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Are seaweed-derived fucoidans possible future anti-cancer agents?

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Abstract Is there a role for brown macroalgae-derived fucoidan in cancer therapeutics? This review discusses the in vitro, in vivo and clinical data concerning fucoidan and cancer. Fucoidans vary according to the species from which they are derived, making direct comparisons between studies difficult. Data from in vitro studies indicate direct activity against some cancer cell lines. In vivo studies indicate cancer inhibitory activity, which may also be partly attributable to increases in innate and specific immunity. A small number of preliminary clinical studies indicate activity and should be followed up. Lastly, to date, there is no reported research into potential interactions between chemotherapy and fucoidan. Other naturally derived pharmaceuticals are known to interfere with certain forms of chemotherapy, and this should not be overlooked during the development of fucoidan.

Keywords Fucan · Chemotherapy · Interaction · Cell lines · Clinical trial

Fucoidans are complex fucose-rich sulphated carbohydrates which can be extracted from brown seaweed (kelp) or echinoderms such as sea urchins. They are negatively charged water-soluble fibres, are of high molecular weight and are highly branched. There are a large number of molecular subtypes depending on their origin (Berteau and Mulloy 2003).

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In recent years, some laboratory and, to a lesser extent, clinical reports have suggested that fucoidans may have a role in the treatment of human cancer. This review will attempt to put these reports in perspective.

Fucoidans have been known for several decades to be biologically active (Fitton 2011). Apart from their purported anti-cancer activity discussed in this paper, they have been reported to have anticoagulant (Irhimeh et al. 2009), anti-thrombotic (Ustyuzhanina et al. 2013), immune modulating (Jin et al. 2014; Myers et al. 2011), pro-apoptotic (Park et al. 2013), viral inhibitory (Hayashi et al. 2008; Prokofjeva et al. 2013) and stem cell mobilising (Irhimeh et al. 2007) actions. However, as many of these studies were carried out with impure or chemically inexact fractions, it does not necessarily follow that fucoidan itself was the active agent.

The principle that pharmaceuticals may be derived from the plant kingdom is well established historically and long precedes the development of modern medicine. Furthermore, of specific relevance to the topic at hand, several highly effective contemporary cancer chemotherapeutic agents are of botanical origin. These include vincristine from the Madagascan periwinkle, a component of the curative treatment for acute lymphoblastic leukaemia (Whitelaw and Kim 1964); etoposide from the mandrake plant widely used to treat various cancers including lymphomas (Vogelzang et al. 1982); and taxanes from the Pacific yew tree, which are active against several metastatic cancers including that of the breast (Slichenmyer and Von Hoff 1991).

Fucoidans were first reported as possibly having anti-cancer activity in the 1980s (Teas et al. 1984). A recent search of the PubMed database (which lists over 23 million medical and biological scientific papers) using the topics ‘fucoidan’ and ‘cancer’ identified 142 relevant publications. The majority of these publications describe laboratory studies such as the addition of fucoidan to in vitro growth of cancer cell lines. Cancer cell lines that have been reported to be inhibited by

fucoidans include those of the liver (Yang et al. 2013), urinary bladder (Park et al. 2014), prostate (Boo et al. 2013), breast (Banafa et al. 2013), colon (Vishchuk et al. 2013) and lung (Lee et al. 2012).

A more realistic study (in the sense of potential relevance to clinical practice) showed that a fucoidan extract added to chemotherapy (cisplatin, tamoxifen or paclitaxel) on a breast cancer cell line induced cell growth inhibition, cell cycle modifications and enhanced apoptosis (Zhang et al. 2013).

The studies described above were all carried out in vitro. Published in vivo studies, which are likely to be of more relevance to clinical practice, have been small in number, but include some that show inhibition of transplantable cancers in mice. They include studies of breast (Xue et al. 2013) and lung cancers (Ale et al. 2011) and melanoma (Ale et al. 2011). One study showed that administration of fucoidan to mice reduced the development of metastases from breast cancer (Hsu et al. 2013).

Even fewer are clinical trials in humans. Of those that have been reported, that of Ikeguchi et al. (2011) is of particular note as it studied patients (n=20) with colorectal cancer who took standard chemotherapy with or without fucoidan. They reported that the patients who took fucoidan had significantly less fatigue and were able to tolerate more chemotherapy. The authors also claimed that those who took the fucoidan had prolonged survival, but this was not significant statistically. Unfortunately, the small size of this study limits its generalisability. In another Japanese study with 13 patients, 6 g fucoidan was taken daily for 6–13 months by subjects infected with HTLV-1, a retrovirus that can lead to adult T cell leukaemia. Viral load levels are positively associated with the risk of developing disease. A 42 % decrease in proviral load was noted over the study period. Once again, the small study size is noted (Araya et al. 2011).

In the 1960s, Italian researchers apparently used a fucoidan preparation intravenously as an experimental treatment for leukaemia, but the research was not followed up (Claudio and Standardo 1965).

Other reports of the use of fucoidans relevant to cancer therapeutics include chemotherapy loading of fucoidan nanoparticles (Lee et al. 2013), enhancement of T cell cytotoxicity (Hu et al. 2010) and use of fucoidan to promote antigen-specific T cell immune responses (Jin et al. 2014). In this last study, several effects of fucoidan were of potential relevance including promotion of maturation of spleen dendritic cells, induction of pro-inflammatory cytokine production, generation of Th1 and Tc1 cells and enhancement of antibody production and T cell responses in vivo. Postulated biological mechanisms by which fucoidans may bring about these effects include nitric oxide release, activation of NK cells (Ale et al. 2011), inhibition of EGFR, anti-caspase effects (Banafa et al. 2013), induction of apoptosis (Ale et al. 2011) and anti-angiogenesis (Ustyuzhanina et al. 2014).

A randomised placebo-controlled study in elderly subjects demonstrated increased immune responses to vaccination in subjects taking 300 mg fucoidan daily. Subjects took fucoidan for 4 weeks prior to vaccination. Antibody production was increased in the fucoidan group (Negishi et al. 2013). This heightened immune response to vaccination may be useful and may also reflect specific immune responses applicable in an oncology setting.

Unfortunately, there are as yet no quality trials of fucoidans in the treatment of human cancer. There are many reasons for this. One difficulty is that fucoidans have a wide diversity of composition (molecular structure) (Ustyuzhanina et al. 2014) depending on, amongst other things, species of seaweed, growth environment, season of harvesting, part of the plant from which the compound is obtained, the degree of sulphation and method of purification. Another issue is the question of the optimum route of administration. When taken orally, absorption is low and may only be of the order of 1 % or less depending on the type of fucoidan, but is not nil (Irhimeh et al. 2005; Tokita et al. 2010).

One aspect that has hardly been addressed is the issue of safety for oncology patients. While dietary brown seaweeds and some commercial fucoidans are categorised ‘generally regarded as safe (GRAS)’ in the USA based on their use as a foodstuff in the human diet for eons and are safely ingested by the general population, the question of possible interference with standard anti-cancer treatments is a separate issue about which evidence is lacking. The basis for raising this as a critical question are the precedents that (1) certain foodstuffs have been found to significantly increase the absorption of standard pharmaceuticals (e.g. grapefruit and various drugs (Bailey et al. 2013)), thus risking toxicity; and that (2) in the cancer chemotherapeutic field, the widely used ‘natural’ anti-depressant St. John’s wort interferes with the efficacy of the chemotherapy agent etoposide (Peebles et al. 2001). In this respect, a relevant recent paper has found interactions between uncharacterised dietary fucoidan and the anti-breast cancer drug lapatinib on growth and growth inhibition of certain cancer cell lines (Oh et al. 2014). This emphasises the need for further interaction studies to be carried out on well characterised fractions.

In summary, fucoidans are biologically active, high MW carbohydrates derived from brown marine macroalgae. Of relevance to cancer therapeutics in vitro, they have been shown to inhibit a wide range of cancer cell lines. A limited number of studies in mice indicate that anti-cancer effects are seen in vivo too. Unfortunately, so far, there are anecdotes, but no quality clinical trials of fucoidan use in cancer patients; clearly, further research is justified.

References

Ale MT, Maruyama H, Tamauchi H, Mikkelsen JD, Meyer AS (2011) Fucoidan from Sargassum sp. and Fucus vesiculosus reduces cell viability of lung carcinoma and melanoma cells in vitro and activates natural killer cells in mice in vivo. Int J Biol Macromol 49:331–336

Araya N, Takahashi K, Sato T, Nakamura T, Sawa C, Hasegawa D, Ando H, Aratani S, Yagishita N, Fujii R, Oka H, Nishioka K, Nakajima T, Mori N, Yamano Y (2011) Fucoidan therapy decreases the proviral load in patients with human T-lymphotropic virus type-1-associated neurological disease. Antivir Ther 16:89–98

Bailey DG, Dresser G, Arnold JM (2013) Grapefruit-medication interactions: forbidden fruit or avoidable consequences? CMAJ 185:309–316

Banafa AM, Roshan S, Liu YY, Chen HJ, Chen MJ, Yang GX, He GY (2013) Fucoidan induces G1 phase arrest and apoptosis through caspases-dependent pathway and ROS induction in human breast cancer MCF-7 cells. J Huazhong Univ Sci Technol Med Sci 33:717–724

Berteau O, Mulloy B (2003) Sulfated fucans, fresh perspectives: structures, functions, and biological properties of sulfated fucans and an overview of enzymes active toward this class of polysaccharide. Glycobiology 13:29R–40R

Boo HJ, Hong JY, Kim SC, Kang JI, Kim MK, Kim EJ, Hyun JW, Koh YS, Yoo ES, Kwon JM, Kang HK (2013) The anticancer effect of fucoidan in PC-3 prostate cancer cells. Mar Drugs 11:2982–2999

Claudio F, Standardo B (1965) Contributo clinico sperimentale sull'uso di un fitocolloide in oncologia. Minerva Med 367:3617–3622

Fitton JH (2011) Therapies from fucoidan; multifunctional marine polymers. Mar Drugs 9:1731–1760

Hayashi K, Nakano T, Hashimoto M, Kanekiyo K, Hayashi T (2008) Defensive effects of a fucoidan from brown alga Undaria pinnatifida against herpes simplex virus infection. Int Immunopharmacol 8: 109–116

Hsu HY, Lin TY, Hwang PA, Tseng LM, Chen RH, Tsao SM, Hsu J (2013) Fucoidan induces changes in the epithelial to mesenchymal transition and decreases metastasis by enhancing ubiquitin-dependent TGFbeta receptor degradation in breast cancer. Carcinogenesis 34:874–884

Hu Y, Cheng SC, Chan KT, Ke Y, Xue B, Sin FW, Zeng C, Xie Y (2010) Fucoidin enhances dendritic cell-mediated T-cell cytotoxicity against NY-ESO-1 expressing human cancer cells. Biochem Biophys Res Commun 392:329–334

Ikeguchi M, Yamamoto M, Arai Y, Maeta Y, Ashida K, Katano K, Miki Y, Kimura T (2011) Fucoidan reduces the toxicities of chemotherapy for patients with unresectable advanced or recurrent colorectal cancer. Oncol Lett 2:319–322

Irhimeh MR, Fitton JH, Lowenthal RM, Kongtawelert P (2005) A quantitative method to detect fucoidan in human plasma using a novel antibody. Methods Find Exp Clin Pharmacol 27:705–710

Irhimeh MR, Fitton JH, Lowenthal RM (2007) Fucoidan ingestion increases the expression of CXCR4 on human CD34+ cells. Exp Hematol 35:989–994

Irhimeh MR, Fitton JH, Lowenthal RM (2009) Pilot clinical study to evaluate the anticoagulant activity of fucoidan. Blood Coagul Fibrinolysis 20:607–610

Jin JO, Zhang W, Du JY, Wong KW, Oda T, Yu Q (2014) Fucoidan can function as an adjuvant in vivo to enhance dendritic cell maturation and function and promote antigen-specific T cell immune responses. PLoS One 9:e99396

Lee H, Kim JS, Kim E (2012) Fucoidan from seaweed *Fucus vesiculosus* inhibits migration and invasion of human lung cancer cell via PI3K-Akt-mTOR pathways. PLoS One 7:e50624

Lee KW, Jeong D, Na K (2013) Doxorubicin loading fucoidan acetate nanoparticles for immune and chemotherapy in cancer treatment. Carbohydr Polym 94:850–856

Myers SP, O'Connor J, Fitton JH, Brooks L, Rolfe M, Connellan P, Wohlmuth H, Cheras PA, Morris C (2011) A combined Phase I and II open-label study on the immunomodulatory effects of seaweed extract nutrient complex. Biogeosciences 5:45–60

Negishi H, Mori M, Mori H, Yamori Y (2013) Supplementation of elderly Japanese men and women with fucoidan from seaweed increases immune responses to seasonal influenza vaccination. J Nutr 143: 1794–1798

Oh B, Kim J, Lu W, Rosenthal D (2014) Anticancer effect of fucoidan in combination with tyrosine kinase inhibitor lapatinib. Evid Based Complement Alternat Med 2014:865375

Park HS, Hwang HJ, Kim GY, Cha HJ, Kim WJ, Kim ND, Yoo YH, Choi YH (2013) Induction of apoptosis by fucoidan in human leukemia U937 cells through activation of p38 MAPK and modulation of Bcl-2 family. Mar Drugs 11:2347–2364

Park HY, Kim GY, Moon SK, Kim WJ, Yoo YH, Choi YH (2014) Fucoidan inhibits the proliferation of human urinary bladder cancer T24 cells by blocking cell cycle progression and inducing apoptosis. Molecules 19:5981–5998

Peebles KA, Baker RK, Kurz EU, Schneider BJ, Kroll DJ (2001) Catalytic inhibition of human DNA topoisomerase IIalpha by hypericin, a naphthodianthrone from St. John's wort (Hypericum perforatum). Biochem Pharmacol 62:1059–1070

Prokofjeva MM, Imbs TI, Shevchenko NM, Spirin PV, Horn S, Fehse B, Zvyagintseva TN, Prassolov VS (2013) Fucoidans as potential inhibitors of HIV-1. Mar Drugs 11:3000–3014

Slichenmyer WJ, Von Hoff DD (1991) Taxol: a new and effective anticancer drug. Anticancer Drugs 2:519–530

Teas J, Harbison ML, Gelman RS (1984) Dietary seaweed (*Laminaria*) and mammary carcinogenesis in rats. Cancer Res 44:2758–2761

Tokita Y, Nakajima K, Mochida H, Iha M, Nagamine T (2010) Development of a fucoidan-specific antibody and measurement of fucoidan in serum and urine by sandwich ELISA. Biosci Biotechnol Biochem 74:350–357

Ustyuzhanina NE, Ushakova NA, Zyuzina KA, Bilan MI, Elizarova AL, Somonova OV, Madzhuga AV, Krylov VB, Preobrazhenskaya ME, Usov AI, Kiselevskiy MV, Nifantiev NE (2013) Influence of fucoidans on hemostatic system. Mar Drugs 11:2444–2458

Ustyuzhanina NE, Bilan MI, Ushakova NA, Usov AI, Kiselevskiy MV, Nifantiev NE (2014) Fucoidans: pro- or antiangiogenic agents? Glycobiology. doi:10.1093/glycob/cwu063

Vishchuk OS, Ermakova SP, Zvyagintseva TN (2013) The fucoidans from brown algae of Far-Eastern seas: anti-tumor activity and structure-function relationship. Food Chem 141: 1211–1217

Vogelzang NJ, Raghavan D, Kennedy BJ (1982) VP-16-213 (etoposide): the mandrake root from Issyk-Kul. Am J Med 72:136–144

Whitelaw DM, Kim HS (1964) Vincristine in the treatment of neoplastic disease. Can Med Assoc J 90:1385–1389

Xue M, Ge Y, Zhang J, Liu Y, Wang Q, Hou L, Zheng Z (2013) Fucoidan inhibited 4 T1 mouse breast cancer cell growth in vivo and in vitro via downregulation of Wnt/beta-catenin signaling. Nutr Cancer 65: 460–468

Yang L, Wang P, Wang H, Li Q, Teng H, Liu Z, Yang W, Hou L, Zou X (2013) Fucoidan derived from *Undaria pinnatifida* induces apoptosis in human hepatocellular carcinoma SMMC-7721 cells via the ROS-mediated mitochondrial pathway. Mar Drugs 11:1961–1976

Zhang Z, Teruya K, Yoshida T, Eto H, Shirahata S (2013) Fucoidan extract enhances the anti-cancer activity of chemotherapeutic agents in MDA-MB-231 and MCF-7 breast cancer cells. Mar Drugs 11:81–98