Carbohydrate Polymers 105 (2014) 97–112

Contents lists available at ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

Review

Carrageenan: A natural seaweed polysaccharide and its applications

Vipul D. Prajapati*, Pankaj M. Maheriya, Girish K. Jani, Himanshu K. Solanki

Department of Pharmaceutics, S.S.R. College of Pharmacy, Saily-Silvassa Road, Saily, Silvassa, U.T. of Dadra and Nagar Haveli 396230, India

ARTICLE INFO

Article history:
Received 11 October 2013
Received in revised form
26 December 2013
Accepted 20 January 2014
Available online 30 January 2014

Keywords:
Carrageenan
Polysaccharide
Properties
Applications

ABSTRACT

Polysaccharides have been gaining interesting and valuable applications in the food and pharmaceutical fields. As they are derived from the natural source, they are easily available, non-toxic, cheap, biodegradable and biocompatible. Carrageenan is one among them, which fulfills the criteria of polysaccharide; it is a natural carbohydrate (polysaccharide) obtained from edible red seaweeds. The name Carrageenan is derived from the *Chondrus crispus* species of seaweed (Rhodophyceace) known as Carrageen Moss or Irish Moss, and Carraigin. A demand based on its application has been widely increasing in food and pharmaceutical sectors. Carrageenan has gained wide applications in experimental medicine, pharmaceutical formulations, cosmetics, and food industries. Through keen references of the reported literature on carrageenan, in this review, we have described about carrageenan, its properties, extraction and refining, and its food and pharmaceutical applications.

Contents

* Corresponding author at: Department of Pharmaceutics and Pharmaceutical Technology, SSR College of Pharmacy, Sayli-Silvassa Road, Sayli, Silvassa, U.T. of Dadra and Nagar Haveli 396 230, India. Tel.: +91 09824284159; fax: +91 0260 2681104.
E-mail address: vippra2000@yahoo.com (V.D. Prajapati).

0144-8617/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.carbpol.2014.01.067

1. Introduction

Natural polymers and their application in the pharmaceutical industry are covered by the presence of synthetic polymers. Natural polymers are preferred above the synthetic as they are inert, safe, non-toxic, biocompatible, biodegradable, low cost, eco-friendly and abundantly available in nature (Guo, Skinner, Harcum, & Barnum, 1998). Probably one of the materials taking more benefit from these advantages is the polysaccharide family, which has been gaining interesting and valuable applications in the biomedical and specifically in biopharmaceutical field. Polysaccharides can be obtained from a number of sources including seaweeds, plants, bacteria, fungi, insects, crustacea, animals and even humans, and can be structurally tuned through genetic engineering (Colquhoun et al., 2001; Coviello, Matricardi, Marianecci, & Alhaique, 2007; D'Ayala, Malinconico, & Laurienzo, 2008; Kost & Goldbart, 1997; Laurienzo, 2010). The polysaccharide term gathers collectively quite diverse large carbohydrates that can be composed of only one kind of repeating monosaccharide (termed homopolysaccharides or homoglycans; e.g. starch, cellulose) or formed by two or more different monomeric units (heteropolysaccharides or heteroglycans; e.g. agar, alginate, carrageenan). The conformation of the polysaccharide chains is markedly dependent not only on the pH and ionic strength of the medium, particularly in the case of the polyelectrolytes, but also on the temperature and the concentration of certain molecules. Polysaccharides are divided into two subtypes: anionic and cationic polysaccharides. Several anionic and cationic polysaccharides are widely available in nature and have gained keen interest in food and pharmaceutical field.

Carrageenan, a naturally occurring anionic sulfated linear polysaccharides extracted from certain red seaweed (Kirk & Othmer, 1992) of the Rhodophyceae family (Chen, Liao, & Dustan, 2002; Rees, 1969; Rochas, Rinaudo, & Landry, 1989; Snoeren, 1976; Stoloff, 1959), particularly from *chondrus cripus*, *euchema*, *gigartina stellate*, *iridaea*, *hypnea*, *solieria*, *agardhiella* and *sarconema* (Chen, McLachlan, Neish, & Shackloch, 1973; Cheney, Luiston, & Brailey, 1987; Chiovitti et al., 1988; McCandles, West, & Guiry, 1982, 1983; Mollet, Rahaoui, & Lemoine, 1988; Mollion, 1983; Murano, Toffanin, Cecere, Rizzo, & Knutsen, 1977; Parekh, Garg, Mehta, & Mehta, 1979; Parekh, Doshi, Rao, & Chauhan, 1988; Parekh, Rao, & Chauhan, 1988). The word "carrageenan" seems to originate from the inhabitants of the country of carraghen, on the south Irish coast where extracts from red algae for food and medicines were already used as early as 600 years ago. The major constituent of such algae is the so-called carrageenans, co-polysaccharides with the linear backbone built up by β-D-galactose and 3,6-anhydro-α-D-galactose with variable density in the sulfated group (Campo, Kawano, da Silva, & Carvalho, 2009). *Chondrus crispus*, *Gigartina stellata*, *Iridaea* spp., *Eucheuma* spp. and *Kappaphycus* spp. (Fig. 1) are the chief raw materials used for carrageenan extraction.

Ideally, each disaccharide in the chain contains a β-delta-galactopyranose (G-unit) with either α-delta-galactopyranose (D-unit) or 3,6-anhydrogalactose (DA-unit). Other carbohydrate residues commonly exist in carrageenan, such as xylose, glucose, and uronic acids. The disaccharide units are variably sulfated, resulting in a sulfate content of 22–38% by weight in commercial carrageenan (Van de Velde & De Ruiter, 2002). Other cations, such as ammonium, calcium, magnesium, potassium, and sodium, are also often present in the form of galactose esters (FAO, 2007; U.S. Pharmacopeia, 2010). Carrageenan is a good source of soluble fibre (Burtin, 2003). There are several different carrageenans with slightly varied chemical structures and properties (McHugh, 2003). The three most prevalent, and of highest commercial interest, polysaccharides of carrageenan are iota, kappa, and lambda carrageenan, serving different properties (FAO, 2007; U.S. Pharmacopeia, 2010; Van de Velde & De Ruiter, 2002). US Food and Drug Administration have "Generally Recognized as Safe" (GRAS) list of products for consumption and topical applications of carrageenan. Carrageenan is an extremely versatile ingredient suitable for use in food and nonfood industries (Van de Velde, Lourenco, Pinheiro, & Bakkerd, 2002). Carrageenan has no nutritional value, but have been widely used in the food industry (Heertje, 1993; Hood & Allen, 1977; Snoeren, 1976; Swaisgood, 1982; Van de Velde et al., 2002) and most recently used in the pharmaceutical industry as excipient in pill and tablets (Campo et al., 2009) and as a potent raw materials of hydrogels (Hoffman, 2002). In pharmaceutical applications (Takamatsu & Tosa, 1993; Van de Velde et al., 2002) and experimental medicine, carrageenan is often used for the testing of anti-inflammatory agents (Zacharopoulos & Phillips, 1997).

The biological activity of carrageenan as a natural occurring polysaccharide has been increasing widely for human applications and creates a strong position in the biomedical field. Due to their different chemical structure and physical properties this natural source can be used in the different applications, varying from tissue engineering to the preparation of drug vehicles for controlled release. This review article is prepared in order to focus on the present use and the diversified applications of carrageenan in pharmaceutical and food sectors.

2. Short summary on types, structure and properties of carrageenans

There are several different carrageenans with slightly varied chemical structures and properties (McHugh, 2003). Carrageenan formed by alternate units of D-galactose and 3,6-anhydro-galactose (3,6-AG) joined by α-1,3 and β-1,4-glycosidic linkage. According to the literature survey, carrageenan can be classified in 3 ways, based on the amount and position of sulphate groups, based on their family and based on its properties. Depending on the amount and position of the SO_3^- groups carrageenan are classified into λ(lambda), κ(kappa), ι(iota), υ(nu), μ(mu), θ(theta) and ξ(Ksi), all containing about 22–35% of sulphate groups (Stanley, 1987). Based on the family, Greer and Yaphe (1984) classified carrageenan mainly into three types as shown in the Table 1 (Anderson, Campbell, Harding, Rees, & Samuel, 1969; Glicksman, 1979; Hoefler, 2001; Hoffmann, Russell, & Gidley, 1996; Imeson, 2000; Moirano, 1977; Rees, 1969). The first family involves *kappa* (κ) family which contain a subclass like Kappa, iota, mu and nu carrageenan. The second class of family involves *lambda* carrageenan which, contain subclass like lambda, Xi and pi and the third class involves *beta* family containing subclass like beta and gamma carrageenan. Whereas Mollion, Moreau, and Christian (1986) introduced another family named *omega* family in which sulphate groups are on the C_6 of the 1,3-1, linked galactopyranosyl units. Alpha carrageenan was included as a subclass in beta family

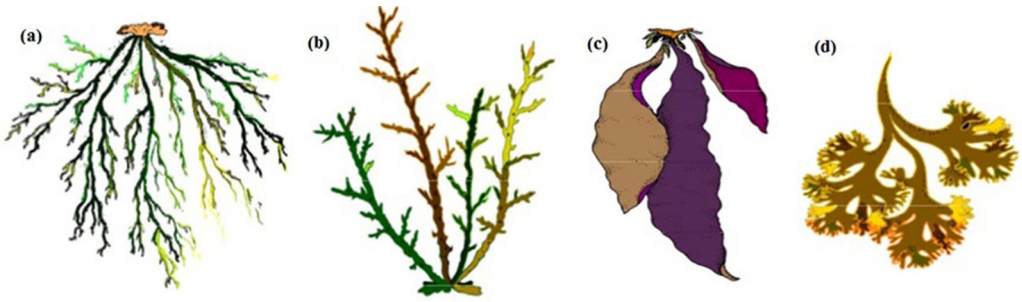


Fig. 1. Different types of seaweeds as a source of carrageenans: (a) *Eucheuma denticulatum* (spinosum) – iota carrageenan, (b) *Kappaphycus alvarezi* (cottonii) – kappa carrageenan, (c) *Gigartina radula* – kappa/lambda carrageenan, (d) *Chondrus crispus* – kappa/lambda carrageenan.

due to 1, 3-linked galactopyranosyl units are not sulphated at C_4 but sulphation was observed at C_2 of 3,6-anhydrogalactose groups. According to the properties of carrageenan, it can split into two groups like, *gelling* (Kappa, iota) and *thickening agent* (lambda).

In recent years, the development of new equipments and techniques has allowed the mechanism of gelation of natural polymers to be studied. In the case of κ-carrageenan, the transition from random coil to double helix has been studied by techniques including rheology (Chen, Liao, & Dustan, 2002; Nishinari & Takahashi, 2003; Mangione, Giacomazza, Bulone, Martorana, & Biario, 2003; Takemesa & Chiba, 2001), polarimetry (Mangione et al., 2003), light scattering (Mangione et al., 2003), photon transmission (Kara, Tamerler, Bermek, & Pekcan, 2003), spectrophotometry (MacArtain, Jaacquier, & Dawson, 2003), low amplitude X-ray scattering (Yuguchi, Thu Thuy, Urakawa, & Kajiwara, 2002; Yuguchi, Urakawa, & Kajiwara, 2003), differential scanning calorimetry (Nayouf, 2003) and laser dispersion during deformation (Takemesa & Chiba, 2001). All these techniques have confirmed the association of two linear κ-carrageenan strands to form a double helix during gelation, reaffirming the mechanism proposed by Rochas (1982).

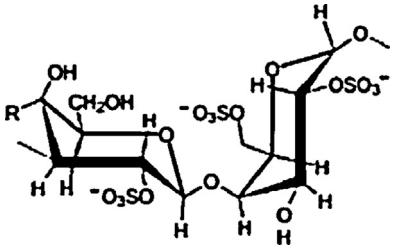
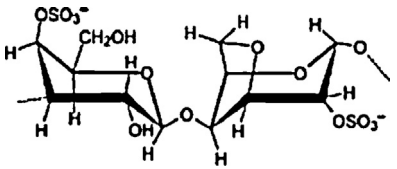
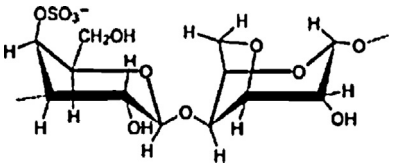
The complex fine structure of carrageenans is still an active field of research. Enzymic, immunological, and ^{13}C NMR techniques have proved to be powerful tools for these investigations (Greer & Yaphe, 1984).

3. Pharmacokinetic properties

3.1. Absorption, distribution, and excretion

Several pharmacokinetics studies regarding the oral administration of carrageenans have been conducted in rats (Arakawa, Ito, & Tejima,1988; Carey, 1958; Chen, Appleby, Weber, & Abraham, 1981; Coulston, Golberg, Abraham, Benitz, & Ford, 1975; Dewar & Maddy, 1970; Grasso, Sharratt, Carpanini, & Gangolli, 1973; Hawkins & Yaphe, 1965; Nicklin & Miller, 1984; Nicklin, Baker, & Miller, 1988; Pittman, Golberg, & Coulston, 1976; Tomarelli, Tucker, Bauman, Savini, & Weaber, 1974), rabbits (Udall, Harmatz, Vachino, Galdabini, & Walker, 1981), guinea-pigs (Engster & Abraham, 1976; Grasso et al., 1973) and Rhesus monkeys (Abraham, Golberg, & Coulston, 1972; Mankes & Abraham, 1975; Pittman et al., 1976). In groups of five rats that received 0.5% native carrageenan (iota-carrageenan from *Eucheuma spinosum*) or 5% degraded carrageenan for 10 days, faecal excretion and weight gain were similar between the two polymers (Dewar & Maddy, 1970), and native carrageenan (kappa/lambda from *C. crispus*), untreated or heat-sterilised in milk, was quantitatively excreted in the faeces of rats (Tomarelli et al., 1974). No carrageenan was found in the livers of rats fed 25% native carrageenan (kappa/lambda from *C. crispus* or *Iridaea crispata*) in the diet for 1 month (Chen et al., 1981), of rats fed diets containing 1% or 5% carrageenan (kappa from *Gigartina* spp., iota from *E. spinosum*) (Coulston et al., 1975), or of rats fed diets containing 5% *Chondrus crispus* carrageenan (kappa/lambda) for 13 weeks (Pittman et al., 1976). No carrageenan was detected in the small or large intestine of rats fed 5% native carrageenan (iota from *E. spinosum*) (Grasso et al., 1973). Nicklin and Miller (1984) stated that orally administered carrageenan (type unidentified) of high relative molecular mass could penetrate the mucosal barrier of adult animals via transport by macrophages in Peyer's patches. Carrageenan did not affect the number or distribution of these cells; however, when antigen was administered systematically to carrageenan-fed rats, the antigen-specific antibody response was suppressed. This result suggested that carrageenan interferes with antigen processing by macrophages and thus mollifies normal immune function. Analysis of liver samples from rats fed 25% native carrageenan (kappa/lambda from *C. crispus* or *C. iridaea*) in the diet for 1 month showed that only the second was stored in the liver in two animals, as determined by the presence of gamma metachromatic reaction sites in the Kupffer cells (Chen et al., 1981). The results of an additional early study suggested that the kappa/lambda form of carrageenan, prepared by a non-standard procedure from either *C. crispus* or *Gigartina stellata*, is not significantly absorbed from the intestine of Wistar rats (Carey, 1958). Two additional studies concerning the absorption of carrageenan have been reported (Arakawa, Ito, & Tejima, 1988; Nicklin et al., 1988); however, in neither report is the identity given of the species from which the carrageenan originated. Moreover, in the latter study the form of carrageenan that was used is unclear (International Food Additives Council, 1997). In the first study, rats quantitatively excreted the carrageenan (kappa form) in the faeces, and it had the same gel filtration distribution pattern as that of the administered material. In the latter study, in male PVG strain rats given radiolabelled carrageenan (iota form), there appeared to have been some uptake into the intestinal wall, Peyer's patches, mesenteric and caecal lymph nodes, and serum; however, the method used to radiolabel the carrageenan with tritium is questionable (International Food Additives Council, 1997). Feeding of guinea-pigs with native carrageenan (iota from *E. spinosum*) at 5% in the diet for 21–45 days resulted in the accumulation of 36–400 pg/g of caecal or colonic tissue. The carrageenan was contained in macrophages (Grasso et al., 1973). Food-grade carrageenan (kappa from *C. crispus*, lambda from *C. crispus*, iota from *E. spinosum*) administered to guinea-pigs as a 1% solution in drinking-water for 2 weeks was not retained in the caecum (Engster & Abraham, 1976). It was reported in an abstract that carrageenan (type and species of origin unidentified) was present in the liver, stomach, and small intestine of new-born rabbits given 40 mg native carrageenan orally. Carrageenan was not detected in the cardiac or portal blood 4 h after treatment (Udall et al., 1981). Rhesus monkeys given 1% native carrageenan (kappa/lambda from *C. crispus*) in drinking-water for 7–11 weeks, with a subsequent 11-week recovery period, showed no evidence of carrageenan storage (Abraham et al., 1972). In another study on rhesus monkeys, no tissue storage of carrageenan (kappa/lambda

Table 1
An overview on types, structure and properties of carrageenan.

S. No.	Properties	Type		
		Lambda	Iota	Kappa
	Chemical structure			
(1)	*Solubility*			
(a)	Hot (80 °C) water	Soluble	Soluble	Soluble
(b)	Cold (20 °C) water	All water soluble	Na^+ salt soluble, Ca^{2+} salt gives thixotropic sols	Na^+ salt soluble, limited swelling of K^+, Ca^{2+} salts
(c)	Hot (80 °C) milk	Soluble	Soluble	Soluble
(d)	Cold (20 °C) milk	Thickens	Insoluble	Insoluble
(e)	Cold milk	Increased thickening or gelling	Thickens or gels	Thickens or gels
(f)	50% sugar solutions	Soluble	Insoluble	Soluble hot
(g)	10% salt solutions	Soluble hot	Soluble hot	Insoluble
(2)	*Gelation*			
(a)	Effect of cations	Non-gelling	Strongest gels with Ca^{2+}	Strongest gels with K^+
(b)	Gel texture		Elastic	Brittle
(c)	Shear reversible gel		Yes	No
(d)	Syneresis		No	Yes
(e)	Hysteresis		5–10 °C	10–20 °C
(f)	Freeze-thaw stable	Yes	Yes	No
(g)	Synergy with locust bean gum	No	No	Yes
(h)	Synergy with konjac flour	No	No	Yes
(i)	Synergy with starch	No	Yes	No
(3)	*Salt tolerance*	Good	Good	Poor
(4)	*Stability in acid*	Hydrolysis	Hydrolysis of solution, Gels are stable	Accelerated by heat
(5)	*Protein reactivity*	Strong interaction increasing at acid pH	–	Specific reaction with kappa-casein

from *C. crispus*) was found when the monkeys were given 1% native carrageenan in the drinking-water for 10 weeks (Mankes & Abraham, 1975). Monkeys receiving daily doses of 500 mg/kg body weight native carrageenan (kappa/lambda from *C. crispus*) for 15 months excreted 12 μg/ml urine. The concentration was reported to be at the limit of detection of the method (Pittman et al., 1976). Monkeys receiving 50, 200, or 500 mg/kg body weight per day native carrageenan (kappa/lambda from *C. crispus*) orally for 7.5 years showed no evidence of storage in the liver or other organs.

3.2. Degradation of carrageenan in the gastrointestinal tract

Since food-grade carrageenan does not have the same effects as degraded carrageenan, it is either not degraded, not degraded to the same molecular mass, or not degraded in the same way. It would appear that carrageenan is only partially degraded, that most of the degradation takes place in the stomach, and that this limited degradation has no effect on the wall of the stomach, where the pH is very low and acid hydrolysis undoubtedly occurs. When a kappa/lambda mixture (from an unidentified species) was incubated in simulated gastric juice at pH 1.2 and 37 °C, breakdown of glycosidic linkages was less than 0.1% after 3 h (Stancioff & Renn, 1975). Breakdown of kappa-carrageenan (unidentified species) was about 15 times greater than that of the iota form; however, the conditions of hydrolysis (6 h at pH 1.0) were more drastic than those that occur normally in the stomach, and the pH would be expected to be considerably higher in a full stomach (Ekstrom & Kuivinen, 1983). There is no evidence that carrageenan is degraded in the lower gut. Incubation of a carrageenan solution with the caecal contents of rats for several hours at 37 °C did not alter its viscosity, suggesting that the microbial flora of the rat gut cannot break down carrageenan (Grasso et al., 1973). Degradation of carrageenan by a large number of intestinal bacteria in vitro has been reported, but the carrageenan used (of an unidentified form from an unidentified species) contained 20% reducing sugar, which would give a positive result in the test method. Among the bacteria claimed to break down carrageenan were *Klebsiella pneumonia* and *Escherichia coli*; however, both these species can be grown on the carrageenan gel (Epifanio, Veroy, Uyenco, Cajipe, & Laserna, 1981). If these bacteria had been able to degrade carrageenan, they would have liquefied the gel medium on which they were grown (Ochuba & Von Riesen, 1980). Breakdown of food-grade carrageenan (kappa, lambda-, and kappa/lambda-carrageenan from *C. crispus* and of iota-carrageenan from *E. spinosum*) isolated from the faeces of guinea-pigs, rats, and monkeys have been reported, but the site of breakdown was not determined. The molecular mass observed (40–50 kDa) was not as low as that of degraded carrageenan (10–20 kDa) (Pittman et al., 1976). In another study the degradation of food-grade kappa- and iota-carrageenan was studied under physiologically realistic conditions in an artificial stomach. Kappa-carrageenan was not hydrolysed at pH 8 or under the severe conditions of pH 1.2 for 6 h, and the relative molecular mass remained at >200 kDa, with no more than 20% having a molecular mass of <100 kDa. It was confirmed that iota-carrageenan is more resistant to degradation than the kappa form. The originating species were *E. cottonii* for kappa-carrageenan and *E. spinosum* for iota-carrageenan. The greater stability of iota-carrageenan to degradation may reflect the conformation of the macromolecule in the medium used (Ekstrom & Kuivinen, 1983; Ekstrom, 1985; International Food Additives Council, 1997). No evidence of fermentation was seen after incubation of rat cecal contents with iota-carrageenan from E. spinosum (Grasso et al., 1973). A study in female Wistar rats fed carrageenan (type and origin unidentified) as an inert polysaccharide does not provide quantitative measures of its degradability (Elsenhans, Blume, & Caspary, 1981). Feeding of 3-week-old male Sprague-Dawley rats for 4 weeks with a diet containing 5% iota-carrageenan originating from *E. spinosum* (International Food Additives Council, 1997) resulted in a significant reduction in the bacterial population of the caecum, as assessed by bacterial counts and the activity of various caecal microbial enzymes; however, the weights of the caecal contents and the caecal wall were increased (Mallett, Wise, & Rowland, 1984). In a study of 154 bacterial species commonly found in the human colon, carrageenan (origin and type unidentified) was one of the polysaccharides most resistant to fermentation (Salyers, West, Vercellotti, & Wilkins, 1977).

4. Extraction and refining

Specific details of extraction processes are closely guarded as trade secrets by the several manufacturers of carrageenans, but broadly these follow a similar pattern. Seaweeds, are usually received to a processing location from the harvesting location. The shipment may be sampled and the sample subjected to a test extraction to evaluate the quality of the extractive. Other need quality factors such as contents of moisture, sand and salt, and non-carrageenophytes are evaluated at this stage.

4.1. Kappa-carrageenan extraction

The different step in the processing of kappa-carragenan is more or less similar to that of agar extraction. Species of *eucheuma, hypnea*, *chondrus* and *furcellaria* can be used as a raw material. The processing of kappa-carrageenan is given in Fig. 2 respectively (Ji Ming Hou, 1990). The sun bleached dry seaweed is treated with 5–10% of NaOH at 80–90 °C for a particular time depending upon the texture of the alga. Then, the seaweed is boiled and the extract is collected in a evaporator to reduce the volume of gel solution. In the case of seaweeds such as *furcellaria* and *eucheuma*, KCl precipitation process is applied. In this case, the filtrate after hot extraction is evaporated to reduce the volume of filtrate and then the filtrate is extruded through the spinnerets into cold 1–1.5% KCl solution. The gelled threads are washed again within the KCl solution. Then it is dehydrated by pressing method, dried and milled to get kappa-carrageenan powder.

4.2. Lambda-carrageenan extraction

Lambda-carrageenan is obtained from different species from the genera *Gigartina* and *Chondrus* (trade name “Irish Moss”) (Van de Velde & De Ruiter, 2002). Lambda-carrageenan exhibits no gelling property and is more hydrophilic. Thus it could be dried by using a drum dryer or alcohol precipitation process. The drum dryer method degrades the product. So, generally alcohol precipitation method is practiced. Propyl alcohol or ethyl alcohol is used as a dehydrating agent. The extraction process regarding lambda-carrageenan is shown in Fig. 2.

4.3. Iota-carrageenan extraction

Iota carrageenan is more hydrophilic than kappa-carrageenan and difficult to produce by the freeze-thaw or gel process. So, the alcoholic precipitation technique is used, similar to that of lambda-carrageenan. After hot extraction, the pH of the alkaline liquor is adjusted and subjected to coarse and fine filtration. The filtrate is then concentrated with double effect evaporator to reduce the volume. The extraction process regarding iota-carrageenan is shown in Fig. 2.

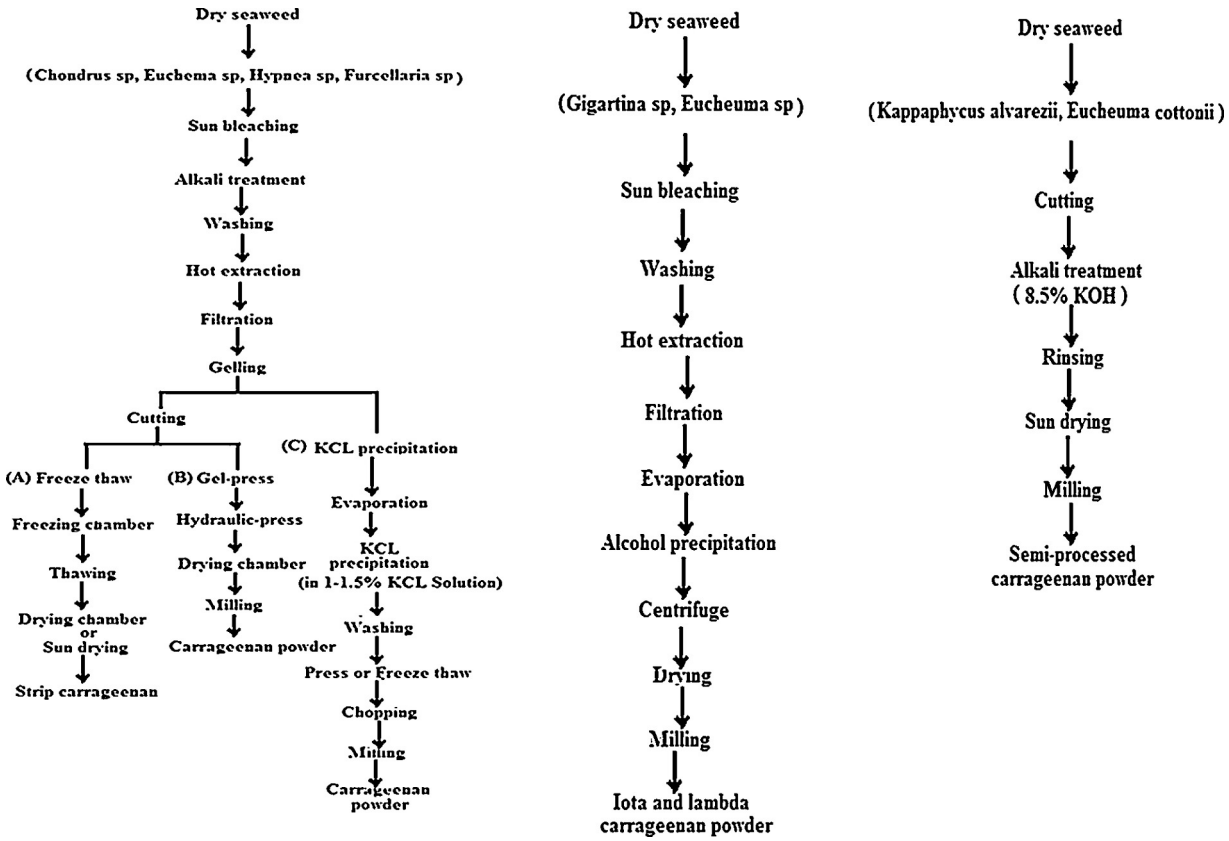


Fig. 2. Flow chart of extraction process for kappa, lambda and iota carrageenan.

4.4. Semi processed/semi refined carrageenan

The semiprocessed carrageenan is produced by alkali treatment of *Eucheuma cottonii* and drying in the farm itself. A basket of seaweeds is immersed and cooked in hot aqueous KOH at 100 °C and then soaked in fresh water to extract the alkali. The procedure is dried and ground to powder. By this process, the quantity of water required to produce the final product is minimized, thereby reducing the cost of the product. This product usually can be substituted for extracting carrageenan, where a little cloudiness due to the small amount of cellulose present does not interfere. The processing technology for semi-processed/crude carrageenan given by Gopakumar (1997) and Kaliaperumal (1984) is shown in Fig. 3 respectively.

5. Biological activity of carrageenan

Sulphated polysaccharides from marine algae can have diverse biological and activities including immunomodulatory, anticoagulant, antithrombotic, antiviral and antitumor effects.

5.1. Carrageenan-induced paw oedema

Carrageenan-induced rat paw oedema is a widely used test to determine anti-inflammatory activity and constitutes a simple and routine animal model for evaluation of pain at the site of inflammation without any injury or damage to the inflamed paw (Henriques et al., 1987; Jain, Patil, Singh, & Kulkarni, 2001; Paschapur, Patil, Kumar, & Patil, 2009; Petersson, Wiberg, Lundeberg, & Uvnas-Moberg, 2001; Sini et al., 2010; Sugishita, Amagaya, & Ogihara, 1981). Mouse paw oedema has been increasingly used to test new anti-inflammatory drugs as well as to study the mechanisms involved in inflammation. In the literature, there are about 400 papers reporting the use of mouse paw oedema (Posadas et al., 2004). A freshly prepared solution of 1–3% carrageenan in saline as an intraplantar injection in doses of 50–150 μl is commonly used (Botting, 2000; Estakhr, Sanchooli, Najafi, & Javdan, 2011; Guay, Bateman, Gordon, Mancini, & Riendeau, 2004; Handy & Moore, 1998; Jain et al., 2001; Nantel et al., 1999; Naude, Cromarty, & Van Rensburg, 2010; Posadas et al., 2004; Rosen, Lundeberg, Bytner, & Nylander, 2000; Salvemini et al., 1996); higher concentrations have been used for the modelling of specific pathophysiological conditions (Porto, Vasconcelos, Silva-Junior, & Souza Andrade, 2010; Radhakrishnan, Bement, Skyba, & Sluka, 2004; Silva et al., 2010).

There are number of mediators involved in inflammation. Histamine, serotonin and bradykinin are the first detectable mediators in the early phase of carrageenan-induced inflammation; prostaglandins (PGs) are involved in the increased vascular permeability and are detectable in the late phase of inflammation. Local and/or systemic inflammation is associated with enhanced levels of the pro-inflammatory cytokines TNF-α, IL-1, and IL-6 (Cuzzocrea et al., 1999). The initial phase of oedema, which is not inhibited by non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin or aspirin, has been attributed to the release of histamine, 5-hydroxytryptamine (5-HT) and bradykinin. The second accelerating phase of swelling has not only been correlated with the elevated production of prostaglandins, but more recently has been attributed to the induction of inducible cyclooxygenase (COX-2) in the hind paw (Nantel et al., 1999). It can be blocked by the NSAIDs (Handy & Moore, 1998). Local neutrophil infiltration and activation also contribute to this inflammatory response by producing, among other mediators, oxygen-derived free radicals such as superoxide anion (O_2^-) and hydroxyl radicals (Posadas et al., 2004; Salvemini et al., 1996).

Another important mediator in acute inflammation is nitric oxide (NO) which is produced in pathological conditions by three

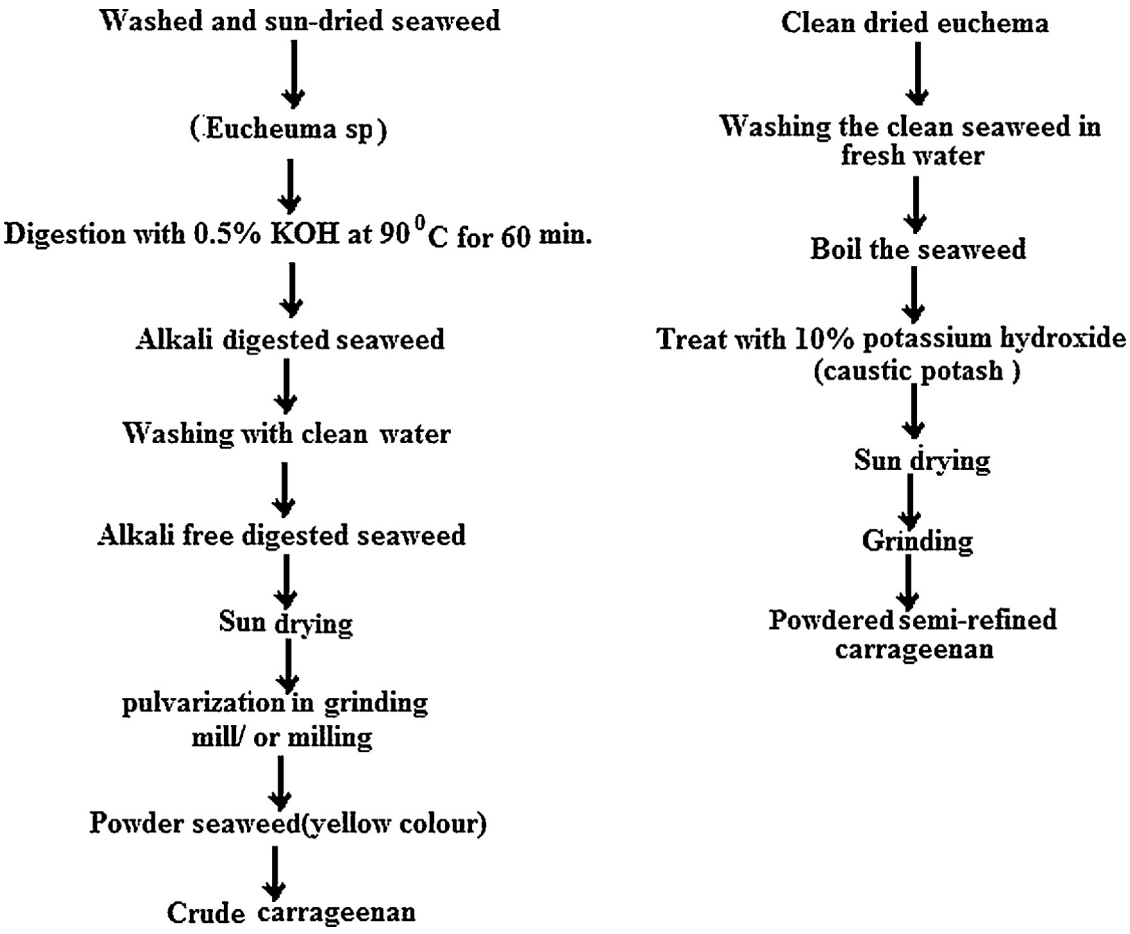


Fig. 3. Flow chart of extraction process for semi-refined carrageenan.

distinct isoforms of nitric oxide synthase (NOS): endothelial NOS (eNOS), neuronal NOS (nNOS) and inducible NOS (iNOS). Carrageenan causes the production and release of NO at the injured site. Perfusion of a non-selective NOS inhibitor, NG monomethyl-L-arginine acetate (L-NMMA), which exhibits some selectivity for inhibition of neuronal and endothelial isoforms, suppressed the release of NO following carrageenan injection in this study. Perfusion of an inducible NOS inhibitor, aminoguanidine hemisulfate (AG), suppressed the release of NO 2.5–8 h after carrageenan injection. Neurectomy completely suppressed NO release for up to 3 h and partially suppressed NO release 4.5–8 h after carrageenan injection. These findings indicate that nNOS contributes to the NO production in both the early and late phase, and that iNOS only contributes to the late phase. The production and release of NO by these NOSs are thought to contribute to tissue injury- and inflammation-induced oedema and hyperalgesia (Handy & Moore, 1998; Omote et al., 2001).

5.2. Intestinal inflammation

Watt and Marcus (1971) described a simple method for inducing the formation of ulcers in the large intestine of the guinea pig requiring only the addition of a degraded carrageenan to the drinking water. The method may be used as an experimental model for the study of various aspects of the pathology of ulcerative lesions in this part of the alimentary tract. Freshly prepared, degraded carrageenan was added to the drinking water for guinea pigs to a concentration of 5%. No greater than 2 g/kg body weight of degraded carrageenan in the drinking fluid for 20–45 days results in ulcerative lesions associated with clinical and pathological changes which in certain respects closely resemble ulcerative colitis in man. Clinically there was loss of weight, loose stools, and occult or visible blood in the faeces. Pathologically, ulceration was found in all parts of the large bowel, extensive lesions occurring in the rectum. Microscopically, the similarities include focal 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 mainly the mucosa, as well as ulcerations in various stages of progression and healing. The ulcerative lesions, however, appear to begin in the caecum and extend distally towards the rectum.

5.3. Anticoagulant and antithrombotic activity

Many reports exist of anti-coagulant activity and inhibited platelet aggregation of carrageenan (Hawkins & Leonard, 1963; Kindness, Williamson, & Long, 1979). Among the carrageenan types, λ carrageenan (primarily from *C. crispus*) has approximately twice the activity of unfractioned carrageenan and four times the activity from κ-carrageenan (*Eucheuma cottoni* and *E. spinosum*). The most active carrageenan has approximately one-fifteenth the activity of heparin but the sulphated galactan from *Grateloupa indica* collected from Indian waters, exhibited anti-coagulant activity as potent as heparin (Sen et al., 1994). The principal basis of the anti-coagulant activity of carrageenan appeared to be an anti-thrombotic property. λ-Carrageenan showed greater anti-thrombotic activity than κ-carrageenan, probably due to its higher sulphate content, whereas the activity of the unfractionated material remained between the two. Similar results were obtained

with λ-carrageenan of *Phyllophora brodiaei* which gave the highest blood anti-coagulant activity (Sen et al., 1994). λ-Carrageenan consistently prolonged the clotting time and was more toxic than κ-carrageenan. The difference in sulphate content between the two carrageenans did not correspond directly to differences in anticoagulation action and toxicity (Shanmugam & Mody, 2000). As stated above, the mechanism underlying the anticoagulant activity of carrageenan involves thrombin inhibition. Amidolytic studies initially indicated that the anti-thrombin activity might be mediated via AT-III (anti-thrombin-III), the major mechanism by which heparin acts. In these studies, carrageenans appeared to inhibit amidolysis of thrombin directly and via AT-III; however, only AT-III potentiated X_a amidolysis was observed (Kindness et al., 1979). These interactions may be influenced by certain critical qualities of the polyanionic polymers, i.e., sulphation, size, pattern of ionic substitution and polymer rigidity (Kindness et al., 1979). However subsequent studies using AT-III-depleted plasma showed residual anti-thrombin activity in the presence of carrageenans. λ-Carrageenan has been shown to potentiate the inactivation of thrombin by 'anti-thrombin BM'. These observations would therefore imply that there is either anti-thrombin potentiation via heparin co-factor II (HC-II) and/or a direct anti-thrombin effect (Kindness, Long, & Williamson, 1980; Kindness, Williamson, & Long, 1980; Wunderwald, Schrenk, & Port, 1979).

5.4. Antiviral activity

New research on the based properties shows that applications of carrageenan gels from *C. crispus* have shown a selective inhibitor of several enveloped viruses and block the transmission of the HIV virus including such human pathogens as human immunodeficiency virus, herpes simplex virus (HSV), human cytomegalovirus, human rhinoviruses (Caceres, Carlucci, Damonte, Matsuhiro, & Zuniga, 2000; Carlucci, Scolaro, & Damonte, 1999; Girond, Crance, Van Cuyck-Gandre, Renaudet, & Deloince, 1991; Marchetti et al., 1995; Stiles, Guptill-Yoran, Moore, & Pogranichniy, 2008; Zacharopoulos & Phillips, 1997) as well as other STD viruses such as gonorrhoea, genital warts (Caceres et al., 2000; Carlucci et al., 1997; Luescher-Mattli, 2003; Shanmugam & Mody, 2000; Witvrouw & DeClercq, 1997). In addition, carrageenans are good candidates for use as vaginal microbicides because they do not exhibit significant levels of cytotoxicity or anti-coagulant activity (Buck et al., 2006; Zeitlin, Whaley, Hegarty, Moench, & Cone, 1997). Results of sexual lubricant gels raised the possibility that use of such lubricant products, or condoms lubricated with carrageenan-based gels, could block the sexual transmission of HPV (human papillomavirus) types that can cause cervical cancer and genital warts. However, carrageenan inhibition of herpes simplex virus and HIV-1 infectivity were demonstrated as about a thousand-fold higher than the IC50s observed for genital HPVs in vitro (Luescher-Mattli, 2003; Witvrouw & DeClercq, 1997). A carrageenan-based vaginal microbicide called Carraguard has been shown to block HIV and other sexually transmitted diseases in vitro. Massive clinical trials by the Population Council Centre began in two severely affected African countries: Botswana and South Africa in 2002. Carraguard entered phase III clinical trials involving 6000 non-pregnant, HIV-negative women in South Africa and Botswana in 2003 (Spieler, 2002).

Carrageenan acts primarily by preventing the binding or the entry of virions into cells (Buck et al., 2006; Grassauer et al., 2008). This finding is consistent with the fact that carrageenan resembles heparan sulfate, an HPV cell-attachment factor. Carrageenan is also active in vitro and in murine model systems against other viruses, including herpes simplex viruses and some strains of HIV-1 (Baba, Snoeck, Pauwels, & de Clercq, 1988; Gonzalez, Alarcon, & Carrasco, 1987; Lynch et al., 1994; Witvrouw & DeClercq, 1997; Zeitlin et al., 1997). Carlucci et al. (1997) and Carlucci, Scolaro, Noseda, Cerezo, and Da-monte (2004) reported that the λ-carrageenan and partially cyclised μ-/ι-carrageenan from *Gigartina skottsbergii* showed potent antiviral effect against different strains of herpes simplex virus (HSV) type 1 and type 2. Similar results were reported by Zacharopoulos and Phillips (1997) who described the ability of carrageenan solutions (lambda, kappa, or iota) to prevent HSV-2 infection (De SF-Tischer et al., 2006). Leibbrandt et al. (2010) tested a commercially available nasal spray containing iota-carrageenan in an influenza A mouse infection model. Eccles et al. (2010) investigated the efficacy and safety of an iota-carrageenan nasal spray in patients with common cold symptoms.

5.5. Anti-tumour and immunomodulatory activities

Several studies have reported that carrageenans have antiproliferative activity in cancer cell lines in vitro, as well as inhibitory activity of tumour growth in mice (Yuan, Song, Li, Li, & Dai, 2004, 2006; Zhou, Sheng, Yao, & Wang, 2006; Zhou et al., 2004). In addition, they have antimetastatic activity by blocking the interactions between cancer cells and the basement membrane, inhibit tumour cell proliferation and tumour cell adhesion to various substrates, but their exact mechanisms of action are not yet completely understood. Yamamoto, Maruyama, Takahashi, and Komiyama (1986) reported that the oral administration of several seaweeds can cause a significant decrease in the incidence of carcinogenesis in vivo. Hagiwara et al. (2001) investigated the modifying effects of carrageenan on colonic carcinogenesis in male rats. No treated related changes in clinical signs and body weights were found. Histopathological examination did not demonstrate any enhancement by carrageenan carcinogenesis, carrageenan does not possess any promoting activity at the highest dietary level of 5.0% for colorectal carcinogenesis under the present experimental conditions.

5.6. Other biological activities

The antioxidant activity of all carrageenans has been studied. λ-Carrageenan exhibited the highest antioxidant and free radical scavenging activity. Rocha de Souza et al. (2007) demonstrated a positive correlation between sulfate content and antioxidant activity. The present findings provide a basis for further experiments on the identification and characterization of specific compounds with relatively high antioxidant activities. Carrageenan from red marine algae is known to be a potent inflammatory agent in rodents and primes mice leucocytes to produce tumour necrosis factor-α (TNF-α) in response to bacterial lipopolysaccharide. Moreover, some types of carrageenans induce potent macrophage activation, while some carrageenans appear to inhibit macrophage functions (Wijesekara, Pangestuti, & Kim, 2011). The feeding of Fischer 344 rats on diets containing 15% kappa/lambda-carrageenan from *G. radula* resulted in a cholesterol-lowering effect (Reddy, Watanabe, & Sheinfil, 1980). Similar effects of the inclusion of carrageenan in the diet may result in reduced blood cholesterol and lipid levels in human subjects (Panlasigui, Baello, Dimatangal, & Dumelod, 2003).

6. Toxicity of carrageenan

It was found that the toxicity of carrageenans depended on the molecular weight and not the sulfate content. Carrageenan can be as low molecular weight, "degraded" carrageenan, or high molecular weight, or "undegraded" carrageenan. US Adopted Names Council (USAN) defines "degraded carrageenan" as "poligeenan" having an average molecular weight of 10,000–20,000 Da, obtained when processed by acid hydrolysis instead of alkali. Poligeenan has no utility in food. Studies have shown that unlike carrageenan, poligeenan has been associated with inflammatory

and proliferative lesions of the GIT, including tumours, at high doses in experimental animals (Oohashi, Ishioka, Wakabayashi, & Kuwabara, 1981; Wakabayashi, Inagaki, Fujimoto, & Fukuda, 1978).

International agency for research on cancer (IARC) has also provided evidence on poligeenan carcinogenicity in lab animals, and classifies degraded carrageenan as group 2B "Possibility carcinogenic to humans" (IARC, 1983). Degraded carrageenan has been widely used in immune system experiments to induce inflammation in immune system experiments (Benford et al., 2008). In 1969, degraded carrageenan was shown to induce cecal and colonic ulceration in guinea pigs (Marcus, & Watts, 1969), the first report of such potential adverse effects (Watson, 2008). Since then, many studies have been published showing that exposure to degraded carrageenan causes bleeding and ulceration of the colon in some laboratory animals (EC SCF, 2003). As a result of these findings, the FDA proposed regulations that commercial-grade carrageenan could not have a molecular weight under 100 kDa (Watson, 2008), though these regulations were never amended and the proposal was withdrawn in 1979 (Tobacman, 2001). Still, the presence of degraded carrageenan in commercially available carrageenan decreased from approximately 25% in 1983 (Benford et al., 2008) to undetectable levels by 2001 (EC SCF, 2003). The molecular weight average of commercially available carrageenan ranges from 453 to 652 kDa. In 2001, Tobacman from the University of Iowa published a review of these 45 studies and concluded that exposure to degraded and/or undegraded carrageenan was associated with intestinal lesions such as ulcerations and neoplasms in several different animal models, including ferret, guinea pig, monkey, mouse, rat, and rabbit (Tobacman, 2001). Animal studies published since 1997 that were not included in Tobacman's review have shown conflicting results. While some studies have verified that carrageenan is associated with induction or promotion of gastrointestinal tract inflammation, ulcerations and/or neoplasms in animal models (Benard et al., 2010) and human tissues (Borthakur, Bhattacharyya, Dudeja, & Tobacman, 2007), other studies have contradicted this finding, e.g., in vivo (Weiner, Nuber, Blakemore, Harriman, & Cohen, 2007) and in vitro (Tobacman & Walters, 2001).

In considering these issues, the Committee took into consideration the recent review of carrageenan by JECFA (2002). Studies on tumour promotion, aberrant crypt cell formation and cell proliferation in the rat colon have been extensively summarized in the recent review by JECFA (2002). The other paper of Tobacman (2001) considered in this review proposes a hypothesis that the increasing incidence of breast cancer in the USA during the twentieth century may be related to consumption of carrageenan. Based on studies which included a three-generation study of reproductive toxicity, short and long-term studies of toxicity in rats at dietary concentrations up to 5%, and short and long-term studies in hamsters, guinea pigs, and monkeys, they concluded that carrageenan may be used safely in the diet and recommended an Acceptable Daily Intake (ADI) of "not specified," which is the highest possible classification from a toxicological point of view. This term is used to refer to a food substance of very low toxicity, which on the basis of the available data (chemical, biochemical, toxicological, and other), the total dietary intake of the substance arising from its use at the levels necessary to achieve the desired effects, and from its acceptable background levels in food, does not in the opinion of the Committee represent a hazard to health. This recommendation was significant since the review was based on extensive safety studies.

The toxicology of carrageenan has been reviewed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the group acceptable daily intake (ADI) for carrageenan and processed *Eucheuma* seaweed was categorized as "not specified" in 2001 (Benford, 2001). JECFA has since maintained the "not specified" ADI classification at the 64th meeting in 2008 they stressed that this classification applied to food additive uses other than infant formula (Benford et al., 2008). JECFA advised that carrageenan should not be used in infant formula intended for children under 13 months of age based on a concern over the narrow margin of exposure between the level of carrageenan consumed through infant formula and the lowest doses reported to cause inflammatory responses in laboratory rats and mice (Benford et al., 2008). Similarly, the European Commission Scientific Committee on Food (now the European Food Safety Authority) concluded in 2003 that there is no evidence of adverse effects in humans from exposure to food-grade carrageenan, yet advised against use of carrageenan in infant formula due to a lack of information regarding possible absorption of carrageenan in the immature gut and effects of carrageenan on the immature immune system (EC SCF, 2003). While the committee noted there was insufficient evidence for lowering the ADI or otherwise limiting carrageenan intake levels, they did suggest a limit be specified that no more than 5% of food-grade carrageenan should fall below 50 kDa (EC SCF, 2003). Conversely, the US FDA does permit carrageenan in infant formula, because it concluded that the health benefit (preventing fat separation and therefore provides uniform nutrition) outweighs the potential risks (Watson, 2008). Authorities worldwide such as JECFA, Scientific Community on Food (SCF), and International Food Additives Council (IFAC) have extensively evaluated the safety of carrageenan. In contrast to the findings presented by Tobacman, all of these authorities agree that carrageenan is safe for use in foods. In addition, the positive effects of carrageenan on human health are begun to explore.

7. Applications of carrageenan

Carrageenan is one of the most abundant polysaccharides in nature that can be used in prepared foods and cosmetics as a gelling, stabilizing and thickening agent due to its biocompatibility, biodegradability, high capacity of water retention and mechanical strength of its gels.

7.1. Application in food and dairy industries

For simplicity, the food applications (Fig. 4) of carrageenan gum have been divided into dairy based and water based. Carrageenan is used as a food additive in the production of a wide range of processed foods, including dairy products, water-based foods, meat products, beverages, condiments, infant formula, and pet food (McHugh, 2003). Carrageenan can function as a bulking agent, carrier, emulsifier, gelling agent, glazing agent, humectant, stabilizer, or thickener (Codex Alimentarius Commission, 2010). Carrageenan is added to processed foods because it can bind water, promote gel formation, thicken, stabilize, and improve palatability and appearance through interaction with other substances in the food (e.g., proteins, sodium or calcium phosphates, starch, galactomannan, carboxylmethyl-cellulose) (Piculell, 2006). Table 2 provides a detailed list of different food products in which carrageenan is commonly found, and the purpose for its addition to those products. In case of dairy products carrageenan improves texture, thickness, and solubility (McHugh, 2003). Carrageenan can successfully prevent separation and maintain texture in dairy products when added in small amounts around 0.3% in milk gels (such as custards, flans, and creamy fillings), whipped cream, yoghourt, and milkshakes, and 0.03% in frozen desserts and liquid milk products (Piculell, 2006).

Carrageenan can be used as a fat substitute in processed meats, as it improves moisture retention and restores tenderness in low-fat processed meats like hamburgers (McHugh, 2003). For example, recent research showed that ground pork patties with

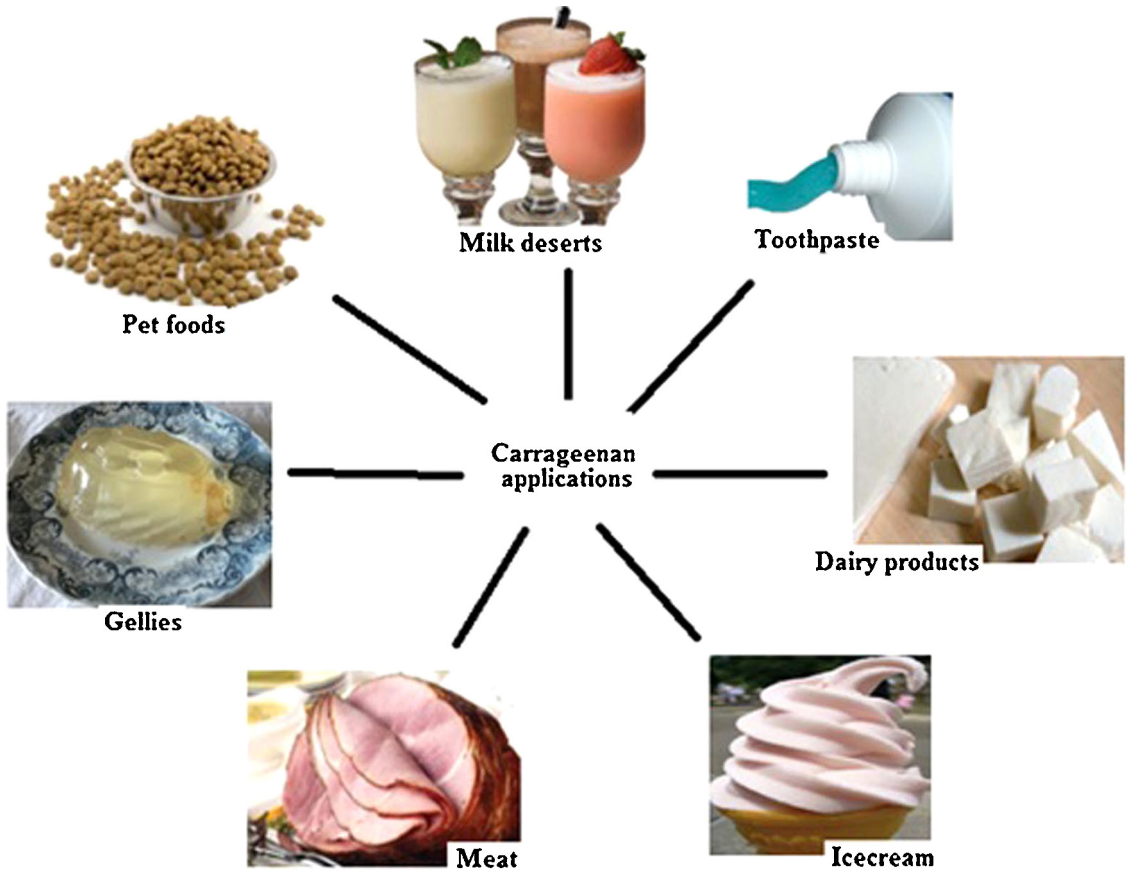


Fig. 4. Illustrative image for application of carrageenan in food industries.

less than 10% total fat and carrageenan at maximum concentrations of 0.75% actually had higher moisture retention after cooking and a similar texture compared to pork patties containing 20% fat and no carrageenan (Kumar & Sharma, 2003). While carrageenan has been used as a fat replacer in processed meat since at least the early 1990s (Ramirez, 1991), food science researchers are still exploring the use and no information was found to indicate exactly how common this use is today.

One newly explored the use of carrageenan in the food industry is as a protective coating on fresh-cut packaged fruits. Carrageenan

Table 2
Various applications of carrageenan in food and dairy products.

Product	Purpose for addition/action in product	References
Cottage cheese	Prevent separation of whey	McHugh (2003)
Ice cream	Prevent separation caused by addition of gums meant to control texture and ice crystal growth, stabilizer and emulsifier	McHugh (2003)
Coffee creamers, evaporated and condensed milk	Prevent separation of fat	McHugh (2003)
Whipping cream	Maintain "lightness"	McHugh (2003)
Low calorie jellies	Replace pectin and sugar with carrageenan, to help set	McHugh (2003)
Drink mixes (powdered lemonade, fruit punch, etc.)	Provide texture when reconstituted in cold water	McHugh (2003)
Low-fat (i.e. low-oil) salad dressings	Suspend herbs and provide thicker texture	McHugh (2003)
Low-fat (i.e. low-oil) mayonnaise	Thicken and stabilize	McHugh (2003)
Pre-cooked poultry products	Injected as brine to improve texture, tenderness and maintain juiciness	McHugh (2003)
Canned pet food	Re-bind meat, create gravy/jelly around meat pieces	McHugh (2003)
Beer	Clarification through precipitating with proteins	McHugh (2003)
Flans, custards, cream fillings	Stabilizer, gelling agent	Piculell (2006)
Cheese	Stabilizer, moisture binding property, improvement of sliceability	Piculell (2006)
Fish	Added prior to processing for water retention	Piculell (2006)
Flavoured milk (i.e. chocolate milk) and milkshakes	Holds cocoa or other flavouring in suspension	McHugh (2003) and Saha and Bhattacharya (2010)
Sorbet	Provide smooth texture (gelling agent)	McHugh (2003) and Piculell (2006)
Low-fat/low-sodium processed meat and poultry	Improves juiciness and tenderness; behaves like fat and retains moisture through cooking; helps bind meat product during cooking	McHugh (2003) and http://applegatefarms.com/
Fresh-cut packaged fruits	Slow/control discoloration, maintain texture	Plotto et al. (2006, 2010) and Bico et al. (2009)

Table 3
Reported carrageenan brands and grades available in market.

S. No.	Brand name	Properties/uses	Manufacturer
1	Danagel™		FMC BioPolymer
	Danagel® AF 9254[a]	Air freshener gel	FMC BioPolymer
	Danagel® PF 3250[a]	Foodstuff application	FMC BioPolymer
	Danagel® CCV[a]	Foodstuff application	FMC BioPolymer
2	Gelcarin®		FMC BioPolymer
	Gelcarin® GP-379NF[a]	Gelling and viscosifying agent	FMC BioPolymer
	Gelcarin® GP-812NF[a]		FMC BioPolymer
	Gelcarin® GP-911NF[a]		FMC BioPolymer
	Gelcarin® ME 7627[a]	Foodstuff application	FMC BioPolymer
3	Isagel™		FMC BioPolymer
	Isagel® PF 38[a]	Gelling agent	FMC BioPolymer
	Isagel® RG 200B[a]	Foodstuff application	FMC BioPolymer
4	Lactogel®		FMC BioPolymer
	Lactogel® FC 3359[a]	Foodstuff application	FMC BioPolymer
	Lactogel® FC 3263[a]	Foodstuff application	FMC BioPolymer
	Lactogel® FX 4264[a]	Foodstuff application	FMC BioPolymer
5	Lactarin™		FMC BioPolymer
	Lactarin® XP 3396[a]	Foodstuff application	FMC BioPolymer
	Lactarin® MV 306[a]	Foodstuff application	FMC BioPolymer
	Lactarin® XP 3342[a]	Foodstuff application	FMC BioPolymer
6	SeaGel®		FMC BioPolymer
	SeaGel® FL 674P[a]	Foodstuff application	FMC BioPolymer
	SeaGel® PS 182[a]	Foodstuff application	FMC BioPolymer
	SeaGel® FL 644L[a]	Foodstuff application	FMC BioPolymer
	SeaGel® PS 316[a]	Foodstuff application	FMC BioPolymer
	SeaGel® FL 512[a]	Foodstuff application	FMC BioPolymer
	SeaGel® GP 713[a]	Foodstuff application	FMC BioPolymer
	SeaGel® XP 3340[a]	Foodstuff application	FMC BioPolymer
	SeaGel® CAP 101[a]	Dietary supplement and personal care	FMC BioPolymer
7	SeaKem®		FMC BioPolymer
	SeaKem® CM 611[a]	Foodstuff application	FMC BioPolymer
	SeaKem® CM 514[a]	Foodstuff application	FMC BioPolymer
	SeaKem® XP 3633[a]	Foodstuff application	FMC BioPolymer
	SeaKem® CM 2610[a]	–	FMC BioPolymer
8	Viscarin®		FMC BioPolymer
	Viscarin® GP-109NF[a]	Gelling and viscosifying agent	FMC BioPolymer
	Viscarin® GP-209NF[a]	–	FMC BioPolymer
	Viscarin® GP-328NF[a]	–	FMC BioPolymer
	Viscarin® TP 389-CP[a]	Toothpaste	FMC BioPolymer
	Viscarin® SD 389[a]	Foodstuff application	FMC BioPolymer
	Viscarin® SD 339[a]	Foodstuff application	FMC BioPolymer
	Viscarin® BF 127[a]	Foodstuff application	FMC BioPolymer
9	GENUGEL® (kappa)	Air freshener gel, cell entrapment	CP Kelco
	GENUGEL® RLV[a]	Air freshener gels	CP Kelco
	GENUGEL® CG-130[a]	Gels, face masks, shower gels, emulsions	CP Kelco
	GENUGEL® C1-102[a]	Moulds, encapsulation, air freshener gels	CP Kelco
	GENUGEL® C1-121[a]	Gelling agent, air fresheners gel	CP Kelco
	GENUGEL® C1-124[a]	Air freshener gels	CP Kelco
	GENUGEL® C1-125[a]	Air freshener gels	CP Kelco
	GENUGEL® C1-153[a]	Air freshener gels	CP Kelco
	GENUGEL® RLV[a]	Air freshener gels	CP Kelco
10	GENUVISCO® (iota and lambda)	Personal care and cosmetics	CP Kelco
	GENUVISCO® CG-131[a] (iota type)	Emulsions, surfactant systems, face masks, shaving products, cosmetics, hair care products, shampoos, dermo-cosmetics, SPA products and nutricosmetics	CP Kelco
	GENUVISCO® CG-129[a] (lambda type)	Lubricants, low viscosity milk and sprayable systems	CP Kelco
	GENUVISCO® C1-123[a] (iota type)	Dish washing detergents, non-acid pH cleaners	CP Kelco
	GENUVISCO® TPH-1[a] (iota type)	Toothpaste, gels and gummies	CP Kelco
	GENUVISCO® TPC-1[a] (iota type)	Toothpaste, gels and gummies	CP Kelco
11	Satiagel™ VPC	Viscosity controlling agent, instant moisturizing, gel forming agent, film forming agent	–
	Satiagel™ UTH[a]	Stabilizer, binder, and thickening agent	
12	Satiagum™ VPC	Stabilizer, binder, thickening agent, gelling agent, moisturizer, sensory enhancer	
	Satiagum™ UTH[a]	Stabilizer, binder, and thickening agent	
13	GRINDSTED™		
14	Aisonschem®		Acroyali Holdings Company
15	Seaspen® PF	Used in reconstitutable suspension, excipient	FMC BioPolymer

[a] Indicates the available grades.

Table 4
Overview on carrageenan patents.

S. No.	Patent No.	Patent title	Published date	Inventor(s)/reference
1	US 3,280,102	Preparation of carrageenan having improved water dispersibility	Oct 18, 1966	Gordon, A.L., Jones, J.J., & Pike, L.F.
2	US 3,907,770	Process of extracting carrageenan from seaweed	Sep 23, 1975	Strong, C. H. G.
3	US 3,962,482	Clear, elastic, water gels based on carrageenan	Jun 8, 1976	Comer, F. W & Strong, C. H.G.
4	US 4,096,327	Modified kappa-carrageenan	June 20, 1978	Guiseley, K. B.
5	US 4,307,124	Composition and method for preparing dessert gel	Dec 22, 1981	Moirano, A. L. & Mountainside, N.J.
6	US 4,443,486	Modified extractive of *Eucheuma cottonii* seaweed and composition containing same	Apr 17, 1984	Guiseley, K. B.
7	US 4,457,908	Stabilization of carrageenan-containing toothpaste	Jul 3, 1984	Scott, G. V.
8	US 4,474,818	Increasing viscosity of carrageenan-containing compositions with microwave radiation	Oct 2, 1984	Scott, G. V.
9	US 4,473,988	Dentifrice packaging process	Oct 2, 1984	Scott, G. V.
10	US 5,002,934	Aqueous gel comprising carrageenan	Mar 26, 1991	Brown, C. R., & Norton, I. T.
11	US 5,502,179	Carrageenan product and a method of producing same	Mar 26, 1996	Larsen, P. F.
12	US 6,187,293	Process for making toothpaste using low levels of carrageenan	Feb 13, 2001	Ballard, A. D.
13	US 6,387,354	Semi-refined carrageenan dentifrice binder	May 14, 2002	Bixler, H. J., & Sanchez-Zaballero, G.
14	US 6,458,405	Gel products with carrageenan	Oct 1, 2002	Roy, S., & Ryan, A. L.
15	US 6,479,649	Production of carrageenan and carrageenan products	Nov 12, 2002	Tsai, A. G., et al.
16	US 6,663,910	Method of preparing food products with carrageenan	Dec 16, 2003	Roy, S., & Ryan, A. L.
17	US 7,018,635	Semi-refined carrageenan	Mar 28, 2006	Tsai, A. G., et al.
18	Indian patent 215567	A toothpaste composition	Mar 14, 2008	Randive, V. B., & Gadkari, V. K.
19	EP 2181115	Process for treatment of kappa carrageenan	May 5, 2010	Trudso, J. E.
20	EP 2181116	Carrageenan	May 5, 2010	Trudso, J. E.
21	EP 2183264	Kappa carrageenan	May 12, 2010	Trudso, J. E.
22	US 7,816,341	Homogeneous, thermoreversible gel containing reduced viscosity carrageenan and products made therefrom	Oct 19, 2010	Sewell, C. J., Riley, P. J., & Blakemore, W. R.

coatings function as a gas barrier, adhering to the cut surface of the fruit and reducing respiration, which slows discoloration (Baeza, 2007). Recent studies have shown that carrageenan is successful in controlling discoloration, maintaining texture through shelf-life, and providing antibacterial protection when used as an edible fruit coating on sliced lychee (Plotto, Narciso, Baldwin, & Rattanapanone, 2006), bananas (Bico, Rapaso, Morais, & Morais, 2009), and mangoes (Plotto, Narciso, Rattanapanone, & Baldwin, 2010).

7.2. Application in pharmaceutical industries

7.2.1. Tetracycline and chlorotetracycline production

Tetracyclines represent one of the most important groups of antibiotics and the method normally used for their industrial production is conventional fermentation. Asanza-Teruel, Gontier, Bienaime, Nava-Saucedo, and Barbotin (1997) used Streptomyces aureofaciens immobilized in κ-carrageenan in an attempt to improve the production of tetracycline and chlorotetracycline.

7.2.2. Semi-synthetic antibiotic production

Semi-synthetic antibiotics are prepared via the coupling of a β-lactam core with the so-called side chain, such as phenylacetic acid, D-phenylglycine, or D-*p*-hydroxyphenylglycine. 6-Aminopenicillanic acid (6-APA) is obtained by the enzymatic hydrolysis of penicillin G produced by fermentation. The suitability of κ-carrageenan as a support for 6-APA production was tested with E. coli cells with penicillin-amidase activity (Nagalakshmi & Pai, 1997). The cells were immobilized with an efficiency of 90% and could be used for 20 repeated cycles retaining 60% of the initial penicillin-amidase activity. The carrageenan gel beads were hardened with gluteraldehyde. Among the side chains, D-*p*-hydroxyphenylglycine is one of the most important precursors, as it is used for the synthesis of amoxicillin and cefadroxil. Recombinant *E. coli* cells expressing both dihydropyrimidinase and carbamoylase were immobilized in κ-carrageenan and were able to convert D/L-hydroxyphenylhydantoin to D-*p*-hydroxyphenylglycine. In a single-step reaction a conversion of 93% was obtained, while a 20% value was observed with the strain of *Agrobacterium radiobacter*, which contained the original dihydropyrimidinase gene cloned into *E. coli* (Chao, Fu, Lo, Chen, & Wang, 1999).

7.2.3. D-Aspartic acid production

A number of D-amino acids have been shown to be important intermediates in drug production. D-Aspartic acid can be used as a component of synthetic penicillins (Takamatsu & Tosa, 1993). When D/L-aspartic acid is used as a substrate for the L-aspartate β-decarboxylase of *P. dacunhae* cells, L-aspartic acid is converted to L-alanine but D-aspartic acid remains unchanged due to the high stereospecificity of the biocatalyst. In this way D-aspartic acid and L-alanine can be produced simultaneously using *P. dacunhae* cells immobilized in carrageenan (Takamatsu & Tosa, 1993). D/L-Aspartic acid is chemically produced from fumaric acid and ammonia. D-Aspartic acid is crystallized by acidification of the reactor effluent and recovered by centrifugation. L-Alanine is also recovered by centrifugation after crystallization by the addition of ammonia to the resulting liquor followed by concentration and cooling. This system for the continuous production of D-aspartic acid and L-alanine using *P. dacunhae* cells immobilized in κ-carrageenan has been industrialized since 1988. Industrial application of immobilized whole cells with the use of κ-carrageenan gels for the preparation of L-aspartic acid was first developed by Chibata (Tanabe Seiyaku, Japan) in 1973. The industrial production of a number of other compounds (L-malic acid, L-alanine, L-tryptophan, 1,5-dimethyl-2-piperidone) for use in food and medical applications is based on the same principles (Van de Velde et al., 2002).

7.2.4. Cleaning of industrial effluents

An efficient integrated nitrogen removal system was developed by the co-immobilization of *Nitrosomonas europaea* and *Pseudomonas* spp. in κ-carrageenan, taking advantage of the oxygen gradient inside the entrapment beads (Dos Santos, Bruijnse, Tramper, & Wijffels, 1996; Dos Santos, Tramper, & Wijffels, 1996). The immobilization of *M. aurum* in κ-carrageenan and its use in an air-bubble fermenter resulted in an improvement of its morpholine-degrading capacity (Poupin, Mazure, & Truffaut, 1996; Swain, Waterhouse, Venables, Callely, & Lowe, 1991). The

carrageenan gel and immobilized microbial cells method was used for 4-chlorophenol degradation (Wang, Li, Shi, & Qian, 1997). Aerobic and anaerobic microbial communities have also been co-immobilized into κ-carrageenan/gelatin gel beads (Gardin and Pauss, 2001). Under air-limited conditions these immobilisates catalyze the degradation of 2,4,6-trichlorophenol. Pentachlorophenol pesticide degradation in contaminated soil was attempted with the use of *Pseudomonas* spp. UG30 cells immobilized in κ-carrageenan (Cassidy, Shaw, Lee, & Trevors, 1997).

8. Different grades of carrageenan

Various grades of carrageenan are available in market to provide the desired characteristics in different food and pharmaceutical sectors. The different brands and their grades are summarized in Table 3.

9. Patents on carrageenan

Various patents on carrageenan are tabulated in Table 4.

10. Conclusion

Different carrageenans have been investigated for more specific applications. Several studies revealed that carrageenan have gained wide interest in food and pharmaceutical fields due to its gelling, thickening and stabilizing properties. A need to enhance controlled delivery of drug by a polymer is still in the development stage. Various research on carrageenan as a polymer is carried out due to their unique properties. Most of the toxicological studies have been carried out on carrageenans and results suggest that carrageenans prepared from different species of seaweed have been shown to be non-toxic. Thus the large varieties of applications as well as its steadily increasing number of research have engaged the researchers to discover new applications of carrageenan and make it versatile polymer and gain more significant interest in future.

Acknowledgment

The authors are thankful to SSR College of pharmacy for providing an excellent library facilities and support for the preparation of review article.

References

Abraham, R., Golberg, L., & Coulston, F. (1972). Uptake and storage of degraded carrageenan in lysosomes of reticuloendothelial cells of the rhesus monkey, *Macaca mulatta*. *Experimental and Molecular Pathology*, *17*, 77–93.

Anderson, N. S., Campbell, J. W., Harding, M. M., Rees, D. A., & Samuel, J. W. B. (1969). X-ray diffraction studies of polysaccharide sulphates: Double helix models for κ- and ι-carrageenans. *Journal of Molecular Biology*, *45*(1), 85–97.

Arakawa, S., Ito, M., & Tejima, S. (1988). Promoter function of carrageenan on development of colonic tumours induced by 1, 2-dimethylhydrazine in rats. *Journal of Nutritional Science and Vitaminology*, *34*, 577–585.

Asanza-Teruel, M. L., Gontier, E., Bienaime, C., Nava-Saucedo, J. E., & Barbotin, J. N. (1997). Response surface analysis of chlortetracycline and tetracycline production with κ-carrageenan immobilized *Streptomyces aureofaciens*. *Enzyme and Microbial Technology*, *21*, 314–320.

Baba, M., Snoeck, R., Pauwels, R., & de Clercq, E. (1988). Sulfated polysaccharides are potent and selective inhibitors of various enveloped viruses, including herpes simplex virus, cytomegalovirus, vesicular stomatitis virus, and human immunodeficiency virus. *Antimicrobial Agents and Chemotherapy*, *32*, 1742–1745.

Baeza, R. (2007). *Comparison of technologies to control the physiological, biochemical and nutritional changes of fresh cut fruit*. Manhattan, Kansas: A report for completion of the Masters of Science degree, Kansas State University.

Ballard, A. D. (2001). Process for making toothpaste using low levels of carrageenan. *US 6,187,293*, FMC Corporation.

Benard, C., Cultrone, A., Michel, C., Rosales, C., Segain, J. P., & Lahaye, M. (2010). Degraded carrageenan causing colitis in rats induces TNF secretion and ICAM-1 upregulation in monocytes through NF-κB activation. *PLoS ONE*, *5*(1), 8666.

Benford, D. J. (2002). Carrageenan and processed Eucheuma seaweed (addendum). In *WHO Food Additive Series: 48. Safety evaluation of certain food additives and contaminants*. Geneva: Prepared by the Fifty-seventh meeting of the Joint FAO/WHO expert committee on food additives (JECFA), World Health Organization.

Benford, D. J., Harrison, R. A., Strobel, S., Schlatter, J., & Verger, P. (2008). Carrageenan and processed Eucheuma seaweed (addendum). In *WHO Food Additive Series: 59. Safety evaluation of certain food additives and contaminants*. Geneva: Prepared by the Sixty-eighth meeting of the Joint FAO/WHO expert committee on food additives (JECFA), World Health Organization.

Bico, S. L. S., Rapaso, M. F. J., Morais, R. M. S. C., & Morais, A. M. M. B. (2009). Combined effects of chemical dip and/or carrageenan coating and/or controlled atmosphere on quality of fresh-cut banana. *Food Control*, *20*(5), 508–514.

Bixler, H. J., & Sanchez-Zaballero, G. (2002). Semi-refined carrageenan dentifrice binder. *US 6,387,354*, Shemberg Marketing Corporation.

Borthakur, A., Bhattacharyya, S., Dudeja, P. K., & Tobacman, J. K. (2007). Carrageenan induces interleukin-8 production through distinct Bcl10 pathway in normal human colonic epithelial cells. *American Journal of Physiology – Gastrointestinal and Liver*, *292*(3), G829–G838.

Botting, R. M. (2000). Mechanism of action of acetaminophen: Is there a cyclooxygenase 3? *Clinical Infectious Diseases*, *31*, 202–210.

Brown, C. R., & Norton, I. T. (1991). Aqueous gel comprising carrageenan. *US 5,002,934*, Van Den Bergh Foods Co., Division of Conopco, Inc.

Buck, C. B., Thompson, C. D., Roberts, J. N., Muller, M., Lowy, D. R., & Schiller, J. T. (2006). Carrageenan is a potent inhibitor of papillomavirus infection. *PLoS Pathogens*, *2*(7), 671–680.

Burtin, P. (2003). Nutritional value of seaweeds. *Electronic Journal of Environmental, Agricultural and Food Chemistry*, *2*(4), 498–503.

Caceres, P. J., Carlucci, M. J., Damonte, E. B., Matsuhiro, B., & Zuniga, E. A. (2000). Carrageenans from Chilean samples of *Stenogramme interrupta* (*Phyllophoraceae*): Structural analysis and biological activity. *Phytochemistry*, *53*, 81–86.

Campo, V. L., Kawano, D. F., da Silva, D. B., & Carvalho, I. (2009). Carrageenans: Biological properties, chemical modifications and structural analysis. *Carbohydrate Polymers*, *77*, 167–180.

Carey, P. L. (1958). *The digestibility of polysaccharides by rats* (Thesis). Purdue University. Submitted to WHO by Gray, R. J. H. International Food Additives Council, Atlanta, Georgia, USA, and P. Couchoud, Marinalg, Paris, France

Carlucci, M. J., Pujol, C. A., Ciancia, M., Noseda, M. D., Matulewicz, M. C., Damonte, E. B., et al. (1997). Antiherpetic and anticoagulant properties of carrageenans from the red seaweed *Gigartina skottsbergii* and their cyclized derivatives: Correlation between structure and biological activity. *International Journal of Biological Macromolecules*, *20*, 97–105.

Carlucci, M. J., Scolaro, L. A., & Damonte, E. B. (1999). Inhibitory action of natural carrageenans on herpes simplex virus infection of mouse astrocytes. *Chemotherapy*, *45*, 429–436.

Carlucci, M. J., Scolaro, L. A., Noseda, M. D., Cerezo, A. S., & Da-monte, E. B. (2004). Protective effect of a natural carrageenan on genital herpes simplex virus infection in mice. *Antiviral Research*, *64*, 137–141.

Cassidy, M. B., Shaw, K. W., Lee, H., & Trevors, J. T. (1997). Enhanced mineralization of pentachlorophenol by k-carrageenan-encapsulated *Pseudomonas* sp. UG30. *Applied Microbiology and Biotechnology*, *47*, 108–113.

Chao, Y. P., Fu, H., Lo, T. E., Chen, P. T., & Wang, J. J. (1999). One-step production of D-p-hydroxyphenylglycine by recombinant *Escherichia coli* strains. *Biotechnology Progress*, *15*, 1039–1045.

Chen, J., Appleby, D. W., Weber, P., & Abraham, R. (1981). Detection of a carrageenan in rat liver homogenates after feeding in the diet. *Toxicologist*, *1*(Abstr), 133.

Chen, L. C. M., McLachlan, J., Neish, A. C., & Shackloch, P. F. (1973). The ratio of kappa and lambda carrageenan in nuclear phases of the *Rhodophycean* algae, *Chondrus crispus* and *Gigartina stellata*. *Journal of the Marine Biological Association of the United Kingdom*, *53*, 11–16.

Chen, Y., Liao, M. L., & Dustan, D. E. (2002). The rheology of K^+-κ-carrageenan as a weak gel. *Carbohydrate Polymers*, *50*, 109–116.

Cheney, D. P., Luiston, A. H., & Brailey, P. M. (1987). Carrageenan analysis of tissue culture and whole plant of *Agardhiella subulata*. *Hydrobiologica*, (151/152), 161–166.

Chiovitti, A., Bacic, A., Craik, D. J., Kraft, G. T., Liao, M. L., Falshaw, R., et al. (1988). A pyruvated carrageenan from Australian specimens of the red alga *Sarconema filiforme*. *Carbohydrate Research*, *310*, 77–83.

Codex Alimentarius Commission. (2010). *GSFA Online: Food Additive Details, Carrageenan*.

Colquhoun, I. J., Jay, A. J., Eagles, J., Morris, V. J., Edwards, K. J., Griffin, A. M., et al. (2001). Structure and conformation of a novel genetically engineered polysaccharide P2. *Carbohydrate Research*, *330*, 325–333.

Comer, F. W. & Strong, C. H. G. (1976). Clear, elastic, water gels based on carrageenan. *US 3,962,482*, Uniroyal, Ltd.

Coulston, F., Golberg, L., Abraham, R., Benitz, K. F., & Ford, W. (1975). *Carrageenans (Hercules Incorporated). Safety evaluation. Nine-month study*. Albany, NY, USA: Unpublished interim progress report from Institute of Comparative and Human Toxicology, Center of Experimental Pathology and Toxicology, Albany Medical College. Submitted to WHO by Gray, R. J. H., International Food Additives Council, Atlanta, Georgia, USA, and Couchoud, P., Marinalg, Paris, France.

Coviello, T., Matricardi, P., Marianecci, C., & Alhaique, F. (2007). Polysaccharide hydrogels for modified release formulations. *Journal of Control Release*, *119*, 5–24.

Cuzzocrea, S., Sautebin, L., De Sarro, G., Costantino, G., Rombola, L., Mazzon, E., et al. (1999). Role of IL-6 in the pleurisy and lung injury caused by carrageenan. *Journal of Immunology*, *163*, 5094–5104.

D'Ayala, G. G., Malinconico, M., & Laurienzo, P. (2008). Marine derived polysaccharides for biomedical applications: Chemical modification approaches. *Molecules*, *13*, 2069–2106.

De SF-Tischer, P. C., Talarico, L. B., Noseda, M. D., Guimaraes, S. M. P. B., Damonte, E. B., & Duarte, M. E. R. (2006). Chemical structure and antiviral activity of carrageenans from *Meristiella gelidium* against herpes simplex and dengue virus. *Carbohydrate Polymers*, *63*, 459–465.

Dewar, E. T., & Maddy, M. L. (1970). Faecal excretion of degraded and native carrageenan by the young rat. *Journal of Pharmacy and Pharmacology*, *22*, 791–793.

Dos Santos, V. A. P. M., Bruijnse, M., Tramper, J., & Wijffels, R. H. (1996). The magic-bead concept: An integrated approach to nitrogen removal with co-immobilized micro-organisms. *Applied Microbiology and Biotechnology*, *45*, 447–453.

Dos Santos, V. A. P. M., Tramper, J., & Wijffels, R. H. (1996). Dynamic modelling of an integrated nitrogen removal system using co-immobilized microorganisms immobilized cells. *Progress in Biotechnology*, *11*, 486–493.

EC SCF (European Commission Scientific Committee on Food). (2003). *Opinion of the Scientific Committee on Food on carrageenan*. SCF/CS/ADD/EMU/199 Final.

Eccles, R., Meier, Ch., Jawad, M., Weinmüllner, R., Grassauer, A., & Prieschl-Grassauer, E. (2010). Efficacy and safety of an antiviral iota-carrageenan nasal spray: A randomized, double-blind, placebo-controlled exploratory study in volunteers with early symptoms of the common cold. *Respiratory Research*, *11*, 1–10.

Ekstrom, L. G. (1985). Molecular-weight-distribution and the behaviour of kappa-carrageenan on hydrolysis. Part II. *Carbohydrate Research*, *135*, 283–289.

Ekstrom, L. G., & Kuivinen, J. (1983). Molecular weight distribution and hydrolysis behaviour of carrageenans. *Carbohydrate Research*, *116*, 89–94.

Elsenhans, B., Blume, R., & Caspary, W. F. (1981). Long-term feeding of unavailable carbohydrate gelling agents. Influence of dietary concentration and microbiological degradation on adaptive responses in the rat. *American Journal of Clinical Nutrition*, *34*, 1837–1848.

Engster, M., & Abraham, R. (1976). Cecal response to different molecular weights and types of carrageenan in the guinea pig. *Toxicology and Applied Pharmacology*, *38*, 265–282.

Epifanio, E. C., Veroy, R. L., Uyenco, F., Cajipe, G. J. B., & Laserna, E. C. (1981). Carageenan from *Eucheuma spiratum* in bacteriological media. *Applied and Environmental Microbiology*, *41*, 155–163.

Estakhr, J., Sanchooli, N., Najafi, S. H., & Javdan, N. (2011). Anti-inflammatory activity of ethanolic extract of *Physalis alkekengi*. *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, *2*, 421–425.

FAO. (2007). *FAO JECFA Monographs 4. Specifications: Carrageenan*. , available at: http://www.fao.org/ag/agn/jecfa-additives/details.html?id=830

Gardin, H., & Pauss, A. (2001). Kappa-carrageenan/gelatin gel beads for the co-immobilization of aerobic and anaerobic microbial communities degrading 2,4,6-trichlorophenol under air-limited conditions. *Applied Microbiology and Biotechnology*, *56*, 517–523.

Girond, S., Crance, J. M., Van Cuyck-Gandre, H., Renaudet, J., & Deloince, R. (1991). Antiviral activity of carrageenan on hepatitis A virus replication in cell culture. *Research in Virology*, *142*, 261–270.

Glicksman, M. (1979). Gelling Hydrocolloids in Food Product Application. In J. M. V. Blanshard, & J. R Michell (Eds.), *Polysaccharides in Food*. Boston: Butterworths.

Gonzalez, M. E., Alarcon, B., & Carrasco, L. (1987). Polysaccharides as antiviral agents: Antiviral activity of carrageenan. *Antimicrobial Agents and Chemotherapy*, *31*, 1388–1393.

Gopakumar, K. (1997). Seaweed farming and utilization in Philippines. In *Proc. Workshop, National Aquaculture Week* (pp. 64–69).

Gordon, A. L., Jones, J. J., & Pike, L. F. (1966). Preparation of carrageenan having improved water dispersibility. *US 3,280,102*, National Dairy Products Corporation.

Grassauer, A., Weinmuellner, R., Meier, C., Pretsch, A., Prieschl-Grassauer, E., & Unger, H. (2008). Iota-carrageenan is a potent inhibitor of rhinovirus infection. *Virology Journal*, *5*, 1–13.

Grasso, P., Sharratt, M., Carpanini, F. M. B., & Gangolli, S. D. (1973). Studies on carrageenan and large-bowel ulceration in mammals. *Food and Cosmetics Toxicology*, *11*, 555–564.

Greer, C. W., & Yaphe, W. (1984). Characterization of hybrid (beta-kappa-gamma) carrageenan from *Eucheuma gelatinae* J. Agardh (Rhodanhyta, Solieriaceae) using carrageenases, infrared and ^{13}C-nuclear magnetic resonance spectroscopy. *Botinica Marina*, *27*, 473–478.

Guay, J., Bateman, K., Gordon, R., Mancini, J., & Riendeau, D. (2004). Carrageenan-induced paw edema in rat elicits a predominant prostaglandin E2 (PGE2) response in the central nervous system associated with the induction of microsomal PGE2 synthase-1. *Journal of Biological Chemistry*, *279*, 24866–24872.

Guiseley, K. B. (1978). Modified Kappa-carrageenan. *US 4,096,327*, FMC Corporation.

Guiseley, K. B. (1984). Modified extractive of *Eucheuma cottonii* seaweed and composition containing same. *US 4,443,486*, FMC Corporation.

Guo, J. H., Skinner, G. W., Harcum, W. W., & Barnum, P. E. (1998). Pharmaceutical application of naturally occurring water soluble polymers. *PSTT*, *1*, 254–261.

Hagiwara, A., Miyashita, K., Nakanishi, T., Sano, M., Tamano, S., Asai, I., et al. (2001). Lack of tumor promoting effects of carrageenan on 1,2-dimethylhydrazine-induced colorectal carcinogenesis in male F344 rats. *Journal of Toxicology and Pathology*, *14*, 37–43.

Handy, R. L. C., & Moore, P. K. (1998). A comparison of the effects of L-NAME, 7-NI and L-NIL on carrageenan-induced hindpaw oedema and NOS activity. *British Journal of Pharmacology*, *123*, 1119–1126.

Hawkins, W. W., & Leonard, V. G. (1963). Antithrombic activity of carrageenan in human blood. *Canadian Journal of Biochemistry and Physiology*, *41*(5), 1325–1327.

Hawkins, W. W., & Yaphe, W. (1965). Carrageenan as a dietary constituent for the rat: Faecal excretion, nitrogen absorption, and growth. *Canadian Journal of Biochemistry and Physiology*, *43*, 479–484.

Heertje, I. (1993). Structure and function of food products: A review. *Food Structure*, *12*, 343–364.

Henriques, M. G. M. O., Silva, P. M. R., Martins, M. A., Flores, C. A., Cunha, F. Q., Assreuy-Filho, J., et al. (1987). Mouse paw oedema. A new model for inflammation? *Brazilian Journal of Medical and Biological Research*, *20*, 243–249.

Hoefler, A. (2001). *Carrageenan: Chemistry, functionality, and applications*. PA: Oxford.

Hoffman, A. S. (2002). Hydrogel for biomedical applications. *Advanced Drug Delivery Reviews*, *43*, 3–12.

Hoffmann, R. A., Russell, A. R., & Gidley, M. J. (1996). Molecular weight distribution of carrageenans. In G. O. Phillips, P. J. Williams, & D. J. Wedlock (Eds.), *Gums & stabilisers for the food industry* (Vol. 8) (pp. 137–148). Oxford: IRL Press at the Oxford University Press.

Hood, L. F., & Allen, J. E. (1977). Ultrastructure of carrageenan-milk sols and gels. *Journal of Food Science*, *42*, 1062–1065.

Imeson, A. P. (2000). Ch. 5: Carrageenan. In G. O. Phillips, & P. A. Williams (Eds.), *Handbook of Hydrocolloids* (Vol. 740) (pp. 87–102). Boca Raton, FL: CRC Press.

International Agency for Research on Cancer (IARC). (1983). . *Monographs on the evaluation of the carcinogenic risk of chemicals to humans* (Vol. 31) World Health Organization.

International Food Additives Council. (1997). *Unpublished monograph prepared by the International Food Additives Council, Washington, DC*. Submitted to WHO by Gray, R.J.H., International Food Additives Council, Atlanta, Georgia, USA, and Couchoud, P., Marinalg, Paris, France.

Jain, N. K., Patil, C. S., Singh, A., & Kulkarni, S. K. (2001). A simple technique to evaluate inflammatory pain along with anti-inflammatory studies in carrageenan-induced paw edema. *Indian Journal of Pharmacology*, *33*, 114–115.

JECFA. (2002). *Carrageenan and processed Eucheuma seaweed (addendum). Safety evaluation of certain food additives and contaminants*. Geneva: WHO Food Additives Series: 48 Prepared by the 57th Meeting of the Joint FAO/WHO Expert Committee on Food Additives, World Health Organization., pp. 91–101.

Ji Ming Hou. (1990). . *Processing and extraction of phycocolloids. Report on the regional workshop on the culture and utilization of seaweeds* (Vol. II) Bangkok, Thailand: NACA.

Kaliaperumal, N. (1984). *Report on the training in eucheuma culture at the Marine Sciences Center*. Manila: University of the Philippines., pp. 1–25.

Kara, S., Tamerler, C., Bermek, H., & Pekcan, O. (2003). Cation effects on sol–gel and gel–sol phase transitions of κ-carrageenan–water system. *International Journal of Biological Macromolecules*, *31*, 177–185.

Kindness, G., Long, W. F., & Williamson, F. B. (1980). Anticoagulant effects of sulphated polysaccharides in normal and antithrombin III-deficient plasmas. *British Journal of Pharmacology*, *69*, 675–677.

Kindness, G., Williamson, F. B., & Long, W. F. (1980). Involvement of antithrombin III in anticoagulant effects of sulphated polysaccharides. *Biochemical Society Transactions*, *8*, 82–83.

Kindness, G., Williamson, F. B., & Long, W. F. (1979). Effect of polyanetholesulphonic acid and xylan sulphate on antithrombin III activity. *Biochemical and Biophysical Research Communications*, *13*(88), 1062–1068.

Kirk, R. E., & Othmer, D. F. (1992). J. I. Kroschwitz, & M. Howe-Grant (Eds.), *Encyclopedia of chemical technology* (Vol. 4) (p. 942). New York: John Wiley & Sons.

Kost, J., & Goldbart, R. (1997). Natural and modified polysaccharides. In A. J. Domb, J. Kost, & D. M. Wiseman (Eds.), *Handbook of biodegradable polymers* (pp. 275–289). Amsterdam: Harwood Academic Publisher.

Kumar, M., & Sharma, B. D. (2003). The storage stability and textural, physico-chemical and sensory quality of low-fat ground pork patties with carrageenan as a fat replacer. *International Journal of Food Science and Technology*, *39*(1), 31–42.

Larsen, P. F. (1996). Carrageenan product and a method of producing same. *US 5,502,179*, Grinsted Products A/S (Danisco A/S).(Copenhagen, DK).

Laurienzo, P. (2010). Marine polysaccharides in pharmaceutical applications: An overview. *Marine Drugs*, *8*, 2435–2465.

Leibbrandt, A., Meier, Ch., Konig-Schuster, M., Weinmullner, R., Kalthoff, D., Pflugfelder, B., et al. (2010). Iota-carrageenan is a potent inhibitor of influenza a virus infection. *PLoS ONE*, *5*, 1–12.

Luescher-Mattli, M. (2003). Algae, a possible source for new drugs in the treatment of HIV and other viral diseases. *Current Medicinal Chemistry*, *2*, 219–225.

Lynch, G., Low, L., Li, S., Sloane, A., Adams, S., Parish, C., et al. (1994). Sulfated polyanions prevent HIV infection of lymphocytes by disruption of the CD4-gp120 interaction, but do not inhibit monocyte infection. *Journal of Leukocyte Biology*, *56*, 266–272.

MacArtain, P., Jaacquier, J. C., & Dawson, K. A. (2003). Physical characteristics of calcium induced κ-carrageenan networks. *Carbohydrate Polymers*, *53*, 395–400.

Mallett, A. K., Wise, A., & Rowland, I. R. (1984). Hydrocolloid food additives and rat caecal microbial enzyme activities. *Food and Chemical Toxicology*, *22*, 415–418.

Mangione, M. R., Giacomazza, D., Bulone, D., Martorana, V., & Biario, P. L. (2003). Thermoreversible gelation of κ-carrageenan: Relation between conformational transition and aggregation. *Biophysical Chemistry*, *104*, 95–105.

Mankes, R., & Abraham, R. (1975). Lysosomal dysfunction in colonic submucosal macrophages of rhesus monkeys caused by degraded iota carrageenan. *Proceedings of the Society for Experimental Biology and Medicine*, *150*, 166–170.

Marchetti, M., Pisani, S., Pietropaolo, V., Seganti, L., Nicoletti, R., & Orsi, N. (1995). Inhibition of herpes simplex virus infection by negatively charged and neutral carbohydrate polymers. *Journal of Chemotherapy*, *7*, 90–96.

Marcus, A. J., & Watts, J. (1969). Ulcerative colitis in the guinea-pig caused by seaweed extract. *Journal of Pharmaceutical sciences and Pharmacology*, *21*, 187.
McCandles, E. L., West, J. A., & Guiry, M. D. (1982). Carrageenan patterns in the *Phyllophoraceae*. *Biochemical Systematics and Ecology*, *10*, 275–284.
McCandles, E. L., West, J. A., & Guiry, M. D. (1983). Carrageenan patterns in gigartinaece. *Biochemical Systematics and Ecology*, *11*, 175–182.
McHugh, D. J. (2003). Ch. 7: Carrageenan. In *A guide to the seaweed industry: FAO fisheries technical paper 441*. Rome: Food and Agriculture Organization of the United Nations.
Moirano, A. L. (1977). Sulfated seaweed polysaccharides. In H. Graham (Ed.), *Food Colloids*. Westport: AVI Publishing.
Moirano, A. L. & Mountainside, N. J. (1981). Composition and method for preparing dessert gel. *US 4,307,124*, FMC Corporation.
Mollet, J. C., Rahaoui, A., & Lemoine, Y. (1988). Yield, chemical composition and gel strength of agarocolloids of *Gracilaria gracilis*, *Gracilariopsis longissima* and the newly reported *Gracilaria vermiculophylla* from Roscoff, France. *Journal of Applied Phycology*, *10*, 59–66.
Mollion, J. (1983). Exploitation of algal carrageenans: Global situation and perspectives in Senegal. In J. M. kornprobst (Ed.), *Marine chemistry for development* (pp. 84–95).
Mollion, M. J., Moreau, S., & Christian, D. (1986). Isolation of a new type of carrageenan from *Rissoeulla verruculosa* (Bert) J. Agardh (Rhodophyta, Gigartinales). *Botinica Marina*, *29*, 549–552.
Murano, E., Toffanin, R., Cecere, E., Rizzo, R., & Knutsen, S. H. (1977). Investigation of the carrageenans extracted from *Solieria filiformis* and *Agardhiella subulata* from Mar. Piccolo. Taran. *Marine Chemistry*, *58*, 319–325.
Nagalakshmi, V., & Pai, J. S. (1997). Immobilisation of penicillin acylase producing *E. coli* cells with κ-carrageenan. *Indian Journal of Microbiology*, *37*, 17–20.
Nantel, F., Denis, D., Gordon, R., Northey, A., Cirino, M., Metters, K. M., et al. (1999). Distribution and regulation of cyclooxygenase-2 in carrageenan-induced inflammation. *British Journal of Pharmacology*, *28*, 853–859.
Naude, P. J., Cromarty, A. D., & Van Rensburg, C. E. (2010). Potassium humate inhibits carrageenan-induced paw oedema and a graft-versus-host reaction in rats. *Inflammopharmacology*, *18*, 33–39.
Nayouf, M. (2003). *Étude rhéologique et structurale de la qualité texturante du système amidon/kappa-carraghénane en relation avec le traitement thermomécanique* (Thèse de Doctorat). Nantes, France: École Nationale des Ingénieurs des Techniques des Industries Agricoles et Alimentaires.
Nicklin, S., & Miller, K. (1984). Effect of orally administered food-grade carrageenans on antibody-mediated and cell-mediated immunity in the inbred rat. *Food and Chemical Toxicology*, *22*, 615–621.
Nicklin, S., Baker, K., & Miller, K. (1988). Intestinal uptake of carrageenan: Distribution and effects on humoral immune competence. *Advances in Experimental Medicine and Biology*, *237*, 813–820.
Nishinari, K., & Takahashi, R. (2003). Interaction in polysaccharide solutions and gels. *Current Opinion in Colloid and Interface Science*, *8*, 396–400.
Ochuba, G. U., & Von Riesen, V. L. (1980). Fermentation of polysaccharides by *Klebsiellae* and other facultative bacteria. *Applied and Environmental Microbiology*, *39*, 988–992.
Omote, K., Hazama, K., Kawamata, T., Kawamata, M., Nakayaka, Y., Toriyabe, M., et al. (2001). Peripheral nitric oxide in carrageenan-induced inflammation. *Brain Research*, *912*, 171–175.
Oohashi, Y., Ishioka, T. T., Wakabayashi, K., & Kuwabara, N. (1981). A study of carcinogenesis induced by degraded carrageenan arising from squamous metaplasia of the rat colorectum. *Cancer Letters*, *14*, 267–272.
Panlasigui, L. N., Baello, O. Q., Dimatangal, J. M., & Dumelod, D. B. (2003). Blood cholesterol and lipid-lowering effects of carrageenan on human volunteers. *Asia Pacific Journal of Clinical Nutrition*, *12*, 209–214.
Parekh, R. G., Doshi, Y. A., Rao, A. V., & Chauhan, V. D. (1988). Phycocolloid from marine red alga, *Hypnea musciformis* (wulf.). *Indian Journal of Marine Sciences*, *17*, 242–243.
Parekh, R. G., Garg, S. K., Mehta, B. R., & Mehta, D. J. (1979). Studies on extraction of κ-carrageenan from hypnea and its characterization. In *International symposium on algae of the Indian Ocean region* Bhavnagar, (p. 42).
Parekh, R. G., Rao, A. V., & Chauhan, V. D. (1988). Carrageenan from marine red alga, *Hypnea valentiae* (Turn.) Mont. *Phykos*, *26*, 146–151.
Paschapur, M. S., Patil, M. B., Kumar, R., & Patil, S. R. (2009). Evaluation of anti-inflammatory activity of ethanolic extract of *Borassus flabellifer* L. male flowers (inflorescences) in experimental animals. *Journal of Medicinal Plants Research*, *2*, 49–54.
Petersson, M., Wiberg, U., Lundeberg, T., & Uvnas-Moberg, K. (2001). Oxytocin decreases carrageenan induced inflammation in rats. *Peptides*, *22*, 1479–1484.
Piculell, L. (2006). Chapter 8: Gelling carrageenans. In A. M. Stephen, G. O. Phillips, & P. A. Williams (Eds.), *Food polysaccharides and their applications* (2nd ed., Vol. 4, pp. 239–288). Boca Raton, FL: CRC Press.
Pittman, K. A., Golberg, L., & Coulston, F. (1976). Carrageenan: The effect of molecular weight and polymer type on its uptake, excretion and degradation in animals. *Food and Cosmetics Toxicology*, *14*, 85–93.
Plotto, A., Narciso, J., Baldwin, E. A., & Rattanapanone, N. (2006). Edible coatings and other surface treatments to maintain color of lychee fruit in storage. *Proceedings of the Florida State Horticultural Society*, *119*, 323–331.
Plotto, A., Narciso, J., Rattanapanone, N., & Baldwin, E. A. (2010). Surface treatments and coatings to maintain fresh-cut mango quality in storage. *Journal of the Science of Food and Agriculture*, *90*, 2333–2341.
Porto, G. G., Vasconcelos, B. C., Silva-Junior, V. A., & Souza Andrade, E. S. (2010). The use of carrageenan for limiting the mandibular movement in rats: A preliminary experimental study. *Medicina Oral, Patologia Orally Cirugia Bucal*, *15*, 653–657.
Posadas, I., Bucci, M., Roviezzo, F., Rossi, A., Parente, L., Sautebin, L., et al. (2004). Carrageenan-induced mouse paw oedema is biphasic, age-weight dependent and displays differential nitric oxide cyclooxygenase-2 expression. *British Journal of Pharmacology*, *142*, 331–338.
Poupin, P., Mazure, N., & Truffaut, N. (1996). Morpholine degradation by strain *Mycobacterium aurum* MOI: Improvement of cells growth and morpholine degradation rate by cells immobilization. *Progress in Biotechnology*, *11*, 770–776.
Radhakrishnan, R., Bement, M. K. H., Skyba, D., & Sluka, K. A. (2004). Models of muscle pain: Carrageenan model and acidic saline model. *Current Protocols in Pharmacology*, *25*, 1–28.
Ramirez, A. (1991). Fast food lightens up but sales are often thin. *New York Times*,. March 19.
Randive, V. B. & Gadkari, V. K. (2008). A toothpaste composition. *Indian Patent 215567*.
Reddy, B. S., Watanabe, K., & Sheinfil, A. (1980). Effect of dietary wheat bran, alfalfa, pectin and carrageenan on plasma cholesterol and fecal bile acid and neutral sterol excretion in rats. *Journal of Nutrition*, *110*, 1247–1254.
Rees, D. A. (1969). Structure, conformation and mechanism in the formation of polysaccharide gels and networks. In M. L. Wolfrom, R. S. Tipson, & D. Horton (Eds.), *Advances in carbohydrate chemistry and Biochemistry* (Vol. 24). London: Academic Press.
Rocha de Souza, M. C., Marques, C. T., Dore, C. M. G., da Silva, F. R. F., Rocha, H. A. O., & Leite, E. L. (2007). Antioxidant activities of sulfated polysaccharides from brown and red sea-weeds. *Journal of Applied Phycology*, *19*, 153–160.
Rochas, C. (1982). *Etude de la transition sol-gel du kappa-carraghenane. These Docteur es Sciences Physiques*. Grenoble, France: Universite Scientifique et Medicale et Institute National Polytechnique de Grenoble.
Rochas, C., Rinaudo, M., & Landry, S. (1989). Relation between the molecular structure and mechanical properties of carrageenan gels. *Carbohydrate Polymer*, *10*, 115–127.
Rosen, A., Lundeberg, T., Bytner, B., & Nylander, I. (2000). Central changes in nociceptin dynorphin B and Met-enkephalin-Arg-Phe in different models of nociception. *Brain Research*, *857*, 212–218.
Roy, S., & Ryan, A. L. (2002). Gel products with carrageenan. *US 6,458,405*, General Mills, Inc.
Roy, S., & Ryan, A. L. (2003). Method of preparing food products with carrageenan. *US 6,663,910*, General Mills, Inc.
Saha, D., & Bhattacharya, S. (2010). Hydrocolloids as thickening and gelling agents in foods: A critical review. *Journal of Food Science and Technology*, *47*(6), 587–597.
Salvemini, D., Wang, S. Q., Wyatt, P. S., Bourdon, D. M., Marino, M. H., Manning, P. T., et al. (1996). Nitric oxide: A key mediator in the early and late phase of carrageenan-induced rat paw inflammation. *British Journal of Pharmacology*, *118*, 829–838.
Salyers, A. A., West, S. E. H., Vercellotti, J. R., & Wilkins, T. D. (1977). Fermentation of mucins and plant polysaccharides by anaerobic bacteria from the human colon. *Applied and Environmental Microbiology*, *34*, 529–533.
Scott, G. V. (1984a). Dentifrice packaging process. *US 4,473,988*, Colgate-Palmolive Company.
Scott, G. V. (1984b). Increasing viscosity of carrageenan-containing compositions with microwave radiation. *US 4,474,818*, Colgate-Palmolive Company.
Scott, G. V. (1984c). Stabilization of carrageenan-containing toothpaste. *US 4,457,908*, Colgate-Palmolive Company.
Sen, A. K., Das, A. K., Banerji, N., Siddhanta, A. K., Mody, K. H., Ramavat, B. K., et al. (1994). A new sulfated polysaccharide with potent blood anti-coagulant activity from the red seaweed *Grateloupia Indica*. *International Journal of Biological Macromolecules*, *16*(5), 279–280.
Sewell, C. J., Riley, P. J., & Blakemore, W. R. (2010). Homogeneous, thermoreversible gel containing reduced viscosity carrageenan and products made therefrom. *US 4,096,327*, FMC Corporation.
Shanmugam, M., & Mody, K. H. (2000). Heparinoid-active sulphated polysaccharides from marine algae as potential blood anticoagulant agents. *Current Science*, *79*(12), 1672–1683.
Silva, F. R. F., Dore, C. M. P. G., Marques, C. T., Nascimento, M. S., Benevides, N. M. B., Rocha, H. A. O., et al. (2010). Anticoagulant activity, paw edema and pleurisy induced carrageenan: Action of major types of commercial carrageenans. *Carbohydrate Polymers*, *79*, 26–33.
Sini, J. M., Yaro, A. H., Ayanwuyi, L. O., Aiyelero, O. M., Mallum, S. M., & Gamaniel, K. S. (2010). Antinociceptive and anti-inflammatory activities of the aqueous extract of the root bark of *Combretum sericeum* in rodents. *African Journal of Biotechnology*, *9*, 8872–8876.
Snoeren, T. H. M. (1976). *Kappa-carrageenan. A study of its physico-chemical properties, sol–gel transition and interactions with milk*. (PhD Thesis), Wageningen, The Netherlands.
Spieler, R. (2002). Seaweed compound's anti-HIV efficacy will be tested in southern Africa. *Lancet*, *359*(9318), 1675.
Stancioff, D. J., & Renn, D. W. (1975). Physiological effects of carrageenan. *American Cancer Society Symposium Series*, *15*, 1–12.
Stanley, N. F. (1987). Carrageenans. In D. J. McHugh (Ed.), *Production and utilization of products from commercial seaweeds*. Australia: FAO Fisheries Technical Papers. ISBN: 9251026122.
Stiles, J., Guptill-Yoran, L., Moore, G. E., & Pogranichniy, R. M. (2008). Effects of κ-carrageenan on in vitro replication of feline herpesvirus and on experimentally

induced herpetic conjunctivitis in cats. *Investigative Ophthalmology and Visual Science*, *49*, 1496–1501.
Stoloff, L. (1959). Carrageenan. In R. I. Whistler (Ed.), *Industrial Gums*. New York: Academic Press.
Strong, C. H. G. (1975). Process of extracting carrageenan from seaweed. *US 3,907,770*, Uniroyal Ltd.
Sugishita, E., Amagaya, S., & Ogihara, Y. (1981). Antiinflammatory testing methods: Comparative evaluation of mice and rats. *Journal of Pharmacobiodynamics*, *8*, 565–575.
Swain, A., Waterhouse, K. V., Venables, W. A., Callely, A. G., & Lowe, S. E. (1991). Biochemical studies of morpholine catabolism by an environmental mycobacterium. *Applied Microbiology and Biotechnology*, *35*(1), 110–114.
Swaisgood, H. E. (1982). Chemistry of milk protein. In P. F. Fox (Ed.), *Developments in dairy chemistry* (Vol. 1) (pp. 1–59). London, New York: Applied Science Publishers.
Takamatsu, S., & Tosa, T. (1993). Production of L-alanine and D-aspartic acid. *Bioprocess Technology*, *16*, 25–35.
Takemesa, M., & Chiba, A. (2001). Gelatin mechanism of k and i-Carrageenan investigated by correlation between the strain-optical coefficient and the dynamic shear modulus. *Macromolecules*, *34*, 7427–7434.
Tobacman, J. K. (2001). Review of harmful gastrointestinal effects of carrageenan in animal experiments. *Environmental Health Perspectives*, *109*(10), 983–994.
Tobacman, J. K., & Walters, K. S. (2001). Carrageenan-induced inclusions in mammary myoepithelial cells. *Cancer Detection and Prevention*, *25*(6), 520–526.
Tomarelli, R. M., Tucker, W. D., Jr., Bauman, L. M., Savini, S., & Weaber, J. R. (1974). Nutritional qualities of processed milk containing carrageenan. *Journal of Agricultural and Food Chemistry*, *22*, 819–824.
Trudso, J. E. (2010a). Process for treatment of kappa carrageenan. *EP 2181115A1*, CP Kelco U.S., Inc.
Trudso, J. E. (2010b). Carrageenan. *EP 2181116A1*, CP Kelco U.S., Inc.
Trudso, J. E. (2010c). Kappa carrageenan. *EP 2183264A1*, CP Kelco U.S., Inc.
Tsai, A. G., et al. (2002). Production of carrageenan and carrageenan products. *US 6,479,649*, FMC Corporation.
Tsai, A. G., et al. (2006). Semi-refined carrageenan. *US Patent 7,018,635*, FMC Corporation.
U.S. Pharmacopeia. (2010). *2010–2011 Food Chemical Codex* (7th ed.). Rockville, MD: The United States Pharmacopeial Convention.
Udall, J. N., Harmatz, P., Vachino, G., Galdabini, J., & Walker, W. A. (1981). Intestinal transport and liver uptake of a food additive present in infant formulas (Abstract). *Pediatric Research*, *15*, 549.
Van de Velde, F., Lourenco, N. D., Pinheiro, H. M., & Bakkerd, M. (2002). Carrageenan: A food-grade and biocompatible support for immobilisation techniques. *Advanced Synthesis and Catalysis*, *344*, 815–835.
Van de Velde, I. F., & De Ruiter, G. A. (2002). Chapter 9: Carrageenan. In S. De Baets, E. J. Vandamme, & A. Steinbuchel (Eds.), *Biopolymers, Volume 6, Polysaccharides II: Polysaccharides from Eukaryotes* (pp. 245–273). Wiley-VCH: Weinheim, Germany.
Wakabayashi, K., Inagaki, T., Fujimoto, Y., & Fukuda, Y. (1978). Induction by degraded carrageenan of colorectal tumors in rats. *Cancer Letters*, *4*, 171–176.
Wang, J. L., Li, P., Shi, H., & Qian, Y. (1997). Immobilization of microorganisms using carrageenan gels coated with chitosan and application to biodegradation of 4-chlorophenol. *Journal of Environmental Sciences*, *9*, 283–287.
Watson, D. B. (2008). Public health and carrageenan regulation: A review and analysis. *Journal of Applied Phycology*, *20*(5), 505–513.
Watt, J., & Marcus, R. (1971). Carrageenan-induced ulceration of the large intestine in the guinea pig. *Gut*, *12*, 164–171.
Weiner, M. L., Nuber, D., Blakemore, W. R., Harriman, J. F., & Cohen, S. M. (2007). A 90-day dietary study on 824 kappa carrageenan with emphasis on the gastrointestinal tract. *Food and Chemical Toxicology*, *45*(1), 98–106.
Wijesekara, I., Pangestuti, R., & Kim, S. K. (2011). Biological activities and potential health benefits of sulfated polysaccharides derived from marine algae. *Carbohydrate Polymers*, *84*, 14–21.
Witvrouw, M., & DeClercq, E. (1997). Sulfated polysaccharides extracted from sea algae as potential antiviral drugs. *General Pharmacology: The Vascular System*, *29*(4), 497–511.
Wunderwald, P., Schrenk, W. J., & Port, H. (1979). Antithrombin BM from human plasma: An antithrombin binding moderately to heparin. *Thrombosis Research*, *15*, 49–60.
Yamamoto, I., Maruyama, H., Takahashi, M., & Komiyama, K. (1986). The effect of dietary or intraperitoneally injected seaweed preparations on the growth of sarcoma-180 cells subcutaneously implanted into mice. *Cancer Letters*, *30*, 125–131.
Yuan, H., Song, J., Li, X., Li, N., & Dai, J. (2004). Immunomodulation and antitumor activity of κ-carrageenan oligosaccharides. *Pharmacological Research*, *50*, 47–53.
Yuan, H., Song, J., Li, X., Li, N., & Dai, J. (2006). Immunomodulation and antitumor activity of κ-carrageenan oligosaccharides. *Cancer Letters*, *243*, 228–234.
Yuguchi, Y., Thu Thuy, T. T., Urakawa, H., & Kajiwara, K. (2002). Structural characteristics of carrageenan gels: Temperature and concentrations dependence. *Food Hydrocolloids*, *16*, 515–522.
Yuguchi, Y., Urakawa, H., & Kajiwara, K. (2003). Structural characteristics of carrageenan gels: Various types of counter ions. *Food Hydrocolloids*, *17*, 481–485.
Zacharopoulos, V. R., & Phillips, D. M. (1997). Vaginal formulations of carrageenan protect mice from herpes simplex virus infection. *Clinical and Diagnostic Laboratory Immunology*, *4*, 465–468.
Zeitlin, L., Whaley, K. J., Hegarty, T. A., Moench, T. R., & Cone, R. A. (1997). Tests of vaginal microbicides in the mouse genital herpes model. *Contraception*, *56*(5), 329–335.
Zhou, G., Sheng, W., Yao, W., & Wang, Ch. (2006). Effect of low molecular-carrageenan from *Chondrus ocellatus* on antitumor H-22 activity of 5-Fu. *Pharmacological Research*, *53*, 129–134.
Zhou, G., Sun, Y. P., Xin, X., Zhang, Y., Li, L., & Xu, Z. (2004). In vivo antitumor and immunomodulation activities of different molecular weight lambda-carrageenans from *Chondrus ocellatus*. *Pharmacological Research*, *50*, 47–53.