POTENTIAL ANTI-INFLAMMATORY DRUG TARGETS FROM MARINE ALGAE- AN OVERVIEW

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ABSTRACT: Inflammation is viewed as one of the major cause for the development of several diseases such as cancer, cardiovascular disease, osteoporosis, diabetes, obesity, rheumatoid arthritis, psoriasis and CNS related diseases. The use of modern medicines and steroids has been known to cause a lot of side effects and people these days are resorting to plant based natural medicines for their treatments. Compared to the natural sources from their terrestrial counterpart, the sources from the ocean has been less studied and treating diseases with these marine sources has been so far limited. Over the years, it has been known that seaweeds are abundant in curatively efficient bioactive constituents which are grouped under polyphenols and sulfated polysaccharides. These bioactive constituents could act as potential drug candidates paving way for research based on marine products. Inspite of these vast resources enriched with chemicals, the marine floras are largely unexplored for anti-inflammatory lead compounds. This review aims to explore how some natural sources from the marine ecosystem can be used in treating chronic inflammatory diseases.

Key Words: Anti- inflammatory, Marine algae, Polyphenols, Sulfated polysaccharides, Auto-immune diseases.

INTRODUCTION:

Inflammation since the early times has been known to be a well -known symptom for a lot of infectious diseases. It has also been linked with non-infectious diseases as well (Philip, 2012). Hence, by studying the role of these inflammatory process, we can hopefully generate new drugs which will help in the prevention of cancer, auto-immune diseases and other disorders. These days, commercially available synthetic drugs and medicines cause a lot of side effects in humans. Around 100,000 people die each year due to the toxic effects of synthetic drugs. It has been found that over the years, there are lots of fatalities from over the counter medicines. (Ali *et al*., 2015). Hence the need arises to develop new potent drugs from natural resources. According to the World Health Organization (WHO) more than 80% of the world population especially people living in the developing countries are resorting to herbal medicines for their illness. Almost 60% of the drugs which are approved for cancer and other chronic inflammatory diseases are made up of natural origin. (Sithranga and Kathiresan, 2010). Most of the medicinal plants possess anti-oxidant activity and has been shown to be effective in treating many conditions including cancer, alzheimer, atherosclerosis, diabetes and other cardiovascular diseases.

Antioxidants play a crucial role in the later stages of cancer development. Several herbs and spices such as turmeric, nutmeg, ginger, rosemary, sage , thyme, chilli, pepper, cayenne, cinnamon and cloves

have been shown to exhibit antioxidant and anti-inflammatory activity. Majority of the bioactive antioxidant and anti-inflammatory compounds from plants contain flavanoids, isoflavone, flavones, anthocyanins, coumarins, lignans, catechins and isocatechins. Moreover, vitamins C and E, β carotene and α tocopherol present in natural foods, are known to contain anti-oxidant properties. Hence, the potent antioxidant and anti-inflammatory activity of plants or any natural source can probably be explored for developing anti-inflammatory drugs. (Kaur and Kapoor , 2002).

MARINE ALGAE- AS AN IMPORTANT SOURCE OF DRUGS:

The ocean is a very complex eco-system where all organisms live in a collaborative way. Seaweeds are commonly marine macro algae that are attached to rocks and coral reefs. Marine algae which are basically classified into Chlorophyta (green algae), Phaeophyta (brown algae) and Rhodophyta (red algae) are termed as seaweeds based on their size, multicellular form and attachment to a firm substrate (Wong and Cheung, 2000). Marine macro algae are widely distributed around the world in a variety of habitats and have attracted the attention worldwide due to their potential as a source of food to fish, cattle and man. Marine algae are a famous delicacy in some parts of Asia and also a well-known source of important food phlorotannins, pigments and sulfated polysaccharides. Seaweeds are considered as a source of bioactive compounds and produce a great variety of secondary compounds characterized by a wide range of biological activities. In India, so far 650 species of marine algae, with a total of 320 species of rhodophyta, followed by 165 species of chlorophyta and 150 species of phaeophyta have been recorded. Compared to the terrestrial plants and animal-based foods, seaweed is rich in some health-promoting molecules and can be harvested and eaten as vegetable. Various compounds with antiviral, antibacterial, antihelminthic, antifungal activity have been detected in green, brown and red algae (Jayashree *et al*., 2013).

In addition marine algae are considered sea vegetables not only for consumption but also as an alternative medicine since ancient times for skin- related diseases (Noel and Se Kwon, 2013). In other words, the marine environment is many folds richer in its biodiversity, thereby making marine organisms and their metabolites unique and valuable. To date, many chemically unique compounds of marine origin with various biological activities have been isolated, and some of them are under investigation, and are being used to develop new pharmaceuticals.

ANTI-INFLAMMATORY AGENTS FROM MARINE HABITAT:

MARINE MICROORGANISMS:

Marine microorganisms offer a wide range of possibilities and new source of drugs which ultimately can lead to the development of new drugs and targets. Antibiotics are produced by living organisms and are active against other living systems at low concentrations. Many are secondary metabolites. Their chemical structures are diverse and complicated, and they exhibit selective activity against certain biological systems. After wide and frequent use of therapeutic antibiotics, resistant organisms have appeared. So, new agents are needed to treat these resistant organisms. In addition, there is a great need for new agents capable of inhibiting viral infections and neoplastic growth. Furthermore, agents which at low concentration could selectively regulate various functions in living systems are of main interest, e.g., novel hypotensive and anti-inflammatory agents. Thus, microorganisms help to meet the demand for useful compounds because of their capacity to produce diverse and selective agents through secondary metabolism.

Probiotic bacteria such as lactobacilli and bifidobacterioum contributes mainly in the control of pathogenic microbes through the production of the antibacterial protein bacteriocin. (Kathiresan and Thiruneelakandan, 2008). Most of the marine micro flora produce toxins and these toxins are useful in the studies related to neurophysiological and neuropharmacological activities. For example, bacteria present in

Noctiluca scintillans are responsible for causing red tides. The major metabolite, macrolactin-A, produced by the bacteria inhibits B16-F10 murine melanoma cancer cells, mammalian herpes simplex virus (HSV) (types I and II), and protects T lymphocytes against human immunodeficiency virus (HIV) replication (B.K Carte, 1996).

Only a few marine bacteria could be isolated under laboratory conditions and there's always been an urgent need to develop new culture techniques to isolate slow-growing bacteria that helps in the production of novel natural products. Among the antibiotic-producing microbes, marine actinomycetes within the family Micromonosporaceae seems to be very promising. These microbes are known to be potent sources of anticancer agents that targets proteasome function and their industrial potential is validated by several pharmaceuticals and research scientists. As far as marine fungi are concerned, they still seem to be an unexplored source and are studied less compared to their terrestrial counterparts. Recently, more interest has been focused on studying the biologically active metabolites from higher fungi (Basidiomycetes), endophytic fungi and filamentous fungi from marine flora. Marine derived fungi are known to be a valuable source for anti-oxidative natural products (Sithranga and Kathiresan, 2010).

MARINE MICRO ALGAE:

Marine micro algae especially cyanobacteria are considered to be the richest sources of bioactive compounds which has various therapeutic and pharmaceutical applications. Some of these cyanobacteria are useful in the production of vitamins such as vitamin B and vitamin E. For example, the cyanobacterium Stigonema sp. produces a compound called scytonemin which acts as a protein serine kinase inhibitor. This compound is known to have a yellow-green ultraviolet sunscreen pigment and is known to be present in the extracellular sheaths of different aquatic and terrestrial blue green algae. It is involved in cell cycle control and inhibits the profiferation of endothelial cells and human fibroblasts. Thus this compound scytonemin which is a protein kinase inhibitor may act as an excellent drug for anti-proliferative and anti-inflammatory activity. (Stevenson *et al.*,2002)

More than 50% of the marine cyanobacteria are potentially exploitable for extracting the bioactive substances. These bioactive substances are known to be effective in killing cancer cells by instigating apoptotic death or by affecting the cell signaling through activation of the members of protein kinase-c family of signaling enzymes. A compound called Curacin A, which is isolated from the organic extracts of Curacao collections of *Lyngbya majuscula* is an exceptionally potent antiproliferative agent as it inhibits the polymerization of the tubulin and it also shows the inhibitory activity selectively on colon, renal, and breast cancer-derived cell lines (B.K Carte,1996).

MARINE MACRO ALGAE:

Marine seaweeds have been recognized as an important source of antibiotic substances. Seaweeds are an essential source of iodine, proteins, minerals and hence their metabolites have been known to show promising activities towards several chronic diseases. In the past few decades many scientists have been working on anti-oxidant, anti-tumor, anti-microbial and immunomodulating effects of seaweeds. The alcoholic extract of the marine red algae *Acanthophora spicifera* exhibits tumoricidal activity on Ehrlich's ascites carcinoma cells when developed in mice at a dose of 20mg/kg, comparable to the standard drug, 5-flurouracil. This is signified by an increase in the mean survival time, decrease in tumor volume, and viable cell count. The smear study reveals membrane blebbing, vacuole formation, and reduction in staining intensity, which further ascertains the tumoricidal activity. The seaweeds *Acanthaphora spicifera, Ulva reticulata,Gracilaria foliifera, and Padina boergesenii* of Gulf of Mannar region are apparently exhibiting cytotoxic activity in their alcoholic extracts.

Owing to their various biological properties algae have gained special interest among scientists. There have been many reports which goes on to show the anti-inflammatory and anti-tumor activites of algae. An extract from the brown seaweed *Sargsassum thunbergii* has shown anti-tumour activity and inhibition of

tumour metastasis in the rat mammary adeno carcinoma cell (13762 MAT) (Sithranga and Kathiresan, 2010). Fucoidans exhibit antitumor, anticancer, antimetastatic and fibrinolytic properties in mice. Two compounds, meroterpenes and usneoidone, showing antitumor properties have been isolated from *Cystophora* sp.

Table 1: Some of the marine floral derivatives and their anticancer and anti-inflammatory activities

Marine Algae

Cancer

1. ***Cyanobacteria***- Apratoxins present here, inhibits a variety of cancer cell lines. (Luesch *et al.*,2001)

2. ***Nostoc linckia***- Cytophycin 1 shows cytotoxicity effect against human tumor cell lines and human solid tumors (R.E Moore,1996)

3.***Sargassum thunbergii*** -

Crude extract reveals antitumor activity, inhibiton of tumor,metastasis in rat mammary adeno carcinoma cell -13762 MAT (Zhuang *et al.*,1995)

4. ***Ascophyllum nodosum***- It contains fucoidan compound which exhibits anti-tumor and anti-proliferative, anti-cancer activity,anti-metastatic activity (Vischer and Buddecke,1991)

Inflammation

1. ***Stigonema sp.*** - Sctyonemin exhibits anti-proliferative and anti-inflammatory activity. (C.S Stevenson *et al.*, 2002).

2. ***Sargassum wightii***- Fucoidan exhibits anti-inflammatory and anti-bacterial activity. (Balachandran *et al.*,2016)

3.***Turbinaria ornata***-Crude extract contains anti-inflammatory activity and anti-oxidant activity. (S.Ananthi, 2011)

Neurogenic Pain

1. ***Acanthophora Spicifera*** - The compound Apigenin exhibits antinociceptive activity and analgesic effects. (Gihan *et al.*, 2016).

2. ***Caulerpa cupressoides***- Lectin from this algae exhibits antinociceptive activity (Edfranck *et al.*, 2010)

3. ***Hypnea cervicornis***-Mucin binding agglutinin isolated from the red algae exhibits antinociceptive activity. (Flavio *et al.*, 2008).

4. ***Gracilaria caudata***- Sulfated polysaccharide fraction exhibits antinociceptive activity. (Luciano *et al.*, 2013).

BIOACTIVE CONSTITUENTS OF SEAWEEDS:

Polysaccharides: Over the decade, pharmaceutical industries and research companies have shown a great deal of interest in seaweed derived polysaccharides. Seaweeds contain large amounts of polysaccharides mainly cell wall structural polysaccharides such as alginate from brown seaweeds, carrageenans and agar from red seaweeds. Other minor polysaccharides are found in the cell wall such as fucoidans from brown sea weeds, xylans from certain red and green seaweeds, ulvans in green seaweeds (Patricia, 2003). The active components present in algal polysaccharides are mainly sulfated ones. Most studies suggest that sulfated polysaccharides can enhance the innate immune response by promoting the tumoricidal activities of macrophages and natural killer cells. Sulfated polysaccharides can enhance the adaptive immune response by promoting such process. Sulfated polysaccharide can bind to CD2, CD3, and CD4 in T lymphocytes and enhance the proliferative response of T lymphocytes. B-1, a sulfated polysaccharide isolated from the culture filtrate of marine *Pseudomonas* sp., induces apoptosis of human leukaemic cells (Sithranga and Kathiresan, 2010). Among polysaccharides, fucoidans are particularly studied as they show a lot of increasing biological activities such as anti-cancer, anti-proliferative, anti-viral, anti-thrombotic and anti-inflammatory activity.
(Patricia, 2003).

Polyphenols: Polyphenols are broadly distributed in plants and they generally act as free radical scavengers and as anti-cancer agents. Marine flora such as seaweeds, sea grass, and mangroves also contain high amounts of polyphenols such as phenolic acids, flavonoids, anthocyanidins, lignin, tannins, catechin, epicatechin, epigallocatechin, and gallic acid. These polyphenolic compounds has been shown to have many health benefiting bioactivities, such as antioxidant, anticancer, antiviral and anti-inflammatory activities (Sithranga and Kathiresan, 2010) . Algal polyphenols are also called phlorotannins and these differ from terrestrial plant polyphenols. Polyphenols from terrestrial plants are derived from gallic and ellagic acid, whereas the algal polyphenols are derived from phloroglucinol units (1,3,5-trihydroxybenzine). Phlorotannins constitute an extremely heterogeneous group of molecules (struture and polymerisation degree heterogeneity) and these provide a wide range of potential biological activity (Patricia, 2003).

Alkaloids: Alkaloids are a group of biological amine and cyclic compounds having nitrogen in the ring and they are naturally occurring in plant, microbes, animals and marine organisms. These cyclic nitrogen compounds in halogenated form are predominantly found in marine organisms and algae (Irwandi and Hammed, 2011). Due to their prominent physiological activities in animals and humans, alkaloids have gained pharmaceutical importance and have attracted researchers interest. Indole alkaloids from marine sources have been reported to have anti-inflammatory potentials.

Another compound 'Caulerpin' is known to be the only investigated alkaloid from seaweed with anti-inflammatory activities. Caulerpin, which is a Bisindole alkaloid contains 2 indole groups (benzylpyrrole derived from tryptophan) linked together by 8 carbons cyclic ring with two carboxyl groups. Caulerpin has been isolated from mainly green and red algae. Isolation of this Caulerpin (CLP) from seaweed (Caulerpa spp) was first conducted as far back as 1970 and tagged as CLP I and 21 years later other analogues were isolated from *Caulerpa racemosa.* These are referred to as CLP II and CLP III while in 1994 crystal structure of CLP I was determined by Lu *et al.* in 1994. Various investigations has been carried out on the *in-vivo* anti-inflammatory activities of Caulerpin by examining its potency against ear edema and peritonitis in mice (Irwandi and Hammed, 2011).

Carotenoids: Carotenoids are known to be powerful anti-oxidants. Latest studies have shown and proved that there is a correlation between a diet rich in carotenoids and a diminishing risk of cardio-vascular disease.(β-carotene, lycopene), as well as opthalmological diseases (lutein, zeaxanthin). Brown seaweeds are particularly rich in carotenoids especially in fucoxanthin, β-carotene, violaxanthin . The main carotenoids present in the red algae are the β-carotene and α-carotene and their dihydroxylated derivatives namely zeaxanthin and lutein. The carotenoid composition of the green algae is similar to that of higher plants which constitutes β-carotene, lutein,

violaxanthin, antheraxanthin, zeaxanthin and neoxanthin. A lot of studies demonstrated the antioxidant properties of the algal carotenoids and the role they play in preventing many pathologies linked to oxidative stress (Okuzumi *et al.,* 1993).

DISEASES ASSOCIATED WITH CHRONIC INFLAMMATION:

Cancer: Rudolf Virchow, in 1863 suggested that chronic inflammation signifies the foremost pathological starting point for tumor growth and carincogenesis. Later many studies conducted have reinforced this proposition and shown that over 20% of all cancer related deaths are due to chronic inflammation and infection. Autoimmune diseases (inflammatory bowel disease and colon cancer), microbial infections (*Helicobacter pylori* and gastric cancer), viral infections (Hepatitis B, C and hepatocellular carcinoma) and inflammatory conditions of unidentified sources are acknowledged as significant causes for chronic inflammation related with cancer development (Durgaprasad *et al.,* 2013). Several reports have suggested that TNF-α plays a dual role in carcinogenesis where its high concentration is able to kill endothelial as well as tumor cells. In certain tumor models, TNF-α has been observed to stimulate fibroblasts or tumor cell growth (Mantovani,2008) and most evidences have demonstrated its potential involvement in metastasis. It has also been observed that macrophages support invasiveness of tumor cells by a TNF-α dependent matrix metalloproteinase induction *in vitro* (Gaiotti *et al.,* 2000).

Obesity: The prevalence of obesity is increasing worldwide resulting in an association with major health disorders such as type 2 diabetes, ischemic heart disease, stroke, asthma, cancer and neuro-degeneration (Hotamisligil, 2006). It is therefore necessary to treat obese individuals by both lifestyle interventions and pharmacological therapy. The relation between obesity and inflammation has been derived from the finding that proinflammatory cytokines are over-expressed in obesity. Main proinflammatory cytokines such as TNF-α, IL-6 are produced by macrophages. TNF-α levels increase with obesity and decrease with weight loss. IL-6 also plays a significant role in the regulation of whole body energy, homeostasis and inflammation (Hotamisligil *et al.,* 2006). One of the most important roles of IL-6 is that it controls hepatic CRP production which is one of the most important inflammatory markers related to obesity in humans and also linked positively with the degree of obesity (Pradhan *et al.,* 2001).

Cardiovascular disease: The predominant relationship between cardiac risk and CRP was first documented in 1954. It was established that myocardial infarction (MI) causes a significant increase in the circulating CRP levels (Anzai *et al.,* 1997). As a result, it was observed that pre-infarct increased CRP levels were interrelated with an amplified threat of future cardiac actions and unexpected death and the elevated circulating levels of IL-6, IL-18, 1-antitrypsin and ICAM-1 have been linked with augmented threat of cognitive heart failure in aged patients even before confirmation of CVD (Vasan *et al.,* 2003).

Atherosclerosis is an inflammatory disease and the consequential cardiovascular disease is more widespread in patients with chronic inflammatory diseases like rheumatoid arthritis than in the healthy population. Therefore, CVD mortality has a strong linkage with the high levels of inflammatory markers such as IL-6 and C-reactive protein, as revealed by the study of pravastatin drug in the aged people. (Durgaprasad *et al.,* 2013).

Inflammatory bowel disease: Inflammatory bowel disease is a chronic intestinal inflammatory condition caused by multi-factorial circumstances. It is primarily characterized by two major forms such as ulcerative colitis and crohn's disease. In addition to the non-immune contributing factors, the breach of the intestinal epithelial barrier and dysfunction of both innate and adaptive immunity that predominates during the inflammatory process is considered to be one of the earliest etiological factors involved in IBD (Kaser *et al.,* 2010).

Depression: For over a decade, the association between stress, inflammation and behavioral signs of depression has been greatly recognized (Raison et al 2006). Depressed and anxious persons display elevated blood levels of inflammatory cytokines TNF-α and IL-6 as well as other markers of inflammatory state, for e.g. soluble ICAM-1, CRP and MCAP-1. In addition to people exhibiting signs of depression, the function of individuals undergoing stress has also been evaluated. On examining the leukocytes, an increased activity of NF-κβ has been found among individuals who reported loneliness (Cole *et al.,* 2007).

Psioriasis: Psoriasis is a genetically determined chronic inflammatory skin disease which is characterized by red, scaly and raised patches, and it affects 2.3% of the worldwide population. Psoriasis is a disorder of the skin, which occurs when the immune system sends out faulty signals, resulting in the speeding-up of the skin cell's cycle. (Afzar and Gelfand, 2002). Psoriasis is primarily characterized by marked keratinocyte hyper-proliferation, a dense inflammatory infiltrate of T cells and neutrophils, and vascular dilation and proliferation. In psoriasis, abnormal keratinocyte differentiation, angiogenesis with vasodilation and excess Th-1 and Th-17 inflammation can be observed. Psoriatic skin is also characterized by an advanced state of lipid peroxidation , thus, it has been suggested that an antioxidant treatment could be part of a more specific and effective therapy for the management of this skin disease.

CONCLUSION:

Inflammation has long been associated with the development of diabetes, cardiovascular disease, cancer, some auto-immune disorders, CNS related disorders and other chronic diseases. Recent studies on anti-inflammatory potentials of seaweed compounds have shown a great deal of success and promising future. It has been shown that marine seaweeds seems to have a lot of therapeutic efficacy. Future work should be mainly focused on in depth investigation of pharmacological properties and toxicity regarding the short term and long term effect of the compound isolated from the marine algae. While, a wide array of drugs and natural compounds have been proved to be useful in reducing the inflammatory process by various mechanisms, further studies are still required so as to signify and validate the pre-clinical and clinical effectiveness of such drugs and natural compounds against these inflammatory ailments.

TABLES AND FIGURES:

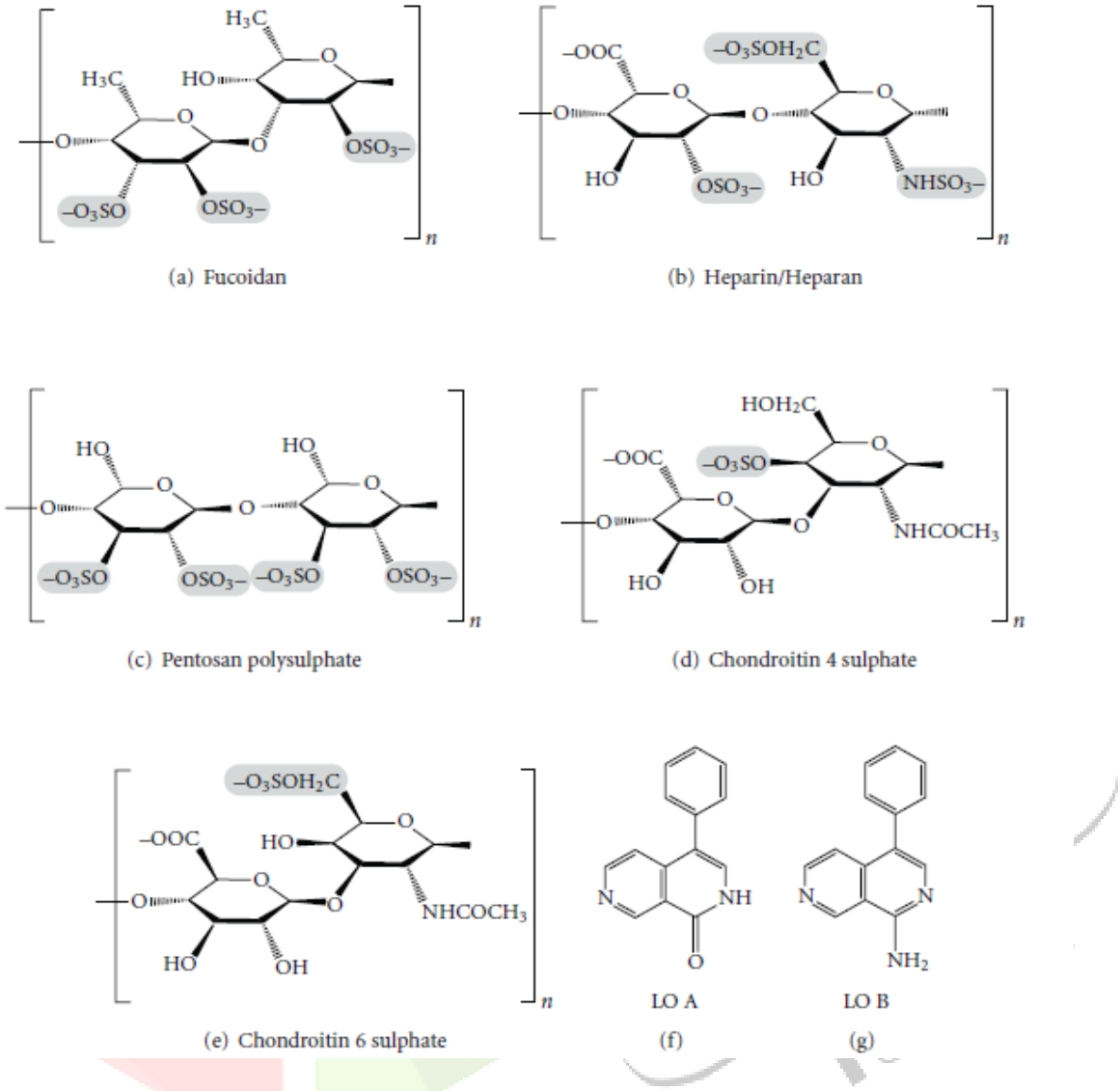

Figure 1: Anticancer Polysaccharides from marine flora (Sithranga and kathiresan, 2010)

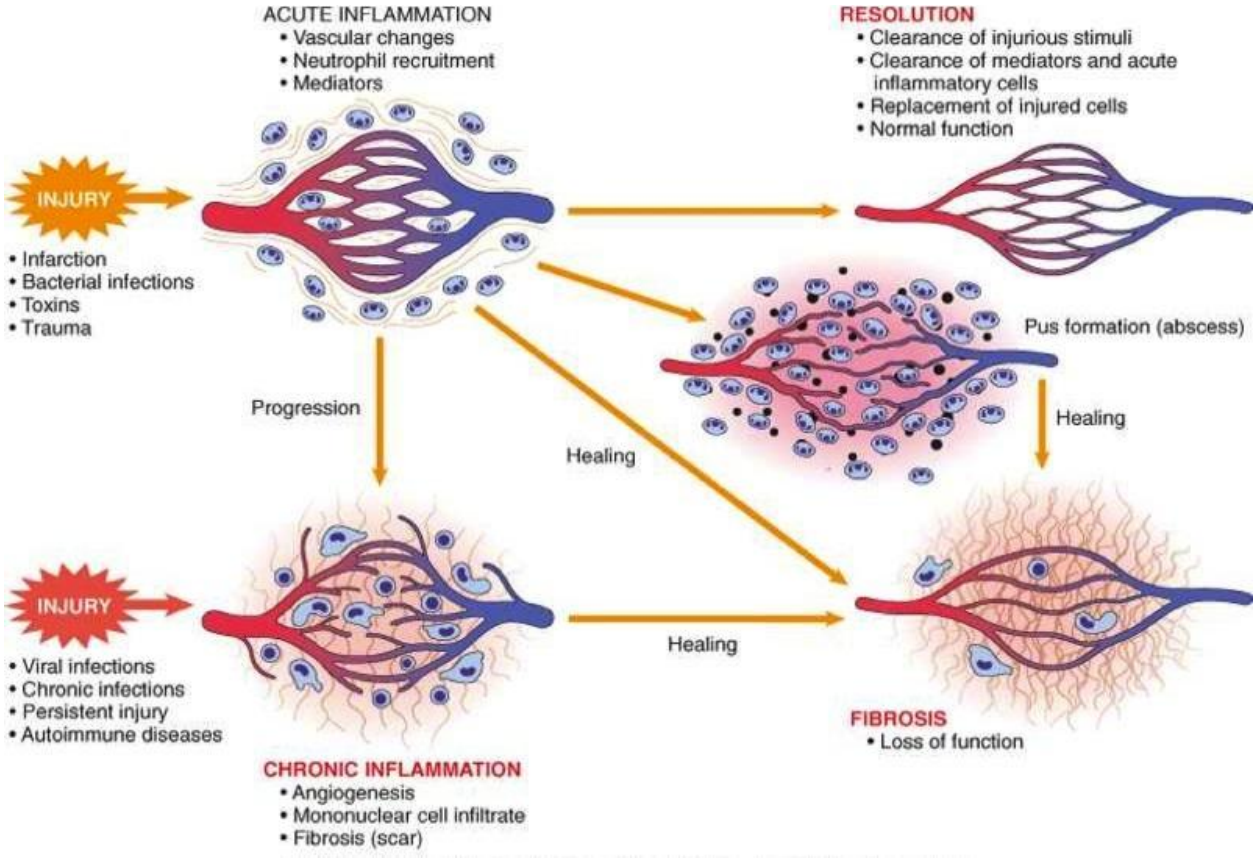

Figure 2: Pathophysiology of Inflammation (Kumar *et al.*, 2013)

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