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Health Benefits of Edible Seaweeds and Their Nano-Applications

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Abstract: Edible seaweeds have historically been consumed by coastal populations across the globe. Today, seaweed is still part of the habitual diet in many countries and a total of 145 species of red, brown and green seaweeds are used worldwide. Seaweed contains fiber and sugars, both of which can be used as food sources for the bacteria in human gut. Seaweed may help to lose weight and a good source of essential amino acids and omega-3 fats. Seaweed contains a wide range of vitamins and minerals, including iodine, iron, zinc, magnesium and calcium. In addition to containing a wide range of antioxidants, such as vitamins A, C and E, carotenoids and flavonoids. As part of a healthy diet, seaweed can help to protect against oxidative stresses and prevent chronic diseases such as cancer and digestive problems. Some types can even contain high amounts of vitamin B12. Seaweed may help to reduce cholesterol, blood pressure and risk of blood clots. Seaweeds have broad spectrum of biological activities such as antimicrobial, antiviral, anti-inflammatory, anti-allergic, anticoagulant anticancer, and antifouling activities. Recently, seaweeds and their bio-products are getting greater attention toward the treatment of diabetes. Current development of nanotechnology has an advantage in the Nano-science field and it has become popular in the past twenty years. Seaweeds possess both primary and secondary metabolites to carry out green synthesis. Silver nanoparticles synthesized via green methods are widely used for many applications such as anti-diabetic, antimicrobial, antioxidant, and were found to be an appropriate Nano-medicine for Nano-biomedical. Therefore, seaweeds are believed to be a potential source to provide novel biologically active substances for human health and the development of pharmaceuticals.

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Introduction

Seaweeds (Marine macro-algae) are classified into Green seaweeds (*Chlorophyta*), Brown seaweeds (*Phaeophyta*), Red seaweeds (*Rhodophyta*). Studies have shown that most of the seaweeds discovered are red (6000 species) followed by brown (2000 species) and green (1200 species) (Raja *et al.,* 2013; Kochi, 2012). Seaweeds are commonly utilized as a source of food with a total of 145 species of red, brown and green seaweeds used globally. They are also utilized in industrial applications and fertilizers, especially in Asian countries. In marine ecosystems, seaweeds are a primary source of energy. They are rich in compounds that are essential in the food cycle of phytoplankton and zooplanktons (Perumal *et al.,* 2019). Since prehistoric times, Asian countries have relied on seaweeds as a source of food, fertilizers, fungicides and herbicides (Fleurence, 1999; Sanchez-Machado *et al.,* 2004). In Japanese meals, more than 20 species of seaweed are used, including Nori (*Porphyra* sp.), Kombu (*Laminaria* and *Saccharina* sp.) and Wakame (*Undaria pinnatifida*). Seaweed polymers are also used as thickening and gelling agents in food and drug industries in western countries (Mabeau and Fleurence, 1993; Ruperez *et al.,* 2012). In Ireland and Scotland, the red seaweed *Palmaria palmata, Porphyra* and *Chondrus crispus* are widely used. Oats are mixed with Laverweed (*Porphyra*) to make laver bread in California and Maine in the US, British Columbia, Nova Scotia in Canada, and in the cuisines of Brittany and Wales. Other forms of seaweed, such as Dulse, is dried and eaten as a snack or mixed in salads, bread dough and curds in Iceland (Warwier *et al*., 2012).

Macroscopic seaweed been closely connected with day to day human life since time immemorial. Seaweeds possess an economically important phycocolloids (Levering *et al.,* 1969; Sumayya and Murugan, 2019). They are usually collected or harvested for food consumption and especially known for their high nutritional value and health benefits. Seaweeds are used in medical and pharmaceutical fields due to their richness in antioxidant, antimicrobial, anti-inflammatory and antidiabetic activities (Elsie and Dhanarajan, 2010). It has been concluded that seaweed contain many useful and essential compounds including fatty acids, sterols, phenolic compounds, terpenes, polysaccharides, alkaloids, flavonoids. Among the three main divisions of seaweed (*i.e.*, *Chlorophyta, Phaeophyta*, and *Rhodophyta*) red seaweed was not studied thoroughly until recently where it was determined that they contain many active ingredients, particularly those that are medically useful. Interestingly, various mechanisms of action have been proposed but the structural details of the active compounds are not yet properly elucidated. Among other benefits of seaweeds, they possess reactive antioxidant compounds such as ascorbate, glutathione (GSH), secondary metabolites including carotenoids, aminoacids, phlorotannins (phloroglucinol), Tocopherols (Yuan *et al.,* 2005a).

Seaweeds are ecologically important sources of food, dairy, pharmaceutical, cosmetic, and industrial applications; in addition, they are a naturally important source of nutrition. They are a source of carbohydrate, protein enzymes, fiber, vitamins including: A, B1, B2, B6, niacin and C, and are rich in iodine, potassium, iron, magnesium and calcium (Raja *et al.,* 2013). Production of bioactive compounds is majorly through seaweed culture and the reason for being an important type of aquaculture. They are used in printers' inks, paints, cosmetics, insecticides, and pharmaceutical preparations. Seaweeds are generally photosynthetic organisms which are heterogeneous and benthic in nature. Entirely, seaweeds have commonality in the general character of higher green plants, however they are structurally different from each other (Vadas, 1979). With the similarities in the function and habitat of marine ecosystem, marine higher plants like salt marsh grasses and seagrasses are considered seaweeds. Seaweeds are recognized as a sustainable source of naturally occurring bioactive compounds. Seaweeds are rich in antibacterial and antifungal agents, and thus utilized in the treatment of diseases caused by effective against Gram-positive and Gram-negative organisms (Kolanjinathan *et al.,* 2014; Gnanavel *et al.,* 2019). They can be easily cultivated in different aquatic environments and have a short generation cycle (John *et al.,* 2011; Jang *et al.,* 2012). The importance of seaweeds as biologically active metabolites is due to their availability, diversity, and productivity (Kim and Chojnacka, 2015). Their richness in phenolics (Montero *et al.,* 2018), terpenoids (Pérez et al., 2016), alkaloids (Güven et al., 2010), flavonoids (Hamed et al., 2015), and polysaccharides (Garcia-Vaquero et al., 2017), makes them important source of nutrition, especially that they possess specific characteristics that are rare or absent in terrestrial plants. Studies on seaweeds found that have effective antioxidant (Chew et al., 2008), antimicrobial (Shanmughapriya et al., 2008; Lu et al., 2019), anti-flammation (Lin et al., 2016; Kazłowska et al., 2010), antidiabetic (Lin *et al.,* 2017; Sharifuddin *et al.,* 2015) and anticancer activities (Moussavou *et al.,* 2014).

Epidemiological researches state that seaweed-containing diets plans are inversely associated with all-cause mortality and cardiovascular disease mortality in Japanese adults (Nanri *et al*., 2017; Cherry *et al*., 2019). However, studies on Korean men with metabolic syndrome reported that they consume higher quantities of seaweed than those without metabolic syndrome, while no mechanistic insight has been published (Shin *et al*., 2009). *Porphyra* spp. consumption was also inversely associated with breast cancer risk in studied premenopausal women but not in postmenopausal women. However, no association was found between consumption of *Undaria pinnatifida* and breast cancer risk (Yang *et al*., 2010). Michikawa *et al.,* (2012) identified a positive correlation between seaweed intake and thyroid cancer risk (especially papillary carcinoma) in postmenopausal women. On the other hand, a study by Wang *et al*., (2012) concluded no association between seaweed intake and thyroid cancer in either premenopausal or postmenopausal women. Stomach and colon cancer also demonstrated an inverse relationship with seaweed intake in Case-controlled studies by Hoshiyama and Sasaba, (1992) and Hoshiyama *et al*., (1993). Recently, *Palmaria palmata* was studied in an intervention study in a European population and concluded that its consumption could improve iodine status in adults, as serum TSH was significantly increased (within the normal clinical range) following *Palmaria palmata* intake of 5 g/d for 28 days (Allsopp *et al*., 2016).

Nutritional and Bioactive constituents of seaweeds

Various types of seaweeds considered novel foods in Europe, although the nutritional composition of brown, red, and green seaweeds differs between species, season, and ecology of the harvesting location (EC, 2018). Therefore, there is a need to characterize the composition of seaweeds in relation to the influence of location and seasonality on seaweed content. Current efforts to catalog information on the variability of nutritional composition will facilitate the identification of optimal harvesting periods and/or locations for a given species. When the perfect harvesting conditions are studied, it could aid the functional food industry in targeting the best conditions in which specific bioactive components present can be isolated (Madden *et al.,* 2012; Schiener *et al.,* 2015; Vieira *et al.,* 2017). The marine ecosystem have been recently exploited as a rich source of new agents used in different medical fields (Chew *et al.,* 2007; Mayer *et al.,* 2007). Studies have succeeded in isolating numerous novel compounds from marine organisms which resulted in the discovery of interesting biological activities present in the extracts (Ely *et al.,* 2004; Dubber and Harder, 2008).

In fact, seaweeds are one of the most remarkable marine organisms that are highly beneficial and used in human and animal nutrition (Dawczynski *et al.,* 2007a). In addition, they produce structurally different and biologically active secondary metabolites that act as a defense mechanism against fouling organisms and herbivores (Bhadury and Wright, 2004). The presence of bioactive compounds obtained from seaweeds make them a primary tool in pharmaceutical industries, such as their antimicrobial, antiviral, antifungal, anticancer and antioxidant activities (Kolanjinathan *et al.,* 2014; Lavanya *et al.,* 2017).

A primary natural resource of the oceans is seaweeds as they represent 27% of the global production from aquaculture (FAO, 2016). They are also a source of hydrocolloids, fertilizers, and animal feed (Stengel and Connan, 2015; Torres *et al*., 2019). The medicinal properties of seaweeds have been known anciently in the traditional Chinese tests of medicine and Ayurveda (Mouritsen, 2013). However, the attention on studying marine seaweeds have only peaked recently especially on the bioactivities and bioprospecting of these organisms (Hafting *et al.,* 2015). Seaweeds are loaded with a range of compounds, such as pigments (e.g., phycobiliproteins and carotenoids), phenolic compounds (e.g., phlorotannins and bromophenols), nitrogen compounds (e.g., alkaloids), polysaccharides (e.g., agarans, carrageenans, and alginate), and terpenoids (e.g., diterpenes and sesquiterpenes) (Stengel and Connan, 2011). The biological activities of these compounds include but do not exclude antioxidant, antibacterial, antiviral, anti-aging, anti-inflammatory, and anticancer compounds (Michalak and Chojnacka, 2015).

Different dietary supplements, functional foods, pharmaceuticals, cosmetics, and other industrial applications greatly use seaweeds due to the presence of these bioactive components (Ariede *et al.,* 2017; Lerat and Cornish, 2018). In the nutraceutical industry, for instance, macroalgae–rich diets were reported to provide significant health benefits including a reduction in diseases risk and improvement in the overall well-being (Cornish *et al.,* 2017; Wells *et al.,* 2017). In addition, in the cosmetic industry, seaweed extracts are known to induce benefits to the skin due to the bioactives in them (Ariede *et al.,* 2017). Seaweeds are found in complex habitats and are at risk of fluctuations in temperature, salinity, light, nutrients, contaminants such as heavy metals etc. Therefore, the circumstances of their habitat make them prone to unfavorable environmental conditions and thus capable of producing a wide range of unique primary and secondary metabolites that are not normally found in organisms living in terrestrial environments (Rodrigues *et al.,* 2015, Sumayya and Murugan, 2019).

Seaweeds are filled with different nutrients such as proteins, lipids, polysaccharides, minerals, enzymes, antioxidants, phytonutrients and vitamins (A, E, C and Niacin). These nutrients are essential for human nutrition and growth, which has been reported in various literatures (Perumal *et al*., 2019). However, seaweeds nutritional status differs with their ecological and physiological conditions. Moreover, they possess many essential elements like potassium, magnesium, iron and zinc. Green and red seaweed primarily contain vitamins of B12, B1, pantothenic acid, folic and colonic acids and are rich sources of protein and fiber (Berna *et al.,* 2013). These compounds make seaweeds not only significant in on the nutritional level, but also have pharmaceutical importance. Many studies experimented and reported their varying photochemical profiles and important biological applications. Many microbial infections can be treated with the phytochemicals in seaweeds (Okigbo and Omodamiro, 2006). The pharmaceutical importance of seaweeds is known as the development of antibacterial, antifungal and antiviral substances from their extract; however, it is still in the rapidly growing step of research and development.

The recently studied bioactive secondary metabolites and the chemically modified marine compounds obtained from the marine seaweeds like carotenoids, polyunsaturated fatty acids, phycocolloids and sterols have proven their significant pharmacological activities in preventing and treating various diseases (Gnanavel *et al.,* 2019). They are also considered healthier food ingredients that are used in the manufacture of nutraceuticals throughout the world. Diverse pharmacologically effectual bioactive metabolites that are present in natural seaweeds makes it unique and indispensable in the identification of lead molecule for new drug discovery, such as antimicrobial, antiviral, antibacterial, and antifungal, anti-allergic, anticoagulant, anticancer, antifouling, and anti-oxidant (Perumal *et al*., 2019). The functions of these secondary metabolites are defense mechanism against pathogens that can increase mortality rates among humans. Almost all of the secondary metabolites extracted from seaweeds are known to have bacterial or the antimicrobial compounds, viz., phenols, oxygen heterocyclic, terphenols, sterols, polysaccharides, dibutenolides peptides and proteins (Watson and Cruz-Rivera, 2003).

Dietary Fiber

Seaweeds contain an assorted variety of fiber components. Brown seaweeds are known to contain alginate (Brownlee *et al*., 2005) laminarin (Devillé *et al*., 2007) and fucoidan polysaccharides (Li *et al*., 2008); while red seaweeds contain agar, carrageenan, porphyran, and xylan (Usov *et al*., 2011) and green sea weeds contain ulvan, xylan, and cellulose (Lahaye and Robic, 2007). With many populations failing to meet daily requirements for dietary fiber intake (EFSA, 2010a; SACN, 2015), seaweeds can be an essential resource in every individuals diet. The viscous and water-binding properties of fiber within the gastrointestinal tract is the potential functional properties of dietary fiber (EFSA, 2010b). As a result, fiber has been suggested to promote satiety and weight loss; as it works on delaying gastric emptying to improve glycemic control; enhance stool bulking to reduce gut transit time and increase defecation frequency; and enhance bile acid excretion, resulting in reduced low-density lipoprotein cholesterol (LDL-C) in blood (EFSA, 2010a; EFSA, 2011; Clark and Slavin, 2013). To improve health, dietary fiber components are recommended via their fermentation by the colonic microbiota, which can positively alter the microbial composition of the gut and enhance the production of health-associated volatile fatty acids such as acetate, propionate, and butyrate. Fiber-induced alterations to the microbiota composition and the associated metabolites produced can promote the gastrointestinal, cardiometabolic, immune, bone, and mental health (Gibson *et al*., 2017).

Seaweed, with its high fiber content, is a promising candidate to achieve so. There is an increasing interest from food industries that identify seaweeds as a sustainable alternative source of dietary fibers, especially owing to the range of proposed beneficial health effects associated with consumption of dietary fiber (Clark and Salvin, 2013). However, the contribution of whole seaweed to the currently recommended intake of dietary fiber, i.e, 25 g/d, is limited, with a 5-g serving of brown, red, or green seaweed contributing up to 14.28%, 10.64%, or 12.10% of dietary fiber intake, respectively (EFSA, 2010c). This has led to increasing interest in the industrially applicable extraction and isolation of individual fiber components from seaweed.

Although some seaweed-derived fibers (alginate, carrageenan, and agar) have been used for decades for their emulsifying, stabilizing, and thickening characteristics for their ability to improve the sensory properties of food, there is a limited interest in their application as functional dietary fibers. However, their extensive use in the food industry ensures they are safe for human consumption, according to the European Food Safety Authority (EFSA) and the US Food and Drug Administration. Thus, alginate isolated from brown seaweeds, long used by the food industry, is a leading candidate for application in the functional food market (ONFL, 2016; EFSA, 2017). EFSA recently classified Fucoidan as a novel food, (EC, 2017) making it another viable candidate for an emerging functional food ingredient. On the other hand, suggestions that low-molecular-weight carrageenan components (< 50 kDa) may negatively impact health (on the basis of pro inflammatory properties) have negatively impacted the potential interest of using carrageenan as a functional ingredient (Burges Watson, 2009).

The majority of studies that focused on the health benefits of seaweed-derived dietary fiber components in humans was fixated on potential antiobesogenic effects, including improved satiation, delayed nutrient absorption, and delayed gastric emptying (El Khoury *et al*., 2015; Chater *et al*., 2016). Peters *et al*., (2011) concluded that an alginate drink enhanced self-reported satiety and reduced the feeling of hunger in a dose-dependent manner. Another parallel study by Hall *et al*., (2012) in overweight men demonstrated that an intake of an *Ascophyllum nodosum* enriched (4%) bread reduced energy intake by 109 kcal and 506 kcal at 4 hours and 24 hours post consumption, respectively, compared with an isocaloric placebo. This concludes that Alginate seems to affect appetite and food intake.

Beta glucan, another fiber, have received favorable EFSA opinions for its ability to reduce postprandial glucose absorption by slowing the rate of gastric emptying (EFSA, 2011). However, there is a lack of literature on the effect of alginate on glucose metabolism, particularly the postprandial insulinemic response. The recent label of fucoidan as Generally Recognized as Safe (GRAS) by the US Food and Drug Administration (OFAS, 2016) and as a novel food by the European Union, (EC, 2017) along with accumulating in vitro and in vivo evidence of fucoidan's potential antiobesogenic effects (Kim *et al*., 2014) make fucoidan an attractive ingredient for the functional food industry (Lim *et al*., 2017). A randomized, double-blind, parallel, placebo-controlled trial in an overweight/obese group revealed that participants who consumed fucoidan (500 mg/d) for 3 months had decrease in their diastolic blood pressure and LDLC compared with those who received placebo (Hernandez-Corona *et al*., 2014). However, no changes in weight, waist circumference, body mass index (BMI), adiposity, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol

(HDL-C), blood glucose, or blood triglycerides were observed in the study. Whilst blood insulin and homeostasis model assessment of insulin resistance (HOMA-IR) were positively increased in the fucoidan consuming cohort compared with baseline values. They suggested that fucoidan consumption down regulated expression of the transcription factor peroxisome proliferator-activated receptor-c (PPARc) to suppress adipocyte differentiation and insulin signaling.

Contrariwise, evidence from experimental animals of obesity and diabetes suggests that low-molecular-weight fucoidan could enhance dyslipidemia and improve insulin sensitivity through activating insulin signaling pathways in adipocytes and hepatocytes (Kim *et al*., 2014; Lin *et al*., 2017). Further, experimentation from human intervention trials is essential to understand how dietary fucoidan may modulate host glucose and lipid metabolism to induce antiobesogenic and antidiabetic effects. The anticoagulant properties of fucoidan are gaining the attention of the pharmaceutical industry. The anticoagulant properties in Fucoidan, serving as a catalyst for antithrombin mediated and heparin cofactor II–mediated inhibition of thrombin (Dockal *et al*., 2011). In a study by (Irhimeh *et al.,* 2009) on oral administration of *Undaria pinnatifida* extract (9 g/d) with 75% fucoidan (molecular weight 713 kDa) for 12 days increased activated partial thromboplastin time, decreased thrombin time, and increased antithrombin-III. Another study by Ren *et al*., (2013) researched oral administration of fucoidan extracted from *Laminaria japonica* (molecular weight 300 kDa) at a dosage of 400 mg/d for 5 weeks and reported a significant reduction in thrombus lysis time. On the contrary, a fucoidan-specific monoclonal antibody enzyme-linked immunosorbent assay was not successful in detecting fucoidan in the blood of study participants in the same study. Therefore, it is suggested that fucoidan may not be bioavailable in humans, although in vitro and in vivo experiments found fucoidan to be absorbed through the small intestine (Nagamine *et al*., 2014).

There is plenty of evidence that supports an anticancer activity of fucoidan, but the majority of evidence is from in vitro or animal experiments (Atashrazm *et al*., 2015). A recent clinical study in patients of colon cancer investigated the effect of an oral fucoidan supplement (4g twice daily) administered in conjunction with chemotherapy (Tsai *et al*., 2017). Patients who were treated fucoidan had a significantly better disease control rate compared with placebo control patients however showed no change in overall response rate, progression-free survival, overall survival, adverse effects, or quality of life.

There is an increasing interest on the potential effect of prebiotics from seaweed-derived fiber, which can change the composition and metabolism of the colonic microbiota. Numerous studies of in vitro fecal batch culture have demonstrated the ferment ability of seaweed fiber components and noted an increase in the production of short-chain fatty acids and modulation of the microbial gut communities (Bai *et al*., 2017; Bajury *et al*., 2017; Fu *et al*., 2018). Modulation in the gut microbiota and production of short-chain fatty acids have been observed in animal studies using a seaweed fiber–containing diet by Deville *et al*., (2007). The only health benefit correlated to the prebiotic effects of seaweed fibers is that it slows the weight gain in animals that are on a high-fat diet (Nguyen *et al*., 2016).

Protein

The protein content of seaweed has been a source of attention due to the emerging challenges faced to improve food security through identifying alternative and sustainable protein sources (Harnedy and FitzGerald, 2011). The protein content ranges from 5.02% to 19.66% in brown seaweeds; from 0.67% to 45.0% in red seaweeds; and from 3.42% to 29.80% in green seaweeds. A 5-g portion of dried brown is a maximum of 1.97%, red 4.5%, and green 2.98%, and of the Reference Nutrient Intake for protein. On a gram-for-gram basis, seaweeds have protein and amino acid contents similar to those of beef; however, seaweeds are consumed in much minor amounts (Greenwood *et al.,* 1951). To determine the value of proteins to the human diet, the amino acid composition of proteins is critical, particularly in achieving an adequate intake of essential amino acids. However, the nutritional value of the protein will be significantly affected by the digestibility of seaweed protein within the gastrointestinal tract, with protein–polysaccharide interactions reducing digestion efficiency considerably.

Using seaweeds as nonanimal protein sources may be possible through planning harvests that optimize protein and amino acid contents. Seaweeds are a source of lysine, which is an important amino acid often found in limited quantities in terrestrial plant protein sources such as corn, maize, soy, rice, and wheat (Misurcova *et al.,* 2014; EFSA, 2012) An 8-g portion of *Palmaria palmata* contains up to 21.9% of the recommended daily intake of cysteine, yet the total protein content of *P. palmata* varies seasonally (Misurcova *et al.,* 2014). For instance, the protein content reported in winter/spring was as 21.9% and as 11.9% in summer/autumn, with essential amino acids making up to 26% to 50% of the protein (Galland-Irmouli *et al.,* 1999).

Protein extracts from seaweeds holds an importance as a viable source of protein, providing their bioactivity is validated in humans. The digestibility of protein in edible species of seaweeds, estimated by in vitro methods, is reported as follows: *Fucus vesiculosus*, 14.7%; *Laminaria digitata,* 16.9%; *Undaria pinnatifida*, 28.0%; *Chondrus crispus*, 45.0%; *Porphyra tenera*, 69.4% (Urbano and Goni, 2002); *Palmaria palmata*, 56.0% (Galland-Irmouli *et al.,* 1999); and *Porphyra columbina*, 74.3% (Cian *et al.,* 2014). Studies have reported that the digestibility of *Undaria pinnatifida* and *Porphyra tenera* protein in rodents is reported as 86.1% and 86.2%, respectively, while the digestibility of *Undaria pinnatifida* protein in humans is reported as 70.0%, which is similar to the digestibility of protein from terranean plants (Urbano and Goni, 2002; Cerna, 2011). Although data on in vivo digestibility suggest that seaweed protein is bioaccessible, protein polysaccharide interactions within the seaweed matrix could prevent the formation of enzyme–substrate complexes and hinder proteolysis of seaweed proteins. Certainly, treatment via enzymes with xylanase and cellulase polysaccharidases improved *Palmaria palmata* protein bioaccessibility 1.7-fold and 3-fold, respectively (Maehre *et al.,* 2016). These results support the utilization of protein extracts from seaweed to provide the maximal protein and amino acid content, with possible food, feed, supplement, and nutraceutical applications (Cerna, 2011; Beasley *et al.,* 2013). There are several methods of protein extraction from seaweed and they're described comprehensively in other studies; for example, the use of different proteolytic and sac charolytic enzymes such Celluclast or Shearzyme are reported to improve both protein extraction yield and endogenous digestion (Kadam *et al.,* 2017; Bleakley and Hayes, 2017).

Until now, reports on the bioactivities in literature are related to peptides extracted from red seaweeds such as *Palmaria palmata* and *Porphyra* spp. and from brown seaweeds such as *Undaria pinnatifida* and were associated with antihypertensive, antioxidant, and antidiabetic effects (Admassu *et al.,* 2018). They are known to possess cardioprotective effects such as reduced blood pressure through the inhibition of angiotensin-converting enzyme, (Sato *et al.,* 2002; Jimenez-Escrig *et al.,* 2011; Fitzgerald *et al.,* 2014); additionally, antidiabetic activities through inhibition of dipeptidyl-peptidase (Bouga and Combet, 2015; Harnedy *et al.,* 2015) and promoting iron absorption (Cian *et al.,* 2016). Applying seaweed peptides as food preservatives have also been suggested as peptides contain antioxidant properties (Harnedy *et al.,* 2017; Sato *et al.,* 2002).

Fat

The fat content in seaweed tends to be relatively low to total dry weight. However, in winter the percent fat content is the highest and is lowest during summer but the fatty acid composition varies by season (Madden *et al*., 2012). For instance, both the lipid concentration and the polyunsaturated fatty acid (PUFA) content of *Saccharina latissima* grown in integrated multitrophic aquaculture were highest in March and November, yet lowest in January (Marinho *et al*., 2015). Furthermore, lipids derived from seaweed are highly digestible. For example, up to 98% of the fat content of *Undaria pinnatifida* (1.5% dry weight) is proven digestible in adults (Yamada *et al*., 1991).

Sargassum polycystum has a total lipid content ranging from 0.29% (Matanjun *et al*., 2009), 8.88% in *Porphyra* spp. (Paiva *et al*., 2014). *Porphyra* spp. have the lowest saturated fatty acid (SFA) content (17.4% of total fatty acids), whereas *Plocamium brasiliense* has the highest (74% of total fatty acids) (Gressler *et al*., 2011). Monounsaturated fatty acid content relative to total fatty acid content ranged from 3.3% in *Ochtodes secundiramea* to 47.1% in *Fucus vesiculosus* (Maehre *et al*., 2014). The PUFA content of total fatty acids ranges from 6.7% in *Ulva lactuca* (Yaich *et al*., 2011) to 69.1% in *Undaria pinnatifida* (Sanchez-Machado *et al*., 2004). *Undaria pinnatifida* also has the highest PUFA:SFA ratio (3.39). *Palmaria* spp. is reported to have the lowest ratio of n-6 to n-3 fatty acids (Maehre *et al*., 2014) whereas *Gracilaria gracilis* has the highest (Francavilla *et al*., 2013).

Maintaining blood LDL-C within normal concentrations can be achieved through foods with a greater ratio of PUFAs to SFAs concentrations (EFSA, 2011). However, dietary reference values have not yet been established for PUFAs collectively, but an intake of 4% of total energy is recommended for n-6 linoleic acid (EFSA, 2010d). Reports on male KK-Ay mice treated with 1% *Undaria pinnatifida* lipid for 4 weeks showed a significant reduction in body weight when compared with controls, whereas total weight of white adipose tissue was reduced in mice who consumed both the *Undaria pinnatifida* lipid and n-3 PUFA-rich scallop phospholipids (Okada *et al.,* 2011). Seaweed lipids are known to have anti-inflammatory activities, which include the inhibition of lipopolysaccharide induced inflammation in human THP-1 macrophages by lipids derived from the red seaweeds *Porphyra dioica, Palmaria palmata*, and *Chondrus crispus* (Robertson *et al.,* 2015). Lipids extracted from *Gracilaria* spp. also inhibited lipopolysaccharide in murine RAW 264.7 macrophage cells and decreased the viability of human T-47D breast cancer cells and of 5637 human bladder cancer cells (da Costa *et al.,* 2017). The fatty acid C18 extracted from *Ulva lactuca* was reported to exert an anticancer effect via activation of the Nrf2-ARE pathway to promote scavenging of reactive oxygen species (Wang *et al.,* 2013). Seaweeds may be considered as a viable and sustainable source of extractable PUFAs that can be potentially applied as dietary supplements or nutraceutical products.

Carotenoids

Carotenoids are a group of tetrapenoid compounds in seaweeds that contribute to photosynthesis. Carotenoids are generally a highly conjugated natural pigments present in all types of plants typically made up of 40 carbon structures which are enzymatically polymerized from the five carbon isoprene units (Cardozo, 2007). Due to animals being unable to obtain carotenoids endogenously, through diet is the only route or primary source for all the animals to achieve essential carotenoids. Among their essentialities is that their antioxidant properties aid in protection from UV damage. The linear polyenes of carotenoids functions as a potential antioxidant which reduces the level of reactive oxygen species (ROS) and also proceeds as a light energy harvester (Von Elbe and Schwartz, 1996). There are around 600 identified carotenoids, however about only 50 carotenoids are known to have property of provitamin A and thus carotenoids are a primary source of provitamin A for all animals and humans (Von Elbe and Schwartz, 1996). Carotenoids can also be effectively utilized in treatment of diseases and even protection against heart diseases, cancer and ulcer, mainly owing to its provitamin A and antioxidant properties (Li and Chen, 2001).

Carotenoids are likewise used in the food industries in the production of finished food products and also in the nutraceuticals industries. In the food industry, they are also utilized as a food coloring agent which are usually obtained from the isolation of natural sources and can also be prepared synthetically. Astaxanthin and β-Carotene are the important carotenoids obtained from the microalgae and these bioactive molecules are predominantly present in the microalgae sources and also have significant pharmacologically activity. β-Carotenes are mostly found in the plant tissues which have potential provitamin A activity (Gregory and Vitamins, 1996). It is clearly evident that there is a significant difference in the concentration proportion of β-Carotene among the marine plants and seaweeds. There are many factors which play a major role in the concentration difference proportion of β-Carotene among the marine plants and seaweed but the most important factors include salt concentration, nitrates level and increased light intensity.

Fucoxanthin is the main carotenoid with potential application in the food industry is extracted from brown seaweeds (Mikami *et al.,* 2013)**.** Studies suggests that fucoxanthin possess antioxidant activities that can potentially be used as food preservatives to prevent lipid peroxidation in meat (Sellimi *et al.,* 2017). Other carotenoids are present in various red seaweeds) lutein, b-carotene, and zeaxanthin (as well in green seaweed (lutein, b-carotene, echinenone, violaxanthin, and neoxanthin) which calls for investigation on their potential antiobesogenic, antidiabetic, or antioxidant bioactivities (Parjikolaei *et al*., 2016; Pirian *et al*., 2016).

Fucoxanthin can be used as a functional food ingredient to reduce the risk of diabetes and obesity, although the evidence is derived predominantly from in vitro and animal studies. Fucoxanthin's mechanism is thought to be by inhibiting the digestive enzymes a-amylase and a-glucosidase, which in turn affects lipid metabolism by modulating leptin and adiponectin, resulting in down regulation of lipogenesis and upregulation lipolysis (Nagappan *et al.,* 2017)**.** Several in vivo animal studies reported that fucoxanthin supplementation was proven to reduce blood glucose, plasma insulin, body weight gain, and accumulation of lipid in the liver; to decrease insulin resistance; and to improve the plasma lipid profile (Muradian *et al.,* 2015). However, studies investigating the impact of fucoxanthin on cholesterol metabolism in mice have differed. Beppu *et al.,* (2012) reported an increase in HDL-C, non-HDL-C serum and total cholesterol, while Jeon *et al.,* (2010) reported a decrease in the cholesterol serum and an increase in fecal cholesterol following fucoxanthin diets.

In a human intervention trial, the antiobesogenic effects of fucoxanthin have been reported in which consumption of fucoxanthin over a course of 4 weeks have significantly decreased BMI, body weight, and visceral fat area in mildly obese adults (BMI, 25–30 kg/m^2) (Hitoe, 2017). An investigation by Abidov *et al*., (2010) found evidence to support a role for a proprietary product containing brown seaweed fucoxanthin, n3 fatty acids, and punicic acid to exert antiobesogenic effects. Consumption of fucoxanthin product over 16 weeks by premenopausal woman with nonalcoholic fatty liver disease and premenopausal women with normal liver fat showed a significant reduction in body weight, by 5.5 kg and 5 kg, respectively, compared with the placebo group. Furthermore, statistically significant improvements in liver fat content were observed in both groups, along with improved systolic and diastolic blood pressure, and C-reactive protein, but not in the placebo group. Additionally, significantly reduced waist circumference and serum triglycerides were observed only in the intervention group with nonalcoholic fatty liver disease. Interpretation of the role of fucoxanthin in this study is confounded by the additional components (omega-3 fatty acids, punicic acids derived from pomegranate seed oil) present in the treatment, and thus further study is needed to verify the effects of fucoxanthin alone.

Polyphenols

Polyphenols are highly complex, structural components of the cell wall. Polyphenols are bound to cell wall polysaccharides, which protects against oxidative damage (Heffernan *et al.,* 2015). There are different categorize of polyphenols, which are phenolic acids, flavonoids, tannins, catechin, anthocyanidins, epigallocatechin, lignin, epicatechin, epigallate, and gallic acid (Bandaranayake, 2002). They're known for their ability to reduce the mitotic index and decrease the levels of cellular proteins needed for cancer cell proliferation and colony formation. Phenols have anti-inflammatory activity, antiviral effects, and inhibited the human platelet aggregation (Mohsen and Ammar, 2009). Edible seaweed *Palmaria palmata* is rich in polyphenols with antioxidant and anticancer properties (Yuan *et al.,* 2005b). These polyphenols showed metabolic inhibition of xenobiotic-metabolizing enzymes (Zhao *et al.,* 2007), which leads to changes of the mitotic process in the telophase and therefore disruption of cell division (Gawron and Kruk, 1992).

Seaweeds are loaded with polyphenols, such as catechins, flavanols, and phlorotannins. However, mostly red and green seaweeds are a source of bromophenols, phenolic acids, and flavonoids (Gomez-Guzman *et al*., 2018), while phlorotannins are the most abundant polyphenol in brown seaweeds. Most recent researches investigates the bioactivity of phlorotannins, a class of polyphenol in brown algae included of phloroglucinol monomers and categorized as eckols, fucols, fuhalols, ishofuhalols, phloroethols, or fucophloroethols. The studied bioactivities of seaweed polyphenols are concerning its mitigation ability of risk factors related to type 2 diabetes and cardiovascular disease, including hyperglycemia, hyperlipidemia, inflammation and oxidative stress (Murray *et al*., 2018), and also anti-microbial activity (Eom *et al*., 2012).

Flavonoid and phlorotannin polyphenols are present in brown seaweeds that vary in structure, molecular weight, and level of isomerization (Murugan *et al.,* 2015). The bioactivities of seaweed polyphenols include potential anticancer (Yang *et al.,* 2010) and antioxidant activities (Fernando *et al.,* 2016). However, the bioavailability of polyphenolic compounds in food differs greatly but is relatively known to be low (Bohn, 2014). Literature and information on the bioavailability of seaweed derived polyphenolic compounds was limited, until a recent human intervention trial studied the bioavailability of polyphenols extracted from *Ascophyllum nodosum* provided initial indications of interpersonal variation in polyphenol uptake. Polyphenols detected in serum ranged from 0.011 to 7.757 mg/ml, while the total concentration of urinary phlorotannin and its metabolites ranged from 0.15 to 33.52 mg/ml (Corona *et al.,* 2016).

Most plant-based polyphenols undergo intestinal biotransformation by endogenous enzymes and the gut microbiota before being absorbed across enterocytes. These enzymatic transformations eliminate glycosidic bonds, for example, flavonoids are converted to glycones (sugars) and aglycones (non-sugars–polyphenols) by endogenous -glucosidases in the small intestine (Lewandowska *et al*., 2013). The transport of aglycones to the liver is through the portal vein and leads to phase II biotransformation (coupling reactions, chiefly hepatic conjugation to O-glucuronides and O-sulfates) to help in urinary and biliary elimination. The phase II metabolites are either absorbed into the systemic circulation, or defecated in bile and re-enter the duodenum (namely hepatic recycling), where subsequent glucuronidase, glycosidase, or sulphatase-mediated deconjugation by the colonic microbiota usually favors the reabsorption of aglycone (Opara *et al*., 2014).

Around 90–95% of dietary polyphenols reach the colon whole (Clifford, 2004), as the metabolism and biotransformation by the gut microbiota occurs through reduction, hydrolysis, decarboxylation, demethylation, dehydroxylation, isomerisation, and fission (Selma *et al*., 2009). This helps in the production of low-molecular weight compounds with less chemical heterogeneity than the polyphenol parent compound (Lewandowska *et al*., 2013). Moreover, the bioactivities associated with dietary polyphenol intake may be dependent on the catabolic capacity and composition of the gut microbiota, due to the biological activity of metabolites rather than the parent polyphenol compound present in food (Williamson *et al*., 2017; Espin *et al*., 2017), while a synergistic effect between prebiotic polyphenols and probiotic bacteria may occur (Gibson *et al*., 2017).

Glucose and lipid digestion and metabolism studies on animals support the evidence that seaweed polyphenols have an impact on them, giving rise to suggestions that these polyphenols may have potential in preventing diabetes and obesity-associated complications. Evidently, diabetic rats fed a water extract (300 mg/kg) or an ethanol extract (150 and 300 mg/kg) from *Sargassum polycystum* showed significant reductions in blood glucose, glycated hemoglobin, total cholesterol, blood triglycerides, and plasma atherogenic index (Motshakeri *et al.,* 2014)**.** A study by Iwai, (2008) on polyphenols from both *Ecklonia stolonifera* and Zhang *et al.,* (2007) on *Ascophyllum nodosum* have both shown to favorably alter glucose and insulin metabolism in diabetic mouse models, while *Ecklonia cava* polyphenols significantly reduced serum and liver triglycerides and total cholesterol in a diabetic mouse model (Kim and Kim, 2012). Another study by Kang *et al.,* (2016) demonstrated that a *Gelidium amansii* phenolic-rich extract reduced blood glucose and serum insulin and helped in protecting against the different impacts of a diet-induced obesity in mice via decreased blood triglycerides and total cholesterol. Until now, the mechanism of action is undetermined, however current evidence supports a role in the inhibition of digestive enzymes, including a-amylase, a-glucosidase, and lipase (Austin *et al.,* 2018). There is limited literature on seaweed polyphenols exerting anti-obesogenic effects or that they may play a role in maintaining glucose homeostasis in healthy humans. Elsewhere, neither a 500-mg nor a 2000-mg dose of *Fucus vesiculosus* polyphenol-rich extract reduced postprandial glucose or insulin responses beyond that of the cellulose placebo after a 50-g carbohydrate load (white bread) in healthy adults (n 1⁄4 38) (Murray *et al.,* 2018a). The total cholesterol LDL-C, and C-reactive protein was reduced in adults with increased cholesterol following treatment with a dosage of 400 mg/d *Ecklonia cava* polyphenol extract for a period of 12 weeks (Lee *et al.,* 2012). The mechanism of action may be due to the inhibition of adipogenesis, as the phlorotannin dieckol has been shown to down regulate AMP-activated protein kinase (AMPK) signaling in 3T3-L1 preadipocytes.

A recent meta-analysis concluded that marine extracts rich in polyphenol extracts could decrease fasting blood glucose, total cholesterol, and LDL-C in humans, but the few studies conducted on humans have reported non reliable findings for the effect of seaweed polyphenols on other biomarkers associated with risk of type 2 diabetes and cardiovascular disease, including postprandial blood glucose, fasting insulin, HDL-C, and triglycerides (Murray *et al.,* 2018b). However, *Ecklonia cava* phlorotannins were deemed safe for use as food supplements by the European Union (EFSA, 2017). Further evidence on at risk and healthy human populations is essential to determine the bioactivities of seaweed polyphenols (Murray *et al*., 2018a). Such efforts are crucial for maximizing the potentiality of seaweed polyphenols as food ingredients (Li *et al.,* 2017).

Polysaccharides

Polysaccharides compounds are abundantly present in several marine organisms, primarily alginates, agar, and carrageenans (Khalifa *et al*., 2019). The mechanism of action of polysaccharides cytotoxic effect is presumed to be the activation of the innate immune system (Zhou *et al*., 2005), which leads to the attraction of macrophages and natural killer cells to the target damaged sites and production of tumoricidal cytokines (Yim *et al*., 2005).

Seaweeds contain 2.97–71.4% complex polysaccharides (Cherry *et al*., 2019; De Jesus Raposo *et al*., 2016). Brown seaweeds include fucoidan, alginate, and laminarin; while red seaweeds xylan and sulphated galactans, such as agar, carrageenan, and porphyran; whilst ulvan and xylan are found in green seaweeds. Polysaccharides extracted from seaweeds are atypical in structure to terrestrial glycans, and are understood to resist gastric acidity, host digestive enzymes, and gastrointestinal absorption (O'Sullivan *et al*., 2010). Seaweed glycans can be utilized to serve as fermentation substrates for specific gut microbial populations or help substrate cross-feeding of partially broken-down intermediates, such as oligosaccharides and metabolic cross-feeding of SCFAs to cause indirect proliferation of specific bacteria (Ríos-Covián *et al*., 2017).

Brown Seaweed Polysaccharides

Brown seaweeds are commercially abundant and commonly used as food ingredients (Usman *et al*., 2017). The brown seaweeds are characterized by the dominance of different types of polysaccharides such as alginate, fucoidan, and laminarine.

Alginate

Alginates are composed of 1,4-linked ff-l-guluronic (G) and -d-mannuronic acid (M) residues to form GM, GG and MM blocks, and represent 17-45% dry weight of brown seaweeds (Vera *et al*., 2011). Alginates contain many properties that have wide applications in food processing, biotechnology, medicine and pharmaceutical industries (García-Ríos *et al*., 2012), while degraded sodium alginate is an approved item of "foods with specified uses", under the categories of "Foods that act on cholesterol plus gastrointestinal conditions" and "Foods that act on blood cholesterol levels" in Japan (Maeda-Yamamoto, 2017). In the faeces of pigs fed alginate, the presence of water soluble alignate oligosaccharides was found which is an indication of alginate lyase activity by the luminal or mucus adherent gut microbiota (Jonathan *et al*., 2013), although an adaptation period of > 39 days is reported for the degradation of G blocks by the porcine microbiota whilst M blocks are readily degraded (Jonathan *et al*., 2015).

Alginate's capacity to modulate the gut microbiota of Japanese individuals was discovered over 20 years ago (Terada *et al*., 1995), where alginate supplementation (30 kDa, 10 g/day, n = 8) significantly increased faecal *Bifidobacterium* populations in healthy male cohorts after both one and two weeks, besides, it significantly increased acetic and propionic acids after two weeks. Deleterious metabolites, including faecal sulphide, phenol, p-cresol, indole, ammonia and skatole had decreased compared to the control (free living) diet. Notably, faecal *Bifidobacterium* counts and SCFA concentrations returned to baseline in the week after alginate diet cessation, which highlights the transient nature of the gut microbiota and the need for greater powered long-term human intervention studies.

Alginate oligosaccharides (AOS) (~3.5 kDa) can be obtained via acidic or enzymatic hydrolysis of alginate polysaccharides (Vera *et al*., 2011), and enzymatically derived AOS has promoted the growth of *Bifidobacterium bifidum* ATCC 29521, *Bifidobacterium longum* SMU 27001 and Lactobacilli, in vitro (Han *et al*., 2016). In a two week study, supplementation of 2.5% AOS significantly increased faecal *Bifidobacterium* in rats compared to control and 5% FOS supplemented diets (13-fold and 4.7-fold increase, respectively), while faecal *Lactobacillus* were 5-fold greater in rats who consumed AOS compared to FOS. *Enterobacteriaceae* and *Enterococcus* populations were significantly decreased following AOS supplementation. Elsewhere, the hydrolysis of alginate, mannuronic acid oligosaccharides (MO) and guluronic oligosaccharides (GO) during a 48 h batch culture fermentation with the faecal microbiota of Chinese individuals demonstrated increased production of acetate, propionate, butyrate, and total SCFAs compared to the substrate-free control, where GO generated the greatest increase (Li *et al*., 2016). Subsequent strain isolation from the stools of individuals who demonstrated alginate degradation during fermentation identified Bacteroides xylanisovlens G25, Bacteroides thetaiotomicron A12, Bacteroides ovatus A9, and Bacteroides ovatus G19 as strains capable of hydrolysing alginate and AOS, where Bacteroides ovatus G19 expressed -1,4-guluronanlyase and -1,4-mannuronanlyase CAZymes (Li *et al*., 2017).

Fucoidan

Fucoidan is a sulfated polysaccharide (sulfated L-fucose) found in the brown seaweed cell wall (Berteau *et al*., 2003). Fucoidans are water soluble polysaccharides made up of sulphated 1,2 or 1,3 or 1,4- ff-l-fucose which exist as structural polysaccharides and occupy 5–20% of algal dry weight (Vera *et al*., 2011). The structural heterogeneity of fucoidan involves different degrees of branching, sulphate content, polydispersity, and irregular monomer patterns, which can include fucose, uronic acid, galactose, xylose, arabinose, mannose, and glucose residues (Zaporozhets *et al*., 2014).

Atherosclerosis, angiogenesis, and metastasis were changed by Fucoidan (Boisson-Vidal *et al*., 2007), when tested against human lymphoma HS-Sultan cell line. This impact is due to the consequent activation of caspase-3 and down regulation of the kinase pathway (Asia *et al*., 2005). Fucoidan is capable of disrupting heparansulfate-growth factor/cytokine complexes and substitute the cell surface heparansulfates by stabilizing the interaction between growth factors and their receptors (Sithranga Boopathy and Kathiresan, 2010).

A study on mice tested the anti-obesogenic effects of brown seaweeds, where supplementation of 5% (w/w) *Saccorhiza polyschides* extract, containing 12% dietary fiber was utilized and caused a reduction in body weight gain and fat mass of mice with diet-induced obesity (Huebbe *et al*., 2017). The fermentation of alginate and fucoidan complex polysaccharide components can be the cause behind the anti-obesogenic, presumably due to reduced microbial bile salt hydrolase activity; however, no gut microbial compositional data were found. Elsewhere, the in vitro evidence indicates that whole brown seaweeds and their extracted complex polysaccharide components are fermented by the ex vivo faecal microbiota. A corresponding increase in populations, such as *Bifidobacterium, Bacteroides, Lactobacillus, Roseburia, Parasutterella, Fusicatenibacter, Coprococcus, Fecalibacterium* was also reported (Fu *et al*., 2018).

A greater increase in *Bifidobacterium* and *Lactobacillus* was observed in an vitro fermentation study of fucoidan extracted from *Laminaria japonica* following 24 h and 48 h fermentation relative to >30 kDa fucoidan (Kong *et al*., 2016), while fucoidan from *Ascophyllum nodosum* (1330 kDa) and *Laminaria japonica* (310 kDa) were shown to increase *Lactobacillus* and *Ruminococcaceae,* respectively, in the caecal microbiota of mice administrated with 100 mg/kg/day (Shang *et al*., 2016). Fucoidan also reduced serum LPS-binding protein levels in this study which indicates a reduction in the antigen load and reduced inflammatory response. In contrast, fucoidan with a fucose-rich and highly sulphated fucoidan extracted from *Cladosiphon okamuranus* was not fermented by the rat gut microbiota (An *et al*., 2013).

Laminarin

Laminarin is known as a water-soluble storage polysaccharide consisting of 1,3 or 1,6 glucose with an average molecular weight of 5 kDa (Kadam *et al*., 2015) and accounts for 10–35% of the dry weight of brown seaweeds (Vera *et al*., 2011). An in vitro batch culture fermentation study on laminarin concluded an increase in Bifidobacteria and Bacteroides after 24 h (Seong *et al*., 2019), while another demonstrated an increase in propionate and butyrate production after 24 h (Devillé *et al*., 2007). Another in vivo rat study using 143 mg laminarin per kg body weight per day for 14 days demonstrated that laminarin was not selectively fermented by *Lactobacillus* and *Bifidobacterium*, however it was proved to modify jejunal, ileal, caecal and colonic mucus composition, secretion, and metabolism to protect against bacterial translocation. Researchers suggest that increased luminal acidity and/or catabolism of laminarin by mucolytic commensals could influence such effects, which corroborates the evidence that a complex polysaccharide-rich diet maintains mucus layer integrity to promote gut barrier function (Desai *et al*., 2016).

Future studies on modulation of intestinal mucus via laminarin may wish to characterize gut microbiota compositional and functional changes following laminarin ingestion, to detect the abundance and metabolic activity of glycan degraders, such as Bacteroides (Salyers *et al*., 1977a; Salyers *et al*., 1977b) or mucolytic species associated with health, such as *Akkermansia muciniphila* or *Ruminococcus* (Dao *et al*., 2016). On the other hand, laminarin increased L-cell GLP-1 secretion to attenuate diet-induced obesity in mice, and improved glucose homeostasis and insulin sensitivity (Yang *et al*., 2017). The authors suggested that the observed cytosolic Ca^{2+} cascade caused GLP-1 secretion, which is in agreement with GPR41/43 receptor activation by SCFAs produced by gut microbial fermentation (Everard and Cani, 2014).

Red Seaweed Polysaccharides

Among the characteristics of red seaweeds are the presence of a special type of galactans polysaccharides (Carrageenan, Agar, and Porphyran) (Usman *et al*., 2017). Red seaweeds, such as *Gelidium* spp. and *Gracilaria* spp., are found useful in commercial production of agar and carrageenan food additives, including thickening, stabilizing and encapsulation agents.

Carrageenans

Carrageenans are composed of sulphated 1,4-d-galactose, 1,3--d-galactose, and 3,6anhydro-d-galactose (Weiner *et al*., 2014), and comprises 30-75% dry weight of red seaweeds (Vera *et al*., 2011). In a study where rats were fed 2.5% *Chondrus crispus*, which is rich in carrageenan as a major polysaccharide component, faecal *Bifidobacterium breve*, and acetate, propionate, and butyrate SCFAs were observed in an increasingly manner alongside a significant decrease in the pathogens *Clostridium septicum* and *Streptococcus pneumonia*, as compared to the basal diet (Liu *et al*., 2015). Furthermore, a 1:1 mixture of polysaccharide extracts from *Kappaphycus alvarezii* seaweed that contains carrageenan and *Sargassum polycystum* (a brown seaweed) was observed to lower serum lipids in rats (Dousip *et al*., 2014). In a study by Li *et al*., (2017), carrageenase activity in a *Bacteroides uniforms* 38F6 isolate complex of *Bacteroides xylanisolvens* and *Escherichia coli* hydrolysed carrageenan oligosaccharides into 4-O-sulfate-d-galactose, carratriose, carrapentaose, and carraheptaose, which could facilitate cross-feeding to promote the growth of *Bifidobacterium* populations.

Agar

Agar contains sulphated 1,3d-galactose and 1,43,6-anhydro-l-galactose (Lahaye and Rochas, 1991) and can be divided into agarose and agaropectin (O'Sullivan *et al*., 2010). Low molecular weight agar of 64.64 kDa has demonstrated a bifidogenic effect alongside increased acetate and propionate SCFA concentrations after 24 h in vitro fermentation with human stool inoculum (Ramnani *et al*., 2012). However, in a study where mice fed with 2.5% (w/v) neoagarose oligosaccharides for 7 days demonstrated increased caecal and faecal *Lactobacillus* and *Bifidobacterium*. The utilisation of agaro-oligosaccharides was noted in vitro by *Bacteroides uniforms* L8, isolated from Chinese individuals, which secreted a -agarase CAZyme to breakdown agarooligosaccharides into agarotriose and subsequently facilitated the growth of *Bifidobacterium infantis* and *Bifidobacterium adolescentis* via the cross feeding of agarotriose (Hu *et al*., 2006).

Porphyran

Porphyran is made up of sulphated 1,3 -d-galactose, 1,4--l-galactose-6-sulfate and 3,6-anhydro--l-galactose (Hehemann *et al*., 2010). An in vitro study on faecal fermentation demonstrated that porphyran did not significantly increase SCFAs, but instead stimulated *Lactobacillus* and *Bacteroides* populations (Seong *et al*., 2019). While pure cultures of *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Bifidobacterium adolescentis*, but not *Bifidobacterium bifidum*, were able to ferment dried *Porphyra yezoensis* (Nori) that contained low protein content (25%), whereas Nori with a high protein content (41%) was not fermented (Muraoka *et al*., 2008). This may be due to that carbohydrate content was highest in the low protein Nori, thus seasonal and species-variation and in seaweed macronutrient content should be considered a fixed factor to determine the fermentability of whole seaweeds (Kravchenko *et al*., 2018).

Phycocolloids

Phycocolloids is a type of hydrocolloids usually obtained from seaweeds (FAO, 2004). The polysaccharides are made with the polymer of simple sugars which are connected jointly with the glycosidic bonds. They are very essential for the mechanism of identification among the pathogens and seaweeds (Potin, 1999). There are found in numerous polysaccharides derived from the phycocolloids which are known to possess various pharmacological activities such as antiviral, anticoagulant, antioxidant and antitumor (Mayer *et al.,* 2007). The important polysaccharide obtained from phycocolloids includes alginate, agar and carrageenan that are useful commercially in both the pharmaceutical and nutraceuticals industries.

Fatty acids

For the normal maintenance and function of cell, polyunsaturated fatty acids are very much essential as seaweeds are the main chief sources for the production of polyunsaturated fatty acids as marine sources. The most important constituents like docosahexaenoic acid and eicosapentaenoic acid are primarily obtained from the marine seaweeds (Ohr, 2005). Cardiovascular can be treated with the polyunsaturated fatty acids. In addition, they possess a wide range of applications in the pharmaceutical and nutraceutical industries (Sayanova and Napier, 2004). For the normal cellular metabolic function, polyunsaturated fatty acids are important. They're also helpful in the regulation of electron transport, oxygen transport, cellular membrane fluid level (Funk, 2001). The important constituents like docosahexaenoic acid and eicosapentaenoic acid obtained from the seaweed sources have a significantly better oxidative stability when compared to oils obtained from fish sources (Sijtsma and De Swaaf, 2004). Nowadays, α-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid are majorly used in the nutraceuticals industries due to their vital medicinal characteristics in preventing cardiovascular diseases, colorectal cancer, memory disorders and arthritis (Michele Greque de Morais *et al*., 2015).

The lipid content of seaweed involves n-3 PUFAs, such as eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA) (Robertson *et al*., 2015). They're linked with the anti-inflammatory activity that reduce cardiovascular disease risk and may also apply beneficial properties on brain function and behavior, as mediated by the microbiota-gut-brain axis (Costantini *et al*., 2017). Dietary EPA and DHA intake are reported to improve microbial diversity, reduce the Firmicutes/Bacteroidetes ratio, reduce LPS-producing bacteria, and increase populations of *Bifidobacterium, Lachnospiraceae*, plus lipopolysaccharide (LPS)-suppressing bacteria in both animals and human models (Menni *et al*., 2017; Robertson *et al*., 2018). Although up to date, studies has focused on fish-derived n-3 PUFA, great scope exists to evaluate the prebiotic effect of n-3 PUFA obtained from seaweeds.

Vitamins

Multivitamin supplements are used daily by many people to achieve recommended daily intakes. Seaweeds contain an abundant source of both fat and water-soluble vitamins, which makes it a good sustainable and natural alternative. For example, the vitamin A content of a 5-g portion of dried seaweed *Ulva rigida* (retinol equivalents of carotenoid content, determined by high-performance liquid chromatography) varies from 14.5lg (2% of Reference Nutrient Intake RNI) (Taboada *et al*., 2010) to 70.5 l.0 g in *Fucus spiralis* (10% of RNI) (Paiva *et al*., 2014). Similarly, the vitamin C content in *Ascophyllum nodosum* varies from 0.41 mg (1% of RNI) to 9.24 mg (23% of RNI) in *Undaria pinnatifida*. Reported vitamin B9 (folate) content varies also varies among different seaweed species, from 7.5 lg (3.75% of RNI) in *Ulva* spp. 1 to 5400 lg (2700% of RNI) in *Ulva rigida* (Taboada *et al*., 2010). This could be attributed to both seasonal and geographical variations that cause such differences within the same genus.

There is a lack of literature on vitamin D3 content in seaweeds. A study worked on analyzing the vitamin D3 content of seaweeds and reported amounts of 0.83 mg/100 g of dry weight in *Fucus spiralis* and 1.05 mg/100 g of dry weight in *Porphyra* spp. (Paiva *et al*., 2014). This equates to 41.5l g (415% of RNI) and 63.5l g (635% of RNI) in a 5-g dried portion of *Fucus spiralis* and *Porphyra* spp., respectively (EP, 2011). However, further studies on characterization are required to verify these results that accounts seaweed as a valuable dietary source of vitamin D.

Seaweed is among a few non-animal based sources of vitamin B12. *Enteromorpha* spp. and *Porphyra* spp. are reported to contain 63.58l g and from 32.26 (Watanabe *et al*., 1999) to 133.8l g (Miyamoto *et al*., 2009) per 100 g of dry weight, respectively. This equates to 3.18l g (212% of RNI) and from 1.6l g (107% of RNI) to 6.69l g (446% of RNI) in a 5-g dried portion of *Enteromorpha* spp. and *Porphyra* spp., respectively. Further studies are required on vitamin B12 content of seaweeds to specify whether the vitamin B12 is present in the active form that can be absorbed and utilized in humans. Individuals following vegan diets can use seaweeds containing active vitamin B12 to reduce their risk of vitamin B12 deficiency. For example, a research on a group study in children following a vegan diet for 4 to 10 years certified healthy vitamin B12 status to nori consumption (*Porphyra* spp.) (Suzuki and Serum, 1995). However, other seaweeds studied, such as hijiki, wakame, and kombu, are comprehended to contain limited amounts of vitamin B12 or to contain vitamin B12 analogs that due to structural differences, do not have vitamin B12 activity in humans (Watanabe *et al.,* 2002). Drying methods of *Porphyra* spp. has also been reported to inactivate vitamin B12; therefore, processing methods may impact vitamin bioavailability (Yamada *et al*., 1999).

Iodine

Iodine is a trace element essential for the production and function of triiodothyronine (T3) and thyroxine (T4) thyroid hormones. In Japan, a country where approximately 20 different types of seaweed are consumed, the majority being wakame (*Undaria* spp.), kombu (*Laminaria* spp.), and nori (*Porphyra* spp.), iodine intake varies from 0.1 to 20 mg/d (average intake, 1–3 mg/d). These consumption habits can exceed the upper tolerable limits of 600 mg/d (EFSA) and 1100 mg/d (World Health Organization) (EFSA, 2014). The iodine content of the seaweed ranges from 0.06 mg/100 g of dry weight (*Ulva lactuca*) to 624.5 mg/100 g of dry weight (*Laminaria digitata*), however many characterization studies do not consider iodine. Desideri *et al*., (2016) found that consumption of 3.3 g of *Laminaria digitata* would provide 4017% of the permissible daily intake for iodine and suggested that excessive intake of seaweed with high iodine content exceeding 45 mg/kg of dry weight could impair thyroid function.

Static in vitro digestion studies have reported the bioavailability of iodine in seaweed as follows: *Laminaria* spp. (17%–28%), *Sargassum fusiforme* (12%), *Palmaria palmata* (10%), *Undaria pinnatifida* (2%– 12%), *Himanthalia elongata* (4%), *Porphyra* spp. (5%), *Ulva rigida* (2%), and cooked *Himanthalia elongata* and *Sacchoriza polyschides* (below the limit of detection) (Dominguez-Gonzalez *et al*., 2017). On the other hand, boiling can be implemented to reduce the iodine content of *Alaria esculenta* (from 670 mg/g to 165 mg/g), *Palmaria palmata* (97 mg/g to 66 mg/g), and *Ulva intestinalis* (92 mg/g to 79 mg/g). This information may be beneficial for industry to provide to consumers for implementation (Nitschke and Stengel, 2015). A study in humans tested urinary excretion of iodine following *Ascophyllum nodosum* ingestion and was reported as only 33% (excretion of potassium iodide control 1⁄4 59%) (Hou *et al*., 2000). The reduced iodine bioavailability was attributed to reduced release of iodine from the seaweed food matrix (i.e iodine bound to proteins, polysaccharides, polyphenols, and pigments).

From *Gracilaria verrucosa* and *Laminaria hyperborean,* urinary excretion of iodine was reported as 101% and 90%, respectively, in an iodine-sufficient population, yet as 85% and 61.5% in an iodine-deficient population (Aquaron *et al*., 2002). Reduced urinary iodine excretion in the deficient group was due to an increase in iodine storage in the thyroid (Lightowler and Davies, 1998); thus, consuming seaweeds may improve iodine status in those at risk of iodine deficiency, as demonstrated in vegan populations (Krajcovicova-Kudlackova *et al*., 2003).

In *Laminaria japonica*, iodine absorption was estimated as 57% to 71%, although serum thyroid stimulating hormone (TSH) was significantly increased above the normal limits in 4 of 6 participants who consumed 15 g of *Laminaria japonica* daily for 7 to 10 days, in 4 of 14 who consumed 30 g/d for 7 to 10 days, and in 1 of 3 who consumed 15 g/d for 55 to 87 days (Miyai *et al*., 2008). These findings agree with previous evidence that kelp supplementation increased serum TSH over 4 weeks (Clark *et al*., 2003). Urinary iodide excretion increased 30-fold and 44-fold from baseline (in subgroups that received 15 g and 30 g, respectively), but returned to baseline 7 to 40 days after seaweed consumption ceased. Moreover, when 500 mg of *Ascophyllum nodosum* containing 356 mg of iodine was given to healthy women for 14 days, the iodine content improved without compromising thyroid function (Combet *et al*., 2014). The urinary iodine concentrations increased significantly, reflecting sufficient intake and subsequent renal excretion. Plasma concentrations of T3, T4, free T3, and free T4 were unchanged between pre and post intervention, while serum TSH increased significantly, albeit within the normal range. The numerous variations in iodine concentration between seaweed species, season, and harvest location act as a challenge to the food industry, since there is a lack and misleading information about how individual seaweeds may impact iodine status and thyroid health.

Micronutrients

Seaweed consumption contributes to dietary mineral intake (Desideri *et al*., 2016), and a higher consumption of foods containing seaweed has been linked with sufficient calcium intake to prevent osteoporosis in postmenopausal women (Lim *et al*., 2015). In contrast, a report concluded no significant contribution to dietary intakes of sodium, potassium, magnesium, phosphorus, calcium, iron, manganese, zinc, selenium, or copper when considering a daily portion of 5 g (dry weight) of 17 brown seaweed and 17 red seaweed food products obtained from Japan, China, and South Korea (Dawczynski *et al*., 2007a). This explains that there are wide differences in mineral content between sources of seaweed.

Seaweeds are important source of iron, as *Sargassum* spp. are reported to contain 9 mg of iron per 100 g of dry weight (Lee *et al*., 2012), and thus adding this seaweed to wheat or maize-based bread increases the proportion of absorbed iron (Garcia-Casal *et al*., 2009). In another study, *Sargassum* spp. improved iron absorption when added in a rice meal, with the iron content of the *Sargassum* spp. used ranging from 81 to 290 mg/100 g of dry weight over 12 months (Gracia-Casal *et al*., 2007).

Magnesium can also be obtained from seaweeds as they're a rich source of it. However, the bio accessibility of magnesium varies between seaweeds types and sources. The magnesium content of *Ulva pertusa*, *Laminaria japonica*, and *Gloiopeltis furcata* is 10.47 mg/kg (41.8% bio accessible), 6.55 mg/kg (60.8% bio accessible), and 8.18 mg/kg (72.5% bio accessible), respectively, under simulated gastrointestinal conditions (Nakamura *et al*., 2012).

Seaweed metabolites in food

Globally, especially in Asian coastal communities, seaweed have been traditionally consumed as a readily available whole food (Yang *et al*., 2010). In Japan, it has been reported that the Japanese consume 5.3 g of seaweed in their daily diet (Matsumura, 2001). Additionally, seaweed is used in many ailments in various traditional Asian medical systems. Awareness regarding dietary seaweed intake is generally low in other regions (Kadam and Prabhasankar, 2010). However, consumers of East-Asian diet worldwide have gradually showed public interest in seaweed as a food source, relatively due to their associated health benefits. Their interest can be attributed to the fact that currently a healthy lifestyle is in vogue and thus an increase of consumers' interest influences the food industry. Consumption of seaweed and seaweed-based products are rising similar to the trend observed with fresh fruits and vegetables. Some consumers are still limiting their utilization of seaweed to extracts and food additives (Carvalho *et al*., 2009), as well as isolates, such as carrageenan and alginate, which are normally used in various applications (Cofrades *et al*., 2010). Optimistically, there is increasing awareness on the function of food beyond the basic nutritious value they provide, but health benefits and reducing the risk of various illnesses including diabetes have encouraged consumers to choose their feed cautiously.

Seaweed consumption in high amounts daily has been associated with lower risk of diseases, such as cardiovascular disease and hyperlipidemia (Iso, 2011), as well as breast cancer (Kim *et al.,* 2009). Furthermore, there has been dietary changes involving reduction of daily seaweed consumption due to a more Westernized diet in Asian societies that traditionally consumed seaweed. The changes indicated an increased incidence of chronic lifestyle overlooked as a good source of functional food and are under-utilized dietary source of novel as well as structurally diverse bioactive compounds with high biomedical potential that are not commonly present in terrestrial plants (Sharifuddin *et al*., 2015).

The oils extracted from some seaweeds have high levels of unsaturated fatty acids. For example, *Parietochloris incisa* is very high in arachidonic acid, where it reaches up to 47% of the triglyceride pool. Some varieties of seaweed favored by vegetarianism and veganism have the long-chain, essential omega-3 fatty acids, Docosahexaenoic acid (DHA) and Eicosapentaenoic acid (EPA) that are essential in their daily diet. In addition to health benefits, the natural pigments produced by seaweed can be used as an alternative to chemical dyes and coloring agents (Bigogno *et al*., 2002). Seaweeds have been consumed in Asia since older times more than the rest of the world. In recent years, many marine resources have examined in the search for bioactive compounds to develop new drugs and health foods. Edible seaweeds are a rich source of dietary fiber, minerals, and proteins (Kuda *et al.,* 2002). Seaweeds are now considered a rich source of antioxidants (Nagai and Yukimoto, 2003). Some active antioxidant compounds from brown seaweed were identified as phylopheophytin in *Eisenia bicyclis* (arame) (Cahyana *et al*., 1992) and fucoxantinein Hijikia fusiformis (hijiki) (Yan *et al.,* 1999). However, usually, these seaweed are usually boiled and/or steamed, dried and stored in process. A study by Jimènez-Escri *et al*. (2001) reported that the radical scavenging activity of a brown seaweed *Fucus* was decreased by 98% after drying at 50^{o} C for 48 h. In addition, red seaweeds such as *Gracilaria* are used to extract Agars and are used in the food industry and in laboratory media culture. Carrageenans, extracted from red seaweeds such as *Chondrus, Gymnogongrus*, and *Eucheuma* among others, are used to provide particular gel qualities.

Biological activity of seaweeds

Seaweeds have been considered in the past years as a potential source of bioactive compounds, mainly attributing to the fact that they are able of producing a series of secondary metabolites with varying interesting biological effects, such as antimicrobial, antiviral and antioxidant activity (Laurienzo, 2010; Sirbu *et al*., 2019). Certainly, several species of seaweed have been characterized by the presence of sulfated polysaccharides, polyphenolic compounds and antioxidant enzymes (Keyrouz *et al.,* 2012). Secondary metabolites known as phytochemicals have been studied numerously as a source of medicinal agents. These phytochemicals contain antimicrobial activity and are thus used as a treatment for many microbial infections (Okigbo and Omodamiro, 2007).

Antimicrobial activity

Antimicrobial substances originating from green seaweed from various seas and oceans have been studied in the past years (Priyadharshini *et al*., 2011; Elnabris *et al*., 2013). Seaweed contain a high number of antibacterial compounds, such as fatty acids (Wang *et al*., 2009), phenols (Wang *et al*., 2009), steroids (Patra *et al*., 2008) and halogenated compounds (Pinteus *et al*., 2017; Elshouny *et al*., 2017). Due to their properties, seaweed extracts have been widely used in the prevention and treatment of bacterial and viral disease in aquatic animals (Bansemir *et al*., 2006). Their extracts have shown great antibacterial activity against aquatic pathogenic bacteria (Thanigaivel *et al*., 2014). The antimicrobial activity is considered an indicator to detect the potent pharmaceutical abilities of seaweed to be utilized in synthesis of bioactive secondary metabolites (Gonzalez *et al.,* 2001). Seaweeds are rich in several bioactive compounds like antiviral, antibacterial, antifungal, antioxidant and hypertensive properties in seaweeds from different parts of the world (Perumal *et al.,* 2019).

Antimicrobial mechanism is usually to kill microorganisms or to slow down their growth (Sirois, 2016). Severe side effects and the development of drug-resistant strains of microorganisms implement the need to search for new antimicrobial agents for combating infectious diseases, such as pneumonia, tuberculosis, herpes, malaria, and AIDS (acquired immunodeficiency syndrome) (WHO, 2018). In a study by Torres *et al*. (2019), bacteria, fungi, protozoa, and viruses were the most frequently evaluated microorganisms in studies with *Gracilaria* species. The assays against bacterial and fungal pathogens were performed mainly by disk or well diffusion assay (> 89%). *Gracilaria* species were found to be among the most active seaweed against at least one bacterium or fungus. In another study, a promising result was obtained with the methanolic extract from *G. changii* (Al-Zahrani *et al.,* 2014). Methanolic extract was found among the most active against a pathogenic bacterium responsible for many hospital-acquired infections, the antibiotic-resistant *Staphylococcus aureus.*

Bioactive compounds such as flavonoids, terpenoids, tannins, carbohydrates and highly phenolic compounds present in methanolic extracts could be the key behind the observed highest antimicrobial activity of *S. vulgare* extracts; whereas, terpenoids, phenols and highly saponins compounds were found in hexane extracts (Torres *et al*., 2019). These compounds create an important class as secondary metabolites reported to display strong antimicrobial activity. Perez *et al.* (2016) reviewed the antimicrobial potential effect of seaweed in-relation to the different bioactive constituents found in them such as polysaccharides, fatty acids, phlorotannins, pigments, lectins, alkaloids, terpenoids and halogenated compounds.

Selective exploitation of seaweeds as potential source of pharmaceutical agents has been increasing recently. Many seaweeds possess bioactive compounds that inhibit the growth of some Gram-positive bacteria and Gram-negative bacterial pathogens. The seaweed extracts are used as treatments and preventive agents for various diseases such as antibiotics, antihelminthic, cough remedies, antihypertensive, antitumor and antidiarrheal. Recently, many researchers have focused on chemically investigating seaweed with a special accent on their bioactive properties (Siddha *et al*., 1991).

Vijayabaskar and Shiyamala (2011) tested the methanol extracts of brown seaweed *Sargassum wightii and Turbinaria ornate* against various Gram-positive and Gram-negative human harmful microbes. Their finding visualizes that methanol extracts of *Turbinaria ornate* could be a good source of antimicrobial agent in the pharmaceutical industry. Priyadharshine *et al.* (2011) evaluated the in vitro antimicrobial and hemolytic activity of micro seaweed *Ulva fasciata* methanol and aqueous extracts were tested against selected fish pathogens, *Aeromonas hydrophila, Pseudomonas fluorescent, Proteus* sp*., Vibrio alginolyticus and Enterobacter sp., and fungal pathogens Rhizopus* sp*., Asperillus flavuus, Asperillus* sp*., Aspergillus niger* and *Candida* sp. The extract was subjected to TLC to determine the presences of peptides and amide groups and the hemolytic activity was assayed. The inhibition zone varied between a maximum of 16 mm inhibition zone observed against *Vibrio alginolyticus,* and the minimum 12 mm against *Enterobacter* sp.*,* respectively. *Ulva fasciata* showed poor activity against the fungal pathogens. These results demonstrated the use of seaweeds as antimicrobial agents in pharmacology or as a health promoting food found in aquacultures. The screening confirmed that these seaweeds need further studies to be utilized as a possible source of antimicrobial compounds.

Most of the secondary metabolites that seaweeds produce possess antibacterial compounds derived from seaweeds that consist of a diverse group of bacteriostatic properties (Banu and Mishra, 2019). Compounds with antibacterial activity have been detected in green, brown and red seaweed. (Jose *et al.,* 2002) recommended that the active compounds from red seaweed *T. requienii* can be used to develop drugs that can fight against pathogens responsible for infectious diseases. Banu and Mishra (2019) demonstrated in a study that out of six pathogens tested, the extract exhibited prominent zone of inhibition against three pathogen i.e., *P. aeruginosa*, *S. aureus* and *P. mirabilis* (The maximum zone of inhibition was observed against *S. aureus* (42 mm) followed by *P. aeruginosa* (30 mm) and minimum in *P. mirabilis* (25 mm). This may be attributed to active components present in extracts of seaweed.

In human pathogens, two are Gram-negative and one is Gram-positive. When comparing Gram-positive and negative, the Gram-negative bacteria had more inhibition activity against the selected solvents (Sujatha *et al*., 2019). *A. hydrophila,* a fish pathogen, had more inhibition activity than *V. vulnificus* in selected solvents. Methanol residue is the most effective antibacterial activity than other solvents in human pathogenic bacteria and ethanol extract is a higher antibacterial activity than other solvents in fish pathogenic bacteria. Brown seaweeds are richer in more bioactive components than either green or red seaweeds (Gupta *et al.,* 2010). Inhibitory effect of *S. polycystum* and *P. australis* (brown) seaweed against 3 Gram-negative bacteria isolates was reported using methanol, dichloromethane and n-hexane solvents, showed that *S. polycystum* seaweed was more potent as compared to *P. australis* (Madkour *et al*., 2019). The differential antibacterial activities of seaweeds may be attributed to the presence of different antibacterial active compounds which are easily extracted with organic solvents. The highest inhibitory action among all extracts was obtained with isopropyl alcohol extract. Although isopropyl alcohol is known as a solvent for a wide range of non-polar compounds compared to other organic solvents (e.g. methanol), it was not seemed as a preferable solvent in the studies dealing with antimicrobial activities of algal extracts. The finding of the present study suggests that the isopropyl alcohol crude extracts of brown algae could be contained a new antibacterial compounds showed high activity against human pathogenic bacteria and further studies are required to purify the active principles.

The solvent extracts of 4 different seaweeds (*Sargassum vulgara, Sargassum aureus, Sargassum fusiforme and Padina pavonia)* were tested in a significant inhibitory action against multidrug resistant (MDR) bacteria (Lavanya *et al.,* 2017). Among the 4 seaweeds screened for their antibacterial activity the 100 µl diethyl ether extract of brown seaweed *Sargassum fusiforme* and 50 µl ethanol extract of *Sargassum vulare* showed more inhibitory activity against *Sargassum aureus* and *Kelbsiella peneumonia,* respectively. The phytochemical screening of seaweeds demonstrated the presence of dolestrepans acetogenis phenols fatty acids and volatile halogenated hydrocarbons in the selected species. The changes in ultrastructure of tested (MRD) bacteria *Sargassum aureu* and *Kelbsiella pneumonia* due to *Sargassum fusiforme and Sargassum vulgare* extract were investigated by transmission electron microscope which showed the shrinking of protoplasm cytoplasmic vacuolation deformation in cell structure and damage of the outer cell boundary (Shimaa *et al.,* 2016).

Lavanya and Veerappan (2011) investigated the antibacterial activity of six selected seaweed. Extracts of seaweed *Codium decorticatum, Caulerpa scalpelliformis, Gracilaria crassa, Acanthophora spicifera, sargassum wightii and Turbinaria conoides* were used for testing their antibacterial activity against selected human pathogens such as species *Vibrio parahaemolyticus, salmonella* sp*., Shewanella* sp., *Escherichia coli, Kelbsiella pnenmonia, Staphylococcus aureu, Enterococcus faecalis, Pseudomonas aeruginosa* and *Proteus mirabilis*. Results demonstrated that, all the seaweeds extracts have shown moderate antibacterial activity < 10mm zone of inhibition, out of which only methanol extract has shown significant activity. The research showed that the higher antibacterial activity was found in *Acanthophora spicifera* and the minimum was found in *Codium decorticatum.*

Earlier studies worked on antibacterial screening of different solvent extracts concluded that the crude acetone extracts of different seaweeds reacted positively against selected human bacterial pathogens (Venugopal *et al.,* 2014; Moorthi and Balasubramanian, 2015; Rosaline *et al.,* 2017). However, ethanol extracts revealed insufficient antibacterial activity, showing inhibitory action only against Gram-positive bacteria (*S. aureus*). In a study by Ambreen *et al.* (2012), 5 screened ethanol extract of seaweeds were tested for antibacterial activity, and 9 tested against root rotting fungi and found that the ethanol extract of most of the species was less active against tested fungi. This could be attributed to the more complex structure and composition of Gram-negative bacterial cell wall (Rosell and Srivastava, 1987). Mendes *et al.* (2013) demonstrated that the outer membrane and the thick murein layer of Gram-negative bacteria act as a barrier which prevents the entrance of outer environmental substances including antibiotics and inhibitors.

Antifungal activity

Aruna *et al.* (2011) screened the antifungal activities of six different seaweeds, namely the green seaweed *Cladophora glomerata, Ulva lactuca* and *Ulva reticulata,* the red seaweed *Gracilaria corticata* and *Keppaphycus alvarezii,* and the brown seaweed *Sargassum wightii* against fungal pathogens *Aspergillus niger, Aspergillus flavus, Aspergillus fumigatus, Saccharomyces cerevisiae* and *Mucor indicus*. The zone of inhibition ranged between 56-58 mm in aqueous extract, and 54-56 mm in methanol extract. The maximum activity (56 mm) was recorded with 200 mg aqueous extract of *Ulva lactuca* against *Aspergillus flavus* and the minimum activity (8 mm) was obtained by *Gracilaria corticata* against *mucroindics* 50 mg level. Whereas, methanol extract showed the maximum activity (56 mm) was recorded from 200 mg of *Ulva lactuca against Aspergillus niger* and minimum (4 mm) by 50 mg of *Ulva reticulata* against *Aspergillus flavor.*

The in vitro antifungal activity of crude seaweeds extracts and those of three purified extract fractions with hexane, ethanol and water as well as the in vivo antifungal efficacy of the cured extract was studied for to exclude possible compounds, which would have antimicrobial activity other than fatty acids, lipids, polysaccharides, polyphenols and phlorotannins (De Corato *et al*., 2017). The findings coming from the in vivo experiments indicate that crude seaweed extracts had a variable degree of antifungal activity in relation to the different fungi/host systems tested here. Extract of *L. digitata* and *U. pinnatifiea,* followed by *P. umbilicalis,* and showed the highest antifungal activity against *B. cinerea* on strawberries and *M. laxa* on peaches followed by *P. digitatum* on lemons. However, *L. diggitata* extract is to be considered the best antifungal to among those tested here due to its higher competitiveness with respect to fenhexamamid and imazalil. The antifungal activity of the crude seaweed extracts could be due to their content of fatty acids rather than the phenolic compounds.

A recent study investigated water extracts and polysaccharides from *Anabaena* sp., *Ecklonia* sp., and *Jania* sp. were tested for their activity against the fungal plant pathogen *Botrytis cinerea* by Righini *et al.* (2019). Controlling fungal diseases is usually based on synthetic pesticides; however, the European Directive 2009/128/EC stated regarding implementation of bio-based strategies their support to the development of sustainable agriculture protection management through different means, among them natural products, such as seaweeds. Extracts obtained from seaweeds may be contributing tools for effective disease control. That is because seaweed extracts showed activity against several pathogens (Roberti *et al*., 2015; Righini *et al*., 2018). Recent studies demonstrated that extracts from the two brown algae *Laminaria digitata* and *Undaria pinnatifida* and from the red one *Porphyra umbilicalis* inhibited both *B. cinerea* mycelia growth and spore germination (Righini *et al.,* 2019), marking them both effective antifungal seaweeds. Thus, seaweed extracts are capable of increasing the transcription and the activity of defense-related enzymes involved in the control of fungal pathogens (Agarwal *et al*., 2016; Esserti *et al*., 2017).

Studies have investigated the activity of the single compounds contained in the extracts such as polysaccharides, phenols, and cyclic peptides (Jaki *et al*., 2001; Vera *et al*., 2011). Particularly, sulfated polysaccharides, such as carrageenan, fucoidan, and ulvan showed antimicrobial activity against human pathogens (Marudhupandi *et al*., 2013; Jun *et al*., 2018). The bioactivity degree of these compounds might be related to their structure, molecular size, and sulfate groups amount (Jun *et al*., 2018). Additionally, polysaccharides plays a role as inducers of plant resistance, since they work on increasing the activity of multiple defense-related enzymes such as chitinase, -1,3-glucanase, peroxidase, polyphenol oxidase, phenylalanine ammonia lyase, and lipoxygenase (Righini *et al*., 2018).

Ulvans are the primary polysaccharides found in the cell walls of green seaweed, whereas agarans and carrageenans are the principal polysaccharides for red seaweed and alginates and fucans for brown seaweed (Rioux *et al*., 2017). The different species of brown seaweed *Laminaria* are sources of laminarin, which is a storage polysaccharide utilized in plant protection and is already commercialized in many EU countries (EU Pesticide Database). That is for their capability of inducing plant resistance. Among phenols, bis (2,3-dibromo-4,5-dihydroxybenzyl) ether displayed antifungal activity of *B. cinerea* fungal growth and decreased the occurrence of fruit decay, in addition to the severity of diseases of strawberry fruits infected with the pathogen (Liu *et al*., 2014). To our knowledge, limited to no studies have been conducted on the antifungal activity of cyanobacterial polysaccharides against plant pathogens, and also their activity against human pathogens is poorly documented (Pugh *et al*., 2001).

Antioxidant property of marine algae

Synthetic antioxidants that are spread in different markets are widely used in food industries. The negative impact of these chemical compounds was revealed by the toxicological reports on the concentrations used (Jayaprakasha *et al.,* 2004). The seek for natural antioxidants due non-toxic properties and cheaper value has attracted considerable attention in the last decade. It was also reported by Huang and Wang (2004) that marine seaweed are a viable source of antioxidant compounds with free radical scavenging activity.

The impacts of light, the presence of oxygen and active free radicals (O_2, OH $^{\bullet}$, LOO $^{\bullet}$) on living systems has become a frequently researched topic (Sdatman, 1992). Oxidative degradation of lipids from raw or processed food products is not only harmful for the loss of nutritious value it causes, but also for contributing to carcinogenesis, atherosclerosis and the ageing process in humans (Barclay, 1993). Phenols are vital efficient antioxidants for polyunsaturated fatty acids; in fact, they can easily transfer a hydrogen atom to the peroxyl lipid radical (LOO), and therefore forming the aryloxy radical (ArO), which cannot act as chain carrier. This couples itself with another radical, thus stopping the chain process (Alkhamaiseh *et al*., 2011). Amongst marine organisms, seaweed represent are amongst one of the richest sources of antioxidants (Sirbu *et al.,* 2019). Phenolic compounds are present in all plants (Pallag *et al*., 2018) however they can be found in significant amounts in seaweed, besides other vital active biologic compounds, such as polysaccharides, fatty acids, proteins, terpenes, and so on, which suggest antitumor, antibacterial, antiviral and antioxidant activity (Abd El Megeed *et al*., 2014). Marine seaweed are globally dispersed in marine environments and can be found attached to rocks or sediments on coastal regions that have a 0.01% availability of photosynthetic light (Appeltans *et al*., 2012). The different species of seaweed can be found in every climate area, from warm tropical waters to polar, freezing regions (Marbà *et al*., 2017). Green seaweed are present worldwide, growing in intertidal zones, attached to a hard substrate or free living (Collin *et al*., 2016). These are considered opportunistic seaweed and they proliferate in eutrophic coastal waters (Teichberg *et al*., 2010). The numbers of studies regarding green seaweed are numerous and increasing (Chakraborty *et al*., 2010). Thus, phenols and active biologic compounds have been found in several green seaweed species which can be observed in various seas and oceans (Pandima *et al*., 2008), making them accessible and useful.

Plenty of the publications found were focused on comparisons between different groups of macro seaweed (red, brown, and green). The evaluation of antioxidant activities of species of *Gracilaria* was mostly made by in vitro assays, mainly against the DPPH (2,2‐diphenyl‐1‐picrylhydrazyl) radical (79.0%), the Folin-Ciocalteu reagent (67.1%), and applying the ferric reducing antioxidant power assay (FRAP) using potassium ferricyanide (28.2%) or TPTZ (tripyridyltriazine) (17.6%). Overall, *Gracilaria* sp. showed moderate to weak antioxidant potential. Some studies that support such remarks include Zhang *et al.* (2007) studying Chinese seaweed, Farvin and Jacobsen (2013) studying Danish seaweed, and Zubia *et al.* (2007) studying Mexican seaweed. Although, sulfated agarans have rarely been studied, promising results have been reported, such as by Seedevi *et al.* (2017) who studied sulfated agarans from *G. corticata*. The researchers found comparable results to those of reference standards (ascorbic acid and butylated hydroxytoluene BHT). In vivo antioxidant studies are rare but offered good antioxidative potential (Chan *et al.,* 2014; Chan *et al.,* 2016). For instance, Murakami *et al.* (2005) reported that the chloroform extract of *Gracilaria blodgettii* was one of the most effective, among several land plants and seaweed, to attenuate the oxidative and nitrosative stress induced in leucocytes.

Seaweeds extracts are considered a rich source of polyphenolic compounds. Moreover, the defensive strategy of many of the red seaweed species prove that they contain many antioxidative and anti-genotoxic constituents in their cells. Therefore, interest in marine seaweed is increasing and valid as they are a promising potential source of pharmaceutical agents. Polyphenols in marine brown seaweed are called phlorotannins and known to act as potential antioxidants. Phlorotannins are formed by the polymerization of phloroglucinol (1,3,5-trihydroxybenzene) monomer units and synthesized in the acetate malonate pathway in marine seaweed (Athukorala et al., 2006). Moreover, sulfated polysaccharides isolated from marine seaweed also have been proven to exert radical scavenging activities in vitro and in vivo.

There is an improved interest in natural substances with valuable medicinal properties, such as terpenoids (Yermakov, 2010) as some of the terpenes are one most potent drugs against life threatening diseases. Triterpenic acids exhibit various biological and pharmacological activities, including anti-inflammatory, antimicrobial, antiviral, cytotoxic, and cardiovascular effects (Shaban *et al.,* 2012; Sumayya and Murugan, 2019). Oxidative stress represents a considerable increase in the intracellular concentration of oxidizing species, such as reactive oxygen species (ROS), which is accompanied by imbalance in antioxidant defense. This activity can cause tissue damage or cell death, which occurs primarily by necrosis and apoptosis. Studies have indicated that macro seaweed have become ideal candidates for sources of natural antioxidants (Lee *et al.,* 2008), especially that seaweed contain several enzymatic and non-enzymatic antioxidant defense systems that works on maintaining the concentration of ROS for protecting the cells from damage (Abd El-Baky *et al.,* 2008).

Anticancer activity of marine algae

According to the World Health Organization-WHO (2018), cancer is reported as one of the leading causes of mortality worldwide, killing more than 8 million people a year. Chemotherapy is one of the main frequently used cancer treatments; however, the side effects can be severe and relatively common, in addition to cases of drug resistance being reported more frequently (Luqmani, 2005; Torres *et al*., 2019). Thus, an intense and justifiable search for new anticancer drugs. Extracts of *Gracilaria* were evaluated mainly in cell viability assays based on metabolic activity (79% of studies) by reduction of tetrazolium salts (67%) or resazurin dye (10%). However, only 29% of studies with *Gracilaria* for anticancer activities were promising. One of the best results was obtained by Costa *et al.* (2017) that studied lipid extracts of an unidentified species of *Gracilaria.* They found that IC50 values of 12.2 μg/ml and 12.9 μg/ml against a human breast cancer cell line (T-47D) and human bladder carcinoma cell line (5637), respectively. Generally, the most studied and active extracts were obtained from organic solvents. As previously seen, Sakthivel *et al.* (2016) and Sheeja *et al.* (2016) identified phytol as one of the responsible components by the anticancer activities of ethyl acetate extracts from *G. edulis.*

An alcoholic extract of the red seaweed *Acanthophora spicifera* was supplemented to mice treated with Ehrlich's ascites carcinoma cells and exhibited anti-tumor activity post an oral dose of 100 and 200 mg/kg (Lavakumar *et al.,* 2012). Similarly, an extract *Sargassum thunbergii* brown seaweed displayed antitumor activity against transplanted tumor such as sarcoma 180 and Ehrlich solid carcinoma (in vivo) (Zhuang *et al.,* 1995). The anti-proliferative effect of fucoidan, isolated from *Ascophyllum nodosum* was demonstrated against sigmoid colon adenocarcinoma cells (COLO320 DM), in comparison to fibroblasts (hamster kidney fibroblast CCL39) (Vischer *et al.,* 1991). Caulerpenyne from *Caulerpa* sp. seaweed attributed to anticancer and antiproliferative effects against neuroblastoma cell line through induction of cells inhibition proliferation with an IC50 of 10 µM (Barbier *et al*., 2001). Condriamide-A, isolated from *Chondria* sp., showed a cytotoxic effect at a dose of 0.5 µg/ml against KB cells and 5 µg/ml against LOVO cells (colon cancer) (Palermo *et al.,* 1992). In addition, two compounds isolated from *Cystophora* sp., namely, meroterpene and usneoidone, have demonstrated antitumor properties (Parent-Massin, 1996). Sulfated polysaccharides purified from the brown seaweed *Eclonia cava* selectively and dose-dependently suppressed the proliferation of murine colon carcinoma (CT-26) and human leukemic monocyte lymphoma (U-937) cell lines (Athukorala *et al.,* 2006). Similarly, stylopoldione, a potent cytotoxic metabolite isolated from *Stypodium* sp., disrupted mitotic spindle formation functioning via inhibiting synchronous cell division using urchin egg assay (*Strongylocentrotus purpuratus* Stimpson) at ED50 = 1.1 µg/ml, and to inhibit cells cleavage via inhibition of tubulin polymerization (Gerwick and Fenical, 1981).

Studies on anti-migration and cytotoxicity effects are rarely evaluated in *Gracilaria* species. Cytotoxicity assays, such as necrosis and apoptosis detection, were reported in 29% of studies. For example, Patra and Muthuraman (2013) researched ethanolic extracts from *G. edulis* and found that the cell inhibition against Ehrlich ascites tumor was due to apoptosis. Anti-migration effects were reported only by Sae-Lao *et al.* (2017). They found that sulphated agaran from *Gracilaria sheri* (B.M.Xia & I.A.Abbott) act against the migration of two lines of cholangiocarcinoma cells, showing IC50 values of 7 µg/ml and 8 µg/ml for HuCCA-1 and RMCCA-1, respectively.

Seaweeds include many pharmacologically vital bioactive elements to include carotenoids, dietary fiber, protein, essential fatty acids, vitamins (A, B, B12, C, D, E), and minerals such as Ca, P, Na, and K (Ibrahim *et al.,* 2016), in addition to polyphenols (Bandaranayake, 2002).

Luis *et al.,* (2010) evaluated the antibacterial and anticancer activities of extract from the seaweeds like *Egregiamenziesii, Codium fragile, Sargassum muticum, Endarachne binghamiae, Centrocera sclavulatum and Laurencia pacifica*. They obtained the organic extract from bacteria, free seaweed and from surface associated bacteria, pathogenic strains of *Staphylococcus aurous, Kelbsiella pneumonia, Proteus mirabilis and Pseudomonas aeruginosa* were used to test antibacterial activity and HCT-116 colon cancer cells for anticancer activity. A total of 35 bacterial strains were isolated from the surface of seaweeds and identified as the phyla Firmicutes, Proteobacteria and Antinobacteria by 16S rDNA sequencing. The strains *Centrocera sclavulatum, Sargassum muticum, Endarachne binghamiae and Endarachne binghamiae* demonstrated anticancer activity.

Fucoidans obtained from brown seaweed *Eclonia cava*, *Sargassum hornery and Costaria costalla*, demonstrates an inhibitory role in colony formation in human stoma and colon cancer cells. Thus, these Fucoidans may be effectively used as antitumor agents (Ermakova *et al*., 2011). Hydrolyzed Fucoidan from sporophyll of *Undaria pinnatifida* were used to determine the molecular weight and hydrolysis condition on cancer cell growth. Negative Fucoidan showed anticancer outcomes. An experiment indicated that the anticancer activity of fucoidan could be significantly enhanced by lowering the molecular weight, however only when they are depolymerized by mild condition (Yang *et al*., 2008). Champiafeldmannii (Cf-pls) didn't show any in vitro cytotoxicity upon experimental exposure but showed in vitro antitumor effect. Cf-pls acts as immunomodulatory agent, which works on producing specific antibodies and increasing the production of ova specific antibodies. Cf-pls was proven to have interesting anticancer activities that could be related with its immune stimulating properties (Lins *et al.*, 2008)**.**

Anti-Diabetic Potentials of Seaweeds

There has always been an essential search for safe and efficient antidiabetic drug. Marine products, especially seaweeds, have become an important source as it provides several compounds of immense therapeutic potential. Recently, seaweeds and their bioproducts are getting greater attention toward the treatment of diabetes as studies have proven their capabilities on that matter (Lordan *et al*., 2013). It is estimated that the isolation, characterization, and pharmacological study of unexplored seaweeds will be helpful in discovering novel antidiabetic compounds that contain high biomedical value. Among seaweed, brown and red seaweed are reported to exhibit antidiabetic activity. Many of the studies on seaweed derived compounds was proven to control the blood glucose levels through the inhibition of carbohydrate hydrolyzing enzymes and protein tyrosine phosphatase 1B enzymes, insulin sensitization, glucose uptake effect and other protective effects against diabetic complications (Unnikrishnan and Jayasri, 2018).

Extraordinary resources of marine bio-actives are usually from species red seaweed (4%), brown seaweed (5%), green seaweed (1%), others (8%). Many marine red and green seaweed are found to be potential inhibitors of α-glucosidase, aldose reductase (AR) and Protein Tyrosine Phosphatase (PTP) (Lordan *et al*., 2013). Bromophenols found in some red seaweed like *Rhodomela confervoides*, *Symphyocladia latiuscula*, *Polysiphonia urceolata* shows significant hypoglycemic potentials by inhibiting PTP, α-glucosidase, and AR apart from its antioxidant activity (Kim *et al.,* 2010; Lee *et al.,* 2010).

Seaweeds and their organic extracts contain various bioactive compounds with potential health benefits (Rindi *et al.,* 2012). Marine seaweeds that are capable of reducing postprandial hyperglycemia by inhibiting enzymes such as *α*-amylase and *α*-glucosidase is found to be an effective strategy for the management of diabetes (Etxeberria *et al.,* 2012). Four green seaweed (*Enteromorpha intestinalis*, *Chaetomorpha aerea*, *Chlorodesmis*, and *Cladophora rupestris*) were chosen to evaluate *α*-amylase, *α*-glucosidase inhibitory, and antioxidant activity in vitro in a study by Unnikrishnan *et al.* (2015). They found that *C. aerea* and *Chlorodesmis* showed important inhibition against alpha-amylase, and *C. rupestris* demonstrated notable free radical scavenging activity. GC-MS analysis of the active extracts reveals the presence of major compounds which gives an insight on the antidiabetic and antioxidant activity of these seaweed. These compounds are known through a phytochemical analysis of the seaweed extracts which indicates the presence of phenols, flavonoids, alkaloids, lipids, glycosides, and tannins (Kumar *et al.,* 2016).

Experiments on the anti-diabetic potential of seaweed is generally non-homogeneous as certain seaweed components, bioactive compounds and mechanisms of action have been studied relatively more extensive than others. Apart from unsaturated fatty acids and dietary fibers, studies on anti-diabetic properties involving polyphenols from seaweed are considerably more noticeable with different polyphenolic compounds isolated against many well-known anti-diabetic targets. Polyphenolic compounds are known to form complexes when interacting with many proteins (Stern *et al.,* 1996), especially those derived from vegetables and fruits exhibit various activities including anti-diabetes (Anhe *et al.,* 2013). The anti-diabetic mechanism of seaweed bioactive compounds is the inhibition of enzymes involved in maintenaning glucose homeostasis such as α-amylase, α-glucosidase, aldose reductase and protein tyrosine phosphatase 1B (PTP1B), inhibition of incretion hormones activities, promotion of glucose uptake by cells, anti-obesity, as well as anti-inflammation and cytoprotection of β-cells.

There is a difference in the effectiveness of various extracts and bioactive compounds derived from seaweed for different purposes, and this can be due to several factors including environmental and seasonal variations as well as experimental procedures. There are many differences in the inhibitory effect of the same compounds isolated from different seaweed species against α-glucosidase activity (Kim *et al*., 2014). Seasonal and within-plant variations of seaweed contents have been reported such as in phenolics against α-glucosidase in *Ascophyllum nodosum* (Apostolidis *et al*., 2011), as well as fatty acid content and composition in *Spatoglossum macrodontum* (Gosch *et al*. 2015). Extraction techniques and other experimental methods can be an influence on the types and quantities of compounds isolated.

Seaweeds and Biomedical Applications of Silver Nanoparticles

Nanotechnology is an emerging field in the scientific studies that involves biotechnology at a nanoscale. A nanoparticle is a microscopic particle, with dimensions less than 100 nm, that can be of different metals such as silver, gold, copper, zinc etc. Silver nanoparticles are usually the most preferred due to their specialized magnetic, electrical and optical properties. Silver nanoparticles are widely utilized for different applications such as in textile industries, in cosmetics, in water treatment and as antimicrobial drugs etc. They are found to possess effective antimicrobial activity **(**Rai *et al.,* 2009**).** Silver nanoparticles can be produced by different techniques but biological synthesis is widely preferred because of their low toxicity, eco-friendly and low cost (Ahamed *et al*., 2010).

However, the physical and morphological features of metal based nanoparticles can be severely affected by the solvents and reducing agents used (Khatoon *et al.,* 2017). Nanoparticles varying in size, shape and morphology influence the applications of the nanoparticles. Synthesizing metal nanoparticles requires special attention due to its specificity and environment friendly approach (Banerjee *et al.,* 2014). Whether the microorganisms or the plants are being employed, it is the biomolecules present in them that are responsible for the biosynthetic mechanism. These biomolecules may be carbohydrates, lipids, DNA and enzymes/proteins or a combination of two or more.

Silver ions are reduced by the various plant metabolites including terpenoids, polyhydroxyphenols, carbohydrates, alkaloids, phenolic compounds, and proteins etc. Fourier transform infrared spectroscopy (FTIR) spectroscopy of biosynthesized AgNPs (silver nanoparticles) has been used to demonstrate that biomolecules present in extract are responsible for synthesis of nanoparticles (Shankar *et al*., 2003).

Seaweeds nanoparticles as antibacterial

There is a need for an alternating antibacterial treatment due to AgNPs exhibiting a promising bactericidal action against both Gram-positive and Gram-negative bacteria (Stoimenov *et al.,* 2002). The antimicrobial activity of AgNPs lays in (a) either forming in the cell wall's pores, which eventually leads to leakage of cellular content or (b) the silver ion penetrating through ion channels that does not harm the cell membranes; rather denatures the ribosome and inhibits the expression of enzymes and thiol containing proteins necessary for the production of ATP and DNA, thus resulting in cell necrosis, i.e, cell death (Pal *et al*., 2007). AgNPs also holds an important role in the respiratory chain by affecting the function of membrane-bound enzymes.

Seaweeds nanoparticles as antifungal

Recently, extreme fungal infections have been contributed to many particular diseases and mortality of immune-compromised patients (Martin *et al.,* 2003). One of the most common pathogens responsible for fungal infections is *Candida* species. It causes nosocomial infection with acmortality rate reaching up to 40% (Panacek *et al.,* 2009). An investigation by Kim *et al*. (2007) showed the antifungal activity of silver nano formulation on a total of 44 antifungal stratins of six fungal species. The literature revealed that AgNPs are effective against *C. glabrata*, *C. albicans*, *C. krusei*, *C. parapsilosis* and *T. mentagrophytes* effectively. Studies showed that the Tulsi (*Ocimum sanctum L.*) mediated AgNPs demonstrated antifungal activity against a possible human fungal pathogen (Khatoon *et al.,* 2015). Hence, AgNPs is considered a promising and a fast-acting fungicide against a wide spectrum of common fungi including *Aspergillus, Candida* and *Saccharomyces*.

Seaweeds nanoparticles as antiviral

The cytoprotective properties of silver is well known and studied. They have been used for the prevention of HIV interaction to the host cells (Sun *et al.,* 2005). AgNPs can also be used to prevent infection after surgery and acting as anti-HIV-1 agents (Elechiguerra *et al.,* 2005). Therefore, AgNPs interaction with microorganisms and viruses is another flourishing field of research. The studies reported that AgNPs interact with HIV-1 by binding preferentially to gp120 glycoprotein knobs (Lara *et al*., 2010). This mechanism of AgNPs specifically inhibits the binding of virus to host cells.

Seaweeds nanoparticles as antidiabetic

Nanomedicine has become a leading research field. Scientists are most concerned with synthesizing safe, eco-friendly, effective, and cheap and less toxic drugs to combat diseases like diabetes, cancer, epilepsy, etc. These nanoparticles use a site specification technique due to which only a secure and a prescribed dosage of drug molecules has to be administered, therefore helping to reduce the undesired toxicity (Balan *et al.,* 2016). These nanoparticles, due to their targeted action, increase the efficacy of the drug. Their tiny size gives them an edge as they can evade immune responses and also gives them the ability to cross relatively impermeable membranes (Uchegbu and Schatzlein, 2010). Green synthesis of nanoparticles is more preferred than chemical synthesis since the latter is more dangerous and involves dealing with hazardous chemicals to reduce metals. Naturally, seaweeds possess both primary and secondary metabolites to carry out green synthesis. Silver nanoparticles synthesized via green methods are widely used for many applications such as antidiabetic (Rajaram *et al.,* 2015), antimicrobial (Bal *et al.,* 2012), antioxidant (Velavan *et al.,* 2012), and anticancer (Babu *et al*., 2014) applications, and also used in industry.

Conclusion

Seaweeds are large group of either unicellular or multicellular eukaryotes belonging to the kingdom Protista. Seaweed-derived compounds have been attributed to a wide range of potential applications for human nutrition and health products. Various seaweeds present in marine water bodies possess several essential nutrients like lipids, minerals, proteins, fiber, fatty acids, polysaccharides, vitamins and many essential amino acids. Marine algae are a rich source of many bioactive molecules which are reported to have many pharmacological properties like antimicrobial, antioxidant, immuno-stimulatory, anti-tumour, antiviral, antiinflammatory, and neurotoxic potential. The seaweed species have proved their efficacy in reducing blood glucose. Biological synthesis of silver nanoparticles is widely preferred due to low toxicity, eco-friendly and low cost. The nanoparticles increase the efficacy of the drug due to their targeted action. Seaweeds are believed to be a potential source to provide not only novel biologically active substances for the development of pharmaceuticals.

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