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A Review On Medicinal Effects Of Fucoidan

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Abstract: Fucoidan is a polysaccharide largely made up of l-fucose and sulphate groups. Fucoidan is favourable worldwide, especially amongst the food and pharmaceutical industry as a consequence of its promising therapeutic effects. It's applaud able biological functions are ascribed to its unique biological structure. Classical bioactivities associated with fucoidan include antioxidant antitumor, anticoagulant, antithrombotic, immunoregulatory, antiviral and anti-inflammatory effects.
Many variety of in vitro and in vivo studies have been carried out to further highlight its therapeutic potentials. This review focuses on the progress towards understanding fucoidan and its biological activities, which may be beneficial as a future therapy. Hence, we have summarized in vitro and in vivo studies also potential effects of fucoidan and its mechanism of action that were done within the current decade. We expect this review can contribute as a theoretical basis for understanding and inspire further product development of fucoidan.[2]

Introduction:

Marine organisms are an important source of bioactive molecules that have been used to treat various diseases. Because of these benefits, much effort has focused on the isolation and characterization of biologically active natural products over the last several decades, numerous compounds with interesting pharmaceutical activities have been identified in marine organisms the diversity of marine environments provides a unique source of bioactive chemical compounds that could lead to potential new drug candidates.
Furthermore, marine-derived polysaccharides have a variety of bioactivities, including antitumor, antiviral, anticoagulant, antioxidant, and anti-inflammatory effects. In this review article we will study about one of the marine aquatic plant fucoidan and its beneficial therapeutic activities.[39]Brown seaweeds (Phaeophyceae) are a large group of multi-cellular macroalgae that are widely distributed in marine aquatic environments. Seaweeds (macroalgae) contain several bioactive compounds such as polyphenols, sulfated polysaccharides, and peptides. Moreover, the cell walls of brown seaweeds such as Ascophylum nodusum, Undaria pinnatifida and Ecklonia cava are considered from the richest sources of fucose-rich sulfated polysaccharides known as fucoidan (FCD)Research studies in human medicine showed that FCD has promising biological functions such as anticancer, antiviral, anti-allergic, anticoagulant, antioxidant, anti-inflammatory, immunostimulant, cardioprotective and hepatoprotective properties.[1]

Structure and chemicals Composition of fucoidan:

Kylin firstly isolated fucoidan in 1913, the structures of fucoidans from different brown seaweeds have been investigated. Fucoidans from several species of brown seaweed, for example Fucus vesiculosus, have simple chemical compositions, mainly being composed of fucose and sulfate. But the chemical compositions of most fucoidans are complex. Besides fucose and sulfate, they also contain other monosaccharides (mannose, galactose, glucose, xylose, etc.) and uronic acids, even acetyl groups and protein. Furthermore, the structures of fucoidans from different brown algae vary from species to species. [37]

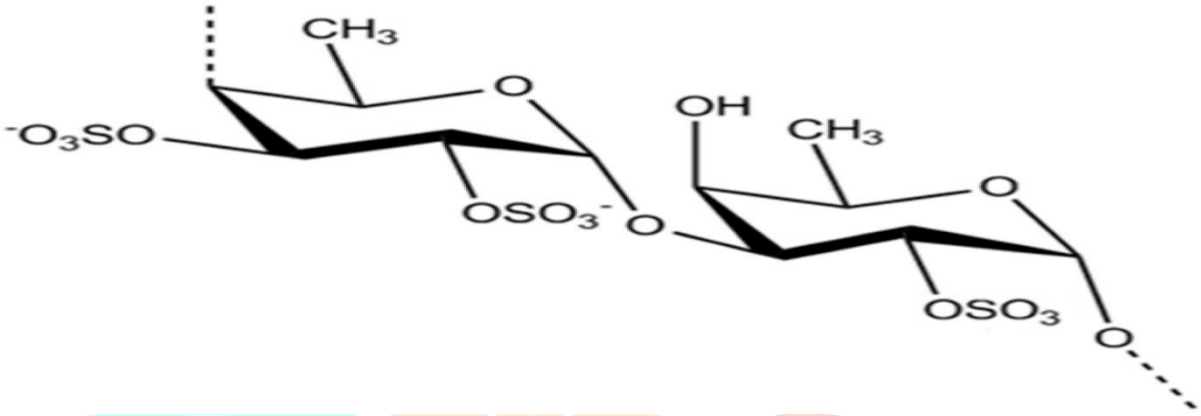

Fig 1 – Structure of fucoidan[44]

1) Role of fucoidan in neurological disease:

a) Fucoidan as memory enhancing activity in Alzheimer's disease:

Attenuating acetylcholinesterase and insulin/insulin-like growth factor-1 signaling in the hippocampus is associated with Alzheimer's disease (AD) development. AD-related pathologies mainly include amyloid-β (Aβ) accumulation, neurofibrillary tangles, and neuronal necrosis. As per Zhang, Ting, et al, Fucoidan and carrageenan are brown and red algae, respectively, with potent antibacterial, anti-inflammatory, antioxidant and antiviral activities. This study examined how low-molecular-weight (MW) and high-MW fucoidan and λ-carrageenan would improve memory impairment in Alzheimer's disease. [41]

b) Fucoidan in treatment of Parkinson disease:

Parkinson's disease (PD) is a degenerative disease of the nervous system that is characterized by the loss of dopaminergic (DA) neurons in the substantia nigra he cause of PD can be related to multiple factors, including aging, genetics, and environmental factors. The major motor symptoms of PD include bradykinesia, rigidity, and resting tremors also associated with many nonmotor symptoms, including olfactory impairment, cognitive impairment, psychiatric symptoms, and autonomic dysfunction. All of these symptoms add up to overall disability the existing drugs to treat PD, such as levodopa and carbidopa, only focus on increasing the concentration of dopamine in the brain to relieve motor symptoms. These drugs do not provide neuroprotection or prevent or delay the degeneration of DA neurons. They also have serious adverse effects, including nausea and vomiting, upright hypotension, sedation, confusion, sleep disturbances, hallucinations, dyskinesia, chorea, and progressive dystonia. There is an urgent need to develop drugs with neuroprotective effects and few side effects to treat PD. Thus, antioxidants are often studied as potential compounds for the protective effects of PD. The great potential of marine-derived glycans to treat neurodegenerative diseases has emerged because marine natural products are rich in the biological activity of antioxidants. Therefore, study have been focusing on finding a potential marine-derived compound as a possible treatment for PD.

Fucoidans are sulphated polysaccharides rich in L-fucose, usually found in brown algae and sea cucumbers. Xing, Meimei, et al, studies showed that fucoidan from Laminaria japonica protected dopaminergic

neu-rons from rotenone-induced PD in rats and reduced behavioral deficits and increased striatal dopamine (Luo et al., 2009; Zhang et al., 2018). Sulfated fucoidan isolated from Saccharina japonica showed better neuroprotective activity than low molecular weight fucoidan. In this study, four kinds of fucoidans isolated and purified with different chemical structures from Holothuria polii (HpF), Laminaria japoni-ca (LjF), Ascophyllum nodosum (AnF) and Fucus vesiculosus (FvF). We found that type II fucoidan (FvF) had the best neuroprotective ef-fect in the MPTP-PD mouse model. Finally, ATP5F1a identified as the target of FvF to protect DA neurons by improving mitochondrial function, suggesting that FvF may be a pluripotent and promising drug for PD therapy.[42]

c) Fucoidan as treatment in depression:

Major depression disorder (MDD) is a significant cause of morbidity and a major contributor to disability worldwide. There is an urgent need to elucidate the pathophysiological mechanisms of depression, and identify novel antidepressants with milder adverse effects and more reliable efficacy.

Chronic fucoidan administration prevents stress-induced increase of caspase-1-IL-1β pathway and reverses stress-induced attenuation of BDNF signaling pathway in the hippocampus of mice, as showed in figure no 7. Eventually produces antidepressant-like effects via regulating the stability of surface AMPARs in mice.[43]

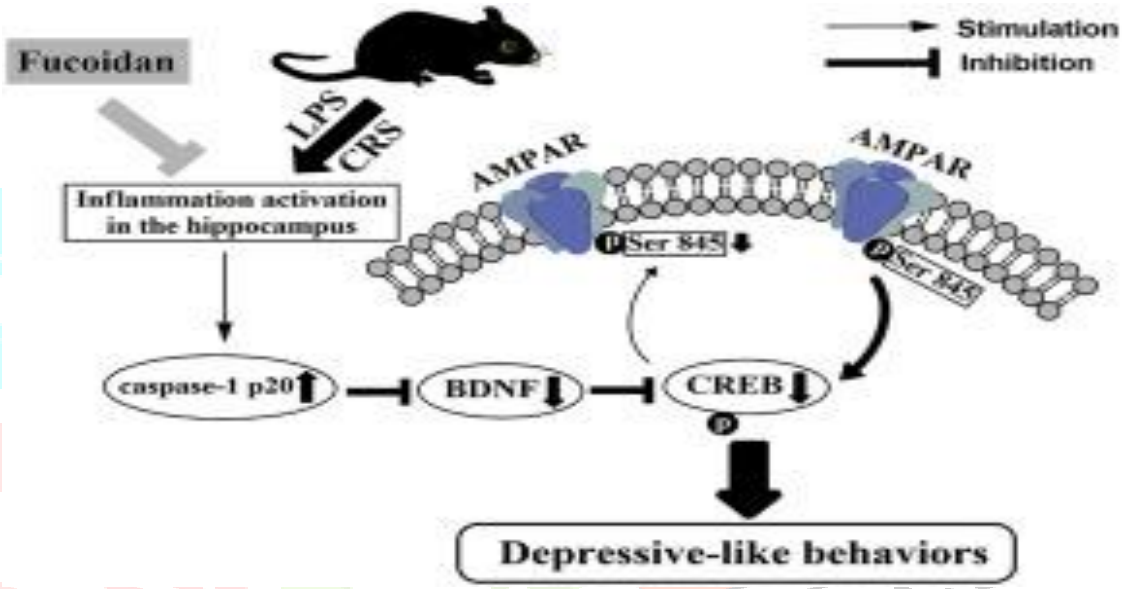

Figure no 2-MOA of fucoidan as antidepressant [43]

d) Fucoidan as treatment in impair cognitive activity:

The earlier study was performed by Gao, Yonglin, et al, that showed the effects of fucoidan on improving learning and memory impairment in rats induced by infusion of Aβ (1–40), and its possible mechanisms. The results indicated that fucoidan could ameliorate Aβ-induced learning and memory impairment in animal behavioural tests. Furthermore, fucoidan reversed the decreased activity of choline acetyl transferase (ChAT), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and content of acetylcholine (Ach), as well as the increased activity of acetylcholine esterase (AchE) and content of malondialdehyde (MDA) in hippocampal tissue of Aβ-injected rats. Moreover, these were accompanied by an increase of Bcl-2/Bax ratio and a decrease of caspase-3 activity. These results suggested that fucoidan could ameliorate the learning and memory abilities in Aβ-induced AD rats, and the mechanisms appeared to be due to regulating the cholinergic system, reducing oxidative stress and inhibiting the cell apoptosis.[45]

2) Role of fucoidan in immunological disease:

a) Fucoidan as treatment in arthritis:

The studies by Phull, Abdul-Rehman, et al, showed that Inflammation inhibition potential of 79.38% was recorded in anti-arthritic complete Freund's adjuvant-induced arthritic rat model. A substantial ameliorating effect on altered haematological and biochemical parameters in arthritic rats was also observed. Therefore, findings of the present study prospects fucoidan as a potential antioxidant that can effectively abrogate oxidative stress, edema and arthritis-mediated inflammation and mechanistic studies are recommended for observed activities. The mechanism of action of fucoidan in arthritis is as followed Effect of fucoidan on Freund's complete adjuvant-induced arthritis is studied. Fucoidan improved the arthritis-induced physical, biochemical and haematological changes. Fucoidan attenuated inflammatory responses in rats. Fucoidan down regulated COX-2 in rabbit articular chondrocytes. Fucoidan exhibited significant antioxidant activity.[46]

b) Fucoidan as anti-allergic activity:

Marine environment covers a huge source of extremely potential secondary metabolites for drug discovery. Among them, fucoidans from brown seaweeds have been evidenced to possess various biological activities and health benefit effects. Notably, a great deal of interest has been expressed regarding anti-allergic activity of fucoidans. Consequently, this contribution presents an overview of potential anti-allergic therapeutics of fucoidans from brown seaweeds to emphasize its functions in prevention as well as treatment of allergic diseases. Fucoidans from brown seaweeds have been studied for anti-allergic activity.Fucoidans suppress the allergic responses and block the leukocyte accumulation. Fucoidans inhibit IgE-expressing and IgE-secreting B cells. Fucoidans modulate TH1/TH2 balance toward TH1 domination and induce dendritic cell function.[26]

c) Therapeutic potential against Human Immunodeficiency Virus (HIV):

Anti-viral activity is dependent on the chemical properties of fucoidan. An investigation found various fucoidans could suppress the infection of Jurkat cells utilizing pseudo-HIV-1 particles which contain envelope proteins of HIV-1. [8]

Therefore, based on the data obtained by Thuy, Thanh Thi Thu, et al, the fucoidans (Saccharina cichorioides (1.3-α-L-fucan) and S. japonica (galactofucan) presented a significant inhibitory effect. This was demonstrated by the efficiency against the lentiviral transduction of fucoidan at rather low concentrations of 0.001–0.05 µg/mL. Another study showed by Thuy, Thanh Thi Thu, et al is potential anti-HIV agent was S. swartzii fucoidan. Bioactive fucoidan fractions (CFF: Crude Fucoidan Fraction; FF1: Fucoidan Fraction 1; FF2: Fucoidan Fraction 2) were isolated from S. swartzii. The fucoidan fractions were placed under investigation for anti-HIV-1 properties. Fraction FF2 significantly exhibited anti-HIV-1 activity at concentrations of 1.56 and 6.25 µg/mL which was observed by >50% reduction in HIV-1 p24 antigen levels and reverse transcriptase activity. These fractions were mainly composed of sugars, sulfate and uronic acid, and the total sugar content in the FF1 and FF2 was 61.8% and 65.9%; the sulfate content—19.2% and 24.5%, uronic acid—17.6% and 13.4%, Mw—45 and 30 kDa, respectively. In addition, Thanh et al. concluded that fucoidans derived from the three brown seaweeds, S.mcclurei (F_{SM}), S. polycystum (F_{SP}) and Turbinara ornate (F_{TO}), also displayed similar anti-HIV activities with a mean IC50 ranging from 0.33 to 0.7 g/mL. While the highest sulfate content was found in F_{SM} when compared to the other two fucoidans, and their anti-viral activities were not significantly different, suggesting that sulfate content is not the essential factor for anti-HIV activities of fucoidan. Those fucoidans inhibited HIV-1 infection when they were pre-incubated with the virus but not with the cells, and not after infection, showing that they were able to block the early steps of HIV entry into target cells as shown in figure no 3 is mechanism of action of fucoidan as anti HIV Hence, such studies are an indication that fucoidans with a naturally high molecular weight are possibly effective as anti-HIV agents regardless of their backbone. Though, the above results may present

a rather positive outlook towards fucoidan as an anti-HIV treatment, more in vitro and in vivo studies are still necessary before proceeding to clinical trials.[10] The MOA to inhibit HIV is as followed.

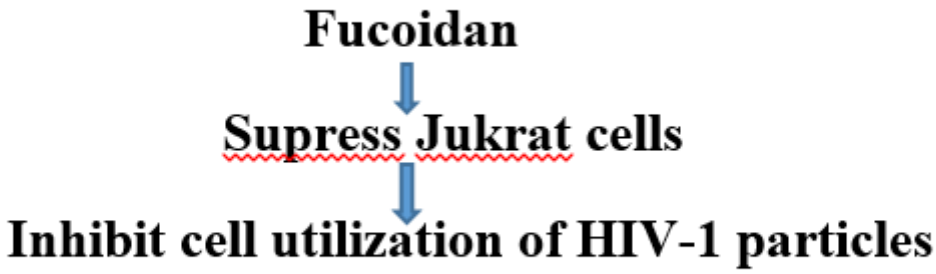

Figure no 3- MOA of fucoidan as anti HIV [8]

d) Immunomodulatory effects of fucoidan:

Fucoidan derived from Fucus vesiculosus enhanced the maturation of dendritic cells, the activation of cytotoxic T cells, the Th1 immune responses, antibody production after antigen challenge, and production of memory T cells [28]. Laminaria japonica, Laminaria cichorioides, and Fucus evanescens fucoidans also could activate the immune defense. Makarenkova et al. [29] demonstrated the interaction of fucoidans with "toll-like receptors" (TLRs), which led to increased production of cytokines, chemokines, and expression of MHC (major histocompatibility complex) molecules. The result was enhanced activity of both specific and innate immune cells. Toll-like receptors are a part of the innate immune system and substances, which bind to TLR to activate the NF-κB signaling pathway. Fucoidans bind to TLR-2 and TLR-4, but not to TLR-5, and enhance the immune response. [30]

3) Role of fucoidan in viral disease:

a) Fucoidan in treatment of influenza A virus:

A study from Wang et al. was undertaken to inhibit IAV infection by Kjellmaniella crassifolia fucoidan (536 kDa, sulfate content 30.1%) targeting the viral neuraminidase and cellular EGFR pathway. The selection of this type of fucoidan was based on one of the other requirements—that the development of anti-IAV drugs must have a high efficacy and minimal or no toxicity , hence the study on fucoidan was rather favorable as a consequence that most studies mention that fucoidan has less or no toxicity and is cost-effective compared to possible alternatives. The results revealed that K. crassifolia fucoidan blocked IAV infection in vitro with low toxicity, it also exhibited a broad spectrum against IAV and showed a low tendency in the induction of viral resistance, outperforming the regular anti-IAV drug amantadine. K. crassifolia fucoidan was able to inactivate virus particles before infection and some stages after adsorption. This was because it could also bind to viral neuraminidase (NA) and inhibit the activity of NA to block the release of IAV. In addition, intranasal administration of K. crassifolia fucoidan significantly improved survival and showed a decreased in the viral titers in IAV-infected mice. In vivo results also indicated that LF1 and LF2 were able to prolong the survival time of virus-infected mice, in addition, it presented an ability to significantly improve the quality of immune organs, immune cell phagocytosis and humoral immunity after intravenous administration of LMWFs.

Fucoidan also has the potential of being a novel nasal drop or spray for influenza therapy and could serve as prophylaxis in the near future.[4]

b) Role of fucoidan as Anti hepatitis B virus treatment:

Fucoidan (130–400 kDa) indeed acted as adjuvants by stimulating the formation of specific antibodies towards the surface of HBV, such as HBs-AG in mice. [5] The mice were immunized with compositions of vaccines contained HBs-AG and fucoidan samples, causing the increase of cytokines (TNF-a, IFN-g and IL-2) in the serum. An increase in the production of such cytokines was detected in the culture of splenocytes stimulated in vitro by fucoidan. A comparison was made that the adjuvant effect of fucoidan and its derivatives was similar to aluminium hydroxide, a traditional licensed adjuvant. Li, Huifang, et al investigation showed that F. vesiculosus fucoidan was able to inhibit the replication of HBV both in vivo and in vitro. Fucoidan suppressed the HBV replication by the activation of the EKR signal pathway and also enhanced the production of type I interferon via the activation of the host immune system. This newly discovered mechanism suggested another approach, which can be effectively employed to inhibit HBV replication. It was further mentioned in Li, Huifang, et al that fucoidan alone and/or synergistically can be used to serve as a new therapeutic drug against HBV. As described in figure 2, The investigation determined that fucoidan significantly inhibited HBV replication in a mouse model in vivo (100 mg of fucoidan at 0, 1, 3, 5 and 7 days post-infection) and in HepG2.2.15 cells in vitro (at the concentration of <200 μg/mL). The results indicated F. vesiculosus fucoidan could activate MAPK-ERK1/2 pathway and subsequently promote the expression of IFN-α, causing a decrease in the production of HBV DNA and related proteins. This may suggest the possibility of using fucoidan as an alternative therapeutic strategy against HBV infection. [6]

The MOA of Fucoidan to inhibit HBV virus is as followed.

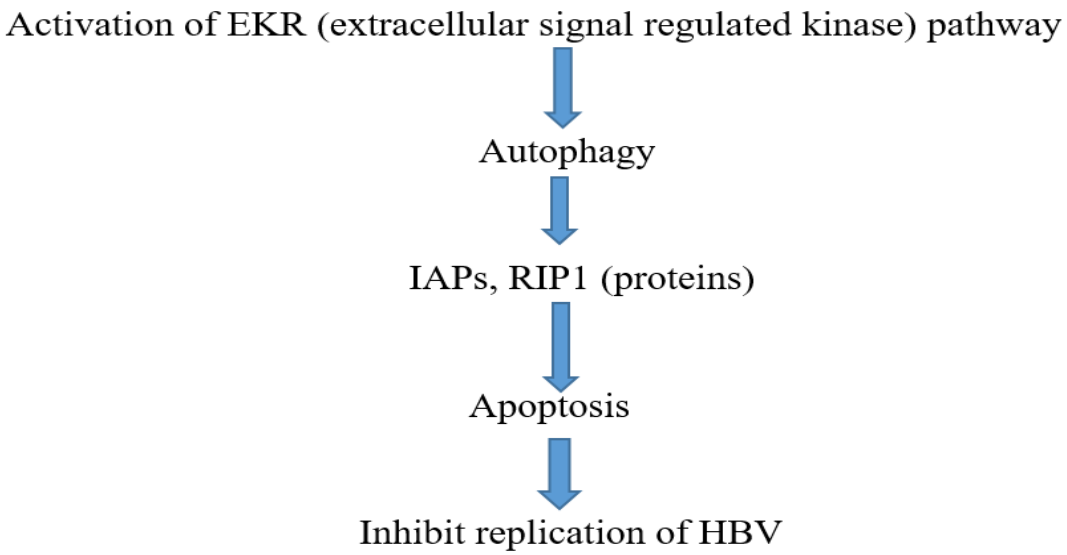

Figure no 4-MOA of fucoidan as anti HBV virus treatment [6]

c) Therapeutic action of fucoidan against canine distemper virus (CDV) in veterinarians:

A study was performed by Trejo-Avila, Laura M., et al to assess the fucoidan's anti-viral activity against CDV, since this type of virus is quite difficult to treat among canines. However, fucoidan may be part of the solution among the strategies and developments that are currently being undertaken,

since the cure is still not available. Trejo-Avila et al. reported that fucoidan extracted from C. okamuranus was able to inhibit CDV replication. This extraction contained 90.4% fucoidan and its mean molecular weight was 92.1 kDa, with fucose (38.6%), sulfate (15.9%) and other sugars (23%). It did not only show a reduction in the number of plaques but reduced the size of them as well. This fucoidan enabled an inhibition of CDV replication in Vero cells at an amount of 50% inhibitory concentration (IC50) of 0.1 µg/mL. The selectivity index (SI50) derived was >20,000. This showed that the fucoidan possesses an ability to inhibit the viral infection by interfering in the early steps and also by inhibiting CDV-mediated cell fusion. Therefore, fucoidan may be useful for the development of pharmacological strategies to treat and control CDV infection. Results such as these and many others to follow could be a stepping stone towards inventing the medication or cure against this deadly disease among canines.[7]

4) Other effects of fucoidan:

a) Fucoidan as treatment for cancer:

Apoptosis is a physiological process that is known as programmed cell death and is essential for embryonic development and homeostasis in organisms, but it can also participate in pathological processes, e.g., cancer.

Low molecular weight fucoidan as a first-line treatment for patients with metastatic colorectal cancer. In Cao, Ling-Min, et al study, the disease control rate was significantly improved by low-molecular weight fucoidan combined with chemotherapy plus target agents.

There are 3 main anticancer mechanisms of fucoidan. First, fucoidan can induce apoptosis, affect the normal mitosis of cancer cells, and inhibit cancer cell proliferation by regulating the growth cycle of cancer cells. By Cao, Ling-Min, et al study, fucoidan can inhibit the formation of vascular endothelial growth factor and tumor angiogenesis, cut off the source of nutrient supply to the tumor, and starve the tumor so as to block the diffusion and metastasis of cancer cells. Third, fucoidan can activate the immune system and enhance the ability of natural killer (NK) cells and T cells to kill tumour cells.[3]

Fucoidan exhibited significant inhibitory effects on the cell proliferation and induction of apoptosis on B16 melanoma cells at 550 µg/mL for 48 h. Such evidence was well executed, which indeed was evidently shown by a strong contention on the side of fucoidan to possess therapeutic potentials.

Luthuli, Sibusiso, et al, 2019 it has been found that The efficiency of fucoidan to inhibit cancer cells through activating apoptosis indicates a promising potential as a therapeutic agent. It is also encouraging to note that a couple of clinical studies have been undertaken to develop fucoidan as an anti-cancer therapy by means of combining it with other anti-cancer agents.[2]

b) Diabetic and Metabolic Syndrome Control:

In recent years, fucoidan has received some intense interest as an agent for treating diabetes and other types of metabolic syndromes (MetS). Fucoidan extracted from F. vesiculosus has been known as an α-glucosidase inhibitor that is able to treat diabetes [11]. In Yang, Wenzhe, et al studies, fucoidan was mentioned to have an ability to attenuate diabetic retinopathy through inhibiting VEGF signaling .[12] Cui, Wentong, et al showed a report of a low Mw fucoidan was noted to provide protection against diabetic associated symptoms in Goto-Kakizaki rats [13] Fucoidan also improves glucose tolerance by modulating AMPK signaling and GLUT4 activity [14]. Hu, Shiwei, et al, Studies mention that Fuc-Pg (fucoidan from the sea cucumber Pearsonothuria graeffei) with an Mw of 310 kDa can be used as a form of functional food to treat MetS [15]. Fuc-Pg enabled weight reduction in high fat diet-fed mice, it also reduced hyperlipidemia, and protected the liver from steatosis. Chen, Qichao, et al, Concurrently stated that Fuc-Pg reduced the

serum inflammatory cytokines combined with reduced macrophage infiltration into adipose tissue. Furthermore, it was declared that the treatment effect for MetS was primarily related to the 4-O-sulfated structure of fucoidan, since it was identified as a tetra saccharide repeating unit with a backbone of [→3Fuc (2S, 4S) α1→3Fucα1→3Fuc (4S) α1→3Fucα1→] n.

With the rapid development of investigations related to intestinal microbes, in some cases, fucoidan is recognized as a prebiotic to regulate the intestinal ecosystem or microbiome [16]. It promotes the growth of beneficial bacteria which represents a mechanism inhibiting the development of MetS [17]. A report by Parnell et al. [18] showed that prebiotics containing fucoidan can regulate blood glucose and metabolism by providing a beneficial environment for the growth stimulation of probiotics. Cheng et al also demonstrated that S. fusiforme fucoidan (SFF) could modify gut microbiota during the alleviation of streptozotocin-induced hyperglycemia in mice. The yield of SFF was 6.02%., with sulfate content up to 14.55% and the average Mw of 205.8 kDa. This study was done with diabetic mice where after a 6-week administration, SFF impressively decreased the fasting blood glucose, diet and water intake. Additionally, SFF attenuated the pathological changes in the heart and liver tissues, hence, improving liver function. Also, SFF suppressed oxidative stress in STZ-induced diabetic mice which are manifestations associated with MetS. Concurrently, SFF significantly altered the gut microbiota in diabetic mice, what was noted is SFF decreased the relative abundances of the diabetes-related intestinal bacteria, which might be the potential mechanism for relieving the symptoms of diabetes [19].

c) Fucoidan effect as anticoagulant:

According to evidence from available studies by Nishino, Takashi, et al, it is mentioned that the anti-coagulant activity of fucoidan is dependent on its Mw, sulfate group/total sugar ratio, sulfate position, sulfate degree, and glycoside branching [20]. Chandria et al. [21] discovered that, by preparing Lessonia vadosa LMWF using free-radical depolymerization, a better anti-coagulant activity is then exhibited than the naive fucoidan in a dose-dependent-manner. Jin et al. [22] discovered that fucoidan's Mw and content of galactose, presented anti-coagulant activity. Documentation based on previous studies by Shanmugam, M., and K. H. Mody, indicates that fucoidans with an Mw of 5–100 kDa present as potential anti-coagulants, while fractions greater than 850 kDa are lack of anti-coagulant activity [23]. The fucoidans with an Mw ranging from 10–300 kDa, are regarded as having by far the strongest anti-coagulant activity. In a previous study [24], the authors performed a comparative study of anti-thrombotic and anti-platelet activities of different fucoidans from L. japonica, where their results showed that the fucoidan of Mw 27–32 kDa exhibited a much better anti-coagulant and anti-thrombin activity than low molecular weight fucoidans (3.7–7.2 kDa) through intravenous administration. A recent study reported by Obluchinsksya, E. D., et al, two dry Fucus extracts, DFE-1 and DFE-2, prepared using ultrasound technique were investigated for their anti-coagulant activity compared to the reference agent heparin. An in vivo experiment on Wistar rats was conducted based on anti-coagulant activities whereby increased blood clotting time was studied—measured by activated partial thromboplastin time (APTT) and prothrombin time (PT). The results indicated that DFE-2 was analogous to the anti-coagulatory effect produced by the reference agent heparin, while DFE-1 showed a weak effect compared to DFE-2 or heparin. The distinct anti-coagulant effect between DFE-1 and DFE-2 might be due to their different physiochemical properties, including fucoidan content, monosaccharide composition and the differences in the contents of polyphenols and sulfate groups. This was indicative that the chemical composition plays an essential role in the anti-coagulant activities of fucoidan.[25]

d) Fucoidan as Antioxidant activity:

Antioxidant activity was measured by Wang, Shao-Hua, et al, the DPPH (2, 2-Diphenyl-1-picrylhydrazyl) scavenging effect as shown in figure no 4. The DPPH scavenging ability of S. Siliquosum fucoidan is shown in Figureno 4. The EC50of purified fucoidan was 2.58 mg/mL DPPH. The crude extract showed

higher antioxidant ability with an EC50of 0.34 mg/mL DPPH. This could be due to the presence of poly-phenolic compounds in the crude extract, which has been removed in the further purification steps [27]

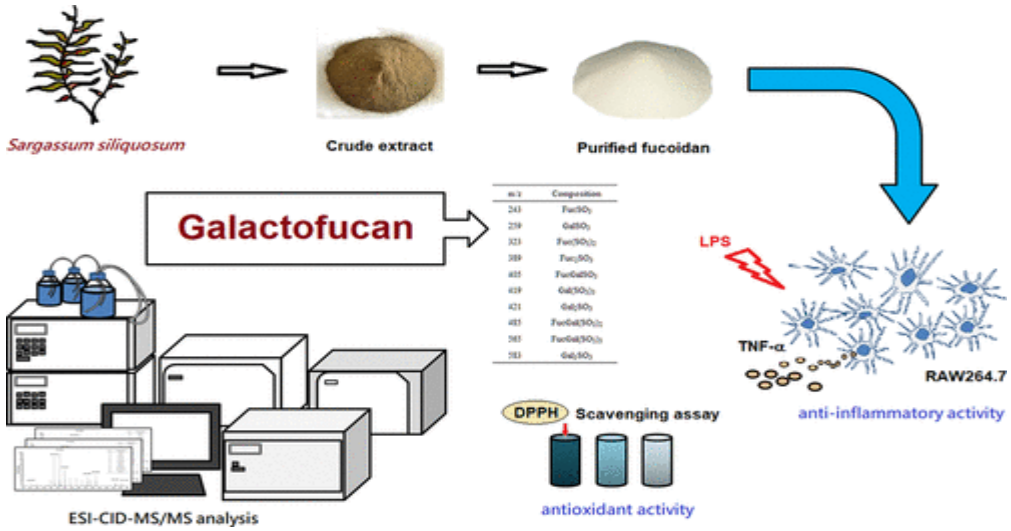

Figure no 5 – Antioxidant and anti-inflammatory activity[27]

e) Fucoidan as anti-inflammatory activity:

Fucoidan was reported to Apostolova, Elisaveta, et al act on different stages of the inflammatory process: Blocking of lymphocyte adhesion and invasion, inhibition of multiple enzymes, induction of apoptosis. The most discussed possible mechanism of action of fucoidan is the downregulation of MAPK and NF-κB (nuclear factor kappa light chain enhancer of activated beta cells) signaling pathways and the following decrease in the production of pro-inflammatory cytokines

Another study focused on the effects of modified fucoidan on LPS-induced nitric oxide production by RAW264.7 macrophages. Methacrylated fucoidan diminished the NO release and CD86 (cluster of differentiation) expression. CD86 are costimulators of the interaction between antigen-presenting cells and T cells and increased level of CD86 leads to enhanced immune response. The effect of fucoidan on the elevated CD86 level after treatment with LPS and IFN-γ was similar to the activity of the anti-inflammatory cytokine IL-10 [30]

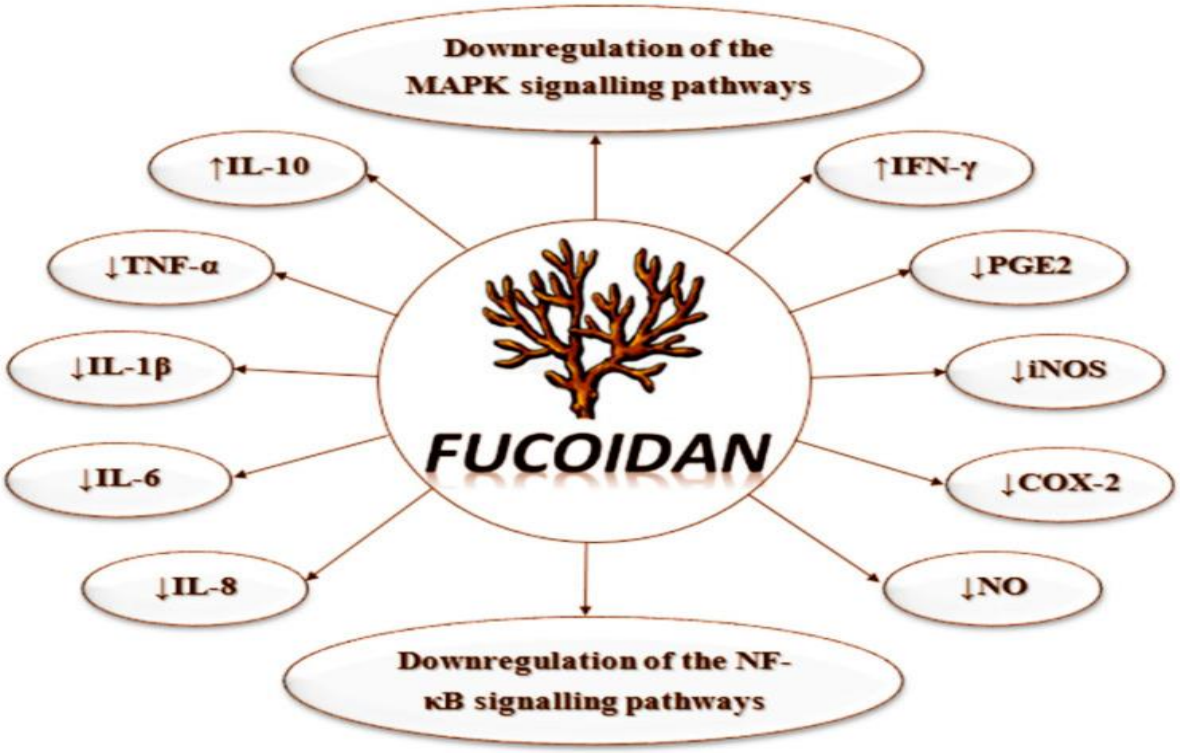

Figure no 6- MOA of anti-inflammatory activity- [30]

Another study by Apostolova, Elisaveta, et al focused on the change in the cytokine levels in BV2 microglial cells after treatment with Fucus vesiculosus fucoidan. The sulfated polysaccharide significantly decreased the levels of NO, PGE2, IL-1β, and TNF-α in LPS-activated microglial cells as showed in figure no 5. The mechanism of the anti-inflammatory effect is related to inhibition of NF-κB, Akt, ERK, p38 MAPK, and JNK pathways.

f) Cardioprotective effect of fucoidan

As per Chang, Po-Ming, Kuan-Lun Li, and Yen-Chang Lin.fucoidan could improve cardiac metabolism and function in aging mice [31], which shows its potential to protect against cardiac impairment.

The heart is the largest energy-consuming organ in the human body, and one of the cells with the most amount of mitochondria is cardiomyocytes. Almost 95% of ATP consumed by the heart comes from the oxidative metabolism of mitochondria [32]. Notably, evidence showed that mitochondrial dysfunction in mouse hearts can induce progressive cardiac hypertrophy with systolic dysfunction [33]. Doxorubicin (DOXO) has been reported to impair cardiac function mainly through oxidative stress and mitochondrial dysfunction [34].Therefore, strategies for mitigating oxidative stress and enhancing mitochondrial function are valuable and can potentially be employed to inhibit the progression and development of DOXO-induced cardiotoxicity. The objective of this study is to assess whether DOXO-induced cardiotoxicity in mice can be prevented by exogenous administration of fucoidan by decreasing oxidative stress and protecting mitochondrial function. The DOXO group and the fucoidan + DOXO group, which is reasonable and sufficient to demonstrate the protective effect of fucoidan against doxorubicin-induced cardiotoxicity. [35]

g) Hepatoprotective effects of fucoidan:

Fucoidan from Fucus vesiculosus may attenuate liver fibrosis in mice by inhibition of the extracellular matrix and autophagy in carbon tetrachloride- and bile duct ligation-induced animal models of liver fibrosis. MMP-9(matrix metallopeptidase), the enzyme that promotes the metabolism of ECM (extracellular matrix), decreased in the model groups and increased after fucoidan treatment. These results showed that

fucoidan can protect against liver injury induced by CCl_4 and BDL (bile duct ligation) through the effective inhibition of ECM production and preventing the change from HSCs (hematopoietic stem cells) to MFBs(myofibroblast), resulting in reduced liver fibrosis. Based on detection of the above indicators, measurement of ALT (alanine amino transferase, AST (aspartate amino transferase), and hydroxyproline suggested that liver function changed with ECM formation. Compared with the model groups, liver biopsy pathology in the fucoidan-treated groups showed less collagen fiber formation and focal necrosis that was dose dependent. In summary, fucoidan inhibited HSCs and reduced ECM formation and α-SMA release to protect against liver fibrosis.

As per Li, Jingjing, et al, Inhibition of autophagy may be a new drug target in the prevention of liver fibrosis. Beclin-1, LC3 (protein light chain), and P62 were assessed to demonstrate the expression of autophagy in this study. The results showed that autophagy was upregulated in the CCl_4 and BDL model groups and decreased with increased fucoidan concentration. Abundant auto phagosomes and auto phagolysosomes were seen in liver tissues of the model groups but were rarely seen following treatment with fucoidan. These findings show that fucoidan can effectively inhibit autophagy, which provides the energy for the activation of HSCs and thus slows down the process of liver fibrosis.

MOA: Fucoidan inhibited HSCs activation that could secrete TGF-β1 (transforming growth factor), thus inhibiting the downstream TGF-β1/Smads pathway. Smad2/3 cannot be transferred from pulp to the nucleus to combine with specific DNA sequences to promote Beclin-1 transcription so that fucoidan hindered the formation of autophagosomes. The autophagy associated with cracked organelles was then activated to induce cell death. [36]

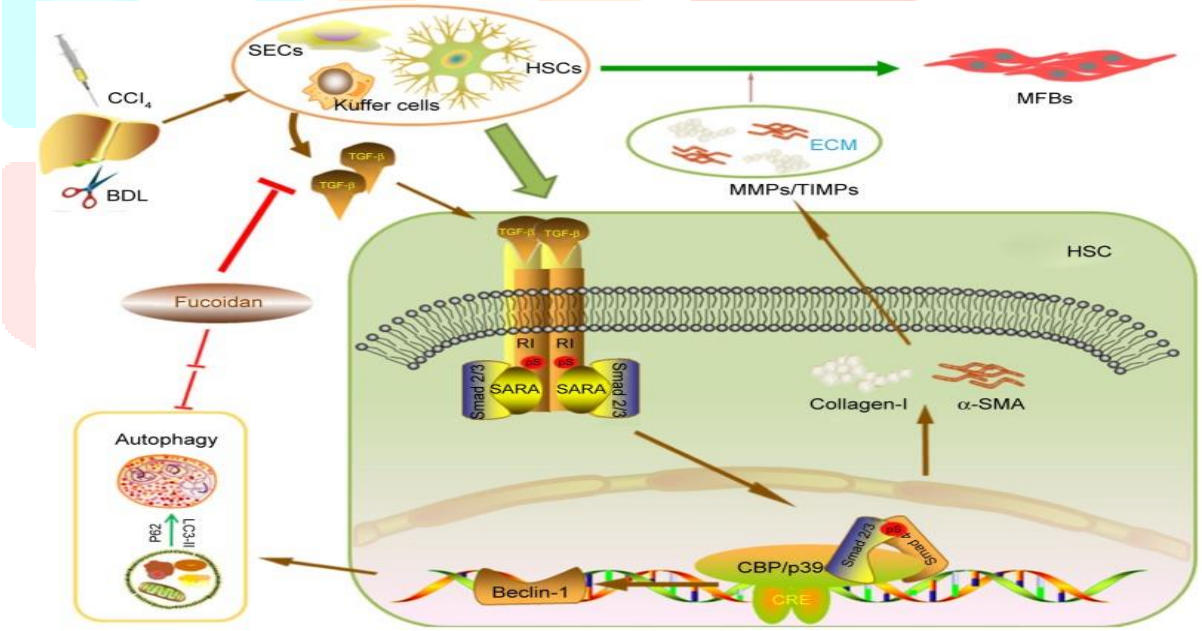

Figure no 7 – hepatoprotective effect of fucoidan[36]

CONCLUSION:

Marine drugs have many beneficial effects with minimum or no toxicity. The mechanism such as anticancer antiviral, hepatoprotective are seen in the marine drugs.

Fucoidan also known as sea weed used in neuroprotective effects .they are used as antiviral, anti-allergic, anticoagulant, antioxidant, anti-inflammatory, immunostimulant, cardioprotective and hepatoprotective properties.[1]

Above we discussed the therapeutic effects and mechanism of fucoidan. That can be used to avoid adverse effects of synthetic drugs.

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