Journal of Medicinal Plants Research Vol. 5(33), pp. 7146-7154, 31 December, 2011
Available online at http://www.academicjournals.org/JMPR
DOI: 10.5897/JMPR11.018
ISSN 1996-0875 ©2011 Academic Journals

Review

Anti-inflammatory compounds of macro algae origin: A review

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Accepted 19 December, 2011

Inflammation, occurs frequently in living tissues, and is responsible for numerous death and precursor to some deadly diseases. This review focus on seaweed derived anti-inflammatory compounds, which have attracted interest and promising replacer of current anti-inflammatory drugs. Macro algae have both pro- and anti-inflammatory compounds, the later include sulphated polysaccharides (fucoidans) from brown seaweeds, alkaloids (Caulerpin I, II and III) from red and green seaweeds, polyunsaturated fatty acids (Docosahexaenoic acid: EDA, Eicosapentaenoic acid: EPA, Stearidonic acid: SA and Eicosatrienoic acid: ETA), carotenoids (fucoxanthin and astaxanthin), Pheophytin A and Vidalols A and B. Anti-inflammatory assays include edema, erythema, tumor necrosis factor (TNF-α), interleukin (IL 1β, 6, 8), Nitric oxide (NO), inducible Nitric oxide synthase (iNOS), Prostaglandin E (PGE 2 and 3), Cyclooxygenase (COX-2), transcription factor (NF-κB) and leukotrienes (LB 3 and 4). Although, *in-vivo* and *in-vitro* studies have been done for crude extracts and specific compounds, but some compounds have not analysed *in-vitro,* and investigation of their pathway need to be studied.

Kew words: Seaweed, anti-inflammatory, fucoidan, sulphate polysaccharide.

INTRODUCTION

Inflammation have been linked with pathogenesis of many diseases like cancer, atheriosclerosis, neurodegenerative diseases, diabetes mellitus, obesity, arthritis, cardiovascular diseases, Parkinson's disease and other deadly diseases (Lee and Weinblantt, 2001; Firestein, 2006; Klegeris et al., 2007; Filippin et al., 2008). Inflammation can result to genetic defects and immunoregulation and mechanism defects which lead to tissue damage (Jones, 2006). Anti-inflammatory UNASD drug was serendipity discovered without thorough investigation and even not effective in term of controlling inflammation and now record several side effect just like other synthetic drugs, thus, safe biological sources are now been considered (Kaboli et al., 2001). Biological sources for active compounds that have medical importance are on the increase in recent time (Kaboli et al., 2001). Also, due to the residual side effects of synthetic compounds that form bulk of the materials used for the production of pharmaceutical products. Aspirin can cause stomach bleeding, acetaminophen can cause liver damage Cox-2 inhbitor Vioxx® and Celebrex® can cause heart problem and non-steroidal anti-inflammatory drugs (NSAID's) was reported to contribute to numerous death yearly (Clegg et al., 2006; Wolf et al., 1999; Singh, 1998). Furthermore, pathogenic organisms are becoming resistance to drug, in recent time. However, living organisms have inherent mechanism to withstand biotic and abiotic factors, therefore they serves as reservoir for various active compounds which can trigger some immunological responses in man (Pomponi, 2001).

This development opens a wider research opportunity to search various living organisms for the purpose of obtaining active compounds of medicinal values in them. Macro algae form part of the few living organisms that have been identified as sustainable sources of bioactive compound (Veena et al., 2007). Macro-algae are generally grown in aquatic environment and have ability to withstand fluctuation in salinity around them, strong tidal current, variation in light intensity and constant fluctuation in temperature (Ehrlich, 2010). These adaptive properties influence its physical (morphology) and biochemical constituents. Analyses of microalgae indicate

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Table 1. Previous works on anti-inflammatory crude extracts of seaweeds obtained using several solvents and their inflammation medium used.

Seaweed species	Extraction solvent	Inflammation medium	References
Sargassum swartzii and *Ulva reticulate*	Methanol	Carrageenan-induced hind paw edema in rats and Peritonitis for acute and chronic inflammatory models	Hong et al. (2011)
Dichotomaria obtusata,	Water	Ear edema induced by TPA and writhing induced by acetic acid	Vázquez et al. (2011)
Turbinaria conoides	Water	EPP-induced ear edema and carrageenin-induced hind paw edema tests	Boonchum et al. (2011)
Phorphyra dentate	Methanol	LPS induced RAW 264.7 macrophages	Kazlowska et al. (2010)
Petalonia binghamiae	Ethyl acetate	LPS induced RAW 264.7 macrophages	Yang et al. (2010)
Sargassum micracanthum	Ethanol fractionated with 5 solvents	LPS induced RAW 264.7 macrophage	Yoon et al. (2009)
37 spp	Methanol	Phorbol myristaten (C14) acetate induced mouse ear edema and erythema	Khan et al. (2008)
Galaxaura marginata	Ethanol:acetic	Croton oil induced mouse ear edema	Rozas and Freitas (2007)
Sargassum thunbergii and *Sargassum fulvellum*	Ethanol, boiling water and Dichloromethane	Taphorbol myriste acetate-induced ear edema, erythema, and blood flow	Kang et al. (2008)
Sagarssum hemiphyllum	Methanol	Phorbol 12-myristate 13-acetate (PMA) and A23187- induced IL-8 and on TNF-α secretion from human mast cells (HMC-1)	Na et al. (2005)

the presence of various bioactive compounds including anti-inflammatory (Gamal, 2010; Bhakuni and Rawat, 2005). However, findings from these studies are numerous in various scientific journals which occlude the extent of scientific researchers on anti-inflammatory potential of seaweed and make it difficult to know the direction and predict future trend. In addition, most reviews on medicinal potential of macro-algae encompass all the medicinal activities with narrowing it down to one specifically. Thus this study reviews the current trends in the anti-inflammatory compounds extracted from macro-algae.

ANTI-INFLAMMATORY COMPOUNDS FROM MARCRO ALGAE

Crude extracts and solvents partitions

Usually, researchers investigated the effectiveness of crude extracts from biological materials prior to embarking on fractionation, isolation and purification. Some studies of anti-inflammatory activities of crude extracts, and some solvent partitions, obtained from seaweeds have been conducted. It is important to note that differences solvent and extraction conditions used in obtaining these crude extracts affect their properties and activities. List of seaweed species, organic solvents used for extraction and inflammation medium used in assays are shown in Table 1. Both *in vivo* and *in vitro* approaches have been used to study crude extracts.

Methanol extract

Out of methanol extracts of 37 seaweeds examined, *Undaria pinnatifida* and *Ulva linza* extracts strongly reduced ear edema/erythema by 85/78% and 84/70%, respectively. U. *pinnatifida* extract has IC_{50} of 10, 15 and 18 mg/ml while U. *linza* extract has 20, 26 and 31 mg /mL, respectively for edema, erythema and blood flow (Khan et al., 2007). More recently, methanoic extracts of

both S. *swartzii* at 175 and 350 mg/kg per body weight applied for 24 h showed 52.12 and 45.85% anti-inflammatory activities respectively against carrageenan induced hind paw edema of acute inflammatory model. Leucocytes and granulomas were significantly reduced by dosages of extract compared, respectively to 25 mg indomethacine/kg body weight and 5 mg predinoson/kg body weight (Hong et al., 2011). Methanoic extract of *Sargassum hemiphylum* was also reported to reduce not only IL-8 but also TNF-α and its transcription factor NF-kB (Na et al., 2005). Methanolic extract of *Petronia dentata* and its phenolic compounds (catechol and rutin but not hesperdidin) was also reported to inhibit secretion of NO and suppress iNOS and NF-κB. (Kazlowska et al., 2010). Reduction in carrageenan induced edema was exhibited by hexane, methanol and butanol extracts of *Sophora wightii*, with butanol having maximum inhibitory effect. Seasonal variation affect anti-inflammatory potential of S. *wightii* possibly due to reduction in nutrient availability during spring compared to winter. All extracts from S. *wightii* harvested in winter causes significant reduction of edema compared to spring harvest (Dar et al., 2007).

Ethanol extract

Crude-ethanol extract of *Sargassum micracanthum* was partitioned into hexane, dichloromethane, ethyl acetate, butanol and water fractions. 20 µg/ml of each of Dichloromethane and hexane fractions, that contained phlorotanin, exhibited 85.6 and 85.2% reduction of NO production, respectively; PGE_2 production was also reduced in LPS induced RAW 246.7 macrophage (Yoon et al., 2009). Likewise, 0.4 mg/ear of dichloromethane of S*argassum fulvellum* and ethanol of *Sargassum thunbergii* extracts inhibited edema/erythma by 79.1/24.1 and 72.1/34.5%, respectively. Analysis of toxicity test at 5 g/kg body weight of extracts did not depict that extracts were toxic and safe at moderate dosages (Kang et al., 2008). Ethanol:acetic acid extract (1mg/ear) of *Galerina marginata* was reported to cause 95±0.5% reduction of mouse ear edema with its 4 Hexane- thin layer chromatography (TLC) fractions inhibited 55, 75, 100, and 100%. EC_{50} of ethanol:acetic extract was reached at 0.31mg/ear and its anti-inflammatory activity was associated to inhibition of PLA_2 (Rozas and Freitas, 2007).

Aqueous extract

Due to concerns over usage of organic solvents for bioactive extraction regarding their safety and environmental impacts, water is prioritized over organic solvent and currently being investigated. Recent study by Boonchum et al. (2011), investigated anti-inflammatory effects of aqueous extract of *Trochomorpha conoides* after being identified as most potent antimicrobial activities. It was reported that the extract significantly reduce carrageenan induced paw edema after oral injection of 500 mg/kg body weight (Boonchum et al., 2011). Also, Vázquez et al. (2011) investigated aqueous extract of red algae *Demoulia obtusata* for anti-inflammatory potential. D. *obtusata* extract inhibited edema and abdominal writhes in a dose depended manner. The aqueous extracts have not been further separated and purified in order to identify the active compound. Likewise, ethyl acetate crude extract of *Petalonia binghamiae* reduced NO and PGE2 production, with IC_{50} of 38.8 and 9.3 µg/mL, respectively, in LPS induced RAW 246.7 (Yang et al., 2010). Both reports agreed that extracts modulated iNOS and COX-2 expression. Although, all 5 fractions used by Yoon et al. (2009) modulated iNOS and COX–2 proteins expression in the macrophages, hexane and dichloromethane caused better modulation in a dose dependent manner. Suppression of iNOS and COX-2 was as a consequence of reduction of their respective Messenger ribonucleic acid (mRNA) by hexane and dischloromethane fractions (Yoon et al., 2009). Also, the two works reported that extracts caused reduction in level of TNF-α, IL-6 (Yoon et al., 2009; Yang et al., 2010), the two potent fractions in Yoon et al. (2009) exhibited dose dependent decrease in IL-1β protein and mRNA of TNF-α, IL-6 and IL-1β (Yoon et al., 2009). IC_{50} of ethyl acetate extract of P. *binghamiae* 19.4 µg/mL for IL-6 (Yang et al., 2010). Extracts were proved to non-toxic by not affecting mRNA of β-actin (a house keeping beneficial protein) (Yoon et al., 2009; Yang et al., 2010) or less toxic because concentration of ethyl acetate extract of *P. binghamiae* below 50 µg/mL did not affect cell viability (Yang et al., 2010).

Sulphated polysaccharide

In animals, sulfated polysaccharides are localized in intracellular space and function as protective barrier against pathogens and cell interaction and adhesion while in algae as protective and support roles (Mestechkina and Shcherbukhin, 2010). Recently, sulfated polysaccharides of macro-algae origin as promising ingredients for functional, nutraceutical, pharmaceutical and cosmeceutical applications due to their potential anti-inflammatory, anti-malaria, anti-coagulant, anti-viral, anti-malaria, anti-thrombotic, anti-parasitic, antioxidant, antilipidemic and high nutritional value (Hwang et al., 2011; Guangling et al., 2011; Mestechkina and Shcherbukhin, 2010; Lee et al., 2004). The types of sulfated polysaccharide from macroalgae are sulfated galactans (carrageenan and agaran) from red algae, fucans (especially fucoidans) from brown algae, ulvan and heteroglycuronan from green algae (Guangling et al., 2011). According to Vitor (2010), green algae also possess sulfated galactans. Carrageenan has

long been identified to act as inflammatory agent and is been used to induced inflammation in animal model experiment. Sulphated polysaccharide obtained from red seaweed *Solieria filiformis* was reported not to show any significant anti-inflammatory effect in carrageenan and dextran induced paw edema in wistar rat, extract showed pro-inflammatory action (de Araújo et al., 2011).

Likewise, water soluble acidic polysaccharide obtained from *Ulva rigida* immunomodulate secretion of pro-inflammation mediators, cytokines and receptors in RAW 264.7 macrophage. It cause increase in secretion of NO and PGE-2, enhance iNOS and COX-2, increase in more than 2-fold of chemokine ligands, increase in expression of IL-12 and TNF-α. Structurally, this extract was similar to glycosaminoglycans which are released after degradation of extracellular matrix at inflammatory site by macrophages (Leiro et al., 2007). Sulfated polysaccharide obtained from cell wall of brown algae with 20 to 60% fructose units are referred to as fucoidans, while those with less than 10% fructose units are referred to as sulfated fucans. Structure of fucoidans of algae origin have alternating α(1→3) and α(1→4) glycosidic bond on their oligosaccharide chain with sulfate group at C-4. There are variations in structure of fucoidans reported previously which include sulfated group at C-3 and presence of α(1→2) glycosidic bond. Variations in monosaccharides content of fucoidans have not been reported, which can affect biosynthesis of difference molecules and their alteration, can be due to different species, seasonal variation (Marinho and Bourret, 2003), and different extraction conditions.

Fucoidans and sulfated fucans (galactofucan) extracted from brown seaweed *Lobophora variegata* have been reported to possess anti-inflammatory potential because they inhibit leucocyte migration to inflammation site (Medeiros et al., 2007; Cumashi et al., 2007). Sulfated fucans from *Laminaria saccharina* was also reported to inhibit adhesion of neutrophil to platelets under flow and also actively inhibit recruitment of leukocytes to inflammation site. Heterofucan extracted from *Laminaria variegate* possessed anti-inflammatory activity in acute zymmosan-induced arthritis in rat by reducing cell infiltration and NO level in Intra-articular lavage fluid, edema injured knee and serum TNF-α (Paiva et al., 2011). Fucoidan extracted blocked induction of acute peritonits by interfering with L- and P-selectins (lectin found on the surface of leukocytes) which support reduction in polymorphonuclear neutrophils (PMN) transmission/transmigration to the abdominal cavity (Croci et al., 2011; Cumashi et al., 2007). Fucoidan, behaving like heparin or haparan sulfate, possibly got attached to L- and P-selectins since both selectins are known to interact with sulfated polysaccharide.

The exact region of fucoidan structure that is involved has not been determined because most extract used are in crude form (Olivier and Barbara, 2003). For instance, fucose-riched sulphated polysaccharide obtained from hot water extraction of *Sargassum hemiphyllum* was reported to reduce pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α) profiles, NO production, expressions of IL-1β, iNOS, and COX-2 and NF-κB (p65) in LPS induced RAW 246.7 macrophage (Hwang et al., 2011). Fucoidan was also reported to interfere with degradation of backbone of basement membrane during inflammation by acting as inhibitor to heparanase and elastases (Senni et al., 2006). Some studies have been conducted *in-vivo* in order to investigate the anti-inflammatory potential of fucoidans using gamma/LPS induced RAW 264.7 macrophage (Yang et al., 2006; Nakamura et al., 2006; Kang et al., 2011), C6 glioma cells (Do et al., 2010), microgial cell purified from whole brains of neonatal (1-dayold) Sprague-Dawley rats, (Cui et al., 2010) and BV2 microglia cells (Park et al., 2011). Fucoidan, when applied to gamma and LPS induced inflammations, acted as anti-inflammation by hindering expression of NO secretion (Nakamura et al., 2006; Yang et al., 2006; Do et al., 2010; Guangling et al., 2011). Likewise, LPS alter the cells' shape to amoeboid which was reportedly inhibited by 62.5 μg/mL of fuocoidan (Cui et al., 2010). Fucoidan significantly reduced NO and COX2 at 50 and 100 μg/ml of fucoidan due to reduction of iNOS and COX-2 (Park et al., 2011). Cui et al. (2010) stated 125 μg/ml of fuocidan caused reduction of NO (75%) and iNOS' mRNA and protein (50%). Also, Kang et al. (2011) reported that purified sulphated polysaccharide from *Ecklonia cava*, fucoidan, reduced NO and PGE2, in a dose dependent manner, by inhibiting iNOS and COX-2, respectively in LPS induced inflammation of RAW 264.7.

Complete blockage of NO production and PGE2 was achieved at 100 and 200 μg/ml of fucoidan respectively (Kang et al., 2011). Although, fucoidan was reported to induce inducible iNOS in RAW 264.7 macrophage cells (Nakamura et al., 2006), induction of iNOS was not significant in BV2 (Park et al., 2011) toward NO production. Since NO has both pro-and anti- inflammatory potential (Vane et al., 1994), slight increase of NO caused by fucoidan can be linked to anti-inflammatory potential. Impact of fucoidans alone on PGE2 production has not been reported. Slight increase of PGE2 production is an act of anti-inflammatory because PGE2 have both pro- and anti- inflammatory activities (Calder, 2009) which have not been reportedly associated with fucoidans. However, anti-inflammatory threshold limit of concentration of NO and PGE2 production needs to be investigated and established.

Effect of fucoidan on pro-inflammatory cytokines, IL-1β and TNF-α, on LPS induced BV2 microglia was investigated. From this experiment, fucoidan not only decrease IL-1β and TNF-α in the supernatants of the cell culture but also decrease mRNA of transcription of these two pro-inflammatory cytokines (Park et al., 2011). Secretion of interleukin (IL)-6, and its mRNA, by LPS induced murine colonic epithelial cell line was reportedly lowered by fucoidan obtained from *Cladosiphon*

okamuranus (Matsumoto et al., 2004). Reduction of mRNA of MCP-1 was also achieved by application of fucoidan, consequently, leading to reduction in MCP-1 production which exhibit concentration dependent pattern of fucoidant (Park et al., 2011). Suppression of Phorylation of p38 and extracellular kinase ERK was reportedly caused by fucoidan treatment of cell (Park et al., 2011; Cui et al., 2010). Furthermore, fucoidan successfully inhibit activation of other pathways known to aid occurrence of inflammation. These pathways include NF-κB, Akt, and JNK (Park et al., 2011). However, JNK pathway was not affected by fucoidan according to Cui et al. (2010).

Alkaloid

Alkaloid is a group of biological amine and cyclic compounds having nitrogen in the ring, naturally occurring in plant, microbes, animals and marine organisms. Cyclic nitrogen compounds in halogenated form are predominantly found in marine organisms and algae. Both halogenated and non-halogenated forms have attracted researchers' interest because of their pharmaceutical importance as bioactives compounds and as biological probes for physiological studies (Kasim et al., 2010). Indole alkaloids from marine sources have been reported to have anti-inflammatory potentials; these include: Oxepinamide A from fungus (Belofsky et al., 2000), Conicamin from tunicate ((Aiello et al., 2003), Plakohypaphorine D from sponge (Borrelli et al., 2004), Manzamines A–F from sponge (Mayer et al., 2005), Symbioimine from dinoflagellate (Kita et al., 2005), Lepadiformines A and B from ascidian (Sauviat et al., 2006) and aplysinopsin-type compound from sponge *Hyrtios erecta* (Aoki et al., 2001) Manzamine from sponge (El Sayed et al., 2008), Carteramine A from sponge (Kobayashi et al., 2007a), Ascidiathiazones A and B from ascidan (Pearce et al., 2007 a, b) and Caulerpin from macro-algae (Carolina et al., 2011; Éverton et al., 2009).

Caulerpin is the only reported alkaloid from seaweed with anti-inflammatory activities. Caulerpin, a Bisindole Alkaloid because it contains 2 indole groups (benzylpyrrole derived from tryptophan) linked together by 8 carbons cyclic ring with two carboxyl groups (Figure 1) (Kasım et al., 2010). Caulerpin has been isolated from mainly green and red algae. Isolation of Caulerpin (CLP) from seaweed (Caulerpa spp) was first conducted as far back as 1970 and tagged as CLP I (Aguilar, 1970), 21 years later other analogues were isolated from *Caulerpa racemosa* and referred to as CLP II and CLP III (Anjaneyulu et al., 1991) while in 1994 crystal structure of CLP I was determined by Lu et al. (1994). Everton et al. (2009) investigated *in-vivo* anti-inflammatory activities of Caulerpin by examine its potency against ear edema and peritonitis in mice, respectively induced by capsaicin (8-methyl-*N*-vanillyl-6-nonenamide) and carrageenan.

Caulerpin caused a significant reduction of plasma extravasation of mice ear with 55.8% reduction in height compared reported rise caused by capasaicin (Everton et al., 2009). Reduction of leukocytes in mice was observed after Caulerpin was injected carrageenan induced cells. Caulerpin significantly reduced 48.3% of number of leukocytes, but, lower to indomethacin that caused 72.1% reduction. Furthermore, Caulerpin was reported to greatly reduce neutrophils recruitment compared to other leukocytes. Structurally, Caulerpin resembles indomethacin, and its anti-inflammatory potential was probably due to presence of indole group as active site (Everton et al., 2009). *In-vitro* was studied to investigate Caulerpin anti-inflammatory potential and mechanisms of its anti-inflammatory action were yet to be reported.

Polyunsaturated fatty acids (PUFAs)

Polyunsaturated (Polyenoic) fatty acids are groups of fatty acids with more than one unsaturated bonds along their carbon chain which are derived from monoenoic followed by desaturation (Michael et al., 2002). Although, most seaweed contain high content of hexadecanoic (palmitic) acid, they also contain reasonable amount of omega 6 (n-6) and omega 3 (n-3) long chain polyunsaturated fatty acids (PUFAs) (Dawczyski, 2007; Noviendri et al., 2011; van Ginneken et al., 2011). Among these 2 groups of PUFAs, Arachidonic acid (C20: 4n-6) (AA), EPA C20:5n-3, Docosahexaenoic acid; C22:6n-3 (DHA), SA C18:4n-3 and ETA C20:n-9 have been linked with inflammation process (Calder, 2009). Arachidonic, an n-6 PUFA, has been associated with pro-inflammatory EPA and DHA rather than α-linolenic acid (ALA), n-3 PUFAs, exhibit anti-inflammatory activities (Simopoulos, 2002). Pro inflammatory PGE2 and leukotriene B4 (LTB4) are produced during the metabolism of AA through cyclooxygenase and 5-lipoxyganase cum leukotriene-A4 hydrolase enzymatic pathway, respectively, while DHA and EPA compete with AA metabolism thus reducing production of PGE2 and LTB4. Although, metabolism of EPA can lead to formation for two pro-inflammatory PGE3 and LTB5 when acted on by cyclo-oxygenase and 5-lipoxygenase, respectively, these two eicosanoid have less inflammatory potential compared to LTB4 and PGE2.

However, PGE2 and PGE3 demonstrated equal inhibitory effect on TNF-α and IL-β. Likewise, metabolism of ETA by 5-lipoxygenase form LTA3 inhibit leukotriene-A_4 hydrolase necessary for production of LTB4, thus act as anti-inflammatory by inhibiting LTB4 production (Calder, 2009). Also, E-series (trihydroxyeicosapentaenoic acid) and D-series (trihydroxydocosahexanoic acid) resolvins mediators derived from EPA and DHA, respectively have been identified to possess anti-inflammatory action in neutrophils, macrophages, dendritic cells and T cells (Arita et al., 2005). Furthermore, action of 15-lipoxygenase with series of reaction on DHA lead to

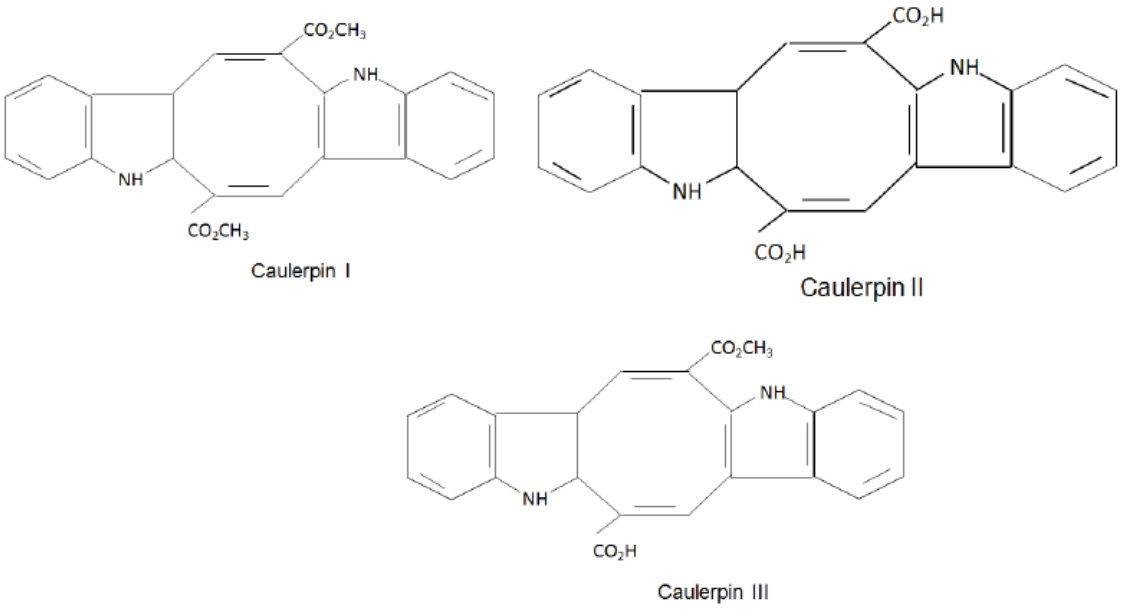

Figure 1. Structure of Caulerpin analogue (Kasim et al., 2010).

generation of anti-inflammatory neuroprotectin D1 (Calder, 2009). Resolvin E1, formed by cell during response to inflammation and microbial infection, protect the tissue from leukocyte mediated injury and counter-regulation of pro-inflammatory injury (Arita et al., 2005). Thus, mediators from EPA and DHA affect peptide mediators (cytokine) among which are mRNA of TNFα, IL-1b and IL-6 and inhibit transcription factors nuclear factor k B (NF-kB) and/or peroxisome proliferator activated receptor (PPAR) (Calder, 2009). PUFAs was reported not to cause significant difference in apoptosis and reduction of iNOS compared to control when tested for modulation of inflammation and necrosis (Caplan and Jilling, 2001). SA and EPA were extracted from brown seaweed *Undaria pinnatifida* exhibited anti-inflammatory against mouse ear edema, eruthema and blood flow induced by phorbol myristate acetate (Simopoulos, 2002). Hexadecatetraenoic and SA extracted from *U. pinnatifida* and *Ulva pertusa* have been reported to suppress production of LTB4, Leukotriene C4 (LTC4) and 5-hydroxyeicosatetraenoic acid (5-HETE) using MC/9 Mouse Mast Cell (Ishihara et al., 1998).

Carotenoids

Carotenoids are naturally occurring lipid soluble pigments (>700) produced by plant, algae, phytoplanktons and some fungi and bacteria. Both fucoxanthin and astaxanthin are among over 700 types of carotenoids and have been identified for their preventive roles in living cells. Although, fucoxanthin and astanxanthin basically function as energy trapping in seaweeds, they have been linked with biological activities in animal systems.

Fucoxanthin

Fucoxanthin extracted from *Ishige okamurae* have been reported to induce apoptosis in human leukemia cells HL-60 by generating reactive oxygen species (ROS) and induced breaking of caspases -3 and -7, poly-ADP-ribose and reduce Bcl-xL levels (Kim et al., 2010a). Fucoxanthin extracted from *Sargassum siliquastrum* provides cytoprotective effect on H2O2 mediated cell damage and UV-B induced cell damage, thus, identified as been able to offer potential therapeutic application towards several diseases (Heo et al., 2008; Heo and Jeon, 2009) in which inflammation was not an exception (Kim et al., 2010; Heo et al., 2010; Shiratori et al., 2005). Inhibition of activities of both iNOS and COX-2, which resulted in reduced NO and PGE2 produced, was reportedly observed when LPS induced RAW 246.7. Reverse transcriptase- polymerase chain reaction (RT-PCR) analysis revealed that mRNA of iNOS and COX-2 were affected by fucoxanthin. Expression of cytokines IL-6, TNF-α and IL-1β were also suppressed by fucoxanthin along with their respective mRNA (Shiratori et al., 2005; Kim et al., 2010b; Heo et al., 2010). Fucoxanthin reduced infiltration of cells into and protein concentration in aqueous humour of LPS induced rat eye in a dose dependent manner (Shiratori et al., 2005). It also reduce of nuclear translocation of P50 and P65 protein and cytoplasmic degradation of inhibitor of B (IκB)-α which lead to low level of nuclear factor (NF)-κB transactivation, and inhibit phosphorylation of mitogen-activated protein kinases (MAPKs; JNK, ERK

and p38) (Heo et al., 2010).

Astaxanthin

Ocular inflammation in LPS induced eye of endotoxin-induced uvetis (EIU) was reportedly suppressed by presence of astaxanthin by causing a significant reduction of infiltrating cells, protein concentration, NO, TNF-α, PGE-2 in aqueous humour (Ohgami et al., 2003; Suzuki et al., 2006) and NF-κB in iris-ciliary body (Suzuki et al., 2006). Although, low concentration of astaxanthin at 1mg/kg body weight of rat NO reduction, higher concentration 10 and 100 mg/kg gave significant reduction of NO. Other responses gave significant reduction in a dose dependent manner when compared with LPS induced without astaxanthin (Suzuki et al., 2006). *In vitro* study of anti-inflammatory potential of astaxanthin, LPS induced RAW 246.7 was used, reduction in secretion of NO, PGE-2 and TNF-α and inhibition of iNOS were reported (Ohgami et al., 2003). Both reports agreed that astaxanthin can be used for ocular inflammation pre-treatment. Furthermore, daily use of extract containing microalgae astaxanthin has been reported to cause reduction in C-reactive protein which usually increases during systemic or silent inflammation (Spiller et al., 2006a). Reduction in lateral humeral epicondylitis (Tennis Elbow pain) has also been linked to intake of astaxanthin (Spiller et al., 2006b). However, other inflammatory tests like edema, erythema and blood flow have not been reported for astaxanthin and fucoxanthin.

OTHERS

Vidalols A and B

Vidalols A and B are bromophenols successively extracted from Caribbean red alga *Vidalia obtusaloba* and possess anti-inflammatory activities. The two compounds were able to inhibit bee venom-derived phospholipase A 2 (96%) and reduce phorbol ester induced mouse ear edema (58 to 82%). However, due to their susceptibility to oxidation during bioassay, it was not clear if the vidalols or their oxidative form ortho-quinnoes were responsible for their anti-inflammatory potentials (Wiemer et al., 1991).

Pheophytin A

Pheophytin A is a derivative of chlorophyll, extracted from *Enteromorpha prolifera*, and was reported to possess anti-inflammatory activities. It suppressed production of formyl-Met-Leu-Phe (FMLP) of human polymorphonuclear leukocytes, superoxide in mouse and edema formation in BALB/c mouse ear, respectively induced by chemotaxis (PMNs) in Boyden's chamber experiment, by 12-O-tetradecanoylphorbol-13-acetate (TPA) using the cytochrome C reduction method, and by TPA-induced inflammation reaction (Okai and Okai, 1997).

Terpenoids

Pacifenol (1), Epitaondiol (3) and stypotriol triacetate (2) are three types of terpenoids and they were isolated from seaweed sourced from Easter Island (Chile) and evaluated for anti-inflammatory potentials. Pacifenol and epitaondiol Inhibit eicosanoids LTB4 (~82%) and TXB2 (~75%) Although, none of the terpenoids affect bee venom PLA2, stypotriol triacetate and epitaondiol reported affect human recombinant synovial PLA2. Edema reduction was achieved by the 3 terpenoids with epitaondiol being the most potent (Gil et al., 1995).

CONCLUSION

Present results on anti-inflammatory potentials of seaweed compound have shown a great success and promising future. Presence of Caulerpin in red and green algae helps in controlling inflammation, sulphated polysaccharide obtained from red and green algae act as pro-inflammatory, fucodans, sulphated polysaccharide, of brown algae origin possessed anti-inflammatory. Future works should focus on in-depth investigation of toxicity regarding both short and long term effect of the compound. Pathway of most of the active compounds have been shown to be multi-dimensional in their performance unlike the UNASD with is only one directional. However, other possible pathway need to be investigated which will provide clue on future drug development.

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