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TRUTH SERIES:

CARRAGEENAN CONTROVERSY

THE TRUTH SERIES

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As a discerning user of natural health products, you want what is best for your health. However, misinformation and deceptive marketing often make it challenging to identify fact from fiction. The Truth Series was created by Advanced Orthomolecular Research (AOR) to share the evidence-based truth about the most controversial and confusing topics within the natural health industry. At AOR, we believe that truth and transparency are the most important values for any organization to uphold. As visionaries, we are committed to continuous innovation so that we can advance the world of natural health. As such, the Truth Series aligns with our vision of providing optimal products without compromise.

Published in Canada by:
Advanced Orthomolecular Research Inc.

Managing Editor:
Cassy Price

Author:
Dr. Nirat Nibber, ND

Publication Design / Art Production:
Leandro Serrano

Reviewer:
Dr. Traj Nibber, PhD

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HISTORICAL AND MODERN USE OF CARRAGEENAN FROM ALGAE

Historical Uses

A fascinating field of botany often overlooked is that of phycology, also called algology or the study of algae.[1] Algae are considered a group of photosynthetic aquatic plants that have tremendous ecological importance, shaping much of the food chain. Types of algae include seaweeds, diatoms, dinoflagellates, phytoplankton, cyanobacteria, and many more.[2] Seaweeds offer an interesting example of the tremendous and varied uses these plants have and can serve. Seaweeds come in many shapes and sizes and are classified based on the colour known as brown, green, and red algae.[2] Each with many subspecies with differing composition and use. Brown algae known as edible giant kelps are commonly found off the west coast of North America.[2] Red and green algae are more common in foods and have long histories of consumption. The first documented historical references to human use or consumption of red algae were made in China as early as 300 BCE.[3] Specific references to consumption of red algae in Japanese cuisines as nori is well known to sushi lovers. Chinese, Greek, and Roman literature also references health and industrial benefits of seaweed as early as 500 AD.[3] In Ireland a type of red seaweed known as Irish moss (Chondrus crispus) was used as an antiviral therapy for livestock, and in humans it was thought to cure upper respiratory symptoms such as colds, flu and congestion. Given the abundance of seaweed along the coast, red seaweed would be collected, and laid out to dry before being boiled and added to flans, tonics and beer.[4]

By the late 1800s seaweed algae or algal derivatives - agar or carrageenan (CGN), were commonly consumed in many recipes as a replacement for the more costly alternative gelatin.[3] Much of the seaweed and agar used in North America before the 1940s was supplied by Japan. However, during World War II, the supply shortage required North American food suppliers to begin extracting their own. This led to the development of an entire commercial industry built on the processing and extraction of algae derivatives from seaweed.

Carrageenan vs. Gelatin

Gelatin, an animal protein derived from the cartilaginous parts, bones, and tendons, of cows, pigs, and fish. Is a very popular and effective coagulant and gelling agent. Used in baking, food processing, and in stabilizing softgels. This ingredient has a few significant drawbacks to its widespread use that drove the need to seek alternatives[6]:

- Concerns regarding sustainability as extraction requires high volumes of animal byproducts
- Ethical and moral concerns have arisen regarding the treatment of animals. Further bones and joints from the meat industry have not been repurposed leading to increased waste.
- While commercial gelatin is usually stable it is not as heat resistant as carrageenan

Investigations into the components of algae ensured a greater use for these plants. A Chicago based dairy producer found that carrageenan from red algae was effective at stabilizing chocolate milk, preventing separation of the chocolate from the milk. This discovery drove further research and by the 1950s carrageenan was widely used in many foods. The effectiveness, environmental sustainability, biodegradability, nontoxicity, ease of access, and low cost for production further drove the desirability of carrageenan as a gelling and stabilizing agent. With the more ubiquitous use of carrageenan researchers and regulatory bodies understandably took a greater interest in understanding the health impacts of carrageenan. As we will discuss later this interest has resulted in an important and nuanced discussion about this ingredient. To fully understand the wide use, we must explore the unique biochemistry of this important ingredient.

What is Carrageenan?

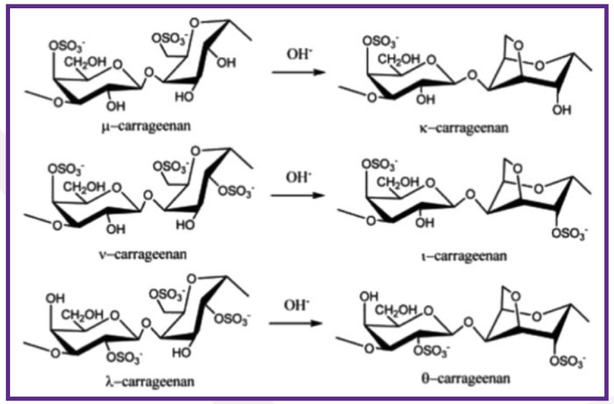
keh• ruh• gee• nuhn (CGN)

Carrageenan was named after Carrigan Head in Northwestern Ireland. Derived from the Irish word "carraigín," meaning "little rock".[4] Carrigan Head was famous for using Irish moss to make a popular pudding, *Blancmange*.

Seaweed algae with significant industrial uses share the common characteristic of having phycocolloids.[7] Phycocolloids are non-crystalline larger molecular structures, derived from seaweeds that when dissolved create thick viscous mixtures.[7] There are three main groups - agars, alginates, and CGN that have been identified and have long histories for industrial and commercial uses. CGN is a naturally occurring anionic and water-soluble polysaccharide fibre, isolated from numerous species of red seaweed.[7,8] These polysaccharides are characterised by the repeating galactose sugar backbone with high molecular weights (Mw200 000 to 800 000 Da) with variable position and number of sulfate groups.[7] The large polysaccharides are resistant to degradation as humans do not have enzymes that degrade these glycosidic bonds, operating similar to dietary fibres.[9]

Forms

The position and location of the sulfate group-galactose linkage determines the CGN type: specifically, lambda (3 sulfates/disaccharide,) iota (2 sulfates,) and kappa.[7] The exposed sulfate groups along with the high molecular weight ensures strong binding capacity and flexibility.[7-9] These linear polysaccharides all have high molecular weight, temperature dependent gelling and stabilizing properties, and are considered viscoelastic (meaning they can thicken while maintaining their flexibility).[7-9] Given the slight structural differences in each form they have differing charge densities and solubilities. Though each still have different commercial and industrial uses. For example, kappa-CGN which is being studied for agriculture as it can form hydrogels that effectively deliver potassium.[7] While lambda CGN does not form a gel and is more effective at thickening. CGN is used as an excipient in drug and gene delivery systems, wound dressing, and tissue engineering as it is included in the approved list in the US FDA Database of Inactive Ingredients.[10] The stability of these gels makes CGN ideal for softgel manufacturing as this viscous hydrogel is stable and strong enough to prevent leakage of ingredients.[7] In commercial food processing the form used depends on the protein, metal, and mineral content of the food as well as the purpose.



What is carrageenan found in? [4,7,9]

- Yogurt
- Cream
- Certain cheeses
- Sauces
- Beers
- Soya products
- Processed meats
- Baby formula
- Toothpastes
- Shampoos

Processing and Extraction:

Carragenophytes (Seaweed species with high carrageenan content):

**Eucheuma spp.*
**Kappaphycus alvarezii Sarcothalia crispata*
Gigartina skottsbergii Chondracanthus chamisoii
Gracilaria chilensis
Pyropia
Chondrus crispus
Calliblepharis jubata

Cultivation or farming of seaweeds for extraction and use is a large and highly profitable industry. Carragenophyte seaweeds are those species of red algae that have high carrageenan content.[5] Historically carragenophytes we harvested, manually collecting, and drying the seaweed where it naturally grows.[4] While these species are present throughout the world Indonesia and the Philippines lead commercial cultivation methods developed in the 1980s.[12] An advantage of cultivation is that a consistent supply and large volume of seaweed can be grown. As large volumes of seaweed are required to extract the carrageenan. Known as fixed off bottom line and the floating raft method of cultivation, large volumes of the two primary carragenophytes: Kappaphycus and Eucheuma can be cultivated with approximately six to eight weeks to harvesting.[12] While this may be the more economical decision there are drawbacks to cultivation. Specifically, that this method has led to over farming and concerns relating to the ecological impact.[12]

Wild harvesting is another method of collection that is more common in Europe, Canada and South America.[13] Wild harvesting is more labour intensive and has lower yields. Yields also have seasonal variation with higher yield for carrageenan from mid spring to summer. The resiliency of seaweeds to climate change and environmental pollutants is admirable. However, there are concerns that we are pushing our limit, with the rise in ocean pollution, microplastics, and lower ocean temperatures.[12] Sustainable options include a hybrid of cultivation methods and wild harvesting.[11-13] Portugal for example is engaging in a sustainable practice known as Integrated Multi-Trophic Aquaculture (IMTA), which reduces aquaculture wastes in "a controlled environment, with organic certification for quality, traceability, stability of supply and a small carbon footprint."[12] Once the carragenophytes are collected, the extraction of carrageenan requires a multi-step process. Manufacturers take the cleaned and dried seaweeds and will engage in semi-refined, refined or mixed processing.[11] Treatment of the dried clean seaweed is done with warm or hot alkali solutions of 5-8% potassium hydroxide solutions to remove the cellulose. Carrageenan is then evaporated; depending on the solution, it can be evaporated using high temperatures precipitated with alcohol or high salt.[11]

Chondrus		
Canada	2 000	
France, Spain, Portugal	1 400	
Republic of Korea	500	
Subtotal	3 900	2.3%
Eucheuma and Kappaphycus		
Indonesia	25000	
Philippines	115 000	
Tanzania (Zanzibar)	8 000	
Others	1 000	
Subtotal	149 000	88.5%
Gigartina		
Chile	14 000	
Morocco, Mexico, Peru	1 500	
Subtotal	15 500	9.2%
Total	168 400	100%

Molecular weight matters...

While the form of CGN is helpful in determining the most appropriate commercial and industrial use; the more important discussion is related to the molecular weight and processing of the polysaccharide.[7,8] CGN (in any form) can be defined as undegraded or degraded (broken into smaller pieces of Mw20 000–40 000 Da.) Further, a molecule derived from CGN called poligeenan (PGN) is characterised by a very low molecular weight of 10 000–20 000 Da and is and sometimes incorrectly labelled as degraded CGN. Both PGN and degraded CGN are produced in laboratory settings and are distinct from the commercially available CGN used in food and drug/nutrient delivery. Degradation from a high molecular weight to a low molecular weight requires acid hydrolysis using a strong acid (pH<2) and high temperature (>80 °C) for four to six hours.[11] This very specific process yields low molecular weight pieces that are more likely to be absorbed through the intestinal lumen, meaning they are no longer "inactive ingredients." As such, regulatory bodies have restricted use of degraded carrageenan or PGN.[14] Animal models have also demonstrated that PGN is a carcinogen and causes gastric ulcerations.[15] The importance of this distinction has largely driven the conversations around safety that we will continue to explore in the next section.

THE CARRAGEENAN CONUNDRUM

Sustainability

As we have seen, both red algae and its derivative CGN, have long and illustrious uses in food, health and manufacturing.[3-5] Given the versatility and attractive properties of CGN its use as an additive has increased drastically. With this increased use, it is important that research and regulatory bodies regularly investigate the safety and efficacy of CGN, particularly as its uses expand to include food packaging and drug delivery systems. While the consensus (based on regulatory reviews) appears to be that undegraded CGN is inert and safe for consumption,[10] it is important to understand the criticism as public opinion on CGN food additives has shifted significantly in the last decade. This criticism began in the 1970s with animal studies and degraded CGN, which has cast doubt as to the safety of long-term consumption.

A review published in 2013 by the Cornucopia Institute outlined concerns based largely on the research of a prominent critic Dr. Tobacman.[16] Critics bring to light three major concerns with the widespread ingestion of carrageenan: the inflammatory response initiated by carrageenan in the human GI tract, the increased exposure with ubiquitous use, and concerns over regulatory bias.[16] In this section, we will review some of the concerns brought and how the scientific community, regulatory bodies and the food processing industry respond.

Can CGN Cause Cancer, Leaky Gut, Ulcers and Inflammation in the GI Tract of Humans?

Concern related to the long-term effects of CGN on proper functioning and overall health of the gastrointestinal (GI) tract, first arose in the 1970s with cell line histological studies.[17] Then in the 1980s, animal studies suggested that CGN may have carcinogenic properties and promoted the development of tumors and ulcerations in the GI tract of rats.[17] Animal studies at this time also suggested that injectable undegraded CGN induces a pronounced inflammatory response.[17] In 2008 once again cell studies reported that cell death and cell cycle arrest occurred when human intestinal epithelial cells were directly exposed to CGN.[18] Researchers from the University of Chicago also proposed that CGN could increase intestinal cell permeability but could not replicate the results when necessary controls were added.[18]

Earlier cell line studies demonstrated that high doses of low molecular weight CGN (that they simply referred to as CGN) could induce cell cycle abnormalities but did not differentiate differences in the undegraded, degraded or PGN, effectively comparing apples to oranges.[7-9] The methodology was questioned and subsequent histological studies using undegraded CGN could not reproduce these results. Three major criticisms revealed in reviews from 2019 and 2020 were identified:

a) there are inconsistencies in defining the causative agent poorly differentiating between low and high molecular weight

b) extrapolating results of injected forms does not mimic actual exposure with oral administration

c) that the results from these studies have yet to be reproduced and often exceed administration or doses that have already been stipulated by regulatory bodies

Let's review these three points in detail.

A. PGN False Equivalency to CGN

One of the greatest points of contention in the discussion around the safety of CGN is the distinction between CGN, degraded CGN and PGN. As mentioned earlier, there are specific differences based on molecular weight, solubility and synthesis. Unfortunately, many researchers are making false equivalencies between effects of degraded CGN and PGN and applying these findings to food grade CGN.[7] While you can see in the table below that PGN is classified based on molecular weight. Molecular weight is important because it determines solubility and absorption into the gut.[7, 8, 19] The larger CGN is not absorbed and depending on the form mentioned above can gel, thicken, or emulsify protein structures. The processing and extraction of CGN also requires alkaline treatment to remove the cellulose encasing the CGN.[7, 11] Thus, it is important to recognise that these are in fact distinct molecules. PGN is derived from CGN and the harsh treatments it is subjected to renders it a completely different molecule.

Property	Carrageenan	Poligeenan
Manufacture	Alkaline extraction at room temperature	Acid hydrolysis (pH 1) at high temperatures, 95°C for up to 6 h
Uses	Food additive, pharmaceutical exipient at <2.0% in food	Medical Imaging in Barium Sulfate slurries at 10% w/w
Molecular Weight % below 50 000 % below 20 000 % below 10 000	200 000 - 800 000 Da. <5% <0.5% <0.1% (not detected)	10 000 - 20 000 Da. >90% About 70% About 50%
Physical Properties	Polydisperse Strongly bound to protein by 3 cross-linking mechanisms including CGN helical formation for complex 3-D CGN-protein structures Gel formation	Polydisperse Bound to protein strongly with no helical formation and complex 3-D structures No Gel formation
Functional Properties in Food	Stabilizer (proteins and emulsions), gelation, thickener	None
Toxicological Properties	Not absorbed by GI tract. Safe via oral exposure in laboratory animals and man Not carcinogenic, tumorigenic, genotoxic No immune system effects Not a tumor initiator or promoter Not a developmental or reproductive toxicant	Absorbed to some extent by GI tract Causes GI ulceration and tumors in laboratory animals via food, water Carcinogen by oral route in animals Immune system tocicity, suppress immune response

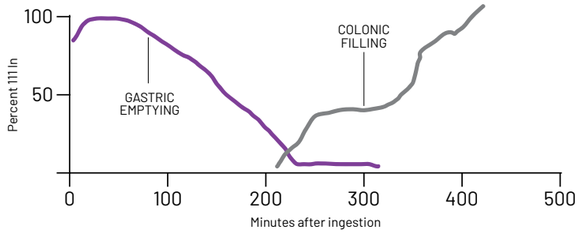
There is a consensus within the scientific community that PGN carries a high risk and has been deemed a category 2b carcinogen by The International Agency for Research on Cancer.[20] While CGN does have GRAS status in both the European Food Safety Authority (EFSA) and the Food and Drug Administration (FDA) as additives.[10] Naturally since PGN is deemed toxic and can cross the GI tract into tissues, the question remains can undegraded CGN become degraded inside the human GI tract?

"There is no evidence of any adverse effects in humans from exposure to food-grade carrageenan, or that exposure to degraded carrageenan from use of food-grade carrageenan is occurring"

- EFSA report, 2003

Acid hydrolysis by the gut

As we know, food that enters the digestive system is subject to acid hydrolysis by HCl, with a pH of 1.5-3.5 with 0.1-0.01 molar concentration, produced in the stomach.[22] Gastric emptying occurs over four to six hours depending on how much was eaten, age, sex and health conditions.[22] These conditions are unique from the lab conditions (high temperature, long period) for PGN production.[7] While it is certainly possible that a small percentage of the undegraded CGN will be hydrolysed to smaller molecular weight products in this time, this is not the same as PGN.[7, 8, 23] This degraded CGN is still of higher molecular weight than PGN and does not exhibit the same absorption and toxic capacity as PGN.[23] The European Commission report stipulated that food-grade carrageenan should be kept below 5% of any CGN used.[21] The production of PGN from CGN in the GI tract has not been demonstrated in a clinical setting. Therefore, reliable and quality manufacturers must test for and limit any degradation of CGN for commercial uses as per regulation.[21] Quality manufacturing and strict enforcement will help alleviate these concerns of further degradation. Further additional studies would provide useful insight into CGN in individuals with gastric conditions that increase acid hydrolysis such as hyperchlorhydria or delayed gastric emptying.



(Adapted from Camilleri, et al. Am J Physiol Gastrointest Liver Physiol 257:284, 1989.)

B. Route of Administration

Animal studies referenced in the Cornucopia review demonstrated induction of an inflammatory response when CGN was injected into the foot pad or intraperitoneal cavity of rats.[16] The review correctly states that research used the CGN to induce inflammation to test anti-inflammatory drugs.[16] However, outside a lab setting CGN as a food additive is acting as a dietary fibre.[24] As such it is not absorbed into confined tissue spaces or accumulating in various organs as proposed by these in vitro studies.[24] Therefore, studies that do extrapolate findings of injected or high dose CGN administration into areas that food grade forms cannot reach are difficult to reliably interpret. Once again, we find ourselves having to compare apples to oranges.

C. Ubiquitous Use Leads to Increased Exposure

Another valid concern brought up by critics for the widespread use of CGN is that given certain gaps in our knowledge there may be increased risk. With a rise in processed foods containing carrageenan, such as milk alternatives, the EFSA set guidelines regarding safe consumption based on body weight in 2018 as 75 mg/kg body weight per day.[25] Further, according to the FDA any "other ingredient" can only be declared as such when it is less than or equal to 2% of the formula or total weight (reg req 21CFR 172.480).[10] While it may be difficult to determine individual consumption of CGN, health care practitioners have consistently promoted the reduction in processed foods in general.

Food	Percent carrageenan (g/100 g food)
Bakery products	0.01 - 0.1
Chcolate milk	0.01 - 0.2
Cottage cheese	0.02 - 0.05
Frosting base mix	3 - 4
Ice cream, frozen custard, sherbets, etc	0.01 - 0.05
Jams and jellies	0.5 - 1.2
Liquid coffee whitener	0.3
Pie filling	0.1 - 1.0
Pimento olive stuffing	2.0
Processed cheese	0.01 - 0.06
Processed meat or fish	0.2 - 1.0
Pudding (nondairy)	0.1 - 0.5
Relishes, pizza, barbecue sauces	0.2 - 0.5
Yogurt	0.2 - 0.5

Government and Regulatory Guidance and Biased Research

It should be reiterated that carrageenan has undergone continual review by expert committees from world-wide regulatory bodies and remains an approved food additive. Regulatory bodies including the FDA, Health Canada, the EFSA, Joint FAO/WHO Expert Committee on Food Additives (JECFA), United States Department of Agriculture (USDA) and more, have all allowed carrageenan to be added as a direct food additive and this additive is considered safe.[9,10,21,25] These regulatory bodies evoke a sense of reassurance and trust given the breadth of the work they do, rigorous guidelines and compliance requirements. Approval from these bodies is subject to regular revision and can be revoked when new data is presented. Certainly, such bodies are not immune to influence or bias, however having multiple organisations and committees increases transparency and helps reach a scientific consensus.

Discussions relating to the versatility, and sustainability of CGN use has certainly brought it to the forefront of conversation. It's important that decisions are made by limiting the scientific biases or industry lobbying.

Timeline: Commercial Use and Regulatory Approval of Carrageenan: [3-5,26]

1830: Carrageenan from Irish Moss published in a popular cookbook

1940: Krim Ko, a Chicago based dairy company, begins using carrageenan derived from red seaweed in chocolate milk

1959: Carrageenan was granted GRAS (Generally Regarded as Safe) status in the United States

1961: FDA approval

1972: Food and Drug Administration, reconsiders status of carrageenan and an amendment to the Code of Federal Regulations for the food additive was proposed

1988: PGN is classified as carcinogen

2001: 57th meeting of the JECFA (Joint Food and Agriculture Organization of the United Nations/World Health Organization Expert Committee on Food Additives) determine CGN safe for trade and use

2008: JECFA declared that carrageenans are not recommended for use in infant formulas

2018: EFSA stipulate safe recommendation on basis of 75mg/kg body weight/day

2018: USDA decision for CGN to remain on the National List, permitted for use in processed organic foods in the US. After NOSB submits its recommendation to remove from list as "not necessary"

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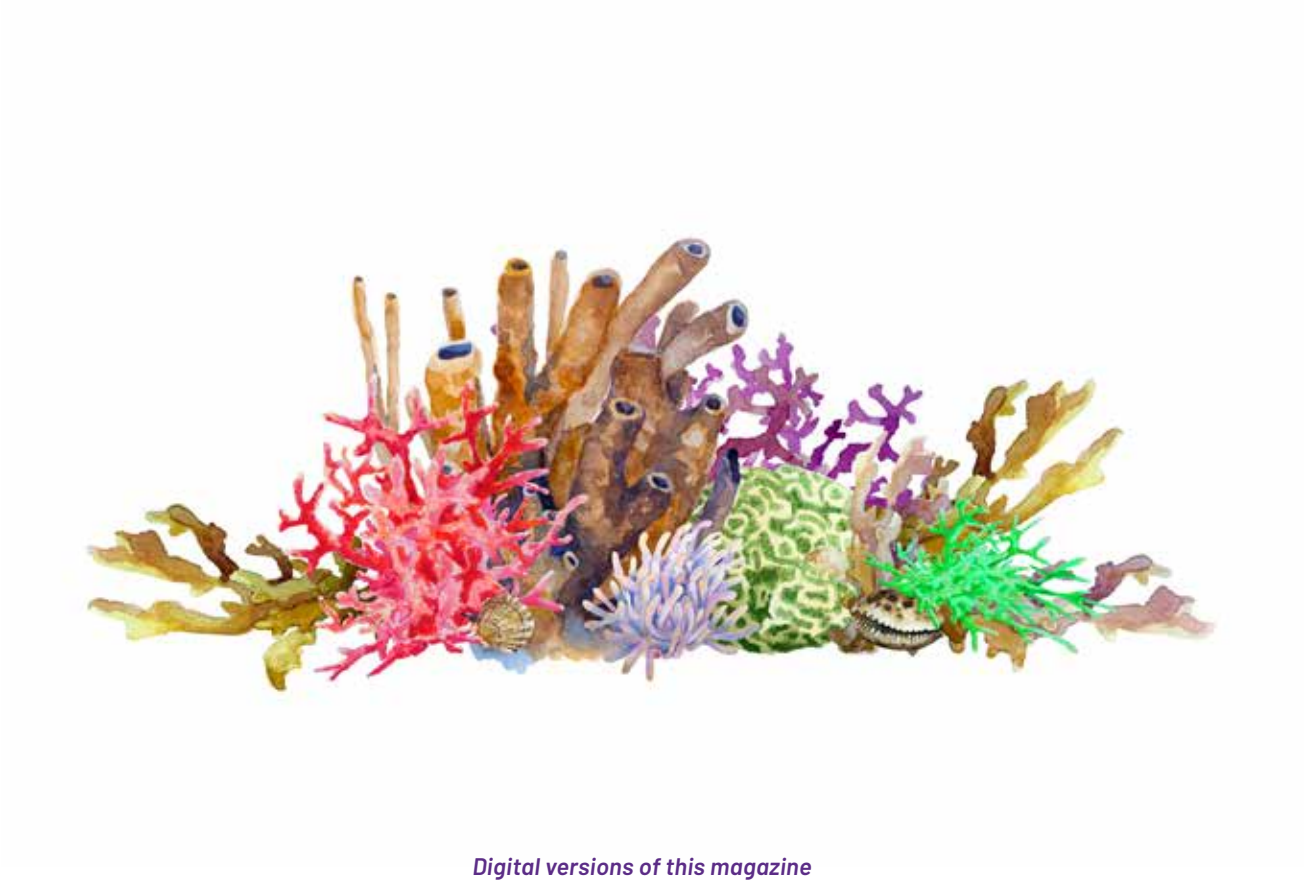

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