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A REVIEW ON THE CHEMOTHERAPEUTIC ROLE OF FUCOIDAN IN CANCER AS NANOMEDICINE

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ABSTRACT: Till date, a wide variety of cancer types, all of them shared some typical molecular and cellular features. Generally, all the chemotherapeutic drugs used in cancer treatment are designed to target common deregulated mechanisms within cancer cells. Recently, there have been remarkable advances and an increasing amount of scientific research and the uses of natural polymeric materials in the drug delivery system due to their biocompatibility and biodegradability. Fucoidan, a natural constituent obtained from brown seaweed, has anti-cancer activity against various cancer types by targeting key apoptotic molecules. Unsurprisingly, nanomedicine has used these compounds to make new therapeutic and diagnostic nanosystems. The applications of fucoidans in nanomedicine as drug carriers, imaging agents or for their intrinsic characteristic are reviewed here after a brief presentation of the primary structural data and biological properties of fucoidan. Fucoidan actively participates in retarding tumor development, eradicates tumor cells and synergizes with anti-cancer chemotherapeutic agents.

KEYWORDS: Cancer, Nanomedicine, Regenerative Medicine, Apoptosis, Metastasis.

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1.INTRODUCTION

Cancer is the second prime root of mortality across the globe. In general, the prevalence of cancer has increased day by day; just in the US alone, approximately 1.7 million people affected from cancer, and around 600,000 of them died due to this ailment by 2014. Therefore, Cancer is a vital

problem which affects the health of all human beings in community. Regrettably, it is a diversification of disease at the tissue level, and this variation is a crucial challenge for its specified diagnosis proceeded by the potency of treatment[1-3]. During the past few decades, and the development of research mainly focused on designing of nanocomposites with its unique characteristic and advanced functionalities acceptable for a wide range of applications, which includes biological and environmental applications [4-6]. A little while back, polysaccharide-based novel nanomaterials have gained a lot of research interest owing to their excellent biological functions. The polysaccharide-based nanoparticles are used as nanocarriers for gene and drug delivery applications in tissue engineering [7]. Fucoidan, a fucose-rich sulfated seaweed polysaccharide, comes under the category of heterogeneous anionic polysaccharides, which is natural biopolymer extricate from marine brown algae composed of anionic sulfate moieties and L-fucopyranose units and structurally looks like heparin[8,9].Fucoidan (e.g., Fucus vesiculosus,Ascophyllum nodosum, Laminaria japonica, and Macrocystis pyrifera). It is predominantly composed of -(1-3)-linked fucose units or repeating disaccharide units of (1-3)- and -(1-4)-linked fucose residues with O-2 branches [10-13]. Fucoidan is considered a worthy candidate for nanomedicine, with an excessive potential for theranostics and a broad range of bioactivities which includes antiviral, antitumor antimicrobial and anticancer [14]. Fucoidan has advantages of very less toxicity, oral bioavailability, and having multiple mechanisms of action. Pharmacologically, fucoidan strikes many pathophysiological processes, including vascular physiology, carcinogenesis, inflammation, and oxidative stress [15, 16]. Research on fucoidan for biomedical applications is at the beginning stage to know its actual function [16-20]. Some research studies have reported that fucoidan itself has the capability of destroying cancer cells by inducing apoptosis [21-28]. Several other investigations have stated that fucoidans can successfully decrease the proliferation and colony formation by cancer cells *in vitro*. Fucoidan-containing drinks or food supplements have been traditionally given to cancer patients in China, Korea, Japan, and other countries [29]. Fucoidan can also eliminate the cancer cells indirectly, e.g., as an antiangiogenic agent. Additionally, fucoidan has immune-stimulating effects on dendritic cells (DCs) [30-33] and natural killer (NK) cells [34, 35]. Thus, fucoidan can actively increase the anticancer immunity by the activation of immune cell and influx and stimulation of the formation of anticancer cytokines. Fucoidan has been communicated to be efficacious *in vivo* upon intraperitoneal, oral or intravenous administration [36-39]. Few experiments have been performed regarding fucoidan-based nanocomposites for the delivery of curcumin, doxorubicin, Cisplatin, and growth factors. That is why a lot of fucoidan-based NPs loaded with anticancer drugs have been developed in the dogging of active cancer therapies [40, 41]. Due to this fantastic feature of fucoidan, it could be a promising polymer that could be entertaining as nanomedicine and coating material as well. The coating of a fucoidan polymer onto the external surface of the core-shell nanoparticles is expected to work as a

pH-responsive shell for the controlled release of encapsulated drugs under acidic pH environments in cancer treatment. The fucoidan coating can serve effectively to protect the payloads from premature leakage and helps them to release under acidic pH environments [42].

2. Fucoidan

Fucoidan is a natural occurring sulfated polysaccharide that is mainly found in the cell wall matrix of different species of brown seaweed like limumoui, bladderwrack mozuku, kombu, and wakame [43]. Many forms of fucoidan have also been identified in few marine invertebrates such as sea urchins [44] and sea cucumbers [45]. The brown seaweeds which possesses fucoidan are mostly consumed as part of the regular diet in East Asia, particularly in China, Japan, and Korea. [46].

2.1. Structure

Fucoidan structurally looks like a heparin-like molecule with a considerable amount of L-fucose, sulfated ester groups, as well as traces of D-mannose, Dxylose, D-galactose, and glucuronic acid [47]. The structures and compositions of fucoidan transmute among various species of brown seaweed and fucoidan are involved in their chemical composition. Low molecular weight fucoidan (LMWF) has more biological action than native fucoidan. The pharmacological profile of fucoidans changes with their molecular weight, which is generally classified as low (< 10 kDa), medium (10–10,000 kDa), or high > 10,000 kDa [48]. That is why LMWF, mostly contained fucose residues and a large number of sulfate groups, possessed higher carcinogenic activity than high-molecular-weight heterofucans with the low degree of sulfation [49, 50]. The polysaccharide was named as “fucoidin” was first discovered by Kylin in 1913 from marine brown algae [51]. Presently it is called as “fucoidan” as per IUPAC rules, but also called as sulfated fucan, fucan, or fucosan [52].

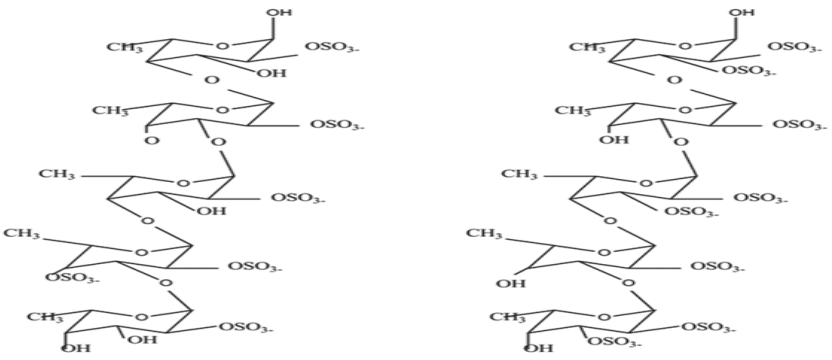

Fig 1: Structure of fucoidan.

2.2. Fucoidan regulation

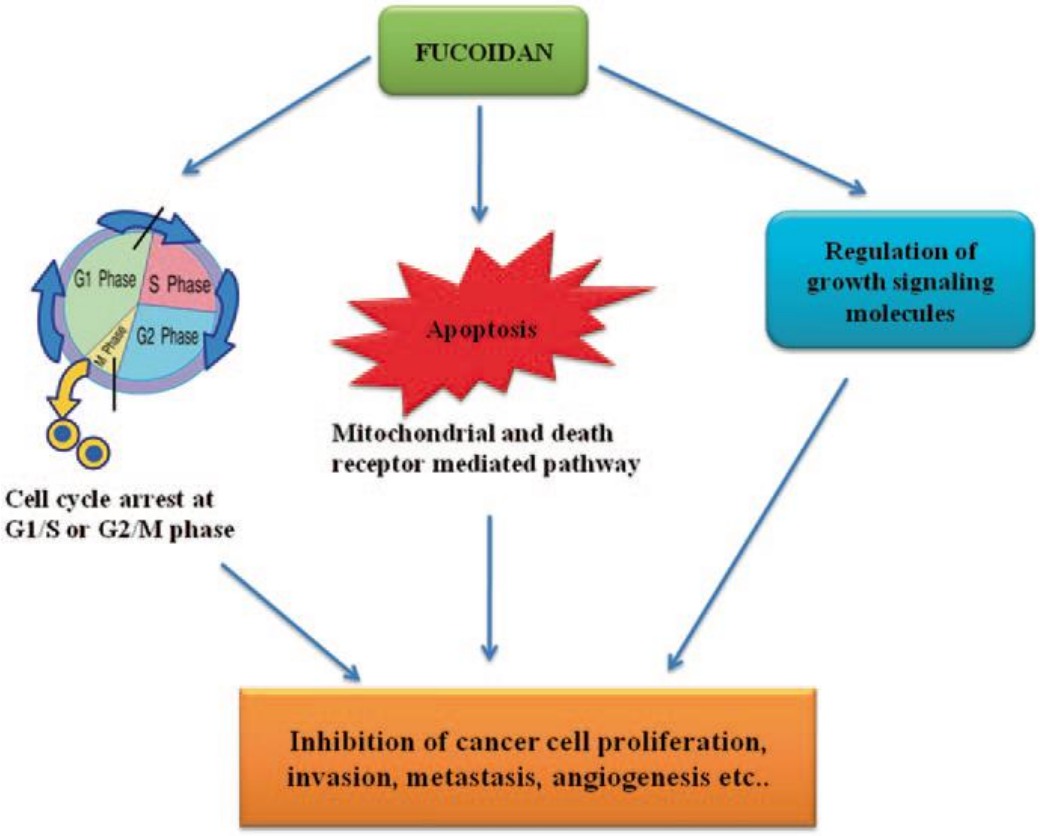

Fig 2: Overview of fucoidan regulation.[53]

3. Fucoidans in Nanomedicine

Nanomedicine, In the biomedical engineering field, is it also called as nanotechnology had earned much attention in the past ten years. Nanosystems like, in a non-exhaustive way, nanotubes, micelles, nanoparticles, polymeric carriers, and liposomes have size-dependent properties and nanometer-scale dimensions which vital characteristic in biological systems. For half a century, fucoidans been continuously developed for therapy and diagnostic uses in the medical industry and more latest have found significant applications in regenerative medicine with the advancement of nanosize biocompatible scaffolds for organization and proliferation of the cell [54]. Additionally, nanotheranostics or theranostic nano drug delivery system have also been used for combining diagnosis and therapy to check both the drug release and the bioavailability of the nano drug at the actual pathological site [55]. The primary interest of medicine is for drug delivery and individualize medicine elucidate as “the right drug to the right patient at the right moment” [56,57]. A lot of these excellent biomedical tools are currently used for treatments through oral or parenteral administration for encounter cancer disease, lack of iron or multiple sclerosis as examples. Lovri´c et al. reviewed the marketed products which contain the enormous potential [54]. Sulfated polysaccharides, especially fucoidans have been added in nanotechnology for imaging, diagnostic, delivery of drugs,

and tissue engineering [58,59]. Some research data shows that Fucoidans also utilized as stabilizers of nanoparticles (NPs) [60-64] or to study the characteristic of the aqueous suspension of chitosan/fucoidan-based NPs [65-67]. In table 1 Construction such applications, importantly with fucoidan-containing nanoparticles (FNPs), and the most suitable are explained in the below text. Moreover, table 2 highlights features of the fucoidan fractions used in nanomedicine related studies.

Table 1: Applications of fucoidan-containing Nanosystems in nanomedicine

Application	References
Small drug delivery	[68-76]
Anti-coagulant	[77,78]
Imaging agent	[79–85]
Protein delivery	[86-90]
Gene delivery	[91,92]
Regenerative medicine	[93-98]

Table 2: Features of the fucoidan fractions used in nanomedicine related studies

Study	Objective	Origin of Fucoidans	Molecular Weight	Sulfate Content	Other Data	Remarks
Changotade et al. [97]	Pretreatment of bone tissue substitute	-	-	-	-	-
Bonnard et al.[80,82]	P-selectin targeting FMPs for SPECT imaging	F.vesiculosus	57 kDa/23 kDa	-	-	Commercial fucoidans from Sigma Aldrich Company
Lee et al. [99]	Electrospun mats for Tissue engineering	U. pinnatifida	-	34.2%	62.12% total polysaccharide	Commercial fucoidans from Haewon Biotech Company
Sezer et al. [91]	DNA delivery with FMPs	F. vesiculosus	80 kDa	-	-	Commercial fucoidans from Sigma

						Aldrich Company
Huang et al. [69]	Gentamicin controlled release	F. vesiculosus	-	-	-	Commercial fucoidans from Sigma Aldrich Company
Huang et al. [74]	Curcumin controlled release	F. vesiculosus	-	-	-	Commercial fucoidans from Sigma Aldrich Company
Lee et al. [71]	DOX controlled release with FNPs	F. vesiculosus	-	-	-	Commercial fucoidans from Sigma Aldrich Company
Kimura et al. [72]	Evaluation of cytotoxic effects of FNPs	C. okamuranus	2–10 kDa	-	-	Fucoidans extracted and purified by the authors
Park et al. [90]	ALA controlled release with FMNs	-	-	-	-	Commercial fucoidans from Haewon Biotech Company
Pinheiro et al. [76]	PLL controlled release	F. vesiculosus	57.26 kDa		40.2% Fuc, 2.98% Xyl, 0.55% Man, 3.6% Gal, 9.17% Ur.Ac, 0.11% Rha, 0.21% Glu	Commercial fucoidans from Sigma Aldrich Company

3.1. Therapeutic Nanosystems of Fucoidans

Firstly, Fucoidan nanocomposites named“fucospheres” engineered by Akbuga and Sezer in the year 2006 from mixtures of fucoidan and chitosan for the delivery drug [86]. After two years, they illustrate the potency of fucospheres from the same origination over chitosan-based Nanoparticles in the therapy of dermal burns in rabbits [100,101]. The fucospheres particle size varies from 300 nanometers to 1000 nm with zeta potential from +6 to +26 mV and were experimentally tested *in vitro* on freshly excised on the black skin of the chicken. After finishing the *in vitro* studies *in vivo* research were started on rabbits with the most structured FNPs and the researchers see the vast improvement of wound healing after 21 days in groups introduced with fucospheres as compared to those treated with chitosan microspheres or FF solution. FF has been found to help in the healing on dermal burns when mixed with chitosan which can re-epithelize and potentiate fibroblast migration to the burn site. During that time, Nakamura et al. engineered FF/chitosan microparticles loaded with fibroblast growth factor 2 (FGF-2) [87]. FF was purified from the precursor material along with calcium chloride. After that microparticle was injected subcutaneously, and neovascularization was seen in ischemic tissue of mice model. Some other another group prepared FGF-2-loaded spherical nanoparticles in 2013, by adding drop by drop mixture of FF and FGF-2 into a solution of chitosan under continuous stirring [88]. This data calculated the release of the growth factor *in vitro* and its potential on the differentiation of PC12 neural progenitor cells noticing a synergistic reaction on nerve cell growth as compared to FGF-2 in solution alone. Huang et al. prepared Chitosan/FF/tripolyphosphate NPs loaded with stromal cell-derived factor-1 (SDF-1) as a therapeutic agent for tissue regeneration [89]. The results show that FNPs were effectively protected the SDF-1 from inactivation by pH, proteolysis, heat, and the release of SDF-1 was able to increase the proliferation and the movement of mesenchymal stem cells rat till seven days [91].

3.2. Diagnostic Nanosystems of Fucoidans

For diagnosis, the nanosystems should be compatible with blood and don’t show any toxicity at concentrations which is sufficient for observing the relevant images of the region of interest. More border, sulfated polysaccharides could meet these conditions as vectors of imaging markers. Among all marine biopolymers, fucoidans have been noticed as excellent candidates for imaging atherothrombosis *in vivo* [79,102], and still, researchers were showing their importance for cancer imaging [81]. Marine-based polysaccharide nanocomposites from dextran and pullulan cross-linked with sodium trimetaphosphate (STMP) in a water-in-oil emulsion developed by Bonnard et al. [80,84].FF was added to the emulsion to make NPs surface functionalized with fucoidans (FNPs) with a mean hydrodynamic diameter of the particle is 358 nm and a surface charge -16 mV. MPFs possess about 1.6% (w/w) of FF and energy dispersive X-ray (EDX) spectrum indicates the presence of FF at the uppermost layer of the nanoparticles. MPFs interaction with activated human platelets was evaluated *in vitro*. MPFs were radiolabeled with 99mTc [81] and used to image an aneurysmal

thrombus in a rat model. Iron oxide embedded MPFs showed a high affinity for activated Human platelets *in vitro* and MRI of aneurysmal thrombus and activated endothelium was also got in murine models. In another research, the authors developed MPFs having USPIO for magnetic resonance imaging [82]. On animal models, significant contrast enhancement of thrombus was taken from 30 min to 2 h after the injection of MPFs [85].

3.3. Fucoidans as Regenerative Medicine

Marine polysaccharides have been utilized for years to design scaffolds for tissue engineering due to their new biological activities and their biocompatibility. Senni et al. reviewed the data in this field [103]. Mainly, fucoidans have increased the interest in the design of nano biocomposites, especially for bone tissue engineering. So it is not surprising to search now the most recent and advanced Scientific developments in this domain although there is still comparatively very few research. Changotade et al. in 2008, treated a commercial bone substitute (Lubboc®) with a low molecular weight FF (LMWF) to improve bone regeneration [97]. The authors found out that the initial treatment of the bone substitute with LMWF enhances human osteoblast proliferation, collagen type I expression and favors alkaline phosphatase activity enhancing the mineralization of the bone tissue. Regarding the origin and structure of LMWF used, the authors also refer to older works without specifying any product parameter used in their study [98]. Puvaneswary et al. in 2015, prepared tricalcium phosphate-chitosan-fucoidan biocomposite scaffold and demonstrated the beneficial effect of FF [96]. Their research data showed that the addition of FF in the scaffold increased the release of osteocalcin allowing the osteogenic differentiation of human mesenchymal stromal cells in vitro. Moreover, FF was found to improve the compression strength and the biomineralization of the scaffolds [59].

4. Anti-Cancer Potential Of Fucoidan

The anti-cancerous Activity of fucoidan has been demonstrated *in vivo* and *in vitro* in different types of cancers. Fucoidan mediates its activity through different mechanisms such as induction of cell cycle arrest, apoptosis, and immune system activation. Additional activities of fucoidan have been reported that may be linked to the observed anti-cancer properties, and these include the induction of inflammation through the immune system, oxidative stress and stem cell mobilization. These activities have been reviewed by Kwak [104].

4.1. Fucoidan action on cell cycle and apoptosis pathway

Fucoidan therapy results in sub G0/G1 cell accumulation (suggestive of dead cells/apoptotic cells) in a variety of cell types. It can also induce cell cycle arrest in other phases; Mourea et al. and Riou *et al.* reported the arrest in G1 phase in a chemo-resistant non-small-cell bronchopulmonary carcinoma line by fucoidan from *Ascophyllum nodosum* and *Bifurcaria bifurcate*, respectively [105-109]. Many studies have been conducted to examining a variety of cancers such as hematopoietic, lung, breast and colon cancers have shown that fucoidan-mediated cell death occurs through

triggering apoptosis (Table 3) [105,110,111,112]. Cell death is characterized by cytoplasmic shrinkage, and chromatin condensation facilitates the removal of cells without inducing inflammation [113]. Apoptosis takes place through either the extrinsic (cytoplasmic) pathway whereby death receptors trigger the apoptosis or the intrinsic (mitochondrial) pathway in which changes in mitochondrial membrane potential (MMP) lead to cytochrome C release and death signal activation. Both pathways activate executive caspases that cleave regulatory and structural molecules [114]. A shallow dose of fucoidan from *F. vesiculosus* (20μg/mL) activated common caspases 3 and 7 in human colon cancer cells [111], whereas it induced the same activity in T-cell leukemia at a much higher concentration (3mg/mL) [115]. Caspase 8 and 9, two of the best-characterized molecules of the extrinsic and intrinsic pathways respectively are activated by fucoidan [111]. Yamasaki-Miyamoto *et al.* demonstrated that pre-treatment with caspase 8 inhibitor completely blocked fucoidan mediated apoptosis in MCF-7 breast cancer cell line [110]. In contrast, in Zhang *et al.* [105] research study, the mediated apoptosis by fucoidan from *Cladosiphon okamuranus* in MCF-7 cell line was shown to be caspase-independent. As cytochrome C and apoptosis-inducing factor (AIF) increased in the cytosol, it was summarized that fucoidan showed its activity through mechanisms altering mitochondrial function [112]. Bcl-2 family members include pro-apoptotic anti-apoptotic, and regulatory proteins, which are mainly involved in the intrinsic apoptosis pathway. Treatment of MDA-MB231 breast cancer cells with 820 μg/mL of low molecular weight fucoidan resulted in a remarkable decrease in anti-apoptotic proteins Bcl-2, Bcl-xl and Mcl-1 [112]. In contrast, no changes in expression of Bcl-xl, Bad, Bim, Bcl-2, and Bik were seen in colon cancer cells when they were treated with 20 μg/mL fucoidan from *F.vesiculosus* [111]. Taken together, the results indicate that fucoidan may interact with several components of the apoptosis pathway [116] as shown in table 3.

Table 3: Effects of fucoidan on cell cycle and apoptosis molecules

Reference	Cell Type	Fucoidan Source	Dose (µg/mL)	Effects on Cell Cycle		Effects on Apoptosis Pathways Extrinsic Intrinsic Common	
[105]	Human breast cancer MCF-7 cells	Cladosiphon novae-caledoniae	82, 410, 820	↑SubG1, No significant changes in cell cycle distribution	No changes in caspase8	Mitochondrial dysfunction, No activation of PARP and caspase-7 No significant changes in cell cycle distribution AIF and cytochrome C release, No cleavage of caspase-9 and Bid. All caspase inhibitors failed to attenuate FE-induced apoptosis ↓ Bcl-2, Bcl-xl,↑ Bax, Bad	All caspase inhibitors failed to attenuate FE-induced apoptosis No activation of PARP and caspase-7
[106]	Human lymphoma HS-sultan cells	F. vesiculosus	100	↑ sub no G0/G1 or G2/M arrest	-	↓ MMP	Caspase 3 activation
[118]	Human Hepatocellular Carcinoma SMMC-7721 cells	U. pinnatifida	1000	Non-significant accumulation in S-phase	Caspase 8 activation	Caspase-9 activation MMP dissipation, Cytochrome C release ↓ Bcl-2, ↑ Bax	Caspase-3 activation

[109]	Human prostate cancer PC-3 cells	U. pinnatifida	100	G0/G1 phase arrest ↑ p21Cip1/Waf	DR5, caspase-8 activation	Caspase 9 activation ↓ Bcl-2	Caspase-3 activation PARP cleavage
[119]	Hela cells	Sargassum filipendula	1500	-	-	No effect on caspase 9 activation cytosol AIF	No effect on caspase 3 (Caspase independent)
[120]	Human acute leukemia NB4 and HL-60 cells	F. vesiculosus	150	↑ sub-G1 fraction	Caspase 8 activation	caspase 9 activation No changes in Bcl-2 or Bax	PARP cleavage Caspase 3 activation
[121]	Human breast cancer MCF-7 cells	F. vesiculosus	400, 800, 1000	G1 phase arrest ↑ Sub G0/G1 ↓ cyclin D1 and CDK-4 gene expression	Caspase-8 activation	↓ Bcl-2 ↑ Bax The release of cytochrome C and APAf-1	Caspase-dependent pathway

4.2. Fucoidan action on angiogenesis

Fucoidan also acts by inhibiting the formation of new vessels by which tumor cells receive their required nutrients and oxygen. Fucoidan has been found to inhibit the binding of VEGF, a key angiogenesis promoting molecule, to its cell membrane receptor [117]. Xue *et al.* examined the anti-angiogenic characteristic of fucoidan in 4T1 mouse breast cancer cells both *in vitro* and *in vivo* and observed a significant dose-dependent decrease in VEGF expression in cells treated with fucoidan. Further, in a mouse breast cancer model using 4T1 cells, intraperitoneal injections of 10 mg/kg body weight fucoidan from *F. vesiculosus* for 20 days markedly reduced the number of microvessels. Using immunohistochemistry, fucoidan was shown to reduce VEGF expression compared to the control group [122]. It is postulated that different effects were seen with fucoidans of various MWs and molecular structures and this is reviewed by Kwak [104,123].

4.3. Fucoidan action on apoptosis

In 1987, Coombe *et al.* demonstrated that fucoidan significantly decreased tumor cells metastasis to the lungs in animals that were intravenously injected with rat mammary adenocarcinoma 13762 MAT cells [123]. It was first reported that fucoidan inhibits cell invasion through competing with

tumor cell binding with laminin in the basement membrane [124]. Subsequent studies then revealed that fucoidan binds to fibronectin with high affinity and prevent attachment of tumor cells. Selectin inhibition by fucoidan interferes with tumor cell-platelet interaction. In Cumashi *et al.* study [125], highly metastatic MDA-MB-231 breast cancer cells were plated in platelet-coated plates in the presence or absence of 100 µg/mL fucoidan. The number of cells attached to the platelets decreased by 80% in the presence of fucoidan. Interaction of tumor cells with platelets is one of the key factors in facilitating the early steps of tumor cell migration. During tumor cell migration, most circulating tumor cells do not survive an attack from immune cells or the shear forces of the bloodstream. However, they can attach to platelets to induce platelet aggregation allowing the tumor cell cluster to survive in the microvascular system. It was concluded that fucoidan inhibited P-selectin residing on the platelet surface and led to a reduced number of attached tumor cells. Fucoidan can also inhibit other adhesion molecules such as integrins residing on the tumor cell surface and can modify the distribution of their subunits [123-127].

4.4. Fucoidan action on the signaling pathway

The extracellular signal-regulated kinase (ERK) pathway (or Ras/Raf/MAPK pathway) is often hyperphosphorylated and upregulated in a variety of human cancers. The potential for developing anticancer agents that cause ERK's dephosphorylation and pathway blockade have been explored. Various studies have shown that fucoidan inhibits tumor cell proliferation by decreasing ERKs activity through reduction of its phosphorylation [106,128] while several studies have proposed that fucoidan causes ERK activation rather than inactivation [128-130].

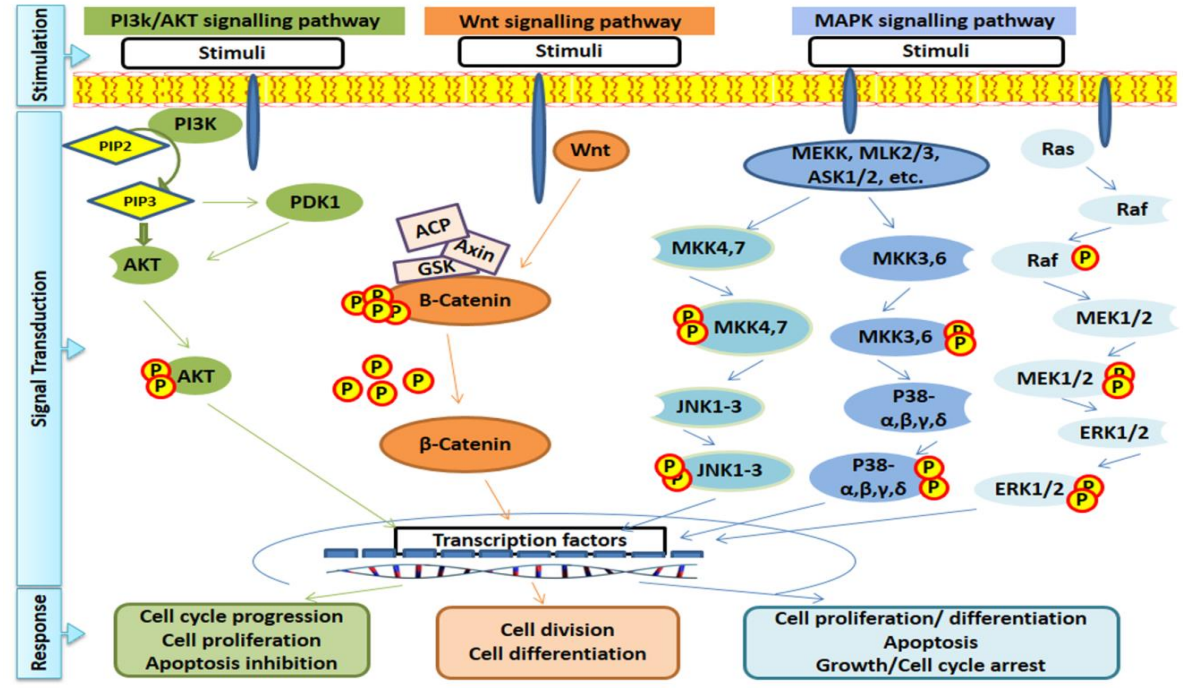

Figure 3: Overview of main signal transduction pathways involved in cell proliferation and apoptosis [131].

4.5. Fucoidan action on the Immune System

The effects of fucoidan on molecules of the immune system have been studied both *in vitro* and *in vivo* and effects on both cellular and humoral elements have been described. Fucoidan increases both activity and number of natural killer (NK) cells *in vivo* [131,132]. Increase in the number of cytotoxic T-cells (CTLs) has also been reported. A high-molecular-weight (HMW) fucoidan from *Cladosiphon okamuranus* (200–300 kDa) induced a substantial increase in the proportion of murine cytotoxic T cells [133]. Investigation of the role of fucoidan on dendritic cell (DC)-mediated T-cell cytotoxicity has revealed that the stimulation of CTLs was more effective in fucoidan-treated DCs as CTLs co-cultured with fucoidan-treated DCs exerted a high level of specific lysis of breast cancer cells [138].

4.6. Fucoidan action on Malignant Transformation *in Vitro* and *in Vivo*

Teas *et al.* fed rats with dietary seaweed (*Laminira*) for 55 days and administrated the carcinogen 7,12-dimethylbenz(a) anthracene intragastrically. Following 26 weeks monitoring, experimental rats showed a significant delay in the median time for tumor appearance (19 *vs.* 11 weeks in the control group) [139]. Transforming growth factor β1 (TGFβ1) is believed to promote tumor development and metastasis through epithelial to mesenchymal transition (EMT), a process that enables epithelial cells to migrate to distant areas during late stages of breast cancer development [140]. To trigger tumor progression, TGFβ1 recruits TGF receptors (TGFR) residing on the cell surface. The investigations of effects of fucoidan on TGFβ1-promoted carcinogenesis in MDA-MB-231 breast cancer cells have indicated that fucoidan decreased the expression of TGFRs and affected the downstream signaling molecules, which are involved in TGFβ1-mediated EMT [129,141].

5. Synergistic action of fucoidan as an anti-cancer agent

The ability of fucoidan to synergize with standard anti-cancer agents and/or reduce toxicity has recently been investigated. Ikeguchi *et al.* examined the synergistic effect of an HMW fucoidan with colorectal cancer chemotherapy agents; oxaliplatin plus 5-fluorouracil/leucovorin (FOLFOX) or irinotecan plus 5-fluorouracil/leucovorin (FOLFIRI). The test patients received 150 mL/day for 6 months of liquid that contained 4.05 g fucoidan. The patients were followed for approximately 15 months, and the survival rate of the patients who received fucoidan was longer than that of the control participants; however, the difference was not significant, probably due to the small numbers [142]. In a xenograft transplantation study, the effect of fucoidan alone or in combination with cyclophosphamide was examined on tumor growth. Nine days after the injection of Lewis lung carcinoma cells into mice, fucoidan from *Fucus evanescens* was administered to animals alone or combined with cyclophosphamide. The fucoidan group showed marked antitumor (33% tumor growth inhibition) and anti-metastatic (29% reduction of the number of metastases) activities. However, fucoidan did not exhibit a synergistic effect with cyclophosphamide on tumor growth but significantly decreased the lung cancer cells metastasis [143].

6. The contribution of fucoidan as an anticancer agent in various treatment plans

6.1. Fucoidan Suppresses Hypoxia-Induced Lymphangiogenesis and Lymphatic Metastasis in Mouse Hepatocarcinoma

In the present study, we demonstrated that fucoidan derived from *Undaria pinnatifida* sporophylls significantly inhibits the hypoxia-induced expression, nuclear translocation, and activity of HIF-1α, the synthesis, and secretion of VEGF-C and HGF, cell invasion and lymphatic metastasis in a mouse hepatocarcinoma Hca-F cell line. Fucoidan also suppressed lymphangiogenesis *in vitro* and *in vivo*. Also, accompanied by a reduction in the HIF-1α nuclear translocation and activity, fucoidan significantly reduced the levels of p-PI3K, p-Akt, p-mTOR, p-ERK, NF-κB, MMP-2, and MMP-9, but increased TIMP-1 levels. These results indicate strongly that the anti-metastasis and anti-lymphangiogenesis activities of fucoidan are mediated by suppressing HIF-1α/VEGF-C, which attenuates the PI3K/Akt/mTOR signaling pathways.

6.2. Fucoidan Elevates MicroRNA-29b to Regulate DNMT3B-MTSS1 Axis and Inhibit EMT in Human

Hepatocellular Carcinoma Cells

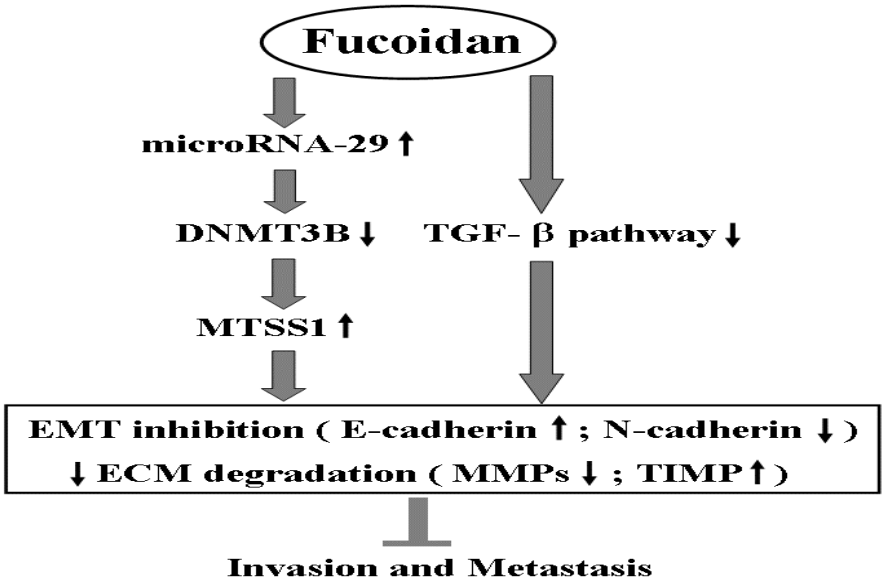

Figure 4: The proposed molecular mechanism of action related to the inhibition of invasion and metastasis of HCC cells by fucoidan. EMT: epithelial to mesenchymal transition; ECM: extracellular matrix. [141]

6.3. The Metabolic Activity of Individual Cell Types in Response to Fucoidan Dose for impairs angiogenesis in bone regeneration and osteosarcoma

The MTS assays were performed to examine a potential effect of fucoidan on the metabolic activities of MSC, MG63, and OEC in monocultures at day 10 using different concentrations of fucoidan. MTS absorbance values were depicted as relative changes of fucoidan treated groups compared to untreated controls (100%). For 100 g/mL, the metabolic activity of MSC and OECs showed only a slight, but no significant reduction in fucoidan treated group compared to controls. The metabolic

activity was further reduced in groups treated with higher concentrations of fucoidan. By first effects of fucoidan on OECs at a fucoidan concentration of 200 g/mL, OECs seemed to be more sensitive compared to MSC (significant effects observed at 300 g/mL) whereas MG63 seemed to tolerate higher concentrations of fucoidan (significant effects at 500 g/mL). Under these observations, all further experiments to assess angiogenesis, as well as osteogenesis, were performed with a fucoidan concentration of 100 g/mL [144,145,146].

7. Metabolism of Fucoidan

The enzyme responsible for fucoidan hydrolysis is Fucoidanase, has only been found in brown seaweed and marine microorganisms like some marine bacteria and fungi [147] and not in humans. In Tokita *et al.* study, the concentrations of fucoidan in the serum and urine were analyzed after oral administration. It was increased to 100ng/mL in serum and 1000 ng/mL in urine 3 hours after administration. The rate of absorption in the small intestine was hugely varied among the participants. The MW of fucoidan in serum was very much close similar to administered fucoidan indicating that fucoidan was not hydrolyzed by digestive enzymes [148]. Nevertheless, the MW of the fucoidan identify in urine was significantly lesser than the ingested fucoidan suggesting that fucoidan is degraded in the excretory system and possibly the kidney and not by intestinal enzymes or normal flora. Regarding the particular ligands by which fucoidan attach to the surface of the cell, several molecules have been implicated such as class A macrophage scavenger receptors for fucoidan attachment to macrophages [149] as well as adhesion molecules such as L-selectin and P-selectin [150] and integrins [151]. However, few reports have shown fucoidan mediates apoptosis through selectin-independent mechanism [106,142,147,148,149,150,151].

2. CONCLUSION

Fucoidans are superabundant polysaccharides with its exceptional biological properties. Their vegetal sources (including that fucoidans extracted from marine animals are a small part of the total amount), the lack of adverse effects, and the low price due to easy-to-handle production processes make them promising for Human health. Till now, fucoidans in nanomedicine have been mainly used for drug or protein delivery with some research about medical imaging; applications to regenerative medicine being still limited to bone tissue regeneration in animals. The utilization of fucoidans in nanomedicine will be legitimated only by a translational strategy from a reproducible starting material with a defined and reproducible structure. The biomedical market picture shows enormous growth and opportunity for fucoidans, as their potential added value can, in principle, justify the inherent risk related to the development and approval of such products. We also discussed the production of various NPs using fucoidan based polysaccharides and their applications in drug delivery. Seaweed polysaccharide-based NPs have exhibits promising results in delivering proteins, peptides, anti-cancer drugs, and other drugs with increased bioavailability and sustained release properties. In the last three decades, lots of scientific research have been carried out on seaweed

polysaccharides both *in vitro* and *in vivo*; these studies have demonstrated the high stability and biocompatibility as well as sustained drug release achievable by these systems, which will support their future use in clinical settings. The introduction of targeting moieties to polysaccharide-based NPs will improve their therapeutic efficacy while also reducing undesired side effects. The goal of cancer treatment is the eradication of tumor cells preferably with less damage to healthy tissues. Because of the side-effects of many present-day treatments, the use of natural substances of low toxicity is of interest. Many *in vitro* and *in vivo* studies have illustrated that fucoidan contains very strong anti-cancer bioactivity. Since fucoidan also possesses immunomodulatory effects, it is postulated that it may have protective effects against the progression of side effects when it is co-administered with chemotherapeutic agents and radiation. In this report, we also reviewed the underlying cellular mechanisms by which fucoidan causes cell death within tumor cells and proliferate the survival rate of tumor-bearing animal models by suppression of metastasis and angiogenesis. Due to the vast dissimilarity of fucoidan structure and to make future research reproducible, it is recommended that the evaluative bioactivity factors such as fucoidan content, sulfate content, monosaccharide constituents, and molecular weight be reported. Focusing on these parameters will be likely to lead to more consistent data and ultimately produce the required evidence to underpin clinical studies shortly.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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