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Fucoidan: A promising target for dyslipidemia - A concise review

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Abstract
Dyslipidemia characterized by altered lipid lipoprotein fractions is a major public health concern. It is the underlying reason for the other diseases to manifest thereby increasing the economic burden, morbidity and mortality index. Several synthetic hypolipidemic drugs are available commercially however, they are often associated with various side effects thus limiting their usage. This has led to search of natural alternatives having antihyperlipidemic potential. The marine macroalage, the seaweeds, provides plethora of natural bioactive compounds with several health benefits. Thus the study emphasizes on the hypolipidemic effects of the fucoidan isolated from brown seaweeds. The structure of fucoidan varies greatly based on different extraction conditions, season and location of harvest thereby affecting its functional capacity and bioactivity. The fucoidan from different seaweeds have shown hypolipidemic effect both *in vitro* and *in vivo* by stimulating the activity of enzymes responsible for lowering serum lipoprotein levels and increasing activity of enzyme involved in lipogenesis. Further fucoidan stimulates reverse cholesterol transport mechanism thereby reducing lipid levels. In addition, more recent studies have focused on the role of fucoidan in influencing gut microbiota thus exhibiting hypolipidemic effect. Thus, fucoidan can be used as promising therapy to target dyslipidemia and other underlying associated complications.

Keywords: Hyperlipidemia, seaweeds, fucoidan, sulphated polysaccharides, triglycerides

1. Introduction
Dyslipidemia is characterized by altered levels of triacylglycerides (TAG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-c) and very low-density lipoprotein cholesterol (VLDL-c). This is often associated with decreased high-density lipoprotein cholesterol (HDL-c). The altered lipidemic profile constitute a primary modifiable risk factor for the development of obesity and related disorders such as atherosclerosis and cardiovascular diseases [1].

Obesity characterized by increased accumulation of adipocytes is associated with various metabolic disorders imposing health risk to obese individuals. The differentiation of preadipocytes into adipocytes involves a highly coordinated and complex involvement of various pathways. This includes stimulation of CCAAR/enhancer binding protein α (C/EBPα) and nuclear peroxisome proliferator activated receptor gamma (PPARγ) [2]. PPARγ is responsible for fat storage in adipose tissues. The reduced activity of lipoprotein lipase (LPL) and mRNA expression of LPL [3] in obesity impairs the lipolysis of triglyceride rich lipoproteins leading to hypertriglyceridemia [4]. This favours the formation of small dense LDL-c. The increased postprandial lipemia also leads to increased free fatty acids (FFA) levels thus increasing the FFA flux from adipocytes to liver. Moreover, the composition of LDL-c changes with a decrease in cholesterol ester content and increase in triglyceride content of LDL-c. This triglyceride is hydrolyzed by hepatic lipase (HL) leading to formation of small dense LDL-c particles [5]. The small dense LDL-c are more susceptible to oxidation [6] and are atherogenic since they are metabolized very slowly with a resistance period of 5 days [7]. Moreover, obesity leads to decreased catabolism of chylomicron remnants [8] and decreased expression of LDL receptors (LDLR) [9] and reduced HDL-c levels [10]. These changes are often associated with visceral obesity and collectively increase the risk of atherosclerosis and other co-morbidities.

Currently, the hyperlipidemia and/or dyslipidemia are treated using various synthetic anti-hyperlipidemic drugs viz., statins, fibrates, ezetimibe, niacin and resins. The statins and ezetimibe acts by inhibiting 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase activity and intestinal cholesterol respectively while fibrates stimulates or activates LPL responsible

for hydrolysis of chylomicrons and VLDL to smaller remnants thereby removing them from the blood stream. On the other hand, niacin acts as lipolysis inhibitors and resins as bile acid sequestrants [11]. These drugs are most likely associated with side effects including myopathy, rhabdomyolysis and hepatic enzyme abnormalities [12].

Seaweeds, the marine macroalgae, grown in extreme conditions of stress are rich in bioactive compounds with myriad of health benefits in addition to good nutritional profile. The seaweeds have been used since ages as phycocolloids viz, agar, carageenan, alginates finding their use in food, pharmaceutical and cosmetics industry. They are affluent source of sulphated polysaccharides. Polysaccharides, as the name suggests, are the polymers made up of various monosccharide units joined together via various glucosidic bonds [13]. They are the most abundant among the natural products produced by plants and exist widely in plants, animals, microorganisms and algae [14, 15]. Sulphated polysaccharides include carrageenan from red algae, fucoidan or fucans from brown algae and ulvans from green algae. They as whole or in their isolated form have various health promoting activities viz., anticancer, anticoagulant, antioxidant, hepatoprotective, immunomodulatory and antidiabetic. Thus, the review will focus on the hypolipidemic effects of fucoidan isolated from brown algae.

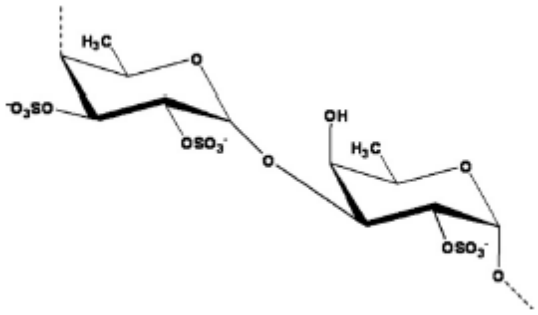

Fig 1: Structure of repeating dimeric units of fucoidan [16]

Fucoidans (Figure 1) are sulphated polysaccharides or sulphated fucans present in and isolated mainly from extracellular matrix of brown macroalgae. Fucoidan is a water soluble and negatively charged polysaccharide [17, 18] and contributes to 0.3% - 1.5% of brown seaweeds wet weight [19]. The amount of fucoidan present varies with the depth at which the seaweed grows with higher content in seaweeds growing at inter-tidal zone and lower content in seaweeds growing in low water line zone [20]. They are composed primarily of sulphated α-L-fucose units ($C_6H_{12}O_5$) in addition to variable amounts of galactose, mannose, xylose, uronic acids and acetyl groups depending on the species of extraction [21].

2. Chemical composition

The fucoidan has a backbone of α-L-fucopyranosyl residues either having (1→3) linkage (Type I) or alternating (1→3) and (1→4) linkages (Type II) [22]. Alternatively, the backbone may be comprised of β-D-galacto with (1→6) linkage and/or β-D-mannopyranosyl units with (1→2) linkages known as sulphated galactofucans having branching of fucose or fuco-oligosaccharide and/or glucuronic acid, xylose or glucose substitutions [19, 23]. However, the detailed structure of fucoidans is not known precisely due to heterogeneity and lack of regularity in its molecule [24, 25]. Moreover, the structure shows considerable variation based on the species from which they have been isolated hence have varied biological activities. The differences in the chemical composition of fucoidan attributes to differences in the species, growing conditions, anatomical region and extraction and analytical procedures used [26, 27]. Shang (2016) [28] observed temperature of extraction as additional factor affecting its composition as higher temperatures of around 150 °C yield glucuronic acid as major monosaccharide while fucose remain dominant at lower temperatures of around 90 °C. Cuong (2015) [29] reported fucose and glucose to be the main sugars of the fucoidan extracted from *Sargassum henslowianum* with sulphation at three positions with different portions. The fucoidan extracted from sporophylls of *Undaria pinnatifida* composed 60% of polysaccharides and 25% of sulphate followed by protein (5%) [30]. Fucoidan from *U. pinnatifida* as isolated by Chen (2019) [31] composed 27.8% of sulphate and 20.3% of fucose. On the contrary, 74.7% carbohydrate and 12.0% sulphate was present in the fucoidan isolated by Yang (2019) [17] from *Ascophyllum nodosum*. The *A. nodosum* fucoidan constitute mannose, fucose, xylose, glucuronic acid and galactose as major monosaccharides present in the molar ratio of 13.0: 25.9: 15.1: 9.5: 1.0 with presence of sulphates at C_2 positions. Major monosaccharides present in the fucoidan isolated from *Kjellmaniella crassifolia* include fucose (31.89%) and galactose (23.54%) with 71.68% of carbohydrate content and 20.04% of sulphate content. Moreover, small amounts of glucose, mannose, xylose, rhamnose and glucuronic acid are also present with sulphate groups at C_4 and C_2/C_3 positions [32]. Huang (2010) [33] reported that majority of sulphate groups are present on the C_4 position in fucoidan polysaccharide sulphuric acid ester (FPS) isolated from *Laminaria japonica* and only minor sulphate groups are present on C_2 and/or C_3 positions of fucopyranose residues. The FPS constitutes 28.1% of sulphate and 59.9% fucose with smaller amount of arabinose (7.89%) and rhamnose residues (0.14%). Lekshmi and Kurup (2019) [34] reported *Padina tetrastromatica* contained both sulphated and non-sulphated mono and oligosaccharides with fucose, xylose, galactose and glucuronic acid as the major monosaccharides.

3. Extraction and/or Isolation

The fucoidan can be extracted from brown seaweeds by several methods depending on the need and the availability of the resources. The basic method includes simple dissolution in water followed by extraction using either dilute acid or alkali, or use of certain enzymes, or solvent extraction, ultrasonic assisted extraction and microwave assisted extraction. However, the combination of two or more methods give better yields [19]. The conventional method involves use of sodium salt such as sodium carbonate (Na_2CO_3) to break down the seaweed biomass which converts the alginic acid to sodium alginate, although it results in impurities along with the extraction of fucoidan. The use of newer extraction techniques such as microwave assisted extraction results in higher yield in less time while, ultrasonic assisted extraction has shown some degradation of fucoidan hence, mild extraction conditions should be followed to avoid structural changes. For enzyme assisted extraction, moderate extraction conditions have resulted in lesser degradation and higher yield. Furthermore, each extraction technique should generally be followed by purification process using various chromatographical techniques to obtain pure fucoidan [19].

4. Anti-dyslipidemic effects of fucoidan

The fucoidan isolated from various brown seaweeds has been studied in the past for their hypolipidemic effects *in vitro* as well as *in vivo*. In animal trials, fucoidan administration to male C57BL/6 mice alongwith high fat diet (HFD) caused lesser weight gain as compared to HFD fed group. The reduction in weight gain was 53.9% and 47.3% respectively for 1% and 2% fucoidan administration with simultaneous significant decrease in food intake (fucoidan 2% group). Further, fucoidan (2%) administration to HFD fed group resulted in significant reduction in hepatic and epididymal tissue weight as compared to control [35]. Similarly, the fucoidan from *A. nodosum* did not resulted in body weight gain of HFD fed C57BL/6J male mice in comparison to fenofibrate treated group (positive control) [17]. Li (2017) [36] reported difference in reduction of body weight gain of Sprague Dawley rats fed on HFD along with sulphated polysaccharides from sea cucumbers. The fucoidan from *Pearsonothuria graeffei* showed minimum body and hepatic tissue weight gain followed by fucosylated chondroitin sulphate (FCS)-*P. graeffei*, FCS-*Isostichopus badionotus* and fucoidan form *I. badionotus* probably due to the structural difference of sulphated polysaccharides.

The protective effects of fucoidan against hyperlipidemia and/or obesity was further confirmed by a remarkable reduction in serum TAG, TC and LDL-c levels and significant improvement in HDL-c levels (43.5% and 43.2% respectively by fucoidan 1% and 2% administered groups) in fucoidan administered groups (1% and 2% fucoidan). The administration of HFD alone, on the other hand, significantly increased the TAG, TC and LDL-c levels with concomitant reduction in HDL-c levels [35]. Cuong (2015) [29] reported that the administration of fucoidan (100mg/kg/day) isolated from *S. henslowianum* showed reduction in serum TC, TAG and LDL-c by 22.85%, 6.35% and 18.74% respectively in HFD fed BALB/c mice group compared to group fed HFD. Further, the liver and adipose tissue weights of the mice showed marked reduction in fucoidan administered group as compared to HFD group. In the same vein, the intraperitoneal administration of fucoidan (50mg/kg b.w.) from *Fucus vesiculosus* significantly reduced TC, TAG, and LDL-c (31%, 41%, and 32% respectively) in P407 induced hyperlipidemic C57BL/6NTacSam mice in dose dependent manner with a simultaneous increase in HDL-c by 92% [37]. Henceforth, reduction in atherogenic index (AI) was observed in fucoidan administered group as compared to atorvastatin group (10 mg/kg) [37]. Similar reductions in TC and TAG levels and fat pad index after fucoidan intervention (100mg/kg b.w.) in C57BL/6J mice has been documented [17]. Huang (2010) [33] reported considerable reduction in serum TAG, TC and LDL-c levels in hyperlipidemic Sprague Dawley rats fed FPS (0.4g/kg b.w.) isolated from *L. japonica*.

Similar results have been observed by Chen (2019) [31] with significant decrease in TC, LDL-c, thiobarbituric acid (TBA) and lipopolysaccharide (LPS) levels in fucoidan (800mg/kg) administered Sprague Dawley rats fed HFD with no variations in TAG levels. On the contrary, Peng (2018) [32] documented significant decrease in TAG levels (53.74% and 64.21% respectively at 100 and 300 mg/kg b.w./day of fucoidan) without any change in TC, HDL-c and LDL-c after 8 weeks of fucoidan administration to male wistar rats. However, group fed higher dose of fucoidan (300 mg/kg b.w./day) showed a considerable improvement in HDL levels (61.03%) and reduction in TC, TAG and LDL-c levels after 12 weeks of supplementation [32]. Similar improvements in lipid profile has been reported for sulphated polysaccharides (fucoidan and FCS from sea cucumbers) [36] and polysaccharides from *L. japonica* in alloxan induced diabetic Kunming mice [38]. Moreover, the sulphated polysaccharides from *P. tetrastromatica* inhibited the *in vitro* oxidation of LDL [34]. Studies have shown that oxidative stress conditions oxidize LDL to fatty streaks formation which in turn leads to development of atherosclerosis.

The hypolipidemic effect of fucoidan has also been mediated by an improvement in the antioxidant enzyme system in animal models. Peng (2018) [32] reported significant increase in superoxide dismutase (SOD) and glutathione peroxidise (GSH-Px) levels with simultaneous reduction in malondialdehyde (MDA) levels in male wistar rats fed HFD diet along with fucoidan from *Kjellmaniella crassifolia*. Similar improvements have been reported for transaminase activities viz., aspartate aminotransferase (AST) and alanine aminotransferase (ALT) [35, 36]. Furthermore, the mRNA expression of PPARγ, adipocyte protein 2 (aP2) and acetyl CoA carboxylase (ACC) were reduced by 40.3%, 30.9% and 25.4% by 1% fucoidan and 34.0%, 36.4% and 28.4% by 2% fucoidan treatment [35] wherein aP2 is expressed primarily in adipocytes and macrophage and acts as a carrier protein for fatty acids. The fucoidan from *A. nodosum* reduced ($p \leq 0.05$) mRNA expression of PPARγ in HFD induced hyperlipidemic mice [17]. Likewise, the HMG-CoA and sterol regulatory element-binding protein-1c (SREBP-1c) levels were reduced significantly while PPARα increased ($p \leq 0.05$) upon fucoidan intake [32]. The SREBP-1c is responsible for regulation of the synthesis of fatty acids and TAG [39, 40] while PPARα regulates the genes responsible to encode proteins that plays a major role in fatty acid uptake and enzymes involved in fatty acid oxidation [41]. The fucoidan from *A. nodosum* hasn't affected the expression of SREBP-2 while increasing the SREBP-1c mRNA expression thus increasing the fatty acids and TAG synthesis which might have abolished by increased PPARγ and CYP7A1 activity [17]. However, the fucoidan from *F. vesiculosus* has decreased the SREBP-2 expression [37] and fucoidan from *C. okamuramus* has down regulated the expression of SREBP-1c which was composed of 1,3-linked α-fucopyranose with a half sulfate substitution at C_4 position, 1,3-linked α-glucuronic acid and 1,3-linked α-fucopyranose [42] further justifying the influence of fucoidan structure on its physiological activity.

Yang (2019) [17] reported no effect on the mRNA expression of PPARα upon fucoidan administration in HFD fed C57BL/6J male mice in contrast to its activation ($p \leq 0.05$) by fenofibrate treatment [17]. However, the fucoidan from *C. okamuranus* has increased mRNA expression of PPARα [43] indicating the role of different monosaccharide composition of fucoidan on its physiological activity. Further, the hypolipidemic effect of fucoidan might be a result of activation of liver X receptor (LXRβ)/ATP-binding cassette transporter (ABC) A1 pathway by fucoidan [17].

Moreover, the hypolipidmeic effects of fucoidan were brought about by increasing the activity of enzymes responsible for lowering serum lipoprotein levels viz., LPL, HL and lecithin cholesterol acyltransferase (LCAT) [33]. Yokota (2009) [44] reported increase in lipoprotein lipase (LPL) secretion from adipocytes after fucoidan administration thus increasing the clearance of the TAG rich lipoproteins from plasma. Park (2016) [37] proposed that fucoidan inhibits enzymes involved in lipogenesis as the probable mechanism to induced

hypolipidemic effect. This was evident from his findings that treatment of HepG2, human hematoma cells, by fucoidan significantly decreased the mRNA levels of fatty acid synthase (FAS) and ACC enzymes by 87% and 89% respectively. FAS and ACC plays pivotal role in lipogenesis. Moreover, since fatty acid synthesis is regulated by SREBP-1c therefore, the effect of fucoidan on its gene expression was also explored. Although, fucoidan did not considerably affected the mRNA levels of SREBP-1c in fucoidan treated HepG2 cells [37]. The fucoidan administration has reduced the mRNA expression of HMG-CoA reductase, LDLR and SREBP-2 responsible for lipogenesis thereby decreasing the lipid synthesis in fucoidan treated cells [37]. The SREBP-2 modulates cholesterol synthesis by stimulating genes responsible for cholesterol synthesis viz., HMG CoA reductase and LDLR [39, 40]. This was further supported by *in vivo* experimentation where fucoidan administration reduced FAS and ACC activity by 70% and 36% respectively in dose dependent manner in P407 induced hyperlipidemic rats compared to P407 treated group [37]. Consequently, the mRNA expression and protein levels of HMG CoA reductase and SREBP-2 were considerably reduced upon fucoidan treatment in P407 induced hyperlipidemic rats [37]. Similar results have been produced by Lekshmi and Kurup (2019) [34] for sulphated polysaccharides isolated from *P. tetrastromatica* in isoproterenol induced myocardial damage experimental animals.

The fucoidan from sporophyll of *U. pinnatifida* significantly inhibited expression of C/EBPα, PPARγ and aP2 at 10µg/ml thus alleviated the preadipocytes differentiation into adipocytes. This was further correlated with the reduced expression of inflammatory cytokines viz., tumor necrosis factor α (TNFα), monocyte chemotactic protein-1 (MCP-1) and plasminogen activator inhibitor-1 (PAI-1) by fucoidan (100 µg/ml) in 3T3-L1 cells and reduced production of reactive oxygen species (ROS) in fully differentiated 3T3-L1 cells [30] explaining the anti-inflammatory role of fucoidan in association with hypolipidemia and antiobesity. The 3T3-L1 preadipocytes treated with fucoidan (isolated from *F. vesiculosus* and sporophyll of *U. pinnatifida*) showed significant reduction in lipid droplets and accumulation of intracellular lipids (16.5% and 72% respectively at the level of 100 µg/ml of fucoidan) [30, 45] and triglycerides (86%) as evident from improved hormone sensitive lipase (HSL) and phosphorylated HSL (p-HSL) levels in fully differentiated 3T3-L1 adipocytes without affecting their viability [45]. HSL are responsible to increase stored TAG hydrolysis into mono-acylglycerol and free fatty acids [46, 47, 48].

Further, Yang (2019) [17] demonstrated that the hypolipidemic effect of the fucoidan was due to stimulation of reverse cholesterol transfer (RCT) in liver wherein the lipids are transported back to liver via bile to be excreted in faeces. In the study, the fucoidan supplementation to C57BL/6J mice significantly increased the mRNA expression levels of LDLR, an enzyme responsible for transfer of non-HDL cholesterol to liver from plasma [49, 50, 51]. The lipid transfer from plasma to liver was further increased by increased mRNA expression of SR-B1 in fucoidan treated group as SR-B1 is responsible to transfer HDL-c from plasma to liver [52]. However the mRNA expression of PCSK9 remained unaffected by fucoidan in contrast to its ~5.5 fold increase by positive control fenofibrate. PCSK9 is responsible to induce LDLR degradation [50, 53]. Additionally, the mRNA expression of CYP7A1, an enzyme involved in conversion of cholesterol to bile acids [50, 54], improved considerably after fucoidan treatment (~4.3 fold) while fenofibrate did not affected CYP7A1 levels.

Alternatively, the hypolipidemic effects of fucoidan extracted from *U. pinnatifida* has been explained by its ability to influence the gut microbiota [31]. The gut microbiota can affect the lipid metabolism in several ways. This may include development of chronic inflammation induced by lipopolysaccharide component of gram-negative bacteria thereby stimulating macrophages which in turn indirectly affects lipid metabolism [55]. Secondly, the gut microbiota produces short chain fatty acids (SCFAs) which stimulate release of peptide YY. This peptide is responsible to suppress lipid absorption and gut mobility [56] thus exerting hypolipidemic effects. Moreover, the propionic acid in the SCFAs can inhibit cholesterol synthesis in liver [57]. Lastly, the host bile acids are metabolized by the enzymes produced by the gut microbiota which in turn influence the rate limiting enzyme of the bile acid synthesis responsible for conversion of cholesterol to bile acid in liver i.e., CYP7A1 [58]. Chen (2019) [31] and Liu (2018) [59] reported an increase in relative abundance of *Firmicutes* with decreased relative abundance of *Bacteroidetes* in HFD fed rats which were altered upon fucoidan supplementation with a decrease in *Firmicutes* and an increase in *Bacteroidetes* in fucoidan supplemented group. Moreover, HFD consumption has disrupted the gut microbiota by increasing the relative abundance of gram-positive bacteria viz., *Corynebacterium*, *Aerococcus* and *Brevibacterium* associated with severe diseases. This effect was reversed to some extent after fucoidan administration with a marked increase in relative abundance of *Enterobacter*, increased intestinal bile salt hydrolase (BSH) levels and increased ($p \leq 0.05$) mRNA and protein expression of CYP7A1 [31]. Liu *et al*._2018 reported growth of three strains of lactic acid bacteria in glucose-free Mann Rogosa Sharpe (MRS) medium in the presence of fucoidan (isolated from *U. pinnatifida*). The fucoidan supplementation decreased TC, LDL-c levels by reducing the synthesis of cholesterol in liver as evident from decreased HMG CoA reductase and SREBP-2 levels [59].

Moreover, the histopathological evaluation further confirmed the hypolipidemic effects of fucoidan as evident from prevention of lipid droplets accumulation and steatosis in liver [32, 35]. Yang (2019) [17] reported HFD fed group showed fatty degeneration which was decreased in fucoidan and fenofibrate treated groups. The fucoidan treatment has reduced the arterial thickening in atherogenic mice [37].

5. Toxicity

Studies have reported that fucoidan is virtually free from toxicity [60, 61]. The fucoidan from sporophyll of *U. pinnatifida* exhibited no cytotoxicity at the levels upto 100 µg/ml. Similar observations have been reported for fucoidan obtained from *F. vesiculosus* on cell viability of HepG2 cells [37].

6. Conclusion

Fucoidan isolated from seaweeds can be used as a therapeutic agent for the treatment and/or prevention of obesity, hyperlipidemia, dyslipidemia and related metabolic diseases. The hypolipidemic effect of fucoidan is mainly attributed to increased activity of the enzymes responsible for lowering serum lipoprotein levels and increased lipogenesis. Moreover, the reverse cholesterol transport mechanism stimulated by fucoidan administration has a marked effect on lowering lipid levels. Additionally, the role of fucoidan in influencing the

gut microbiota which in turn influence lipid uptake and metabolism opens the opportunity for understanding the mode of action of fucoidan and underlying mechanisms. Thus, fucoidan can effectively be used as antihyperlipidemic agent. However, more detailed and in-depth studies on fucoidan and other bioactive compounds isolated from seaweeds needs to be undertaken to explore wide array of mechanisms involved in promoting good health and thus their application in food and pharmaceutical industry.

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