no appreciable anti-proliferation in the human osteosarcoma cell line. Degraded ι-carrageenan inhibited tumor growth, triggered apoptosis, and halted the G1 phase, all of which increased tumor-bearing mice's survival rates. This was caused by a decrease in the Wnt/β-catenin signaling pathway [87].

Angiogenesis is a critical step in the progression of cancer. As a result, anti-angiogenic action is being studied extensively in cancer treatment. Carrageenans have been classified as angiogenesis inhibitors since they exhibit better anti-angiogenic activity than the standard chemical, suramin [88,89]. In ECV304 cells in the chicken chorioallantoic membrane (CAM) model, the anti-angiogenic effect of k-carrageenan oligosaccharides was demonstrated to limit cell proliferation, migration, and tube formation [90]. Furthermore, the oligosaccharides reduced new blood vessel creation in MCF-7 xenograft tumors by negatively regulating human VEGF, bFGF, bFGFR, and CD105. The downregulation of intracellular matrix metalloproteinase (MMP-2) expression by ʎ-carrageenan oligosaccharides at relatively low concentrations (150–300 μg/mL) had a deleterious effect on tumor blood vessel endothelial cell development in human umbilical vein endothelial cells [91].

The amount and position of sulfation, as well as the molecular weight, influence the biological activity of sulfated polysaccharides. That is, changes in the biological activities of carbohydrates are caused by chemical modifications [92]. For example, ʎ-carrageenan can be broken down into five distinct compounds with various molecular weights, all of which have anti-cancer properties, most likely due to immunomodulation. Lower molecular weight products, such as 15 and 9.3 kDa, had better anti-cancer and immunomodulation properties [92]. Chemical sulfation of the carrageenan backbone has a detectable influence on its anticoagulant activity, which is aided by sulfate substitution at C6 of β-d-Galp and C2 of 3,6-anhydro-α-d-Galp units [93]. Sulfate at C2 of the β-d-GalAp units, for example, had a stronger anticoagulant action than sulfate at C4. Furthermore, the partially oxidized molecule increased the k-carrageenan derivative's anticoagulant activity more than the fully oxidized molecule [94]. Sulfation, acetylation, and phosphorylation improved the anti-cancer and immunomodulation properties of k-carrageenan oligosaccharides from *Kappaphycus striatum*, with the sulfated derivative being the most potent. The oxidant activity of k-carrageenan oligosaccharides was also enhanced by chemical changes [54]. The anticancer activity of carrageenan is displayed in Table 1.

3.2.1. Combination with conventional anti-cancer drugs

Polysaccharides are strong anti-cancer agents and excellent adjuvants in cancer immunotherapy, according to toxicity studies. For decades, 5-fluorouracil (5-Fu) as a thymidylate synthase inhibitor has been used to treat cancer. It is, nevertheless, limited by unfavorable side effects [96,97]. The drug was fixed at the 6-position with low molecular weight porphyran to create a water-soluble macromolecule prodrug, which resulted in a delayed release of 5-Fu, extending the period of anticancer effectiveness and reducing adverse effects [96]. In transplanted S180 tumor mice, the combination and conjugation increased 5-Fu's anti-cancer action, and immunocompetence reversed the damage. On transplanted S180 tumor mice, the medical effect of ʎ-carrageenan on anti-cancer activity and immunosuppression by 5-Fu was investigated [98]. Though using the ʎ-carrageenan sample or 5-Fu alone at a low dose had no anti-cancer efficacy, mixing the two samples at the same dose boosted the activity. Meanwhile, ʎ-carrageenan improved 5-Fu-damaged immunocompetence by raising spleen weight, stimulating lymphocyte proliferation, restoring TNF-α levels, and reactivating the reduced spleens and white pulps. In H-22 tumor mice, similar research backs up this conclusion [99].

AuNPs have been employed extensively in catalysis, photothermal treatment, and targeted drug delivery [100]. The k-carrageenan oligosaccharide was used as a reducing and capping agent in the preparation of AuNPs, which were found to have considerable cytotoxic properties against HCT-116 and MDA-MB-231 cells [101]. Furthermore, k-

Table 1
Anticancer activity of carrageenan.

Source	Cell lines	Type of activity	Possible mechanisms	References
ʎ-Carrageenan purchased from Sigma-Aldrich	B16-F10 and 4T1 bearing mice	Inhibition of tumor growth and improving immune system	Increasing the number of tumor-infiltrating M1 macrophages, DCs, and more activated CD4+ CD8+ T lymphocytes and enhancing the secretion of IL17A in spleen and significantly increase the level of TNF-α in tumor	[95]
Carrageenan oligosaccharides derived from *Kappaphycus striatum*	S180-bearing mice	–	Increase macrophage phagocytosis, the form of antibody secreted by spleen cells, spleen lymphocyte proliferation, NK cells activity, serumal IL-2 and TNF-α level.	[53]
k-Carrageenan and ʎ-carrageenan purchased from Sigma-Aldrich	HeLa cells	Cell cycle delayed in G2/M phase or in both G1 and G2/M phase	–	[57]
k-Selenocarrageenan consisted of selenium and k-carrageenan	HepG2 cells	Cell cycle delayed in S phase	Upregulating Cyclin A and chk2 protein and down-regulating Cdc25A and cdk2 expression.	[86]
ι-Carrageenan	Human osteosarcoma cell line	Apoptosis induced and Cell cycle delayed in G1 phase	Downregulation of the Wnt/β-catenin signaling pathway through suppressing LRP6 expression and phosphorylation.	[87]
k-Carrageenan oligosaccharides prepared from k-carrageenan with enzyme	MCF-7 xenograft tumor	Antiproliferation and anti-angiogenic	Negative regulation of human VEGF, bFGF, bFGFR, and CD105.	[90]

carrageenans in the sulfate groups have been observed to electrostatically entrap maghemite nanoparticles [102]. In vitro anti-cancer efficacy of the biocompatible ι-carrageenan-ϒ-maghemite nanocomposite was demonstrated in a human colon cancer cell line by inducing cell apoptosis via the ROS-mediated mitochondrial pathway, along with downregulation of XIAP and PARP-1 mRNA expression and upregulation of caspase3, Bcl-2, and Bcl-xL [102]. The improved anticancer activity of carrageenan and anticancer medication combinations suggests a promising clinical application against a variety of human cancers. However, more research is needed to determine the pre-clinical and clinical efficacy of carrageenan in various cancers. Furthermore, it has the potential to be established as a dietary supplement for cancer patients in the near future.

3.3. Carrageenans triggers immunity via induction of TNF-α

Natural anti-cancer defensive systems in the host, in combination with a variety of therapeutic techniques, such as new anti-cancer medications that boost immunity, play an essential role in cancer treatment [103]. Immune responses are said to be regulated by seaweed polysaccharides, which activate immunological cells and other nonspecific immune responses. Several studies have looked at the immunomodulating potential of carrageenan in the treatment of malignancies. In B16-F10 and 4T1-bearing mice, intratumoral injections of ʎ-carrageenan were found to prevent tumor growth [95]. Meanwhile, boosting tumor-infiltrating M1 macrophages in the spleen, which released larger levels of IL17A in the spleen and TNF-α in the tumor, improved immune response to the tumor. Carrageenan oligosaccharides isolated from *Kappaphycus striatum* were also found to improve tumor immunity and cell-mediated immunity in S180-bearing mice, resulting in significant tumor therapeutic efficacy [53].

Kappa, lambda, and iota carrageenans are sulphated polysaccharides that have been isolated from marine algae and have been shown to significantly reduce immune responses both in vivo and in vitro [104]. The monosaccharide composition of polysaccharides, as well as the quantity, positioning, and distribution of sulphate groups along the galactan chain, are all factors that affect carrageenans' immunomodulatory and anticoagulant activity [105]. Anti-inflammatory IL-10 was secreted as a result of carrageenans in a dose-dependent manner [105]. Depending on the time and route of carrageenan injection in relation to that of the antigen, it either suppressed or enhanced humoral responses to different antigens. The processing of antigen and its presentation to B cells, the production of helper T cells, and the secretion of a proliferative signal to B cells are all crucial steps in the induction of humoral and cell-mediated immune responses [106,107]. Carrageenan appears to have a cytopathic effect on macrophages, which mediates its immunosuppressive effect. Within 36 h of cultured macrophages consuming carrageenan, hydrolytic enzymes are released into the culture medium [108].

3.4. Antidiabetic properties of carrageenan

High blood glucose levels, which may be caused by unusual food intake and are a defining feature of the chronic, life-threatening disease known as diabetes, can cause cardiovascular disease, renal dysfunction, and retinal damage [25]. Around 50.8 million of people are suffering diabetes India due to food habit and will be reaching to 87 million by 2030 [25]. Synthetic antidiabetic drugs displayed several side effects leads to kidney failure, heart problem etc. Searching of natural compounds are more promising [25]. In this regard, seaweeds are more promising and will be fill up the gap.

Seaweed has traditionally been used as a readily available whole-food, particularly among coastal populations in Asia [109,110]. In most other parts of the world, seaweed is only used as an extract or as a food additive [111], as well as isolates, such as carrageenan which are normally used in various applications [112]. Currently, there is a rising knowledge of the significance of food in giving health benefits and lowering the risk of numerous illnesses, including diabetes [113,114].

Human participants who had arroz-caldo (porridge) containing ʎ-carrageenan had considerably lower post-prandial glycemic reactions than controls, indicating that carrageenan and dietary fibre can help manage metabolic illnesses like diabetes [115]. Compared to controls, human subjects who consumed porridge containing lambda-carrageenan had significantly lower post-prandial glycaemic responses, indicating the effectiveness of dietary fibre and carrageenan in treating metabolic diseases like diabetes [115]. Carrageenans from *Eucheuma cottonii* displayed significantly lowered blood glucose and insulin responses, resulting in a 50 % reduction in glucose absorption balance in pigs [116].

3.5. Anticoagulant and antithrombotic activity of carrageenan

The blood coagulation system is made up of intrinsic and extrinsic routes, each with its own set of components. Coagulation factors cause blood to coagulate in order to stop blood from flowing through an injured artery wall in circumstances of aberrant vascular abnormalities or exposure to non-endothelial surfaces at vascular injury sites. Blood coagulation can be prolonged or stopped by using oogenus or exogenous anticoagulants that inactivate or inhibit the activity of coagulation factors [117]. Carrageenan is divided into several kinds, each of which contains 22–35 % sulphate groups has been shown to have anticoagulant properties. λ-Carrageenan, for example, has roughly double the activity of unfractionated carrageenan and four times the activity of κ-carrageenan among the carrageenan types [89]. On the other hand, the most active carrageenan, has only a sixteenth of the activity of heparin [118]. The anticoagulant effect of carrageenan appears to be based on an anti-thrombic characteristic [118]. Because of its higher sulphate concentration, λ-carrageenan showed more anti-thrombic activity than κ-carrageenan, whilst the activity of the unfractionated material was somewhere in the middle. λ -Carrageenan was shown to be more hazardous than κ-carrageenan in terms of clotting time [118].

The variation in sulphate concentration did not equate to changes in anticoagulant effect or toxicity between the two carrageenans [118]. Carrageenan's anticoagulant effect is mediated by thrombin inhibition, as previously indicated. Anti-thrombin action may be mediated through AT-III (anti-thrombin-III), the principal mechanism by which heparin operates, according to early investigations. Carrageenans appeared to inhibit thrombin amidolysis both directly and via AT-III in these trials, while only AT-III potentiated Xa amidolysis [119]. Certain important properties of polyanionic polymers, such as sulphation, size, ionic substitution pattern, and polymer stiffness, may influence these interactions [119]. However, in the presence of carrageenans, further investigations utilizing AT-III-depleted plasma revealed persistent anti-thrombin activity. λ-Carrageenan has been demonstrated to increase the effectiveness of 'anti-thrombin BM' in inactivating thrombin. These findings suggest that either anti-thrombin potentiation via heparin co-factor II (HC-II) or a direct anti-thrombin impact is present [120–122]. The three types of carrageenans—kappa, iota, and lambda—showed variations in pleural exudate volume, which was marked by fluid buildup, a significant neutrophil population, and increased NO production. For kappa and iota carrageenans (100 lg), the activated partial thromboplastin time (aPTT) was 240 s and 132 s, respectively. At 240 s (20 lg), lambda carrageenan outperformed kappa and iota in terms of anticoagulant potency [123]. The concentration and structure of kappa, kappa/beta, kappa/iota carrageenans from Gigartinaceae and Tichocarpaceae can have a significant impact on the cytokine production by human cells. Additional lambda-carrageenan sulphate ester residue raises the calcium level in the cytoplasm and may play a significant part in the activation of the formation of active oxygen forms. The potential anticoagulant activity of kappa/iota carrageenan was very potent at low concentrations. These findings imply that the monosaccharide composition of polysaccharides, as well as the quantity, positioning, and distribution of sulphate groups along galactan chains, influence the anticoagulant

activity of carrageenans [105].

3.6. Carrageenan-induced paw oedema and intestinal inflammation

The onset of oedema in the rat hind paw after carrageenan injection has been described as a biphasic, age-weight-dependent event in which many mediators work in concert to induce the inflammatory response. Carrageenan-induced rat paw oedema is a common test for determining anti-inflammatory activity, and it is a simple and straightforward animal model for assessing discomfort at the site of inflammation without causing any injury or damage to the inflamed paw [124]. Inflammation is mediated by a number of mediators. Prostaglandins (PGs) are implicated in increased vascular permeability and are detected in the late phase of inflammation; histamine, serotonine, and bradykinin are the first detectable mediators in the early phase of carrageenan-induced inflammation. Increased levels of the pro-inflammatory cytokines TNF-α, IL-1, and IL-6 are linked to local and/or systemic inflammation [125]. The release of histamine, 5-hydroxytryptamine (5-HT), and bradykinin is thought to be responsible for the early phase of oedema, which is not prevented by nonsteroidal anti-inflammatory medicines (NSAIDs) such indomethacin or aspirin.

The stimulation of inducible cyclooxygenase (COX-2) in the hind paw has been linked to the second accelerating phase of swelling, which has previously been linked to increased prostaglandin synthesis [126]. It can be blocked by the NSAIDs [127]. Local neutrophil activation and infiltration contribute to the inflammatory response by creating oxygen-derived free radicals such as superoxide anion (O_2^-) and hydroxyl radicals, among other mediators [128]. Nitric oxide (NO) is another significant mediator in acute inflammation, and it is produced by three different isoforms of nitric oxide synthase (NOS) in pathological conditions: Endothelial NOS (eNOS), neuronal NOS (nNOS), and inducible NOS (iNOS). At the wounded site, carrageenan stimulates the production and release of NO. In this investigation, NG monomethyl-larginine acetate (L-NMMA), a non-selective NOS inhibitor with moderate selectivity for inhibition of neuronal and endothelial isoforms, decreased NO release after carrageenan injection. Aminoguanidine hemisulfate (AG), an inducible NOS inhibitor, decreased NO release 2.5–8 h after carrageenan administration. After carrageenan injection, neurectomy totally inhibited NO release for up to 3 h and partially suppressed NO release for 4.5–8 h. These data suggest that nNOS is involved in NO production in both the early and late phases, but iNOS is exclusively involved in the latter. NOSs are hypothesized to contribute to tissue damage, inflammation-induced oedema, and hyperalgesia by producing and releasing NO [129]. The use of mouse paw oedema to test new anti-inflammatory medicines and understand the mechanisms involved in inflammation is becoming more common. There are around 400 studies in the literature that report on the usage of mouse paw oedema [128]. A newly prepared solution of 1–3 % carrageenan in saline is usually utilized as an intraplanar injection in doses of 50–150 μL, with larger concentrations employed for the modelling of certain pathophysiological situations [124,130].

Watt and Marcus [131] described a simple approach for producing ulcers in the guinea pig's large intestine that just required adding a degraded carrageenan to the drinking water. The method could be utilized as an experimental model to investigate several aspects of ulcerative lesions in this section of the gastrointestinal system. Carrageenan, freshly produced and degraded, was administered to the drinking water of guinea pigs at a concentration of 5 %. For 20 to 45 days, a dose of degraded carrageenan of no more than 2 g/kg body weight in the drinking fluid causes ulcerative lesions with clinical and pathological alterations that are similar to ulcerative colitis in humans. Weight loss, loose stools, and occult or obvious blood in the faces were all observed clinically. Ulceration was observed in all regions of the large bowel pathologically, with severe lesions in the rectum. Focused mucosal haemorrhages and cellular infiltrates, oedema, crypt abscesses, irregular dilatation of crypts with loss of mucin-secreting cells and degeneration of the lining epithelium, ulceration involving primarily the mucosa, and ulcerations in various stages of progression and healing are all microscopically similar. However, the inflammatory lesions appear to start in the caecum and spread distally to the rectum.

3.7. Antihyperlipidemic effects of carrageenan

Carrageenan has biological activity in the gastrointestinal tract when taken orally. Carrageenan raises the viscosity of the intestinal material and slows digestion and absorption, reducing the diffusion of enzymes, substrates, and nutrients in the intestinal absorption phase and lowering nutritional absorption, particularly cholesterol absorption [72]. Carrageenan's bioactive potential stems from its ability to reduce cholesterol absorption while increasing endogenous cholesterol production [132]. The effects of kappa-carrageenan, kappa/beta-carrageenan, and iota/kappa-carrageenan on the synthesis of prostaglandin E2 and cytokines (interleukin [IL]-1 β and IL-6) were evaluated in a whole blood model in vitro, both alone and in conjunction with lipopolysaccharide. Carrageenans displayed a significant potential to control prostaglandin E2 synthesis and promote IL-1β and IL-6 synthesis at high doses, indicating the likely mechanism of carrageenan's cholesterol-lowering characteristics [50]. Daily intake of carrageenan for 60 days showed a reduction in serum levels of total cholesterol and LDL-C in women [133]. *Kappaphycus alvarezii* was used as a whole-food supplement to prevent obesity in rats fed a high-carbohydrate, high-fat diet that mimicked symptoms of human metabolic syndrome, such as central obesity, dyslipidemia, hypertension, and impaired glucose tolerance, as well as cardiovascular and liver complications. Furthermore, it has been used as a functional meal with the potential to prevent metabolic syndrome [134]. In male Wistar rats, the red seaweed *Sarconema filiforme* was employed as a functional meal to reverse metabolic syndrome and its probable processes. Iota-carrageenan treatment in rats reduces the symptoms of diet-induced metabolic syndrome. However, it also acts as a prebiotic, as well as having anti-inflammatory effects in organs including the heart and liver [135].

3.8. Antiviral activity of carrageenan

It is been proposed that negatively charged compounds, such as sulphated polysaccharides, exert their inhibitory impact by interacting with positive charges on the virus or on the cell surface, preventing the virus from penetrating host cells. Although carrageenan has been shown to have anti-HIV efficacy, its high anticoagulant properties are considered a negative effect when used as an AIDS treatment [136].

Human pathogens, such as the human immunodeficiency virus (HIV), herpes simplex virus (HSV), human cytomegalovirus, human rhinoviruses, and others are all selectively inhibited by carrageenan [136]. Carrageenan works by blocking virions from attaching to or entering cells [48]. The fact that carrageenan resembles heparan sulfate, an HPV cell-attachment factor, supports this conclusion. In vitro, carrageenan as a seaweed extract is an extremely effective inhibitor of HPV infectivity. Viruses, such as herpes simplex and some strains of HIV-1, are also active against carrageenan in vitro [137]. In vitro IC_{50} values for carrageenan inhibition of HSV and HIV-1 infectivity, on the other hand, are around a thousand times greater than IC_{50} for carrageenan inhibition of genital HPVs.

The antiviral activity of sulphated polysaccharides is determined by their chemical structure, degree of sulphation, sulphate group distribution, molecular weight, constituent sugars, conformation, and dynamic stereochemistry [117]. Sulphated polysaccharides derived from the red algae *Gelidium cartilagenium* were first found to have antiviral effect against the influenza B or mumps virus [138]. The antiviral activity of carrageenan is attributed to the screening of certain cellular structures involved in virus-receptor binding [139]. The antiviral effect of ʎ-carrageenan may be attributed to the irreversible production of stable virion-carrageenan complexes, and therefore carrageenan

occupying the viral envelope sites required for virus binding to host cells, preventing the virus from completing the infectious process (Fig. 4) [140,141].

Several viruses, including the herpes simplex virus (HSV), the human papillomavirus (HPV), the varicella zoster virus (VZV), human rhinoviruses, and others, are selectively inhibited by carrageenan [42,117,141,142]. Carrageenans are strong and specific inhibitors of the HSV-1 and HSV-2, according to several in vitro/in vivo studies (HSV-2) [47,143]. In vitro and in vivo tests, the combination of carrageenan and lectin showed high effectiveness against HSV-2 and HPV [144,145]. Carrageenan has been shown to be effective against HPV, and in cell culture assays, it is 1000 times more powerful against HPV than HSV and HIV. Carrageenan works by blocking HPV virions from attaching to cells [56]. Several studies reported that carrageenan solutions (lambda, kappa, or iota) have the ability to prevent HSV-2 infection [63,146]. λ-Carrageenan and partially cyclized carrageenan (μ/ι) from *Gigartina skottsbergii* had effective antiviral effects against several strains of HSV type 1 and type 2 [51,147].

Carrageenans have been combined with other active compounds to boost or direct their anti-HPV and anti-HSV-2 bioactivity. An intravaginal ring of ʎ/k-carrageenan with four active ingredients was described, including zinc acetate, levonorgestrel, and MIV-150 (microbicide); this formulation had a long-lasting effect and protected against HIV-1, HSV-2, HPV, and unplanned pregnancies [148]. In a cohort of fertile patients with genital human papillomavirus, the antiviral impact of a novel carrageenan-based vaginal microbicide was recently studied. In women who have a positive HPV-DNA test, carrageenans help to speed up the usual clearance of genital HPV infection [149].

The ability of kappa-carrageenans inhibits the 2009 H1N1 influenza virus in the swine flu pandemic [150]. The finding showed that kappa-carrageenans inhibited H1N1 (SW731) reproduction by interfering with a few replication phases in the SW731 life cycle, such as adsorption, transcription, and viral protein expression. After internalization into cells, kappa-carrageenans reduced SW731 mRNA and protein expression suggesting that kappa-carrageenans could be useful to fight against H1N1/2009 and other viruses [151].

In vitro, iota-carrageenans were active against respiratory viruses, and clinical trials showed that it was useful as a nasal spray, treatment with iota-carrageenans in patients with early common cold symptoms. Their findings showed a significant reduction in cold symptoms in the iota-carrageenans group compared to the placebo group during the first four days, when symptoms were the most severe. They also confirmed that iota-carrageenans inhibits the virus-induced cytopathic effect of infected HeLa cells and reduces the growth of human rhinoviruses (HRVs). It also works by stopping virions from attaching to or entering host cells [48,152]. Iota-carrageenans were evaluated as a possible influenza A virus infection inhibitor. Iota-carrageenans had a 10 times stronger inhibitory capacity than kappa-carrageenans, with IC_{50} values of about 0.2 μg/mL in H1N1 and 0.04 μg/mL in H3N2 infections. The authors confirmed that iota-carrageenans inhibited influenza virus spread in affected animals' surface epithelia, giving enough benefit for the animals to encourage survival. Clearly, this study found that iota-carrageenans were safe and effective in the treatment of influenza infection, even when compared to other types of carrageenans, making it a viable antiviral contender for the prevention and treatment of this virus [153].

Mice infected with a fatal dose of influenza A PR8/34 H1N1 virus were treated with iota-carrageenan for up to 48 h after infection and showed equivalent protection to mice treated with oseltamivir. Because alternative influenza therapy options are limited, a nasal spray

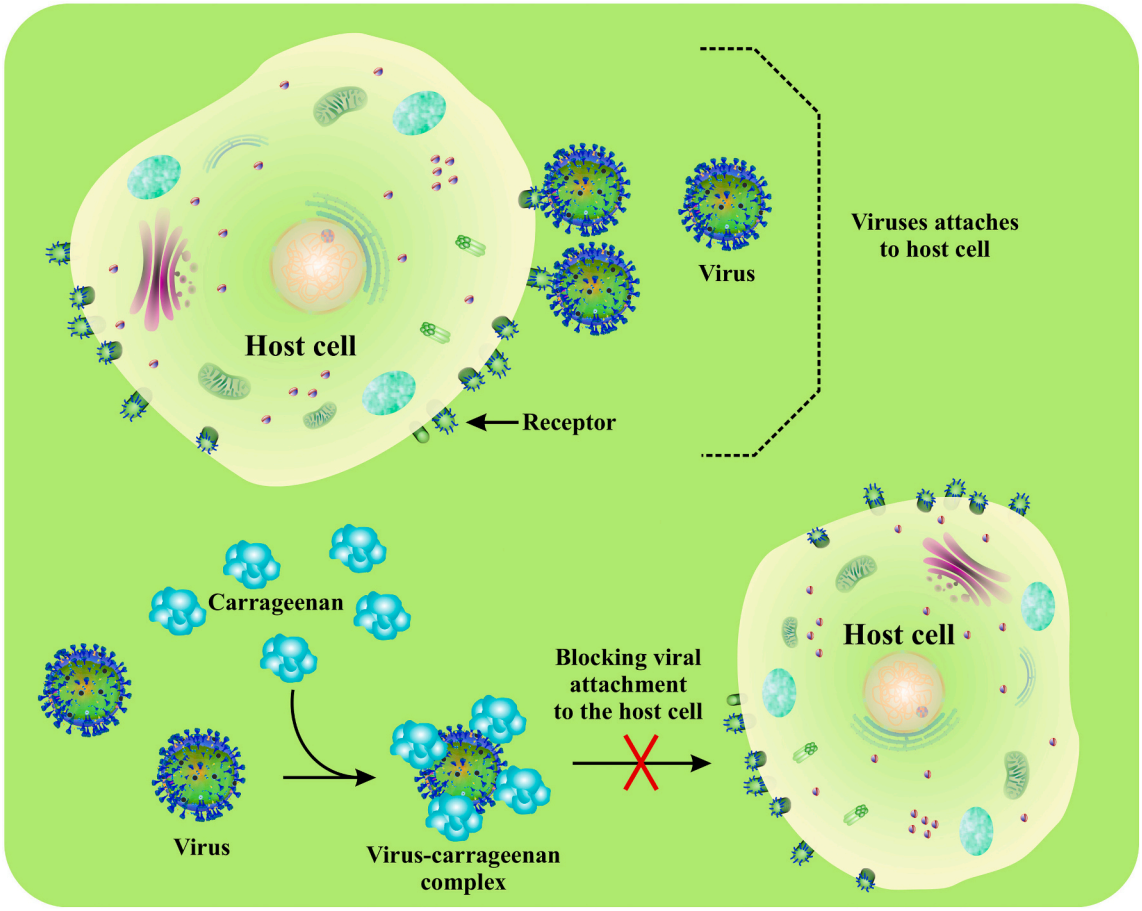

Fig. 4. Carrageenan modulates viral inhibition via blocking viral attachment to the host cell.

containing iota-carrageenan should be studied in human clinical trials as an alternative to neuraminidase inhibitors for the prevention and treatment of influenza A [153]. The efficacy and safety of an iota-carrageenan nasal spray in people who had a common cold and nasal sprays appear to be a potential medication for treating early symptoms of the common cold in a safe and effective manner [154]. The antiviral effect of carrageenan with inhibitory concentration (IC_{50}) is displayed in Table 2.

3.8.1. Mechanisms of antiviral activity

According to reports, carrageenans work best against viruses with envelopes. Herpes simplex virus types 1 and 2 (HSV-1 and 2), cytomegalovirus (CMV), varicella zoster virus (VZV), equid herpesvirus 3 (EHV-3), bovine herpesvirus type 1 (BoHV-1), and suid herpesvirus type 1 are the ones that have been studied the most (SuHV-1) [51,163–165]. Additionally, recent research has shown that the carrageenans iota and lambda have strong inhibitory effects on the SARS-CoV2 virus [166–168]. Additional activity against non-enveloped viruses, such as the human rhinovirus, has been reported by some authors (HRV) [48], enterovirus 71 (EV-71) [169], and papillomavirus type 16 (HPV-16) [56]. Direct virucidal effects, effects on viral replication, and/or preventive effects on cells that are susceptible are a few examples of antiviral mechanisms. This section reviews studies on each of these alleged mechanisms.

3.8.2. Direct virucidal effect

Direct virucidal effects are effects on viral replication, and/or preventive effects on cells that are susceptible are a few examples of antiviral mechanisms. Carrageenans extracted from the red alga *Gigartina atropurpurea* and other SPs extracted from *Splachnidium rugosum* and *Plocamium cartilagineum*, as well as to a lesser extent from *Undaria pinnatifida*, had virucidal activity against herpes simplex virus-2 (HSV-2) [158]. Two animal herpesviruses, bovine herpesvirus-1 (BoHV-1) and suid herpesvirus-1, have also been used to demonstrate the antiherpetic activity of λ-carrageenans extracted from other *Gigartina* species, *G. skottsbergii* (SuHV-1) [160]. Additionally, carrageenans derived from *Acanthophora specifira* and *Hydroclathrus cathralus* could be used to inactivate the herpes simplex virus type 1 (HSV-1) and the Rift valley fever virus (RVFV) [155]. Finally, λ-carrageenans reduced VZV infectivity by 85 % [170].

3.8.3. Effect on the viral replication

The viral cycle consists of six steps: cell adsorption or attachment, entry, coating removal, synthesis (viral genome replication and translation), assembly, and release. The majority of studies have looked at how carrageenans affect the first two steps in various virus and cell lines, but it has also been noted that carrageenans have an inhibitory effect on viral synthesis. The studies that focused on preventing each step of viral replication are summarized below.

3.8.3.1. Carrageenans prevents viral replication via inhibition of viral adsorption, internalization/entry, uncoating, synthesis and protective effect on cells. The host cell surface must bind to the virus for infection to occur. Glycans on the protein or lipid surface interact with a large number of viruses, and among the various cell surface components that can influence viral attachment [171,172]. Three families of glycans—sialoglycans, glycosaminoglycans, and histo-blood group antigens—are involved in viral binding (GAGs). GAGs are long polysaccharides made of glucosamine and sulfated uronic acid residues that are recognized by a variety of enveloped viruses, including herpesviruses, dengue, and zika and non-enveloped viruses such as HPV and human parvoviruses [172,173]. It has been demonstrated that carrageenans, particularly the κ, ι, and λ forms, can inhibit the interactions between GAGs, particularly heparan sulphate (HS), and various enveloped and non-enveloped viruses [151,153,157,174]. This blocking ability in enveloped viruses has been reported to be caused by carrageenans' capacity to bind proteins in the viral envelope, such as the herpes simplex glycoprotein or influenza hemaglutinin, preventing virus binding to GAGs [51,151]. A similar mechanism that involves blocking communication between the viral capsid and cell surface receptors by blocking the virion surfaces involved in binding to cellular receptors appears to be the basis for the activity against non-enveloped viruses [48,56].

Table 2
Antiviral effect of carrageenan with inhibitory concentration (IC_{50}).

Type of carrageenan κ, ι, ε, μ	Size of carrageenan	Algal sources	Viruses involved	Inhibitory concentration 50 (IC_{50}) in μg/mL or μM	References
λ-Carrageenan		*Acanthophora specifira*	HSV-1_{Vero}; RVFV	80.5 and 75.8	[155]
k-Carrageenan, k /β-carrageenan,	2.2 kDa and 4.3 kDa	*Chondrus armatus, Tichocarpus crinitus*		-	[156]
k/ι/ν-Carrageenan		*Cryptonemia crenulata*	HSV-$1_{C1, Vero}$; HSV-2; HSV-$1_{C2S3, Vero}$; HSV-2; HSV-$1_{Heparin, Vero}$; HSV-2; HSV-$1_{DS8000, Vero}$; HSV-2	0.5, 1.1, 0.5, 1.9, 3.0, 1.8, 2.8 and 2.5	[157]
k/ι/ν-Carrageenan		*Cryptonemia crenulata*	HSV-$1_{C3, Vero;}$ HSV-$1_{C1S, Vero}$; HSV-$1_{C2-S3, Vero;}$ HSV-$1_{2S-2d, Vero}$	1.0, 0.8, 0.5 and 1.0	[157]
λ-Carrageenan		Gigartina atropurpurea	HSV-$1_{k-C, HFF}$; HSV-2; HSV-$1_{L-C, HFF}$; HSV-2; HSV-$1_{ACV, HFF}$; HSV-2	36, 1, 1.5, 36, 0.3 and 0.4	[158]
λ-Carrageenan		Gigartina skottsbergii	HSV-$1_{T1, Vero}$; HSV-1_{PH}; HSV-$1_{DS8000, Vero}$; HSV-1_{PH}	0.4, 0.8, 1.8 and 0.8	[159]
λ-Carrageenan		Gigartina skottsbergii	BoHV-1_{MDBK}; SuHV-1	1.37 and 73.54	[160]
C1: k/ι carrageenan C3: μ/ν carrageenan		Gigartina skottsbergii	HSV-$1_{k, i-C, Vero}$; HSV-1_{PH}; HSV-$1_{m, n-C, Vero}$; HSV-1_{PH}; HSV-$1_{DS8000, Vero}$; HSV-1_{PH}	3.2, 3.3, 0.9, 0.8, 1.8 and 0.8	[51,159]
k/ι carrageenan	75–124 kDa	Gigartina skottsbergii	HSV-1_{Vero}; HSV-2; HSV-$1_{DS8000, Vero}$; HSV-2; HSV-$1_{Heparin, Vero}$; HSV-2	3.2–4.1, 1.6–2.3, 1.0, 2.1, 1.3 and 2.1	[51]
k/ι carrageenan		*Gymnogongrus griffithsiae*	HSV-$1_{G3, Vero}$; HSV-$1_{G3S, Vero}$; HSV-$1_{G3d, Vero}$; HSV-$1_{G3S-6, Vero}$; HSV-$1_{G2S-2d, Vero}$	0.6, 2.8, 1.0, 2.0 and 1.0	[157]
ι/k/ν-Carrageenan	845 kDa	*Gymnogongrus griffithsiae*	HSV-$1_{G3, Vero}$; HSV-2; HSV-$1_{G3d, Vero}$; HSV-2; HSV-$1_{Heparin, Vero}$; HSV-2; HSV-$1_{DS8000, Vero}$; HSV-2	1.1, 1.2, 1.0, 1.0, 3.0, 1.8, 2.8 and 2.5	[157]
k-Carrageenan	215 kDa	*Hypnea musciformis*	HSV-$1_{KC, Vero}$; HSV-2; HSV-$1_{OKC, Vero}$; HSV-2	13.8, 11.0, 1.7 and 0.98	[161]
ι-Carrageenan	460 kDa	*Hypnea musciformis*	HSV-$1_{KC, Vero}$; HSV-2; HSV-$1_{OKC, Vero}$; HSV-2	0.67, 0.43, 0.40 and 0.40	[161]
ι/k/ν-Carrageenan	957 kDa	*Meristiella gelidium*	HSV-$2_{E1, Vero}$; C6/36 DENV-2_{HT}; HSV-$2_{E2, Vero}$; C6/36 DENV-2_{HT}; HSV-$2_{E2F, Vero}$; C6/36 DENV-2_{HT}; HSV-$2_{Heparin, Vero}$; C6/36 DENV-2_{HT}; HSV-$2_{DS8000, Vero}$; C6/36 DENV-2_{HT}	0.06, 0.79, 0.05, 0.14, 0.04, 0.21, 0.6, 1.9, 0.6 and 0.9	[63]
k-Carrageenan	1.2–3.0 kDa	Kappaphycus alvarezii		NA	[156]
λ-Carrageenan	2 * 10^3 kDa	*Schizymenia pacifica*	HIVMT-4	9.5 * 10^3 IU/mL	[162]
ι-Carrageenan		*Solieria chordalis*	HSV-1_{CE}; acyclovir; HSV-1_{MAE}; acyclovir	0.1, 0.2, 0.3–0.5 and 0.5	[143]

Viral proteins undergo conformational changes after virus attachment to the cell surface, which activate signaling cascades and destabilize the cell membrane, resulting in viral internalization via an endocytic or non-endocytic route [175,176]. Few studies have examined the impact of carrageenans on viral entry, likely because doing so requires the application of more complicated methods. By measuring the amount of viral RNA present inside the cells, λ-carrageenans can prevent DENV-2 nucleocapsid internalization into the cytoplasm [177]. The internalization of the four DENV serotypes in human myeloid U937 and K562 cells is potently inhibited by these compounds in both primary infections and infections caused by antibodies [178]. The internalization of the RABV virus has also been shown to be affected by λ-carrageenan P32 [179]. HSV-1 internalization was reported to be blocked by another type of carrageenans, λ-carrageenans, using radiolabeled viral particles [164]. These substances may also have an inhibitory post-attachment effect on the two non-enveloped viruses HPV and HRV, either by blocking the surfaces of the virion involved in binding to cellular receptors or by impeding the viral particle's necessary conformational changes [48,56].

To the best of our knowledge, only two reports mention carrageenans' antiviral properties at this stage. The blocking of DENV-2 internalization by λ-carrageenans is most likely caused by the viruses' inability to be uncoated and released from endosomes [177]. According to a study by Luo and colleagues, the λ-carrageenan P32 could prevent the RABV glycoprotein from changing its conformation, preventing the protein's role in mediating cell fusion and preventing the uncoating of the virus [179].

Initial studies in the 1980s suggested that carrageenans' polysaccharides influenced HSV-1 and avian mieloblastosis virus (AMV) enzymatic activities and protein synthesis, respectively [162,164]. Carrageenans displayed the decreased in viral protein synthesis in HeLa cells were infected with HSV-1, but cellular proteins were unaffected [164]. The reverse transcriptase activity of AMV was shown to be inhibited by a λ-carrageenan obtained from *Schizymenia pacifica* [162]. More recently, the impact of carrageenans on intracellular replication steps in influenza A virus has been thoroughly investigated (IAV) [151,180,181]. It has been shown that low-molecular-weight (LMW) κ-carrageenans can enter the Madin Darby canine kidney (MDCK) and inhibit IAV transcription as well as protein expression, most likely by preventing viral polymerase activity [151,180]. Additionally, it has been demonstrated that κ-carrageenans can reduce the production of EV 71 mRNA in Vero-infected cells [169]. Finally, it has been hypothesized that ι-carrageenans may have an impact on DENV and VZV intracellular replication steps [170,174]. In Vero cells, there is a 75 % inhibition of VZV intracellular replication by ι-carrageenan. Furthermore, ι-carrageenan might interfere with potential targets in the host cells, preventing DENV replication in the C6/36 HT mosquito-derived cell line [170,174].

The prophylactic activity of carrageenans has not received much attention, likely because the majority of studies found that these compounds have an antiviral effect by binding viruses and preventing them from adhering to cell cultures. Chiu and co-authors discovered that κ-carrageenan pre-treatment of Vero cells for 1 h prior to infection with EV 72 demonstrated a potent viral inhibitory effect (92 %), slightly higher than that of the group treated at the infection time (87 %) or post-infection (82 %), indicating that the carrageenan molecule can bind to both the cell receptor and viral surface [169]. Pre-treatment with ι-carrageenan of C6/36HT mosquito cells reduced virus yield by 1.5 log at 48 post infection, and the EC_{50} value was similar to that attained when the virus and carrageenan were incubated together throughout the entire infection period [174]. In Vero E6 cells that had been pretreated with κ, λ, and ι-carrageenans for 1 h, there was a decrease in the hantavirus PM-95 titer of 1.8, 1.4, and 1.4 log focus forming units (ffu)/mL [182]. On the other hand, when the polysaccharides were present only before virus infection, Vero cells were not protected from HSV-1 or VZV infection [170,183]. Carrageenans modulates antiviral mechanism of via inhibiting virus attachment, penetration, interiorization, uncoating and transcription and translation process (Fig. 5).

3.8.4. Drug synergisms medicated with carrageenan

Several studies recommended that the mixing of carrageenans with other medicines to improve their antiviral activity. The anti-influenza medicine Zanamivir was tested in vitro and in vivo with carrageenans in a nasal formulation, and the results showed that carrageenans and Zanamivir work together against numerous influenza A virus strains (pandemic H1N1/09, H3N2, H5N1, H7N7). In this study, it was discovered that combining two forms of carrageenan (iota- carrageenans and kappa-carrageenans) with an antiviral medicine improves the formulation's efficacy, as the combined use of the compounds dramatically increased the survival of infected animals as compared to monotherapies [184].

A nasal spray containing xylometazoline HCl and iota-carrageenans was tested in a recent study. In vitro tests demonstrated that the drug's vasoconstrictive qualities combined with iota-carrageenans' antiviral activity were effective against human rhinovirus (hRV) 1a, hRV8, and human coronavirus OC43. The combination of iota-carrageenans with the drug does not produce a negative effect in this study; rather, the efficacy and safety of both components remain unchanged, resulting in the desired therapeutic effect, demonstrating that the combination of carrageenans and drugs does not produce harmful interactions. The formulation was well-tolerated at the application site, with no erythema or edoema in any of the rabbits' nostrils, nor any evidence of toxicity in any of the organs or tissues investigated [185]. Carrageenans produced a physical barrier in the nasal cavity against respiratory viruses, preventing them from adhering to host cells, according to these investigations [139]. The anti-enterovirus 71 (EV 71) activity of kappa-carrageenans is powerful and effective, reducing plaque formation, preventing viral reproduction before or during viral adsorption, and inhibiting EV 71-induced apoptosis. They demonstrated that kappa-carrageenans can bind firmly to the EV 71 to create carrageenans-virus complexes in the virus binding experiment, indicating that the virus–receptor interaction is likely to be disturbed [169].

The potential role of ʎ-carrageenan P32 in rabies virus (RABV) inhibition was investigated, and it was discovered to be a promising anti-RABV drug that efficiently inhibited RABV infection in vitro by influencing viral internalization and cell fusion mediated by viral G protein [179]. In a more recent investigation, kappa-carrageenan, iota-carrageenan, ʎ-carrageenan, and other natural polysaccharides were found to prevent VZV infection in vitro. When compared to the reference medication acyclovir, almost all of the polysaccharides examined were very active against VZV and showed dose-dependent behavior. The findings revealed that iota-carrageenan may prevent the early steps of virus infection, such as virus attachment or penetration into host cells, as well as the late steps after virus penetration into host cells, indicating that iota-carrageenan has potent antiviral activity against a variety of viruses [170]. Finally, during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, researchers discovered that marine sulfated polysaccharides like iota-carrageenan can prevent viral binding and penetration into host cells. At doses of >125 μg/mL, iota-carrageenan could prevent infection [186]. As a result, marine polysaccharides have adequate antiviral action against a variety of viruses, blocking viral binding, allowing them to be used in the treatment and prevention of Coronavirus disease (COVID-19) [186–188].

Carrageenan's antiviral activity has been demonstrated to be highly wide in investigations, making it possible to suppress the replication of numerous viruses with or without envelopes. Carrageenan's antiviral impact occurs alone or in combination with other chemicals, such as medicines, and this combination allows for a significant increase in therapeutic efficacy while avoiding interactions. Since various viral strains, such as SARS-CoV-2, are still being studied, and these polysaccharides fulfil this proposed antiviral efficacy, carrageenan's antiviral activity remains promising, but there is still a long way to go in

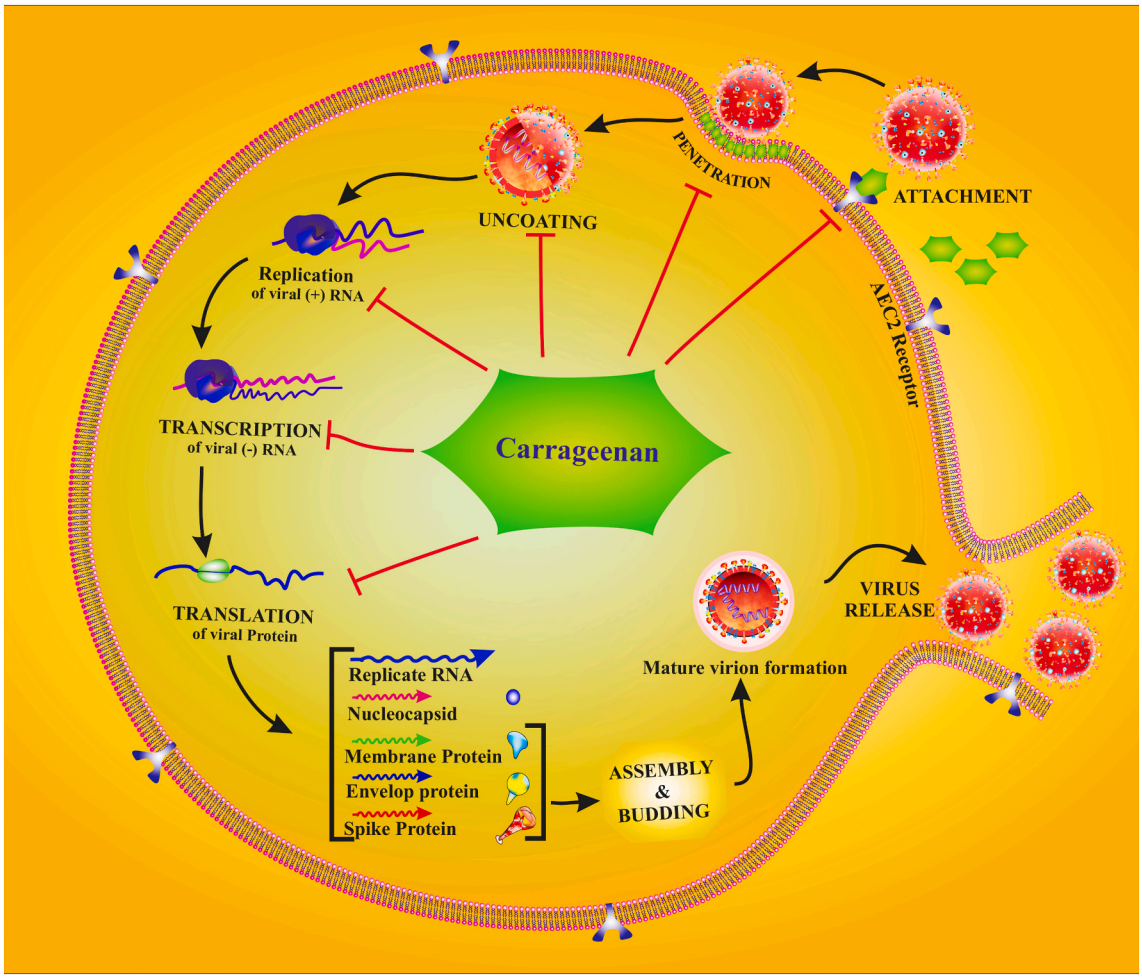

Fig. 5. Carrageenans modulates antiviral mechanism modified from [30] via inhibiting virus attachment, penetration, interiorization, uncoating and transcription and translation process.

fully evaluating the efficacy and safety of these polysaccharides as highly effective antiviral components. The increased antiviral activity of carrageenan and antiviral drug combinations indicates a prospective clinical application against a wide range of human-affecting viruses. However, more research is still needed to open up the carrageenan's pre-clinical and clinical efficacy in diverse human-affecting viruses to be established as a potential antiviral drug.

3.9. Antibacterial activity of carrageenan

Carrageenan has the ability to prevent infection from a range of bacteria. The antibacterial activity of carrageenans was determined by measuring the diameter of the inhibitory zone using kappa-carrageenan oligosaccharides against bacteria *Escherichia coli*, *Staphylococcus aureus*, *Saccharomyces cerevisiae*, *Penicillium citrinum*, and *Mucor* spp. As a result, all kappa-carrageenan oligosaccharides were found to have inhibitory effect against the bacteria tested, with *Saccharomyces cerevisiae* showing the strongest inhibitory activity [49]. However, when carrageenan was modified as an antibacterial agent (oxidized kappa-carrageenan), the bacterial cell wall and cytoplasmic membrane were damaged, and Gram-positive and Gram-negative bacteria's growth was suppressed. The antibacterial activity of oxidized kappa-carrageenan was broad-spectrum, suggesting that it could be a good candidate for the creation of a novel antibacterial agent [49].

In the presence of several *Staphylococcus aureus* strains, kappa-carrageenan was added to a commercially available sinus rinse and applied directly to cultured human primary nasal epithelial cells at the air–liquid interface, as well as to human bronchial epithelial cells. In cells treated with kappa-carrageenan and Flo Sinus Care®, the synthesis of interleukin-6 was reduced when kappa-carrageenan was added to commercially available sinus rinses. In addition, the inclusion of kappa-carrageenan to both Flo CRS® and Flo Sinus Care® rinses lowered intracellular infection rates by an average of 2 % [189]. Yamashita and colleague investigated the antimicrobial effects of dietary polysaccharides on foodborne pathogenic bacteria, finding that carrageenan had the strongest inhibitory impact of all polysaccharides, considerably decreasing the development of almost all of the bacteria tested [72]. A growth-inhibition experiment with *Salmonella enteritidis* revealed that the carrageenan's inhibitory action was bacteriostatic. The elimination of sulphate residues from iota-carrageenan also reduces the bacteriostatic action, implying that the sulphate residue (s) in carrageenan play an important part in this effect [190]. In another study, the effects of iota-carrageenan on ocular *Chlamydia trachomatis* infection revealed a decrease in *Chlamydia trachomatis* infectivity in vitro. In vivo investigations revealed that iota-carrageenan reduced ocular pathology and greatly reduced the shedding of infectious elementary bodies, suggesting that it could be a promising drug for reducing ocular chlamydial infection transmission [191].

PVA, a carrageenan-based hydrogel crosslinked with silane, had high antibacterial activity against *Staphylococcus aureus* and only minor action against *E. coli*. The antibacterial activity could be due to carrageenan molecules interacting with bacterial cell membranes, and more specifically with the carrageenan structure, because carrageenan contains negatively charged SO_4^{2-} suspended groups, and *S. aureus* (Gram-

positive) has an outer covering of mucopeptide and peptidoglycan lipids, whereas *E. coli* has phospholipids and lipopolysaccharides, giving its surface a strongly negative charge. The change of the bacterial cell membrane, which governs bacterial development, is favored by these interaction sites on Gram-positive bacteria. The scientists also mention a second component that could inhibit bacterial growth: the binding of carrageenan and PVA to the bacterial strain's DNA, which would limit transcription and translation by DNA [192].

A recent study detailed carboxymethylating kappa-carrageenan with monochloroacetic acid to achieve various degrees of carboxymethyl-kappa-carrageenan substitution in order to improve the polysaccharide's characteristics. Carboxymethyl-kappa-carrageenan with degrees of substitution of 0.8, 1.0, and 1.2 inhibited the development of *Staphylococcus aureus*, *Bacillus cereus*, *E. coli*, and *Pseudomonas aeruginosa* in antibacterial experiments. The presence of sulphate could explain the antibacterial activity, and carboxylate groups could generate an acidic pH environment; carboxylate groups could also boost the polymer's nucleophilicity. Although the scientists suggested that further research be done on this topic, they did say that antioxidant, antibacterial, and biocompatibility testing could prove the polymer's prospective applications, such as wound dressings and scaffolds [74]. Antibacterial studies are rarer than antiviral studies, which may be due to the fact that the antibacterial action of carrageenan occurs when it is transformed by several processes, such as oxidation or carboxymethylation, allowing the antimicrobial effect to be fulfilled in only a few bacteria.

3.10. Other uses of carrageenan

Carrageenan is referred to as an emulsifier, stabilizer, colloid, or gum by food scientists. Carrageenan is used in many items that we now take for granted, including soymilk, chocolate and other flavored milks, dairy products, newborn formulae, and nutritional supplement beverages. Without this chemical, they could not be created, packed, or stored for long periods of time [193]. Carrageenans are utilized in emulsion stabilization, syneresis control, and bodying, binding, and dispersion because they gel, thicken, or suspend. Foods, particularly dairy applications, are the most common applications [194,195].

Carrageenan is the only gum that can suspend cocoa in chocolate milk at very low concentrations (about 300 ppm); no other gum comes close. The cocoa is said to be held in suspension by a very fine milk gel structure that is unnoticeable when pouring or drinking the milk [195,196]. Practical stabilization necessitates a significant difference between the concentrations at which cocoa settles and those at which visible gelation appears. This is accomplished by meticulous weed type and quality selection. Dessert gel compositions use iota-carrageenans, which have a texture comparable to that of gelatin gels [196]. They have a greater melting point than gelatin gels, making them more ideal for tropical conditions or situations where refrigeration is not available. This is partially compensated by the textural difference, as these gels do not "melt in the mouth" like gelatin [196]. However, iota-carrageenan gels have the advantage of maintaining their sensitive structure over time, whereas gelatin tends to toughen. This is critical for Europe's popular ready-to-eat desserts. Due to its "short," brittle gel structure, kappa-carrageenan or furcellaran is unsuitable for dessert gel applications. This can be mitigated by including locust bean galactomannan in the formulation, and kappa-locust bean or iota-kappa-locust bean blends are also available for this purpose [196]. It is required to utilize a locust bean gum that has been cleared by filtration to obtain sparkling-clear gels. Several of the major carrageenan manufacturers offer clarified gum for this purpose [196].

In addition, carrageenans are used in toothpastes as a "binder" to provide the paste the desired rheological qualities and a "sheen" cosmetic quality. Carrageenan must often be carefully tuned to obtain optimal performance in a given formulation since toothpastes contain chemicals that interact in complex and poorly understood ways. In the United States, sodium carboxymethylcellulose, a considerably cheaper gum, competes fiercely with carrageenan. Despite this, due to the higher quality and appearance carrageenan imparts to toothpastes, business has been kept and even recovered [196]. Carrageenan has maintained a strong position in this application outside of the United States, owing to its resistance to breakdown by enzymes that destroy cellulose gums, among other things. For hundreds of years, gelatinous extracts of the *Chondrus crispus* (Irish Moss) seaweed have been employed as food additives. Carrageenan is a gelatin substitute that is both vegetarian and vegan [197].

Carrageenan is often used as an emulsifier in food products and has the EU additive E407 or E407a when present as "processed eucheuma seaweed". Sugar and additional flavorings such as vanilla, cinnamon, brandy, or whisky are added after it has been heated in milk and filtered. The end result is a jelly that resembles pannacotta, tapioca, or blancmange [197]. A synergistic effect is achieved when iota-carrageenan is coupled with sodium stearoyl lactylate (SSL), allowing for stabilizing/emulsifying not possible with any other form of carrageenan (kappa/lambda) or other emulsifiers (mono and diglycerides, etc.). SSL in combination with iota-carrageenan can produce emulsions in both hot and cold temperatures utilizing vegetable or animal fat [198,199].

Carrageenan's use in the food business is frequently debated in terms of its safety. Carrageenan's safety has been thoroughly assessed by authorities throughout the world, including the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the Scientific Community on Food (SCF), and the International Food Additives Council (IFAC) [200]. All of these authorities concur that carrageenan is safe for use in foods, despite the findings of Tobacman and Tobacman et al. [201,202]. The acceptable daily intake (ADI) of 0–75 mg/kg bw determined for carrageenan by the Joint FAO/WHO and displayed by most effective [203].

4. Conclusions and future prospectives

The current paradigm of human disease therapy has identified a dependable source of bioactive druggable compounds from marine sources with varied therapeutic uses. Carrageenans have a wide range of applications, including not only biomedical but also food. Carrageenans have been shown in studies to have good bioactive properties capable of controlling viral infections like HPV, HSV, or SARS-CoV-2, bacterial infections, cancer suppression, anti-inflammatory activity, and even pathophysiological processes like hyperlipidemia. Carrageenans displayed highly safe, effective, and biocompatible, biodegradable, and non-toxic. In addition to their physicochemical features, these characteristics have led to an increase in their use and promote their future usefulness. However, various therapeutic applications are still in the experimental phase, and there are some limitations in the biomedical field, but the path has been outlined, and new research focused on the use of carrageenans, such as the main components, is currently booming. In recent years, >50 % of the FDA-approved medications have been extracted directly from marine sources or by synthesizing their chemical counterpart. It will be interesting to watch how carrageenans perform in clinical trials to confirm their efficacy and true potency in near future. The bioavailability, diversified chemical makeup, and non-reductant cytotoxicity of these marine-derived bioactive compounds continue to be important targets for separation and use. Carrageenans derived from seaweed act as possible lead pharmacophores in the treatment of numerous human ailments in this setting. The therapeutic application of such prospective agents will flourish in the future with a fresh hope to isolate and screen carrageenans from seaweed as innovative pharmacological agents against diverse human diseases. Furthermore, the development of such therapeutic candidates will add to the existing medication portfolio for future personalized and precision medicine.

CRediT authorship contribution statement

Biswajita Pradhan: Data curation, Conceptualization, Writing - original draft, Writing - review & editing, figure editing, Visualization,

Proof correction. **Jang-Seu Ki**: Supervision, Data curation, Writing - review and editing. Both authors have read and agreed to the published version of the manuscript.

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Informed consent

The corresponding author on behalf of coauthors agrees to accept the informed consent of compliance with ethical standard.

Declaration of competing interest

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

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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