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KAPPAPHYCUS ALVAREZII: PHYTOCHEMICALS AND ETHNOPHARMACOLOGICAL SIGNIFICANCE

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Abstract: *Kappaphycus alvarezii*, a species of red algae (Rhodophyta) formerly known as *Eucheuma cottonii*, has been widely utilised for its nutritional benefits. This comprehensive review highlights the recently published information on the phytochemicals and pharmacological aspects of *K. alvarezii*, which underscore its potential applications in the pharmaceutical, cosmeceutical, and nutraceutical industries. *K. alvarezii* contains high levels of polysaccharide carrageenan, a major component, and other phytochemical constituents, including phenolic compounds, flavonoids, alkaloids, terpenoids, phytosterols, and lectins, which may contribute to its pharmacological activity. Both in vivo and in vitro studies have demonstrated that *K. alvarezii* possesses antioxidant, antibacterial, antiviral, antifungal, anti-inflammatory, antidiabetic, and anticancer properties. Given these phytochemical and pharmacological properties, *K. alvarezii* has the potential to be a valuable source of therapeutically beneficial products in Malaysia, particularly in the pharmaceutical industry.

Keywords: *Kappaphycus alvarezii*, rhodophyta, phytochemicals, pharmacology.

Introduction

Seaweed refers to a variety of marine macroalgae that are commercially available (Janarthanan & Senthil Kumar, 2019). Depending on its nutritional and chemical constituents, it can be classified into many classes and families. It covers 90% of plant species that grow in the sea and serves as a critical food source in the food chain. Seaweed only needs 0.1% of photosynthetic light, which can be found in subtidal and intertidal oceans. Seaweeds have blades, stipes, and holdfasts, but no actual stems, roots, or leaves. Despite their appearance as plants, seaweed belongs to the Eukaryota domain, the most complex organism in the algae family. Brown (Phaeophyta), red (Rhodophyta), and green algae (Chlorophyta) are the three types of seaweeds (Shannon & Abu-Ghannam, 2019). *Kappaphycus alvarezii* (*K. alvarezii*), also known as *Eucheuma cottonii* (Arsianti *et al.*, 2018; Parenrengi *et al.*, 2020), is a red algae and edible species in Malaysia found along the Sabah coast. It is a hairy, thorny shrub with many spherical branches that is brown-red in colour (Figure 1).

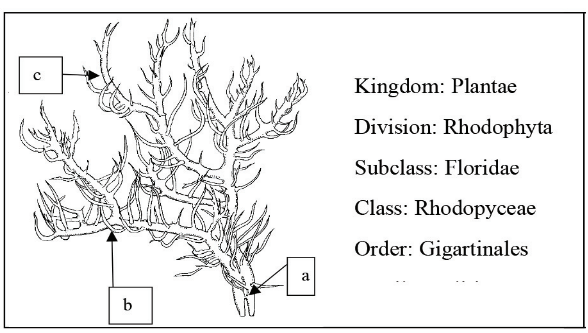


Figure 1: *Kappaphycus alvarezii.* a) main thallus, b) branch, and c) thalli
Figure adapted from https://uses.plantnet-project.org/en/Kappaphycus_alvarezii_(PROSEA)

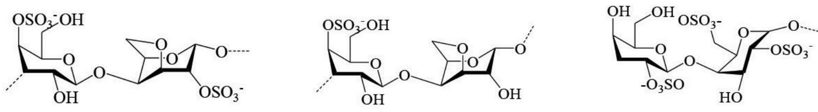
K. alvarezii is one of the largest tropical red macroalgae, which can grow up to two metres long. Among the *Kappaphycus* seaweeds, *K. alvarezii* has the fastest growth rate, making it ideal for food and pharmaceutical uses (Mohammad *et al.*, 2019). Besides Malaysia (Keyimu & Aminah, 2017; Mohammad *et al.*, 2019), *K. alvarezii* is also cultivated commercially in tropical countries, such as India (Kumar *et al.*, 2008; Ranganayaki *et al.*, 2014; Jennifer *et al.*, 2015), Fiji (Wanyonyi *et al.*, 2017), Indonesia (Tirtawijaya, Nur Meinita, *et al.*, 2018), and the Philippines (Chin *et al.*, 2019). Over the past three decades, *K. alvarezii* has been widely cultivated in Malaysia, primarily on the east coast of Sabah. Their cultivation is mainly for export and carrageenan manufacturing. Carrageenan is used as a gelling, thickening, and stabilising ingredient in a wide variety of applications, mainly in the food and beverage industries, including in the production of culinary goods, like frozen desserts, chocolate milk, instant products, yoghurt, jellies, and sauces (Ranganayaki *et al.*, 2014). Apart from that, *K. alvarezii* is used to make bioplastic films to reduce non-degradable plastic (Sudhakar *et al.*, 2021) and act as a bio-stabiliser (Walvekar *et al.*, 2021) and conjugates (Yew *et al.*, 2019) in pharmacological medicine.

This review is a compilation of the data for the phytochemicals and pharmacology report on *K. alvarezii* from scientific sources, such as PubMed, ScienceDirect, ResearchGate, Google Scholar, and Taylor & Francis Online, which focuses only on English articles. The main keywords were *Kappaphycus alvarezii*, phytochemical, pharmacological, antioxidant, antimicrobial, antiviral, antifungal, anti-inflammation, antiobesity, antidiabetic, anticancer, cosmetics, seaweed and red algae. The abstracts of published articles were screened to exclude studies unrelated to the topic. The literature search on these databases yielded 230 articles from 2016 to recently published articles when there is a notable upsurge in studies on *K. alvarezii*. This procedure excluded the 118 articles as they did not meet the inclusion criteria, leaving 112 articles for this review. Therefore, this review aims to provide valuable insights into the potential applications of *K. alvarezii* in the field of natural medicine and the importance of exploring traditional knowledge for the development of new therapies.

Phytochemical Composition

Polysaccharides

The main components of red seaweed are polysaccharides found in the cell walls. The polysaccharides (alginic acid, alginates, carrageenans, agar, laminarans, fucoidans, ulvans and derivatives) comprise a variety of monosaccharides linked by glucosidic bonds (Pérez *et al.*, 2016a). According to the degree of sulphation, there are three general forms: Iota (ɩ), kappa (κ) and lambda (λ) (Figure 2), which vary depending on the seaweed species' seasons, geographic location and age of the population (Nurshahida *et al.*, 2020). Carrageenan is a biodegradable and water-soluble linear sulfated polysaccharide with an alternating backbone composed of D-galactose-4-sulfate, with 3,6-an hydro-D-galactose being the primary polysaccharide in *K. alvarezii* (Teo *et al.*, 2021). It is linked by α-1,3 and β-1,4 glycosidic bonds (Teo *et al.*, 2021). Apart from *K. alvarezii*, carrageenan can be found and extracted from other Rhodophyta, such as *Chondrus crispus*, *Eucheuma spinosum* and *Gigartina* (Teo *et al.*, 2021). κ-carrageenan exhibit 25% of sulphate content, where every two sugar units have one sulphate (Teo *et al.*, 2021). In ɩ-carrageenan, there is an additional sulphate group in the position of anhydrogalactose residue 2, while the most sulphated groups belong to λ-carrageenan (Teo *et al.*, 2021). Previous research has established and reported the presence of polysaccharides in *K. alvarezii* and demonstrated their pharmacological properties, including anti-inflammatory, antioxidant, antibacterial, and immunological activities (Nurshahida *et al.*, 2020).



Iota Kappa Lambda

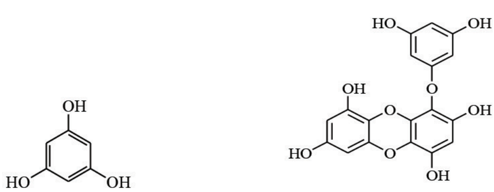
Figure 2: Basic chemical structures for different types of carrageenan (Pérez *et al.*, 2016)

Phenolic and Flavonoid Content

Bromophenols, phenolic acids, and flavonoids are the phenolic compounds primarily found in red algae. Phenolics are secondary metabolites characterised by an aromatic ring with hydroxyl groups (Lomartire *et al.*, 2021). Polyphenols found in red algae could be divided into phloroglucinols and phlorotannins. Simple phenols, such as hydroxycinnamic, benzoic acids, and flavonoids, were found to be present in lower quantities in red algae when compared with green or brown algae (Pérez *et al.*, 2016). In brown seaweeds, the phloroglucinol-based phenolics (1,3,5-trihydroxy benzene), known as phlorotannins (Figure 3), were reported to act as defence compounds. Based on that, the concentration of phlorotannins in brown algae varies depending on the taxonomy of the brown seaweeds and their origins or geographical areas (Nurshahida *et al.*, 2020). Phlorotannins have been shown to have antioxidant, anti-inflammatory, antidiabetic, anti-tumour, anti-hypertensive, and antiallergenic properties (Sumayya & Murugan, 2017a).

Alkaloids

An alkaloid is a chemical that has one or more nitrogen atoms in a cyclic ring. These compounds are divided into three groups: Phenylethylamine alkaloids, indole and halogenated indole alkaloids, as well as other alkaloids like derivatives of 2,7-naphthyridine. (Pérez *et al.*, 2016). For red seaweeds, most of the isolated alkaloids are indole and halogenated indole alkaloids (Pérez *et al.*, 2016). These halogenated alkaloids of algae are not present in terrestrial plants and are specific for algae and sea organisms. There are 44 reported alkaloids in marine algae, including one phenylethylamine, 41 indoles, and one derivative of naphthyridine (Figure 4). In the halogenated indole alkaloid group, there are 25 bromine-containing compounds; among halogenated indole alkaloids, seven have chlorine and the other five have sulphur.



Phloroglucinol Eckol

Figure 3: Structure of phlorotannins

Phenylethylamine N-Acetyltyramine

Figure 4: Structure of common halogenated indole alkaloid

Terpenoids

Terpenes are secondary metabolites composed of five isoprene carbon units. Among others, the Dictyota genus of brown algae was reported to contain a high amount of diterpenes. Typical algal terpenes, such as dictyodial, dictyol C and dictyol H, have been isolated from different species of Dictyota (Manzo *et al.*, 2009). Bromophenols, a volatile halogenated compound, have been isolated from taxonomically diverse marine algae (Xu *et al.*, 2004).

Oxygenated meroterpenoids (Figure 5), namely 1-(3-methoxy propyl)-2-propyl cyclohexane, 3-(methoxymethyl) heptyl 3-(cyclohexyl-3-enyl) propanoate, and 2-ethyl-6-(4-methoxy-2-[(2-oxotetrahydro-2H-pyran-4-yl) methyl) butoxy]-6-oxohexyl-5-ethyloct-4-enoate, were purified from the methanol and ethyl acetate fraction of *K. alvarezii* collected from the southeast coast of peninsular India. They were reported to have antioxidative activities that inhibit 1-diphenyl-2-picrylhydrazyl (DPPH) and ABTS (2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (Chakraborty & Raola, 2018). Similar activities were observed by 2β-ethyl-9-oxo-5α-vinyl-1,2,5,5a,6,7,8,9-octahydroheptalene-10,1-carbolactone and methyl-2-ethyl-9- oxo-5α-vinyl 1,2,5,5a,6,7,10,10a-octahydroheptalene-1α-carboxylate (Chakraborty & Raola, 2018). The crude methanolic extract of *K. alvarezii* analysed by GCMS revealed the presence of some terpenes, with β-amyrin being the predominant one in the extract from this species (Figure 5 and Table 1).

Sterol

Phytosterols are naturally occurring plant compounds with a similar chemical structure to cholesterol, which is only found in animals. The most prevalent plant sterols in the human diet are beta-sitosterol, campesterol, and stigmasterol (Figure 6) (Cabral & Klein, 2017). Clinical studies consistently indicate the intake of phytosterols (2 g/day) is associated with a significant reduction (8- 10%) in levels of LDL cholesterol (Trautwein *et al.*, 2018).

K. alvarezii, collected from Sabah, Malaysia, was reported to be rich in phytosterols (Matanjun *et al.*, 2009). Marine algal phytosterols, particularly fucosterol, have been intensively studied to fight diseases like diabetes, obesity, Alzheimer's, ageing, and cancer, as well as to protect the liver (Ranganayaki *et al.*, 2014; Xia *et al.,* 2019; Hannan & Sohag *et al.,* 2020). Another study also documented phytosterol for

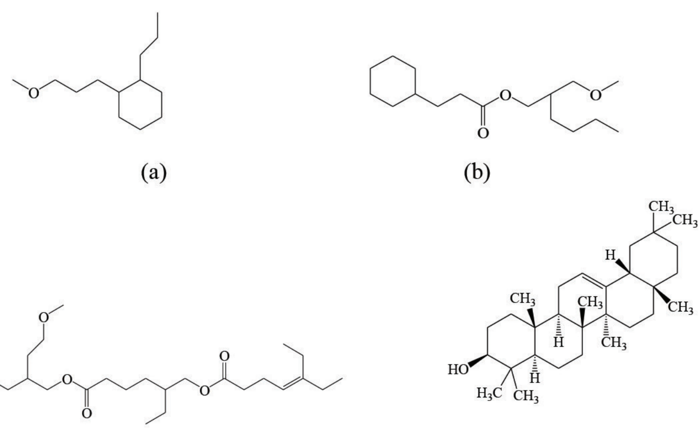


Figure 5: The chemical structure of oxygenated meroterpenoids; (a) 1-(3-methoxypropyl)-2-propylcyclohexane; (b) 3-(methoxymethyl)heptyl 3-(cyclohex-3-enyl) propanoate; (c) 2-ethyl-6-(4-methoxy-2-[(2-oxotetrahydro-2H-pyran-4-yl)methyl)butoxy]-6-oxohexyl 5-ethyloct-4-enoate; (d) beta-amyrin (Sumayya & Murugan, 2017)

Table 1: Terpene and other phytochemical constituents identified from the GC-MS analysis of *K. alvarezii* extract (Sumayya & Murugan, 2017)

Compound Name	Molecular Weight	Molecular Formula	K. alvarezii Area. %	Retention Time (RT)
Hexadecane	$C_{16}H_{34}$	226	1.64	23.330
Eicosane	$C_{20}H_{24}$	282	5.91	32.041
Hepta decane	$C_{16}H_{34}$	226	2.43	25.643
Octadecane	$C_{18}H_{38}$	254	5.30	27.764
Heneicosane	$C_{21}H_{44}$	296	3.07, 4.48, 1.85	34.599,37.316, 39.898
Tricosane	$C_{23}H_{48}$	324	1.35, 2.32	27.880, 42.376
2-Pentadecanone	$C_{14}H_{28}O_2$	228	-	-
Hexadecanoic acid, methyl ester	$C_{17}H_{34}O_2$	270	3.27, 3.72	29.823, 30.005
n-Hexadecanoic acid	$C_{16}H_{32}O_2$	256	-	-
Hexadecanoic acid, ethyl ester	$C_{18}H_{36}O_2$	284	-	-
Beta amyrin	$C_{30}H_{50}O$	426	47.17	44.900
Heptadecanoic acid, methyl ester	$C_{18}H_{36}O_2$	284	-	-
11-octadecanoic acid, methyl ester	$C_{18}H_{36}O_2$	284	-	-

its antioxidant properties and anti-inflammatory, immunomodulatory, and cholesterol-lowering characteristics. These sterols interact with enzymes and other proteins involved in various cellular processes, including the antioxidant defence system, apoptosis and cell survival, metabolism, and homeostasis (Hannan, Sohag *et al.*, 2020). Phytosterols are also recommended for the treatment of hypercholesterolemia, according to international guidelines and consensuses from numerous societies.

Lectins

The term "lectin" is derived from the Latin root "legere", which means "to choose" or "to select" (Fernández Romero *et al.*, 2021). As per its name, lectins are proteins that choose to bind to carbohydrates in glycolipids or glycoproteins involved in non-immune responses (Singh & Walia, 2018). Their interaction can be very selective and specific. In addition, lectins binds stronger to oligosaccharides than monosaccharides (Fernández Romero *et al.*,

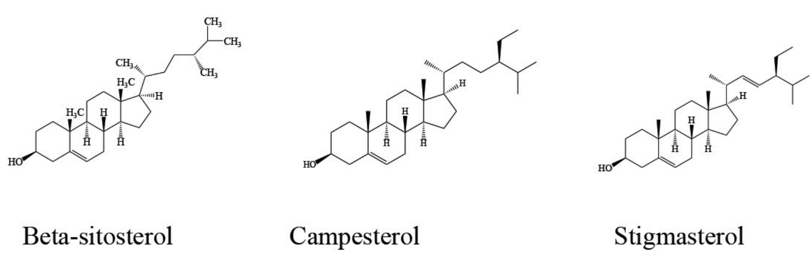


Figure 6: Structure of phytosterol from red algae

2021b). Lectins are ubiquitous and present in different organisms, such as animals, plants, fungi, protists, and microorganisms, such as bacteria, archaea, or viruses (Fernández Romero *et al.*, 2021). Lectins from marine red algae are more sensitive to the enzyme trypsin or pronase upon enzymatic treatment of erythrocyte with a proteolytic enzyme, and the susceptibility of agglutination varies. *K. alvarezii* crude lectins exhibit strong agglutination with enzyme-treated sheep (trypsin and papain) and rabbit erythrocytes compared to native erythrocytes, but they are unable to agglutinate chicken and human erythrocytes.

Pharmacological Properties

Marine organisms produce a variety of active molecules, which leads to pharmacological activities (Pérez *et al.*, 2016), such as anticancer (Suganya *et al.,* 2016; Chang *et al.,* 2017; Yew *et al*., 2019; Baskararaj *et al.*, 2020), antimicrobial (Pérez *et al.*, 2016; Bhuyar *et al.*, 2020; Ruthiran *et al.*, 2020; Siah *et al.*, 2021; Teo *et al.*, 2021), larvicidal (Ruthiran *et al.*, 2020), anti-ageing (Janarthanan & Senthil Kumar, 2019) and antidiabetic activities (Cyriac & Eswaran, 2016; Suganya *et al.*, 2016). As photosynthetic organisms, marine algae are exposed to harmful UV light, oxygen-free radicals, and other stressful factors at their origin (Teo *et al.*, 2021). To survive and live within complex communities that have high competition (space, predation and tide variations) and are hostile (Pérez *et al.*, 2016), they produce complex secondary metabolites (Pérez *et al.*, 2016; Teo *et al.*, 2021). Interestingly, some of the active compounds act as antimicrobials by inhibiting or limiting the development and growth of other competitive microorganisms (Teo *et al.*, 2021). The unique structural components in marine algae protect them from oxidative damage via antioxidative defence systems, thus promoting their antioxidant properties (Teo *et al.*, 2021).

Antioxidant

The antioxidant properties of *K. alvarezii* have been well-investigated (Makkar & Chakraborty, 2018; Araújo *et al.*, 2020; Arsianti *et al.*, 2020; Bhuyar *et al.*, 2020; Papitha *et al.*, 2020; Teo *et al.*, 2021). The DPPH assay is one of the fastest methods to determine antioxidant activity because of its stability and long-lived radical, as well as the simplicity of use (Nurshahida *et al.*, 2020). High antioxidant activity in *K. alvarezii* shows its ability to be a potent scavenger for free radicals, thus having beneficial effects on human health and disease prevention (Keyimu & Abdullah, 2016). *K. alvarezii* was reported to have the highest phytochemical molecules compared with other species (Sharan & Vennila, 2021). The biologically active compounds in *K. alvarezii*, comprising pigments (carotenoid, fucoxanthin, astaxanthin), polyphenols (tannins, flavonoid and phenolic acid), vitamins (A, Bl, B2, B3, B12, C, D, E) and ascorbic acid, have been reviewed to inhibit oxidation when exposed to light and oxygen during storage (Keyimu & Abdullah, 2016). Apart from that, the seawater quality during cultivation also affects the phytochemical properties and antioxidant activities of *K. alvarezii*. A study conducted by Kreckoff *et al.* (2019) indicates that water quality, specifically the pH level during the cultivation of K. alvarezii, has an influence on the percentage of carrageenan found in the plant. The study, conducted in Indonesia, found that the highest concentration of carrageenan was found in *K. alvarezii* harvested from Likupang (63.80%), followed by Talengen Bay (46.14%) and Arakan (44.43%), and this variation was attributed to the water pH conditions in those locations. The study also shows that the *K. alvarezii* collected from these areas have potent antioxidant properties by inhibiting DPPH.

The presence of alkaloids, saponins, steroids, gums, mucilages, carbohydrates, and carrageenan was observed to reduce the antioxidant activity of hydroxyl, nitric oxide (NO), DPPH, and ferric reduction antioxidant power (FRAP) assays. Additionally, the methanolic extract of K. alvarezii was found to contain alkaloids, carotenoids, amino acids, phytosterols, phenolics, flavonoids, terpenoids, phlorotannins, and tannins, which exhibited positive effects in inhibiting DPPH activity. These findings were supported by other studies (Qadri *et al.,* 2019; Kreckhoff *et al.*, 2019; Nurshahida *et al.*, 2020; Bhuyar *et al.*, 2021; Ulfa *et al.*, 2021), in which the DPPH activity is closely related to the content of phenolics, furfural, imidazole, 2-furan methanol, 5-hydroxymethylfurfural, hydrazine, hexadecanoic acid, heptadecanoic acid, 2-heptanol, methyl stearate. Apart from that, the activity of *K. alvarezii* in inhibiting 2,2′-azinobis-(3-ethylenebenzothiazoline)-6-sulfonic acid (ABTS) was documented by a few other researchers (Qadri *et al.*, 2019; Bhuyar *et al.*, 2021). In addition, the ethanolic extract of *K. alvarezii* was also studied and demonstrated to inhibit FRAP activities. It was suggested that this activity was due to the high content of the total phenolic and fatty acids in the extract (Bhuyar *et al.*, 2020b). Another recent study in 2021 supported the ability of *K. alvarezii* extract to inhibit DPPH, NO, superoxide (SO) and hydrogen peroxide (H_2O_2) (Sharan & Vennila, 2021).

Antimicrobial, Antiviral and Antifungal

Metabolites and natural substances present in seaweed or macroalgae include polysaccharides, polyunsaturated fatty acids, phlorotannins and other phenolic compounds, and carotenoids that are able to promote antimicrobial activity (Pérez *et al.*, 2016). *K. alvarezii* has been shown to inhibit the growth of *Escherichia coli* (Syaharuddin *et al.*, 2018; Ruthiran *et al.*, 2020), *Bacillus cereus* (Syaharuddin *et al.*, 2018; Bhuyar *et al.*, 2020) and *Staphylococcus Aureus* (Syaharuddin *et al.*, 2018; Teo *et al.*, 2021) due to the flavonoids content (Syaharuddin *et al.*, 2018b). It was reported that *K. alvarezii* gave the highest zone of inhibition in *E. coli*, *Staphylococcus aureus,* as compared with other species of bacteria, such as *B. subtilis*, *Proteous vulgaris* and *Pseudomonas aeruginosa* (Seetharaman *et al.*, 2016). *K. alvarezii* was also demonstrated to inhibit oral pathogenic microbes, such as *S. aureus, B. subtilis, E. coli, Klebsiella pneumonia, Pseudomonas aeruginosa* and *Candida albicans* that cause gingivitis and periodontitis in humans (Sharan & Vennila, 2021). Besides that, another study revealed that combining *K. alvarezii* with cinnamon essential oil can potentially prevent the growth of *B. cereus*, *S. aureus*, *E. coli*, *Salmonella enterica* serovar *Typhimurium*, *Aspergillus flavus* and *Saccharomyces cerevisiae* in the development of antimicrobial film packaging (Siah *et al.*, 2021).

In contrast, a study by Chan *et al.* (2018) found that different solvent extractions using hexane, chloroform, ethyl acetate, ethanol, methanol and water did not have a significant effect on *S. Aureus*, *Acinetobacter baumannii*, *E. Coli*, and *Pseudomonas aeruginosa*. These contrasting findings might be due to the cultivation (temperature, season) (Li *et al.*, 2019), processing and extraction method of *K. alvarezii,* as well as the concentration and model used for the experiment. In 2019, Cirne-Santos *et al.* reported that *K. alvarezii* extracts inhibit 30% to 98% of Chikungunya virus replication in Vero cells in a dose-dependent manner (1.25 to 50 μg/ml), similar to the effect of other marine algae such as *Caulerpa racemosa*, *Osmundaria obtusiloba*. Apart from that, it was previously reported the antifungal effect of *K. alvarezii* extracted using hexane, chloroform, ethyl acetate, ethanol and methanol was demonstrated to inhibit *Trichophyton rubrum* and *Trichophyton interdigitale* (Sit *et al.*, 2018).

Anti-inflammation

Anti-inflammatory refers to the ability of a substance or treatment to reduce inflammation, which makes up about half of analgesics, and alleviates pain by reducing inflammation (Suganya *et al.*, 2016). A study by Makkar and Chakraborty (2018) demonstrated the inhibition of cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2), and 5-lipoxygenase (5-LOX) by sulphated polygalactans extracted from the aqueous extract of *K. alvarezii*. The presence of polysaccharides and oxygenated meroterpenoids also inhibited COX-1, COX-2, and 5-LOX (Makkar & Chakraborty, 2017; 2018). In vitro, the efficacy against oral diseases was also related to the anti-inflammatory effect of *K. alvarezii* (Sharan & Vennila, 2021; Teo *et* *al.*, 2021). The presence of high flavonoids and phenolic compounds could be related to their bioactivity. Another recent study of *K. alvarezii* aqueous extract shows that the reduction of wound contraction rate in excision-induced wounded mice is comparable to the effect of honey in improving wound closure (Teo *et al.*, 2021).

Anti-obesity, Anti-hypertension and Dyslipidemia

The high carrageenan content in *K. alvarezii* also shows an anti-obesity effect by reducing body weight, total fat mass, systolic blood pressure, left ventricular collagen deposition, plasma triglycerides, and plasma non-esterified fatty acids, along with alleviating fatty liver in obese rats (Wanyonyi *et al.*, 2017). In diet-induced obese C57BL/6J mice, *K. alvarezii* decreased leptin, adiponectin, and total fat, and regulated gut-microbiota composition, which reversed obesity and its related metabolic syndromes (Chin *et al.*, 2019). A review by Hannan *et al.* in 2020 mentioned that *K. alvarezii* interacts with enzymes, activating the antioxidant defence system, apoptosis, cell survival, metabolism, and homeostasis due to fucosterol.

In terms of dietary properties, edible seaweeds are rich and sustainable sources of macronutrients (particularly dietary fibre) and micronutrients (Cherry *et al.*, 2019). The anti-obesity effect of different *K. alvarezii* extracts was reported to lower sterol regulatory element-binding protein-1a *(srebp-1a*) and fatty acid synthase (*fasn)* gene expression levels, thus reducing cholesterol production. Apart from that, the antiobesity mechanism increases acyl-CoA oxidase (*aco)* expression that promotes peroxisomal β-oxidation of fatty acids. This increases the metabolism in colonic tissues through the increase of adiponectin receptor 1 (*adipoR1)* and adiponectin receptor 2 (*adipoR2)* expression levels, mediated by AMPK and peroxisome proliferator-activated receptor alpha (PPAR-α) ligand activities, including lipogenesis. In the liver, PPAR-α plays a central role in the β-oxidation of lipids, which utilise fat as their primary fuel source (Chin *et al.*, 2019). In a study involving obese rats, *K. alvarezii* extract was reported to decrease body weight, triglyceride, total cholesterol, and HDL-C ratio-induced osteoarthritis. This extract also downregulate inflammatory markers, such as tumour necrosis factor-α, interleukin-1β, and leptin, while inhibiting nuclear factor-kappa B and extracellular-signal-regulated kinase-1/2 expression. This leads to a decrease in the levels of matrix metalloproteinases (MMP-1 and MMP-13) and prostaglandin-E2, ultimately attenuating cartilage degradation (Sudirman *et al.*, 2019).

Neurotrophic Activities

Neurotrophic activities of *K. alvarezii* collected from Indonesia were reported in some studies by Tirtawijaya and colleagues (Tirtawijaya *et al.*, 2016; 2019; Tirtawijaya, Mohibbullah, *et al.*, 2018; Tirtawijaya, Nur Meinita, *et al.,* 2018). This study revealed that the ethanolic extract of *K. alvarezii* could promote neurite outgrowth in hippocampal neurons in vitro at a concentration of 1 µg/mL (Tirtawijaya *et al.*, 2016). This study reported that neuronal maturation was accelerated from stage I to stage II within 24 h (Tirtawijaya *et al.*, 2016). On the other hand, a study on phytosterols in *K. alvarezii* ethanolic extract demonstrated that the extract could promote axodendritic maturation by increasing axonal length and the number of secondary axonal collateral primary dendrites and the number of secondary dendritic branches. The extract also increased the number of axodendritic intersections, branching points, and branching tips (Tirtawijaya, Mohibbullah, *et al.*, 2018). The study by the same group shows that *K. alvarezii* had higher neurotrophic activity than other seaweeds, such as *K. striatum* and *E. denticulatum,* cultured under the same conditions.

Cholesterol, isolated from *K. alvarezii* ethanolic extract, was reported to improve dendritic filopodia and spine formations crucial for spinogenesis (Tirtawijaya *et al.*, 2019). The hippocampal neuron also demonstrated an increase in presynaptic, postsynaptic, and colonised puncta, subsequently enhancing synaptic function (Tirtawijaya *et al.*, 2019). A study on the different drying methods of *K. alvarezii*, frozen and shade-dried drying methods, was reported not to affect neuritogenic activities. These findings support the usage of *K. alvarezii* as a functional food for reducing neurological diseases and preventing brain ageing.

Antidiabetic and Antiglycation

Several in vivo and in vitro studies have shown that *K. alvarezii* extract can act as an antidiabetic agent by reducing α-amylase (Makkar & Chakraborty, 2017), α-glucosidase (Suganya *et al.*, 2016; Makkar & Chakraborty, 2017) and dipeptidyl peptidase-4 (DPP-4) (Makkar & Chakraborty, 2017). The inhibition of DPP-4 prolongs GLP-1 half-life, thus stimulating insulin secretion, increasing β-cell mass, inhibiting glucagon secretion, reducing gastric emptying rate, and inducing satiety (Makkar & Chakraborty, 2017). Moreover, the antidiabetic effect of *K. alvarezii* was reported to improve plasma insulin and serum HDL-C while reducing serum cholesterol, triglyceride, phospholipid, and LDL in alloxan-induced diabetic rats at a concentration of 200 and 400 mg/kg body weight (Cyriac & Eswaran, 2016). The inhibition of α-glucosidase enzyme was demonstrated due to the presence of carrageenan extracted from *K. alvarezii*, approximately at a concentration of 500 mg/ml (Suganya *et al.*, 2016) and sulphated polygalactans (Makkar & Chakraborty, 2017).

The fractions from *K. alvarezii* extract were reported to inhibit glycation while reducing glucose, glycated albumin, and Nε-(carboxymethyl) lysine level, and upregulate renal RAGE gene expression in diabetic rats (Yulianti *et al.*, 2021). The decreased glucose level may be attributed to the presence of phytochemicals, namely pheophorbide a cafestol, shogaol, thymol, cinnamic acid, kahweol, *p*-cymene, pyrogallol, (e)-p-coumaric acid, (-)-lupinine, (e)-ferulic acid, putrescine and anacardic acid (Yulianti *et al.*, 2021). Kahweol was reported to induce AMP-activated protein kinase (AMPK) activation that regulates glucose metabolism by increasing glycolysis, activating 6-phosphofructo-2-kinase/fructose-2, 6-bisphosphatase, followed by suppressing glycogen synthesis through inhibition of glycogen synthase. Apart from that, AMPK increases glucose absorption by upregulating glucose transporter 4 and hexokinase II expression in skeletal muscle cells (Ren *et al.*, 2019).

Anticancer

K. alvarezii extract was reported to reduce the growth of breast, colon, liver and osteosarcoma cell lines, which was believed to be related to the presence of alkaloids, saponins, steroids, gums, mucilages, carbohydrates and carrageenan (Suganya *et al.*, 2016). A subsequent study by Chang *et al.* (2017) shows the ability of *K. alvarezii* methanolic extract to reduce the cell viability of breast cancer cells (MCF-7), WBC and growth rate of mammary tumours in DMBA-induces mammary tumours in rats. The presence of flavonoids, triterpenoids, and alkaloids in *K. alvarezii* extract has also been shown to inhibit the growth of cervical HeLa (Arsianti *et al.*, 2018) and lung A-549 cancer cells (Arsianti *et al.*, 2020). A recent systematic review revealed the inhibition of proliferation by *K. alvarezii* of various cancer cell lines (MCF-7, HeLa, MB-MDA231, SK-Lu1, HCT116, HT29, HepG2, MG63) by regulating Chk 1, p53, Birc5, Bag 1 and MDM 2, which induced apoptosis. *K. alvarezii* encapsulated with folate conjugated with PEGylated liposome can inhibit the growth of MCF-7 and induce apoptosis by increased ROS production, mitochondrial transmembrane potential damage or loss and morphological changes of the nucleus of MCF-7 cells (Baskararaj *et al.*, 2020). In addition, another study revealed that the ethanolic, ethyl acetate and chloroform extracts of *K. alvarezii* were able to reduce oral cancer cells' (KB-3-1 cell lines) viability (Sharan & Vennila, 2021).

Table 2: Summary of phytochemicals related to the pharmacological properties of *K. alvarezii*

Properties	Bioactive Compounds	Mechanism	Source	References
Antioxidant	Alkaloids, saponins, steroids, gums, mucilages, carbohydrates and carrageenan	Inhibited the activity of hydroxyl, nitric oxide, DPPH and FRAP	India	(Suganya *et al.*, 2016)
	2β-ethyl-9-oxo-5α-vinyl-1,2,5,5a,6,7,8,9-octahydroheptalene-10,1-carbolactone and methyl-2-ethyl-9- oxo-5α-vinyl-1,2,5,5a,6,7,10,10a-octahydroheptalene-1α-carboxylate	Inhibited DPPH and ABTS radicals	India	(Chakraborty & Raola, 2018)
	Oxygenated meroterpenoids	Inhibited DPPH and ABTS radicals	India	(Makkar & Chakraborty, 2018)
	Alkaloids, carotenoids, amino acids, phytosterols, phenolics, flavonoids, terpenoids, phlorotannins, tannins	Inhibited DPPH activities	India	(Janarthanan & Senthil Kumar, 2019)
	-	Inhibited DPPH activities	Indonesia	(Kreckhoff *et al.*, 2019)
	-	Inhibited DPPH and ABTS radicals	India	(Qadri *et al.*, 2019)
	Phenolics	Inhibited DPPH activities	Malaysia	(Nurshahida *et al.*, 2020)
	Phenolics and fatty acids	Inhibited FRAP activities	Malaysia	(Bhuyar *et al.*, 2020)
	Alkaloids, phenols, sterols, steroids, diterpenoids, flavonoids, saponins, glycosides, proteins, amino acids, carbohydrates	Inhibited DPPH, NO, SO and H_2O_2	India	(Sharan & Vennila, 2021)
	Furfural, imidazole, 2-furanmethanol, 5-Hydroxymethyfurfural, Hydrazine, Hexadecanoic acid, Heptadecanoic acid, 2-Heptanol, Methyl stearate	Inhibited DPPH and ABTS radicals	Malaysia	(Bhuyar *et al.*, 2021)
	-	Inhibited DPPH activities	Indonesia	(Ulfa *et al.*, 2021)

Anti-inflammatory	Isolated bioactive compounds DHA	Isolated bioactive compounds DHA possessed good anti-inflammatory activity, with an inhibition rate of 60% at 0.5ml of concentration, compared with the seaweed extracts, which showed 58% of activity	India	(Suganya *et al.*, 2016)
	Polysaccharides, oxygenated meroterpenoids	Inhibited COX-1, COX-2, and 5-LOX	India	(Makkar & Chakraborty, 2017, 2018)
	-	Promoted wound healing activity by increasing cellular proliferation, wound contraction, granulation tissue formation, and collagen synthesis in burn-induced wound mice	Malaysia	(Chew *et al.*, 2018)
	-	Reduced wound contraction rate in excision-induced wounded mice	Malaysia	(Teo *et al.*, 2021)
	Alkaloids, phenols, sterols, steroids, diterpenoids, flavonoids, saponins, glycosides, proteins, amino acids and carbohydrates	Inhibited oral pathogenic microbes (*Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa* and *Candida albicans*) that promote gingivitis and periodontitis	India	(Sharan & Vennila, 2021)
	Phenolics and phycobilins	Improved body weight, growth and intestinal morphology in broiler chicken Decreased serum catalase and increases lipid peroxidation, TLR2A and NOD1, IL-2 and IL-6	India	(Paul *et al.*, 2021)
Antimicrobial	Flavonoids	Flavonoids from *Bacillus alcalophilus* isolated from *K. alvarezii* inhibited the growth of *S. aureus, B. subtilis and E. coli.*	N/A	(Syaharuddin *et al.*, 2018)
	-	Reduced coliform and staphylococcus count in broiler chicken meat	India	(Qadri *et al.*, 2019)
	-	Inhibited the growth of *E.coli*	India	(Ruthiran *et al.*, 2020)

Antimicrobial	TPC, fatty acids	Inhibited the growth of *B. cereus*	Malaysia	(Bhuyar *et al.*, 2020)
	-	A combination with cinnamon essential oil inhibited *B. cereus*, *Staphylococcus aureus*, *Escherichia coli*, *Salmonella enterica* serovar *Typhimurium*, *Aspergillus flavus,* and *Saccharomyces cerevisiae* for antimicrobial film packaging	Malaysia	(Siah *et al.*, 2021)
		Inhibited the growth of *Staphylococcus aureus*		(Teo *et al.*, 2021)
	Alkaloids, saponin, phenols, Steroids, protein, phytosterols, amino acids, flavonoids, steroids, tannins and absence of terpenoids, sugars and anthraquinone	The highest zone of inhibition was observed in *E. coli* and *Staphylococcus aureus* when compared with other species of bacteria, such as *B. substilis*, *Proteous vulgarius* and *Pseudomonas aeruginosa*	India	(Seetharaman *et al.*, 2016)
Antiviral	-	Inhibited the replication of the Chikungunya virus in Vero cells	Brazil	(Cirne-Santos *et al.*, 2019)
Antifungal	Alkaloids, anthraquinones, flavonoids, saponins, tannins, phenolics and triterpenoids	Inhibited the growth of *Trichophyton rubrum* and *Trichophyton interdigitale*	Malaysia	(Sit *et al.*, 2018)
	-	Inhibited hyphae and zoospores of *Lagenidium thermophilum*, *Haliphthoros sabahensis* and *H. milfordensis*	Malaysia	(Sudirman *et al.*, 2019)
Antiobesity Antihypertension Dyslipidemia	Carrageenan	Reduced body weight, total fat mass, systolic blood pressure, left ventricular collagen deposition, plasma triglycerides, and plasma non-esterified fatty acids, as well as alleviated fatty liver in obese rats	Fiji	(Wanyonyi *et al.*, 2017)

Antiobesity Antihypertension Dyslipidemia	Polysaccharides	Decreased body weight, triglyceride, total cholesterol, and HDL-C ratio induce osteoarthritis in high-fat diet-induced obese rats Downregulated the expression of tumour necrosis factor-α, interleukin-1β, and leptin Suppressed nuclear factor-kappa B and extracellular-signal-regulated kinase-1/2 expression, resulting in a decrease in the levels of MMP-1 and MMP-13 and prostaglandin-E2 and attenuated cartilage degradation	N/A	(Sudirman *et al.*, 2019)
	-	Reduced free fatty acids, peroxide, and cholesterol contents in egg yolk of hens fed with *K. alvarezii*	India	(Mandal *et al.*, 2019)
	-	Reduced leptin, adiponectin, total fat, fat composition, adipose size, total cholesterol, LDL: HDL ratios and regulated gut-microbiota composition	Malaysia	(Chin *et al.*, 2019)
	-	Reduced the cholesterol in the meat of chicks	India	(Qadri *et al.*, 2019)
	Fucosterol	Interacted with enzymes activating the antioxidant defence system, apoptosis and cell survival, metabolism, and homeostasis.	-	(Hannan & Sohag, *et al.*, 2020)
Neurotrophic activities	-	Increased neurite in fetal rat hippocampal neurons *in vitro* by enhancing neuronal maturation within 24 hours	Indonesia	(Tirtawijaya *et al.*, 2016)
	Phytosterols	Promoted axodendritic maturation	Indonesia	(Tirtawijaya & Mohibbullah, *et al.*, 2018)
	-	Increased the length of primary neurite and longest neurite	Indonesia	(Tirtawijaya & Nur Meinita, *et al.*, 2018)

Neurotrophic activities	Ispronicline oleic acid, stigmast-4-ene-3,6-dione, oxysterol, campesterol, cholesterol	Increased dendritic filopodia, spine formations, presynaptic puncta, postsynaptic puncta, and colonised puncta, which enhance functional presynaptic plasticity	Indonesia	(Tirtawijaya *et al.*, 2019)
	-	Increased the number of primary neurites, the total length of the primary neurite and the length of the longest neurite in freeze- and shade-dried *K. alvarezii* ethanolic extract	Indonesia	(Tirtawijaya *et al.*, 2021)
Antidiabetic	-	Improved plasma insulin and serum HDL-C while reducing serum cholesterol, triglyceride, phospholipid, and LDL of the alloxan-induced diabetic rats at 200 and 400 mg/Kg body weight	India	(Cyriac & Eswaran, 2016)
	Polysaccharides	Reduced α-amylase, α-glucosidase and DPP-4	India	(Makkar & Chakraborty, 2017)
	Alkaloids, saponins, steroids, gums, mucilages, carbohydrates, carrageenan	Inhibition of α-glucosidase enzyme	India	(Suganya *et al.*, 2016)
	N/A	Reduced plasma GA and CML levels as well as upregulate RAGE gene expression in the diabetic rats	Indonesia	(Yulianti *et al.*, 2021)
	Kahweol	Induced AMPK and activates 6-phosphofructo-2-kinase/fructose-2, 6-bisphosphatase, followed by suppressing glycogen synthesis through inhibition of glycogen synthase. AMPK upregulates glucose transporter 4 and hexokinase II expression in skeletal muscle cells to enhance glucose absorption		(Ren *et al.*, 2019)
Anticancer	Alkaloids, saponins, steroids, gums, mucilages, carbohydrates and carrageenan	Reduced the growth of breast, colon, liver and osteosarcoma cell lines	India	(Suganya *et al.*, 2016)
	-	Reduced the cell viability of MCF-7, WBC and growth rate of mammary tumour in DMBA-induces mammary tumour in rats	Malaysia	(Chang *et al.*, 2017)

	Flavonoid	Inhibited the growth of cervical HeLa cells	Indonesia	(Arsianti *et al.*, 2018)
	3-hydroxy benzoic acid Cinnamic acid Chlorogenic acid Gallic acid	*K. alvarezii* was encapsulated with folate-conjugated PEGylated liposome that inhibited breast cancer cell, MCF-7 growth and induced apoptosis by increased ROS production, mitochondrial transmembrane potential damage/loss and morphological changes of the nucleus of MCF-7 cells.	India	(Baskararaj *et al.*, 2020)
Anticancer	Triterpenoid and alkaloid	Toxic against lung A-549 cancer cells	Indonesia	(Arsianti *et al.*, 2020)
	Alkaloids, phenols, sterols, steroids, diterpenoids, flavonoids, saponins, glycosides, proteins, amino acids and carbohydrates	Reduced oral cancer cells (KB-3-1 cell lines) viability	India	(Sharan & Vennila, 2021)
	-	Suppressed the proliferation of MCF-7, HeLa, MB-MDA231, SK-Lu1, HCT116, HT29, HepG2, MG63 by regulating proapoptotic proteins (Chk1 and p53) and anti-apoptosis (Birc5, Bag 1 and MDM 2)	-	(Putri *et al.*, 2021)
Cosmetic Application	Alkaloids, carotenoids, amino acids, phytosterols, phenolics, flavonoids, terpenoids, phlorotannins, tannins	Improved fibroblast surface smoothness and proliferation	India	(Janarthanan & Senthil Kumar, 2019)
	Seaweed extract	Anti-photoaging and sunscreen formulations	Indonesia	(Pangestuti *et al.*, 2021)
	Carrageenan production	More than 20% of carrageenan production is used in pharmacy and cosmetology	Indonesia	(Pereira, 2018)

*WBC, white blood cells; FRAP, ferric reducing antioxidant power; DPPH, 2,2-diphenyl-2-picryl-hydrazyl; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; DMBA, 7, 12- dimethylbenz[a]anthracene; ROS, Reactive oxygen species; TPC, total phenolic content; DPP-4, dipeptidyl peptidase-4; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvate transaminase; ALP, alkaline phosphatase; MDA, malondialdehyde; ABTS, 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid; MMP, matrix metalloproteinase; NFκ-B, nuclear factor-kappa B; ERK, extracellular-signal-regulated kinase; TBARS, thiobarbituric acid reactive substance; FFA, free fatty acid; AMPK, AMP-activated protein kinase; N/A, Not accessed, while "-" denotes not performed.

Cosmetic Application

More than 20% of carrageenan production is used in the pharmacy and cosmetology industries (Pereira, 2018). The presence of phytochemicals, such as alkaloids, carotenoids, amino acids, phytosterols, phenolics, flavonoids, terpenoids, phlorotannins and tannins in *K. alvarezii* contributes to its potential as an anti-ageing agent, which has been shown to improve fibroblast surface smoothness and proliferation (Janarthanan & Senthil Kumar, 2019). Apart from that, seaweed extracts could be added to anti-photoaging and sunscreen formulations to prevent oxidative stress and improve the absorption spectra of UV filters (Pangestuti *et al.*, 2021). *K. alvarezii* decreased the levels of mast cell protease-1 and histamine while inhibiting the levels of specific IgE, IL-4 and IL-13. In addition, *K. alvarezii* upregulates Treg cells through the expression of Forkhead box protein 3 (Foxp3) and the release of IL-10, both in in vivo and in vitro models (Xu *et al.*, 2017).

Conclusion

In conclusion, *K. alvarezii* is a red seaweed that has gained significant attention due to its potential as a source of bioactive compounds. The phytochemicals present in *K. alvarezii* have been found to possess various pharmacological activities, such as antioxidant, anti-inflammatory, and anticancer properties. Moreover, seaweed has been traditionally used in various countries for the treatment of ailments, such as cough, cold, and bronchitis. The presence of polysaccharides in *K. alvarezii* has also been shown to have the potential as a natural remedy for diabetes and obesity. Further research on this seaweed is warranted to explore its full potential as a source of natural remedies and to determine its safety and efficacy. In summary, *K. alvarezii* is a promising candidate for the development of novel therapeutic agents, and its ethnopharmacological significance makes it a valuable resource for traditional medicine.

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