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SHORT REVIEW

A Review on the Potential Anti-inflammatory Properties of *Kappaphycus alvarezii*

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Abstract

Inflammation is significant innate mechanism of immunity in our human system. It enables our body to respond to a variety of stimuli, including ischemic, traumatic, physical, chemical, and infectious impulses. A major contributor to global health challenges and a significant driver of rising health expenditures are inflammatory disorders. Naturally occurring substances as well as its chemical structural analogues with anti-inflammatory potential have been discovered in the recent years. Marine life forms have a myriad source of natural molecules that can invoke inflammation as a defense against pathophysiology of illness. Macro and microalgae have been determined to be an undiscovered resource with pro-and anti-inflammatory compounds. Natural substances found in marine species can be employed in novel interventions as treatment modalities as anti-diabetic, anti-inflammatory, anti-bacterial, anti-viral, and antioxidant capabilities. Among these substances, *Kappaphycus alvarezii* is one such marine red algae that can be employed therapeutically to possess biological effects that exhibit strong anti-inflammatory activity and fewer adverse effects. The expanding desire to research marine seaweeds such as *Kappaphycus alvarezii* and its phytochemicals has made it possible to find novel substances with the potential to be used in healthcare in the near future. This review envisages the anti-inflammatory properties of marine algae along with phytochemicals discovered in *Kappaphycus alvarezii* and its biological functionalities.

Keywords: Antioxidants, *Kappaphycus alvarezii,* Phytochemicals, Secondary Metabolites

1. Introduction

Inflammation appears to be the biological response of immune cells in the body. The different factors responsible for inflammation are the microorganisms, chemical components, physical agents, metabolic reactions which result in redness, swelling, chronic pain, or acute pain. These may stimulate the inflammatory reaction in the lungs, heart, pancreas, brain, reproductive system, kidney, intestinal tract, and liver which possibly leads to various diseases and tissue damage[1]. Pro-inflammatory cytokines such as tumor necrosis factor, interleukin-1 and interleukin-6 promote the upregulation of the inflammatory response. Sensitivity to pathogen-associated molecular patterns and damage-associated molecular patterns activates the pro-inflammatory response in monocyte-macrophage cells[2]. Due to rising environmental damage and exposure to hazardous substances, inflammation is currently society's biggest problem. It can be treated by determining its source, removing dead cells, and mending the tissues that have been harmed. There are occasions when bacteria prevent the tissue from remodelling, which leaves a damaged area where it should not be and causes serious health issues. Anti-inflammatory medications are crucial to the development of human history. The creation of innovative, synthetic drugs with the potential to be anti-inflammatory has seen a recent advance owing to the extraction of key elements from living marine organisms[3].

The natural compounds found in marine organisms help in providing anti-diabetic[4], anti-inflammatory[5] and

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can be used in new drug formulations[6]. These natural compounds also possess anti-obesity, anti-oxidant, and anti-cancer properties. Between several marine organisms, algae are one of the highly valued resources in the sea. Algae are rich in bioactive compounds such as proteins, polyunsaturated fatty acids, tocopherols, phycocyanins, antioxidants, soluble dietary fibers, carotenoids, phycocolloids, vitamins, polysaccharides, terpenes, minerals, sterols, phycobilin[7]. It possesses a wide range of medicinal properties, which have an application externally and internally. The brown algae and red algae are seen in the sea, whereas green algae are seen in rocks, the bark of trees in moist environments, and freshwater.

The red algae are rich in polysaccharides, vitamins, unsaturated fatty acids, carrageenans, amino acids, phytoalexins, minerals, and several other bioactive components which have both therapeutic and commercial applications[8]. This investigation primarily focuses on the red algae *Kappaphycus alvarezii,* which is economically valued red algae and commercially it is called 'cottoni'. Its cell wall has carrageenans that have anti-inflammatory, anti-oxidant, anti-diabetic, and many other properties[9]. The fresh and even the dry marine algae are commonly eaten by the people staying near seashores. Those edible algae contain a major amount of nutrients needed for humans[10]. The defending property of red algal species as a promising usage in pharmaceuticals is being explored shortly.

2. Marine Algae and its Classifications

According to the study, an approximation of 72,500 species of algae was found worldwide, that are mostly marine[11]. Marine algae were one of the abundant sources of bioactive metabolites. Alkaloids, micronutrients, carotenoids, polyphenols, chlorophylls, polysaccharides, acetogenins, terpenoids, several amino acids, unsaturated fatty acids are among the substances found in them[12]. The red sea is one of the known marine algae hotspots with high biodiversity[13]. The increasing research towards the exploration of secondary metabolic compounds from marine algae has allowed the discovery of novel bioactive molecules which has the potential for medicinal applications in the future[14]. The benefit of using marine seaweeds is that they do not need high fertile soil. The algal species can grow in hard soil (no moisture), salty soil, and even in sewage effluents. In recent years, numerous biological functions of marine algae have been reported through research studies. Anti-inflammatory, anti-coagulant, anti-microbial, anti-oxidant, anti-cancer, immunomodulatory, tyrosinase inhibitors, and anti-diabetic are only a few of the biological features that might be discovered. Marine seaweeds have attractive shapes, sizes, and colors. In India, the algal species are distributed as 0.2% of brown seaweed, 27% of red seaweed, and 72% of other algae. Marine seaweed growing in harsh environments produces oxidizing agents and other bioactive secondary metabolites which are responsible for biological activities[15]. Based on cellularity, macroalgae, and microalgae are the two main categories of marine algae.

2.1 Marine Microalgae

Unicellular algal species known as microalgae can exist either alone or in colonies. They are an important source of seaweeds that is cultivated and used for the isolation of a wide range of bioactive metabolites. They are photosynthetic single-cell organisms and a primary producer in freshwater or marine which contributes 70% of the global oxygen demand. The abiotic elements such as salt concentrations, intensity of light, temperature variation, and nutrient concentration have an impact on their specific biological activities[16].

2.2 Marine Macroalgae

Multicellular algae are known as macroalgae. Several marine macro algal species are sustainable resources that provide the raw material for the formulation of several bioactive compounds. They are frequently referred to as seaweeds since they have a propensity for rapid growth. The metabolite content varies between species due to its geographical area, heat, wind, amount of rainfall, and also these have an impact on the development and life cycle of seaweeds. The extracts of macroalgae are considered to be an efficient anti-inflammatory biological product, anti-oxidant, and anti-bacterial[17]. Marine macro algae are classified as follows:

- **Green Algae** - (Chlorophyta): They are known for their chlorophyll a and chlorophyll b contents and they have a high source of polysaccharides[18].
- **Brown Algae** - (Phaeophyta): They are a big class of golden-brown seaweed that has fucoxanthin pigments and several polysaccharides that contribute to its color. They are rich in secondary compounds

such as phlorotannin and several other molecules that have biological functions[15].

- **Red Algae** - (Rhodophyta): They are determined based on their photosynthetic pigments. They lack chloroplast endoplasmic reticulum, flagella, and centrioles. The red algae have more anti-inflammatory properties and research has been conducted for the isolation and characterization of potentially bioactive compounds[19].

3. Anti-Inflammatory Properties of Marine Algae

Inflammation is a component of the body's general defensive reaction to adverse stimuli, such as cellular injury, infections, particular disease states, and hazardous substances[20]. An intricate network of soluble substances that may be divided into many categories according to their source or chemical makeup that primarily mediate inflammation; (1) Inflammatory lipid metabolites, which also include platelet activation factor and different arachidonic acid derivatives such eicosanoids, prostaglandins, leukotrienes, and lipoxins that are produced from phospholipids; (2) Plasma protein systems associated with kinin, complement, and the clotting/fibrinolysis systems, which include thrombin, fibrinopeptides, plasmin, as well as other proteins; and (3) Inflammatory (TNF-) and beta (TNF-), chemokines, colony-stimulating factor 2 and 3; nitric oxide produced by vascular endothelia and macrophages, which causes vasodilation and acts as a cytotoxic agent on pathogenic microbes and neoplastic cells; (4) Interleukins, tumor necrosis factor beta and alpha, chemokines, colony-stimulating factor 2 and 3, and other proinflammatory cytokines[21]. Algal bioactive compounds's anti-inflammatory qualities have drawn a lot of attention in medical research since they may offer beneficial protective benefits against the etiology of inflammatory illnesses that might displace currently used synthetic medicines. Table 1 shows the list of marine algae with anti-inflammatory properties.

4. *Kappaphycus alvarezii*

Kappaphycus alvarezii is one of the foremost important sources, which is used as a gelling, thickening, and stabilizing factor in a variety of goods, including frozen desserts, chocolate pudding, yogurt, preserves, and sauce preparation. *Kappaphycus alvarezii* is a robust, meaty,

Table 1. List of marine algae with anti-inflammatory properties

Algae	Scientific name	References
Blue-Green Algae	*Arthrospira platensis*	22
	Grilterinema splendidum	23
	Spirulina platensis	24
Green Algae	*Caulerpa Mexicana*	25
	Ulva prolifera	26
	Chaetomorpha linum	
	Codium fragile	27
	Chlamydomonas hedleyi	28
	Dunaliella bardawil	24
	Ulva conglobate	
	Ulva lactuca	
	Chlorella marina	
	Dunaliella tertiolecta	
	Caulerpa cupressoides	
	Ulva linza	29
	Ulva fasciata	

Table 1 to be continued...

Algae	Scientific name	References
Brown Algae	*Turbinaria decurrens*	30
	Lobophora variegata	31
	Ishige okamurae	32
	Ecklonia cava	24
	Sargassum wightii	
	Spatoglossum schroederi	
	Myagropsis myagrodes	
	Eisema bicylis	
	Ecklonia kurome	
	Sargassum siliquastrum	18
	Sargassum hemiphyllum	
	Sargassum fulvellum	
	Padina tetrastromatica	33
	Sargassum thunbergii	34
	Petalonia binghamiae	
	Turbinaria conoides	
	Sargassum swartzii	
	Laminaria ochroleuca	35
	Sargassum polycystum	36
	Sargassum vulgare	37
	Undaria pinnatifida	38
	Turbinaria ornate	39
	Sargassum ilicifolium	40
	Sargassum micracanthum	41
	Sargassum tenerrimum	17
Red Algae	*Hydropuntia cornea*	42
	Gracilariopsis longissima	
	Gracilaria textorii	24
	Gracilaria tenuistipitata	
	Neorhodomela aculeata	
	Laurencia glandulifera	
	Porphyra yezoensis	
	Laurencia obtusa	
	Lithothamnion corallioides	
	Delesseria sanguinea	
	Bryothamnion triquetrum	
	Gracilaria caudate	
	Gelidium crinale	
	Hypnea cervicornis	
	Pterocladiella capillacea	

Table 1 to be continued...

Algae	Scientific name	References
Red Algae	*Gracilaria cornea*	43
	Gelidium sesquipedale	35
	Gracilaria corticata	44
	Dichotomaria oblusata	45
	Chondrus crispus	46
	Agardhiella ramosissima	47
	Gromphadorhina oblongata	48
	Chondrus armatus	49
	Hyena musciformis	50
	Gracilaria opuntia	51
	Laurencia glandulifera	52
	Porphyra dioica	53
	Palmaria palmata	
	Gracilaria changii	54
	Gracilaria verrucosa	55
	Gracilaria edulis	
	Gracilaria fergusonii	
	Gracilaria salicornia	

hard sea alga that may reach a length of six feet. The anti-inflammatory, diuretic, choleretic, and hemostatic characteristics of *Kappaphycus alvarezii* have led to its usage in herbal therapy[56]. *K. alvarezii* is ubiquitous seaweed that is farmed all over the world, particularly in Indonesia, Malaysia, Tanzania the Philippines. *K. alvarezii* has an enormous proportion of unsaturated fatty acids (44.5% of total; 11.0% oleic acid, 13.5% cis heptadecenoic acid, 2.3% linoleic acid) and saturated fatty acids (37.0%, composed mainly of heptadecanoic acid), and it is plentiful in carbohydrates (27.4% w/w), protein (16.2% w/w), and fiber (29.4% w/w).

Due to the observable ash, proteins, and bulk fiber content, as well as high level of Vitamin E and tiny amounts of niacin and Vitamin B2, *Kappaphycus alvarezii* powder has been recommended as a component for the manufacturing of spices in India, where the utilization of spice is prevalent. Compared to carrageenan oligosaccharides, Kappa carrageenan derivative products from *Kappaphycus striatum*, especially the sulfated modified version at larger dose, demonstrated high antitumor effect and preferred immunostimulatory purpose, which include macrophage phagocytosis as well as cellular immunity, specifically spleen lymphocyte pervasiveness in mouse model[56]. The antioxidant activity of *K. alvarezii*'s acetone extract is substantial. The extracts of *K. alvarezii* showed considerable defense against damages to the DNA caused by H2O2 as well as increased antioxidant capability and resistance towards tissue lipid peroxidation and cellular damage. Extracts made from this seaweed have been shown in studies to decrease tumor cell proliferation, promote wound healing), and up-regulate cancer cell apoptosis. Furthermore, the carrageenan present in, *K. alvarezii* is being used as a soluble fiber to help cleanse the digestive tract, preserve the gastric surface membrane, and also shield the gut against toxins[57]. It has antiviral properties towards enveloped viruses like influenza, HIV (immunodeficiency virus), HSV (Herpes Simplex Virus), and HCMV (Human Cytomegalovirus)[58]. Antitumor activity has also been discovered in *K. alvarezii*[59].

Due to the clear commercial success of large-scale analyses of the carrageenan trade, researchers are optimistic about new potential uses of *K. alvarezii* and its growth tactics based on vegetative propagation. Seaweeds are a low-calorie, high-fiber, high-mineral diet containing considerable levels of protein, vitamins, and trace minerals, as well as a diverse spectrum of secondary metabolites rarely seen in all other species. This source

is particularly appealing due to its extra potential as a natural supply of functional chemicals[57].

5. Phytochemicals Present in *Kappaphycus alvarezii*

The phytochemical content of seaweeds varies depending on the plant species, the period of raw material collection, and environmental conditions including algal nutrient concentration in groundwater, heat, as well as sunlight. Several biological features of various aspects, particularly secondary metabolites, are important in the treatment of a wide range of disorders[60]. The *Kappaphycus alvarezii* has a rich source of bioactive metabolic substances, minerals, polyphenols, vitamins, lipids, and proteins (Table 2) which have various therapeutic properties[56]. Increased availability of several phytochemicals through the extraction process gives rise to the hope of obtaining valuable bioactive compounds from seaweed[61].

Table 2. List of phytochemical characterization through solvent extraction of *Kappaphycus alvarezii*

Raw material	Solvent	Composition	Extract preparation (method/apparatus)	Phytochemicals present	References
Thallus was shade dried and powdered	petroleum ether	20 g of dried powder + 250 ml of solvent	Grinder (powder), Soxhlet apparatus	Reducing sugar, flavonoids, glycosides, alkaloids, steroids, terpenoids	[62]
	Ethanol			Reducing sugar, flavonoids, glycosides, alkaloids, steroids, terpenoids	
	Ethyl acetate			Reducing sugar, flavonoids, alkaloids, steroids	
whole seaweed is shade dried and powdered	Methanol	250 grams of dried powder + solvent	Soxhlet extractor (18-20 hrs.)	Alkaloid, carbohydrate, protein, amino acids, phytosterol, phenolic compounds, flavonoids, terpenoids, tannins	[60]
	Acetone			Alkaloids, saponins, phytosterol, flavonoids, terpenoids	
Seaweed is dried and powdered	Ethanol	10 g of powdered seaweed + 150 ml of ethanol	10 g seaweed powder + 100 ml ethanol (incubated 3 hrs and filtered) + 50 ml of ethanol (incubated 1 hr and filtered)	Saponins, steroids, tannins, quinones, anthraquinones, ketones, reducing sugar, flavones	[61]
Thalli is made into pieces, shade dried, and powdered	Aqueous extract	Seaweed powder + double distilled water	Grinder (powder), seaweed dried powder in double-distilled water (filtered) + residue (2 times re-extracted and filtered) and -20°C freeze-dry the extract	Alkaloids, tannins, phenol, phytosterols, flavonoids, steroids, amino acids, saponins, and proteins	[56]

Table 2 to be continued...

Raw material	Solvent	Composition	Extract preparation (method/apparatus)	Phytochemicals present	References
Shade dried the seaweed and powdered	Methanol	50 g of seaweed powder + 100 ml of methanol	50 mg powder + 100ml methanol (10 days at 37°C), filtered twice using cotton cloth + Whatman filter paper, rotary vacuum evaporator	Carbohydrate, tannin, saponins, alkaloids, quinones, phenol, steroids	63
Seaweed is shade dried and powdered	Hexane	50 g of seaweed powder + 100 ml of solvent	50 mg powder + 100ml solvent (10 days at 37°C), filtered twice using cotton cloth + Whatman filter paper, rotary vacuum evaporator	Carbohydrate, coumarins	
	Chloroform			Carbohydrate, anthocyanin, quinones, phenol, steroids	
	Ethyl acetate			Carbohydrate, tannins, steroids	
Algae is shade dried and powdered	Chloroform	Algae dried powder + solvent	Soxhlet apparatus (8 hours)	Sterols, flavonoids, cardiac glycosides	64
	Ethanol			Flavonoids, cardiac glycosides, sterols, quinones	
Dried seaweed is powdered	Methanol	10 g seaweed powder + 100 ml methanol	10 g of dried powder rinse in 100 ml of methanol (72 hours), filtrate + dried in hot air oven (37°C)	Alkaloids, terpenoids, coumarins, protein, carbohydrate, saponins, phenols, flavonoids, tannins	65

6. Anti-Inflammatory Activity Exhibited by Phytochemicals Present in *Kappaphycus alvarezii*

Kappaphycus alvarezii is used as an herbal medicine due to its anti-inflammatory, hemostatic, anti-diuretic, and anti-choleretic properties and is also used in food supplements in various countries. This red seaweed is rich in bioactive compounds, polyphenols, minerals, lipids, vitamins, and proteins which contribute to several medicinal properties against various diseases[56].

Inflammatory response is a frequent process that occurs as a result of the body's reaction to an infection or damage. *Kappaphycus alvarezii* has powerful anti-inflammatory effects, according to *in vitro* research. Studies show that inhibition of hyaluronidase enzyme activity was maximum in the crude extract of *Kappaphycus alvarezii* followed by amino acids, terpenoids, alkaloids, and flavonoids having appreciable anti-inflammation properties. Hyaluronidase, an enzyme that breaks down chondroitin sulphate and hyaluronic acid, is the constituents in extra cellular matrix of connective tissue components, hyaluronidase increases the distribution of inflammatory mediators across the tissues, leading to the pathophysiology of inflammatory illnesses such as inflammation, allergic reactions, cancer cell relocation as well as high vascular permeability[56]. Sulphated polygalactans, such as 4-O-Sulfo-beta-D-galactopyranosyl-(1->4), were isolated from the red seaweed *Kappaphycus alvarezii*. -3, 6-anhydro-2-O-sulfo-D-galactose inhibits cyclooxygenase-1 (COX-1, IC50 0.01 mg/mL), cyclooxygenase-2 (COX-2, IC_{50} 0.03 mg/mL), and 5-lipoxygenase (5-LOX, IC_{50} 0.24 mg/mL) with an IC_{50} of 0.01 mg/mL. The likeness in DPP-4, COX-2, and 5-LOX repressing procedures, as well as a substantial optimistic connection flanked by DPP-4 inhibitory action (DP1-DP2) and anti-COX and LOX features of sulfated polygalactan from *K. alvarezii* and *G. opuntia,* suggests that these seaweeds are part of the anti-inflammatory and anti-diabetic characteristics[56]. 1-(3-methoxypropyl)-2-propylcyclohexane (C13), 2-ethyl -6-(4-methoxy -2-((2-oxotetrahydro-2H-pyran-4-yl) methyl)butoxy) -6-oxohexyl 5-ethyloct-4-enoate (C29), and 3-(methoxymethyl)heptyl 3-(cyclohex-3-enyl) propanoate (C18) were three antioxidants but

instead anti-inflammatory oxygenated meroterpenoids that have inhibited pro-inflammatory 5-lipoxidase through *in vitro* method (IC_{50}1.04 mg/mL), indicating that it may have anti-inflammatory characteristics against inducing inflammatory mediators that lead to inflammation[66]. Phytochemicals such as flavonoids being a group of polyphenols, are one of the compounds largely accountable for anti-inflammatory properties[61]. Terpenoids extracted from red seaweeds, including *Kappaphycus alvarezii*, *Hypnea musciformis,* and *Gracilaria dura* on LPS induced RAW 264.7 macrophage cell lines on myeloperoxidase, hyaluronidase, lipoxygenase, xanthine oxidase, and cyclooxygenase inhibitory actions reveal significant anti-inflammatory activities through anti-inflammatory enzyme modulation[10]. The use of bioactive compounds from *K. alvarezii* for anti-inflammatory effects is a promising approach in modern medicine.

7. Conclusion

Kappaphycus alvarezii is an effective marine red alga with anti-inflammatory properties. Chronic inflammation is proved to be the breeding ground for many deadly diseases. These marine algae consist of valuable bioactive compounds that can tackle the maladies of inflammation. The use of marine algae-derived natural products has increased extensively during the past decades, due to its low toxicity, economy, availability, and wide range of pharmaco-therapeutic effects. Carrageenan is produced in huge quantities by cultivating *Kappaphycus alvarezii.* It is also reported to possess antioxidant, antimicrobial, anti-inflammatory effects. These marine red algae are known for its anti-inflammatory properties and exploration even then several bioactive compounds from seaweeds are yet to be discovered. This red algae investigation can be value-based research as the secondary metabolites are still not probed. This seaweed can be a promising phytochemical agent which can play a major role in manufacturing effective drugs against many diseases, as contemporary synthetic medicines cause numerous side effects. This review enlightens the eminent properties of this organic life form that can act as a demanding drug in the future.

8. References

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