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Carrageenan: Future Potential Ingredient of Lubricant and Feminine Hygiene Product with Possible Protection Effects against HPV Infection

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Abstract

The discovery that human papillomavirus (HPV) infection is the primary cause of cervical cancer has opened up new avenues for prevention. Carrageenans are attractive candidates for developing potential HPV prevention due to their actions against a wide range of viruses, mainly through the blocking of the viral attachment stage. In addition, they are characterised by low production costs, abundant availability, biodegradability, biocompatibility, and non-toxicity. This review presents an overview of *in vitro* and *in vivo* studies of carrageenan antiviral properties, availability, and future liquid-sexual material. Based on the results of previous studies, both *in vitro* and *in vivo* carrageenan has the potential to be applied as a lubricant and feminine cleanser because it can reduce HPV infection, is non-toxic, and non-allergenic.

Keywords

Cervical cancer, human papilloma viruses (HPV), lubricant, feminine cleanser biomedical products

1 Introduction

Cervical cancer is cancer that grows in the cervix cells and occurs when healthy cells undergo changes or mutations. This mutation causes these cells to grow abnormally and uncontrollably, forming cancer cells.[1] Cervical cancer is one of the most common malignant tumour in women globally, but primarily occurs in underdeveloped or developing countries. In 2020, an estimated 604,127 (3.1 %) women were diagnosed with cervical cancer and about 341,831 (3.4 %) died due to the disease.[2,3] Almost all cervical cancers are mainly caused by high-risk human papillomavirus (HPV) infection. However, the other cofactors of cervical cancer are sexually transmittable infections (HIV and *Chlamydia trachomatis*), smoking, long-term use of oral contraceptives, high age, parity, and low socioeconomic status.[4–6]

The discovery that human papillomavirus (HPV) infection is the primary cause of cervical cancer has opened up new avenues for prevention, including prevention of infection, improved screening methods, and HPV vaccine.[7,8] Cervical cancer treatment is based on the characteristics and stage of cancer. The main treatments for cervical cancer are surgery, gene therapy, radiotherapy, chemotherapy, and immunomodulatory therapy.[9,10]

Gene therapy is understood as the ability of genetic improvement through the correction of altered (mutated) genes or site-specific modifications that target therapeutic treatment.[12] Radiotherapy is a cancer treatment that uses high doses of radiation to kill cancer cells and shrink tumours.[11] Chemotherapy is the use of chemicals to treat disease. Immunotherapy is a type of treatment to encourage the work of the immune system or the immune system to be more effective in fighting cancer.[13] The mechanism of action of each therapy is different for inhibiting cell division and proliferation of rapidly growing cells.[14] Chemotherapy is generally and effectively used in treatment of cancer, destroying not only malignant cells but also normal cells with high-proliferating potential.[15] The most common side effects of chemotherapy are nausea and vomiting, fatigue, loss of appetite, hair loss, dry mouth, and constipation.[16,17] Thus, the discovery of new anticancer drugs with high activity and low side effects is an imperative. According to *Nurgali*,[18] the combination of natural bioactive compounds with traditional chemotherapeutic drugs can enhance anticancer efficacy and reduce side effects of chemotherapy.

Marine organisms provide a rich source of the novel anticancer drug and an alternative source to meet the demand for effective and cut-price drugs.[19,20] Numerous bioactive compounds from marine organisms show various therapeutic effects and pharmacological properties, such as antioxidant, antitumour, anticancer, and antiviral.[21–23] More than 36,000 marine-derived compounds have been reported, and over 1,500 compounds more are delineated each year.[24] There are many marine-derived compounds in preclinical, clinical pipeline, and some marine-derived compounds have been put on the market.[25] In November 2019, six marine-derived drugs for cancer were approved in the clinical marine pharmaceutical pipeline including cytarabine, eribulin mesylate, brentuximab vedotin, trabectedin, plitidepsin, and polatuzumab vedotin.[26]

Seaweeds, also known as marine microalgae, are widely distributed in the ocean including the intertidal, tidal and subtidal regions, respectively.[27] They are divided into three major groups; brown algae or phaeophyceae, green algae or chlorophyta, and red algae or Rhodophyta.[28] Seaweeds contain medicinally potent compounds, including flavo-

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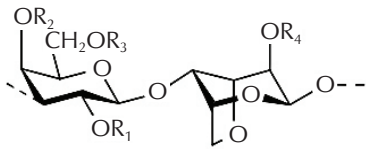

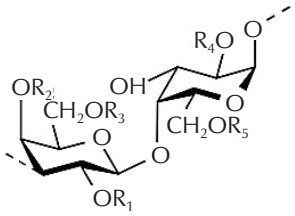

Carrageenan	R_1	R_2	R_3	R_4
κ	H	SO_3^-	H	H
ι	H	SO_3^-	H	SO_3^-
α	H	H	H	SO_3^-
β	H	H	H	H
ω	H	H	SO_3^-	H
θ	SO_3^-	H	H	SO_3^-

Carrageenan	R_1	R_2	R_3	R_4	R_5
μ	H	SO_3^-	H	H	SO_3^-
ν	H	SO_3^-	H	SO_3^-	SO_3^-
λ	SO_3^-	H	H	SO_3^-	SO_3^-
ξ	SO_3^-	H	H	SO_3^-	H
π	SO_3^-	Pyruvate		SO_3^-	H
γ	H	H	H	H	SO_3^-
δ	H	H	H	SO_3^-	SO_3^-
ψ	H	H	SO_3^-	H	SO_3^-
ο	H	SO_3^-	H	SO_3^-	H

Fig. 1 – Structures of carrageenans

noids, phenolics, tannins, terpenes, polyphenols, phlorotannins, polysaccharides, and peptides that have shown anticancer activity.[29–31] Several studies have shown that sulphated seaweed polysaccharides, including carrageenan, have promising effects not only against different cancer cell types *in vitro* and *in vivo,* but also against different types of viruses.[32–34]

Due to its biological activity, the use of carrageenan as a naturally occurring polysaccharide, has been increasing widely for human applications, thus creating a strong position in the biomedical field. The present review is focused on the application of carrageenan biomedical products to prevent and treat cervical cancer.

2 Carrageenan from red seaweeds

Carrageenans are mostly extracted from red seaweeds, particularly from *Chondrus cripus, Kappaphycus alvarezii*, and *Eucheuma denticulatum*. Other genera, including *Gigartina, Iridaea, hypnea, Acanthophora, Porphyra umbilicalis, Meristotheca, Cystocloniaceae*, and *Sarconema* are also used as sources of carrageenan.[35–41] Species of *Eucheuma* and *Hypnea* predominantly produce κ-Carrageenan and ι-Carrageenan;[42,43] the genera of Gigartina and Chondrus are the source of -λ-Carrageenan, and the genera of Cystocloniaceae family mostly produce iota-Carrageenan.[44] In recent years, some processes for the extraction of carrageenan from various red seaweed species have been reported. These processes include enzyme-assisted extraction (EAE), physical processes, chemical extraction (alkaline treatment), and microwave-assisted extraction (MAE).[45]

Carrageenans are a group of linear sulphated polysaccharides that are made up of repeating structure of galactose units and 3,6-anhydro-galactose (3,6-AG). The units are joined by α-1,3 and β-1,4-glycosidic linkage.[46,47] Based on the family,[48,49] carrageenan is classified mainly into four types, including kappa-carrageenan (κ-carrageenan), beta-carrageenan (β-carrageenan), lambda-carrageenan (λ-carrageenan), and omega-carrageenan (ω-carrageenan). The kappa (κ) family contains a subclass such as kappa (κ), iota (ι), mu (μ), nu (ν), and omicron (ο) carrageenans. The beta (β) family comprises beta (β) and alfa (α)-carrageenans and their biological precursors gamma (γ) and delta (δ)-carrageenan. The lambda (λ) family contains a subclass including lambda (λ), xi (ξ), pi (π), and theta (θ) carrageenan, while the omega (ω) family contains a subclass including omega (ω) and its biological precursors psi (ψ) carrageenan.[48–51] The structures of carrageenans are shown in Fig. 1. The structural differences of carrageenan types influence its physical characteristics including hydration characteristics, strength, texture, and temperature of gel formation, as shown in Table 1. Three of the 15 distinct carrageenan structures are primarily employed for commercial purposes: κ, ι, and λ carrageenans.

The ester sulphate percentage of kappa type carrageenan is about 25 to 30 %, and the 3,6-AG concentration is about 28 to 35 %. The ester sulphate level of iota type carrageenan is about 28 to 30 % and the 3,6-AG concentration is about 25 to 30 %. The ester sulphate content of lambda type carrageenan ranges from 32 to 39 %, with no 3,6-AG concentration.[52] The high sulphate concentration of carrageenan is important because it can result in antioxidant or anticoagulant characteristics, which is a vital trait for its use in biomedical applications.[53,54]

Table 1 – Physical characteristics of commercial carrageenans

CG types	Iota (ι)	Kappa (κ)	Lambda (λ)
gelling/°C – effect cations – gel texture	strongest gel with Ca^{2+} elastic	strongest gel with K^+ Brittle	non-gelling –
solubility/80 °C	soluble	soluble	soluble
melting/°C	50–80	40–75	–
pH stability	4–10	4–10	4–10
sources:[49,55]			

The solubility of carrageenan is influenced by various factors, such as temperature, pH, the presence of other solutes, the type of carrageenan (sulphate groups), and their associated cations such as K^+ and Ca^{2+}.[49,56,57] All carrageenans are soluble in hot water. However, λ-carrageenan and sodium salt of κ- and ι-carrageenans are soluble in cold water. The viscosity of the solutions is increased by λ-carrageenan, which does not gel. At low concentrations, κ- and ι-carrageenans produce gels when cooled, depending on the additional cation (calcium or potassium) at low concentration 0.5 %. κ-carrageenan gels are weaker in the presence of Ca^{2+} than K^+. In the presence of Ca^{2+}, κ-carrageenan gels are stronger yet brittle, and they tend to show syneresis (separation of liquid from its gel). In the presence of Ca^{2+}, λ-carrageenan forms flexible gels with little syneresis.[55]

3 Mechanism of antiviral action

Carrageenan has high density of anionic groups from the presence of the sulphate residues in their molecular structure. Ionic interactions between anionic groups in the polysaccharide and basic amino acids of the glycoprotein form the virus-cell complex, while non-ionic interactions rely on hydrophobic amino acids interspersed between the basic ones in the glycoprotein-binding zone.[48] Carrageenans are selective inhibitors of several enveloped viruses (HIV-1, HSV-1, IFV-A, IFV-B, RSV-A, RSV-B, and PIFV-2), and non-enveloped viruses (HAV and HPV), and act predominantly by inhibiting viral binding, inhibiting viral internalisation and un-coating, or inhibiting viral transcription and replication.[58,59] The mechanism of viral inhibition of carrageenan is shown in Fig. 2. Viral infections require binding to the surface of the host cell. Various cell surface components may play a role in viral attachment, and among them, glycans displayed on proteins or surface lipids interact with a large number of viruses. In enveloped viruses, this blocking capacity has been reported, possibly due to the ability of carrageenan to bind to viral envelope proteins, such as herpes simplex glycoproteins. After attachment, carrageenans can block viruses from nucleocapsid internalisation into the cytoplasm, and disable them to uncoat from the endosome. In addition, the presence of carrageenan can inhibit the reverse transcriptase activity of virus.[60]

The virucidal properties of carrageenan may be related to the virus's inability to complete the infection process because the viral envelope sites essential for virus attachment to host cells are occupied by the sulphated polysaccharide.[61] Carrageenan suppresses HPV with over 1,000 times the efficacy of heparin, a highly powerful anti-HPV drug.[62]

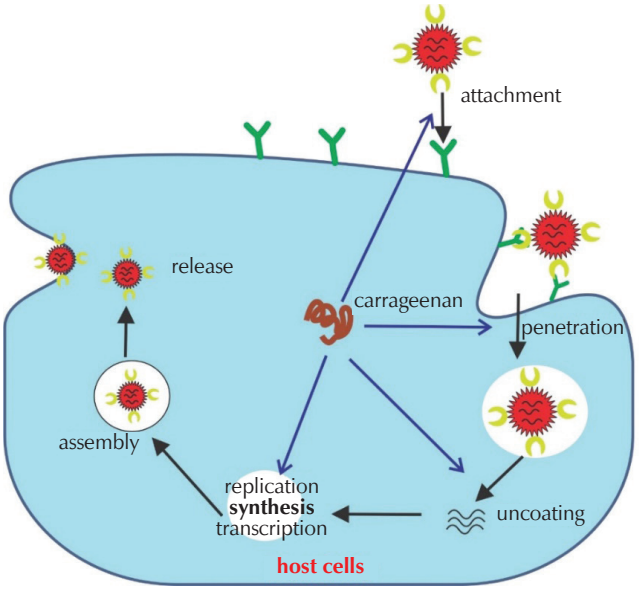

Fig. 2 – Mechanism of viral inhibition of carrageenan[60]

Carrageenan and carrageenan oligosaccharides possess well-known antiviral properties,[63] and are reported to be effective mainly against papillomavirus (HPV) infection. The inhibitory effect of carrageenan on HPV-PsV infection of various cell types was validated by *in vitro* clinical trials (HeLa cells, HaCaT cells, sperm cells, HSPG-deficient PGSA-745 cells, and 293TT cells). The most widely accepted explanation for this effect is that carrageenan binds directly to the capsid.[64] Based on reported studies, thirteen women were enrolled, and thirty samples taken after various time intervals were evaluated. Carrageenans were detected in 87 % of CVL samples, with levels decreasing with time as a result of intercourse. PsV16 inhibition was detected in 93 % of CVL samples, with a median inhibition of 97.5 %. PsV16 inhibition reduced over time but remained high, with median inhibition of 98.1 %, 97.4 %, and 83.4 % after 1, 4, and 8–12 h, respectively. Higher concentrations of carrageenans were found to be related to higher levels of PsV16 inhibition.[65] Using a carrageenan-based lubrication gel can help women avoid genital HPV infections.[66] The lubricating gel can, apart from women, also be used by men for application on condoms or penis.

Carrageenan has been found to be an exceptionally powerful infection inhibitor for a wide spectrum of sexually transmitted HPVs after testing a number of chemicals. Despite the fact that carrageenan can block herpes simplex viruses and some strains of HIV *in vitro*, genital HPVs are around 1,000 times more sensitive, with 50 % inhibitory levels in the low ng ml^{-1} range. Even when diluted a million times, sexual lubricants prevent HPV infectivity *in vitro*. Clinical trials are needed to determine whether carrageenan-based

products are effective as topical microbicides against genital HPVs.[62]

According to *Derby*[67], griffithsin (GRFT) combined with carrageenan (CG) has strong activity *in vitro* and *in vivo* against herpes simplex virus-2 (HSV-2) and human papillomavirus (HPV). They have reported that GRFT/CG in a freeze-dried fast dissolving insert (FDI) formulation for on-demand use protects rhesus macaques from a high dose vaginal SHIV SF162P3 challenge 4 h after FDI insertion. Furthermore, the GRFT/CG FDI also protects mice vaginally against HSV-2 and HPV pseudovirus. The GRFT/CG warrants clinical development. *Prasedya et al.*[68]a consequence of loss of normal cell-cycle control, that underlies tumor growth. Recently there is an increasing interest in potential anticancer agents that affect cell cycle in cancer cells. Thus, in this study we investigated the effects of carrageenan on the tumor cell cycle. Methods: Using human cervical carcinoma cells (HeLa has reported that κ-carrageenan and λ-carrageenan have no significant effect on human umbilical vein endothelial cells (HUVEC). In contrast, both forms of carrageenan were cytotoxic towards HeLa cells (cancer cells).

Carrageenan inhibits not only papillomavirus (HPV) infection but also cofactor viruses of cervical cancer, such as human immunodeficiency virus (HIV)[71] and *Chlamydia trachomatis* infections.[70] Iota-carrageenan could be a promising agent to reduce the transmission of ocular chlamydial infection, and opens perspectives to develop prophylactic approaches to block *C. trachomatis* entry into the host cell.[71] *In vitro* and *in vivo* antiviral activities of carrageenan are shown in Tables 2 and 3.

Table 2 – In vitro evaluation of carrageenan to prevent HPV

CG Type	Virus Type	Cell Line	IC_{50}	Ref.
λ/ι-CG	HPV16	HeLa cells	4–55 ng ml^{-1}	62
κ/λ-CG (PC-515)	HPV16, 18, and 45 PsVs	HeLa cells	1–20 ng ml^{-1}	72
ι-CG	BVP1	C127 cells	1–10 μg ml^{-1}	62
CG (PC-1005)	HPV16 HIV	HeLa cells TZM-bl assay	>100 nM	73
ι-CG HIV MT-4 cells 100 μg ml^{-1}				74
ι-CG	HIVJR-FL	HeLa-CD4-CCR5 cells	1–10 μg ml^{-1}	75
ι-CG	CtB	HCjE cells	N/D	71
CG	CtB	HCjE cells	N/D	76

4 Future prospect of application

Why carrageenan has potential? Carrageenan has many applications in food (dessert mousses, canned food, ice cream, bakery fillings, instant desserts, and salad dressings), and medicine (stabilisers and suspension agents in some other drugs, medicinal creams, and lotions).[81] According to Grand View Research Data[82] in 2021 , the global carrageenan market was worth USD 780.5 million in 2020, and it is predicted to increase at a CAGR of 6.0 percent from 2020 to 2028. Carrageenan's mouthfeel properties to replicate fatty feeling are predicted to enhance market growth during the projected period, resulting in increased product penetration in dairy and processed meat products.

Based on its biological activities, carrageenans have been extensively investigated for their bioactivities such as anticoagulant, anticancer, antiviral, cholesterol-lowering effects, immunomodulatory activity, and antioxidant.[55] Carrageenan possesses promising activity both *in vitro*[62] and *in vivo*,[69–71] showing promising potential to be developed as HPV prevention agents. In addition, previous studies back up the theory that CG aids in the natural clearance of genital HPV infection in women who have a positive HPV-DNA test, acceptable in this population of HIV-infected women, and is nontoxic.[65,73,80]controlled, crossover safety trial in HIV-infected women in Thailand.Methodology/Principal Findings:Participants used each of 3 treatments (Carraguard gel, methylcellulose placebo gel, and no prod-

Table 3 – In vivo evaluation of carrageenan to prevent HPV

CG Type	Virus Type	Experimental System	Effects	Ref.
CG	HPVs	380 participants gbMSM receive treatment CG	Inhibition of infection.	77
CG-based lubricant (Divine 9)	HPV	During each act of vaginal intercourse, 280 women utilised gel plus condoms.	Infection with HPV is less common.	66
λ/κ-CG (carraguard)	HPVs	During each act of vaginal intercourse, 1718 women utilised gel plus condoms.	Infection with high-risk HPV is less common.	78
CG (0.02 %) + Propionibacterium extract (CGP)	HPVs	The study involved 40 healthy, sexually active women between the ages of 18 and 45 who had genital HPV infection. CG-CGP was given to each subject.	CG helps to speed up the usual clearance of genital HPV infection.	79
CG (carraguard)	HIV	60 women enrolled with a median age of 34 years; 25 % were sexually active. CG (carraguard) was given to each subject.	Higher perceived need for protection among HIV-infected women.	80

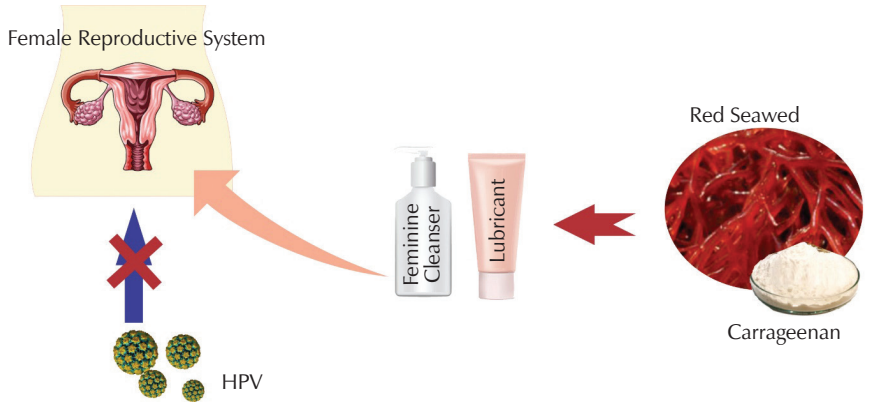

Fig. 3 – Liquid-sexual application of carrageenan

uct Based on its physicochemical properties, biological activities, and abundant availability, carrageenan has the potential as a raw material for medical products such as lubricant gel and feminine cleanser Fig. 3.

Lubricant gel

Most people are safe to use commercial lubricants. However, some lubricant products present risks such as allergic reactions, skin irritation, yeast infections, interfering with fertility, drying up rapidly, and requiring frequent reapplication. Some lubricants may affect function of sperm, decreasing the opportunity of a woman to conceive. Those attempting to conceive should use a sperm-friendly lubricant. Sexual couples wishing to use lubricants and prevent pregnancy can consider using spermicides combined with other contraceptives. A study has shown that the use of lubricants during procreative intercourse does not decrease the chances of conceiving.[83] PC-1005 gel is the MIV-150, ZA, and CG combination. PC-1005 used vaginally for 14 days was well tolerated, low systemic level, and confirmed further development as HIV and sexually transmitted infection prevention gels.[73] Previous studies have confirmed that CG lubricant gel or CG-based lubricant can reduce or prevent infection of HPV.[66,77–79]

Feminine cleanser

Intimate hygiene products are used by women on a regular basis as part of their cleaning routine. Minimising the onset or worsening of an inflammatory illness while maintaining high levels of infection protection, daily feminine hygiene should be approached with care in selecting an appropriate solution.[84] Feminine cleanser has no negative effects on sperm motility.[85] Carrageenan has the potential for application in feminine cleanser products due to its gelling and biological properties . The use of carrageenan in feminine cleanser not only maintains vaginal health against bacterial infections but also prevents HPV infection and inflammation of vaginal areas. A new intimate cleanser, called Saugella Acti3 (SA3), containing antimicrobial ingredients (thymol and zinc) with mild non-aggressive natural surfactants (derived from coconut and the amino acids of wheat) and mucoadhesive agents (xanthan gum and carrageenan) has been formulated. The results showed that women felt significantly better *vs* baseline 70.8 % *vs* 8.3 %.[86]

5 Conclusions

Carrageenans are a group of linear sulphated polysaccharides that are extracted from red seaweed. They are selective inhibitors of several enveloped viruses and non-enveloped viruses including HPV, HIV, and *Chlamydia trachomatis*. The virucidal properties of carrageenan may be related to the virus's inability to complete the infection process, because the viral envelope sites essential for virus attachment to host cells are occupied by the sulphated polysaccharide. Some studies have reported that both *in vitro* and *in vivo* carrageenans have the potential to be applied as a lubricant and feminine cleanser products, because they not only protect against genital HPV and reduce infection of HPV and cofactor viruses of cervical cancer, but are also non-toxic for human cells.

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SAŽETAK

Karagenan: budući potencijalni sastojak lubrikanta i proizvoda za žensku higijenu s mogućim zaštitnim učinkom protiv HPV infekcija

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Otkriće da je infekcija humanim papiloma virusom (HPV) primarni uzrok raka grlića maternice otvorilo je nove načine prevencije. Karagenani su potencijalni kandidati za prevenciju HPV-a zbog njihova djelovanja protiv širokog spektra virusa, uglavnom kroz blokiranje prianjanja virusa. Osim toga, karakteriziraju ih niski troškovi proizvodnje, velika dostupnost, biorazgradivost, biokompatibilnost i nisu toksični. Na temelju rezultata dosadašnjih studija, karagenan (*in vitro* i *in vivo*) ima potencijal za primjenu kao lubrikant i sredstvo za higijenu žena, jer može smanjiti mogućnost HPV infekcije te nije toksičan ni alergen.

Ključne riječi
Rak grlića maternice, humani papiloma virusi (HPV), lubrikant, biomedicinski proizvodi za higijenu žena

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