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[Continued on next page]

(54) Title: COMPOSITIONS AND METHODS FOR TREATING CELLULAR PROLIFERATIVE DISORDERS

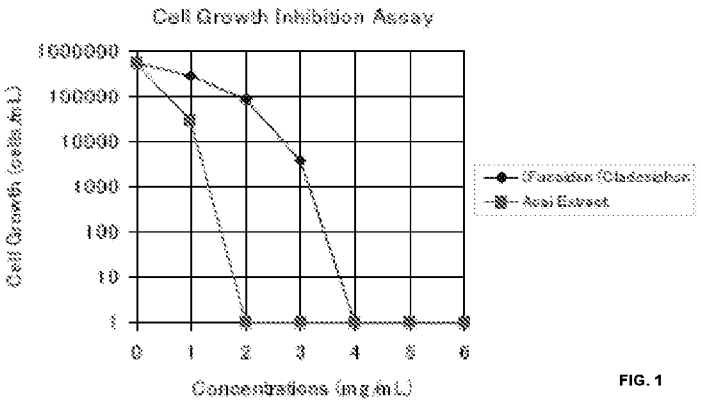

FIG. 1

(57) Abstract: The invention provides compositions and methods for treating cell proliferative disorders by administering a combination of fucoidan and natural antioxidant extracts. Also provided are compositions comprising a fucoidan and one or more natural antioxidant extracts.

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COMPOSITIONS AND METHODS FOR TREATING CELLULAR PROLIFERATIVE DISORDERS

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 61/122,293, filed December 12, 2008, and U.S. Provisional Application No. 61/181,584, filed May 27, 2009; each of which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

[0002] The compositions and methods described herein relate generally to medicine and the treatment of cellular proliferative disorders, and more particularly, to compositions and methods for treating such disorders.

BACKGROUND INFORMATION

[0003] Cancer remains one of the most significant health problems world wide, and ranks second only to heart disease as a leading cause of death in the United States. Cancer, for the most part, involves uncontrolled proliferation and altered differentiation of the involved cells. Although the causes of most cancers are not identified and the mechanisms remain obscure, human, epidemiological, and experimental efforts have generated considerable information on the attributes of cancer. Many factors that are normally important in cell growth and differentiation in healthy individuals can contribute to the genesis or progression of the carcinogenic process in certain disease states.

[0004] Although progress is being made in understanding the biochemical and genetic mechanisms responsible for many cancers, very few successful treatment options currently exist. Unfortunately, even the most effective therapies have significant negative systemic side effects and toxicity that can be intolerable to the patient. Typical negative side effects can include, for example, nausea and vomiting, hair loss, anemia, depression of the immune system leading to infection and sepsis, and other toxic effects. Because these effects on a patient can sometimes be as debilitating as the disease being treated, the effectiveness of these current therapies is severely limited.

SUMMARY OF THE INVENTION

[0005] Provided herein, in some embodiments, are formulations and methods of treating a variety of cellular proliferative disorders such as cancer. Provided herein are methods for treating a cellular proliferative disorder in a subject. Also provided are compositions of fucoidan and a natural antioxidant extract. Also provided herein are methods of treating a cellular proliferative disorder in a subject by administering to the subject a combination of fucoidan

and a natural antioxidant extract. In one embodiment, the cellular proliferative disorder is cancer such as, but not limited to, melanoma, glioma, medulloblastoma, prostate cancer, esophageal cancer, lung cancer, breast cancer, ovarian cancer, testicular cancer, liver cancer, kidney cancer, renal cancer, spleen cancer, bladder cancer, colorectal and/or colon cancer, cervical cancer, pancreatic cancer, gall bladder cancer, stomach cancer, head and neck cancer, carcinoma, sarcoma, hepatoma, lymphoma, mycosis fungoides, leukemia, and a brain tumor. In another embodiment, the cellular proliferative disorder is a neurodegenerative disorder such as, but not limited to, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, Parkinson's disease, Schizophrenia, and Prion diseases. In another embodiment, the cellular proliferative disorder is a neovascular disorder such as, but not limited to, diabetic retinopathy, age-related macular degeneration, rheumatoid arthritis, osteoarthritis, glaucoma, keloids, corneal graft rejection, wound granularization, angiofibroma, Osler-Webber Syndrome, and myocardial angiogenesis. In another embodiment, the fucoidan and the natural antioxidant extract are administered simultaneously. In another embodiment, the fucoidan and the natural antioxidant extract are administered sequentially, such as, for example, the fucoidan is administered up to one, two, or three days prior to administration of the natural antioxidant extract.

[0006] Also provided herein are methods for reducing or inhibiting growth of hyperproliferative cells and/or ameliorating symptoms associated with hyperproliferative cells in a subject by administering to the subject a combination of fucoidan and a natural antioxidant extract. In one embodiment, the hyperproliferative cells are derived from a cellular proliferative disorder such as, but not limited to, melanoma, glioma, medulloblastoma, prostate cancer, esophageal cancer, lung cancer, breast cancer, ovarian cancer, testicular cancer, liver cancer, kidney cancer, renal cancer, spleen cancer, bladder cancer, colorectal and/or colon cancer, cervical cancer, pancreatic cancer, gall bladder cancer, stomach cancer, head and neck cancer, carcinoma, sarcoma, hepatoma, lymphoma, mycosis fungoides, leukemia, and a brain tumor. In another embodiment, the hypoproliferative cells are derived from a cellular proliferative disorder such as, but not limited to, anemia and ischemia. In another embodiment, the fucoidan and the natural antioxidant extract are administered simultaneously. In another embodiment, the fucoidan and the natural antioxidant extract are administered sequentially, such as, for example, the fucoidan is administered up to one, two, or three days prior to administration of the natural antioxidant extract.

[0007] Provided herein, in some embodiments, are methods of delaying and/or inhibiting growth of a hyperproliferative cell by contacting the cell with a combination of fucoidan and a natural antioxidant extract. In one embodiment, the hyperproliferative cells are derived from a cellular proliferative disorder such as, but not limited to, melanoma, glioma,

medulloblastoma, prostate cancer, esophageal cancer, lung cancer, breast cancer, ovarian cancer, testicular cancer, liver cancer, kidney cancer, renal cancer, spleen cancer, bladder cancer, colorectal and/or colon cancer, cervical cancer, pancreatic cancer, gall bladder cancer, stomach cancer, head and neck cancer, carcinoma, sarcoma, hepatoma, lymphoma, mycosis fungoides, leukemia, and a brain tumor. In one embodiment, the method is performed *in vivo*. In another embodiment, the method is performed *in vitro*. In another embodiment, the fucoidan and the natural antioxidant extract are administered simultaneously. In another embodiment, the fucoidan and the natural antioxidant extract are administered sequentially, such as, for example, the fucoidan is administered up to one, two, or three days prior to administration of the natural antioxidant extract.

[0008] Further provided herein are methods of identifying hyperproliferative cells amenable to treatment with a combination of fucoidan and a natural antioxidant extract. The method includes detecting inhibited cell proliferation in a sample of hyperproliferative cells as compared to cell proliferation in a corresponding untreated sample, thereby identifying a cell proliferative disorder amenable to treatment with fucoidan in combination with a natural antioxidant extract. In one embodiment, the method is performed *in vivo*. In another embodiment, the method is performed *in vitro*.

[0009] The natural antioxidant extract used in any of the aformentioned methods is a combination of one or more natural antioxidant extracts. Exemplary natural antioxidant extracts include one or more extracts selected from acai berry extract, green tea extract, coffee bean extract, blueberry extract, grape extract, cherry extract, blackberry extract, cranberry extract, raspberry extract, strawberry extract, huckleberry extract, lemon extract, melon extract, kiwi extract, grapefruit extract, orange extract, apple extract, apricot extract, prune extract, watermelon extract, mangosteen extract, plum extract, date extract, banana extract, tomato extract, tumeric extract, broccoli extract, green barley leaf extract, red chili extract, carrot extract, and safran. In some embodiments, where a sample of cells is contacted with a composition described herein, the sample of cells is any sample, including, for example, a tumor sample obtained by biopsy of a subject having the tumor, a tumor sample obtained by surgery (*e.g.*, a surgical procedure to remove and/or debulk the tumor), or a sample of the subject's bodily fluid.

[0010] Also provided herein are compositions comprising fucoidan and one or more natural antioxidant extracts. In one embodiment, such compositions further include a pharmaceutically and/or neutraceutically acceptable carrier. The preparation is in the form of a tablet, capsule, granule, powder, suspension, emulsion, elixir or solution.

INCORPORATION BY REFERENCE

[0011] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] Figure 1 is an illustrative graphical diagram showing the results from a cell growth inhibition assay comparing concentrations of fucoidan and acai berry extract.

[0013] Figure 2 is an illustrative graphical diagram showing the results from a cell growth inhibition assay demonstrating synergy of inhibition with combinations of fucoidan and acai berry extract.

[0014] Figure 3 is an illustrative graphical diagram showing the results from a cell growth inhibition assay demonstrating synergy of inhibition with combinations of fucoidan/green tea extract and fucoidan/coffee bean extract.

[0015] Figure 4 is an illustrative graphical diagram showing the results from a cell growth inhibition assay demonstrating synergy of inhibition with combinations of fucoidan and blueberry extract.

[0016] Figure 5 is an illustrative graphical diagram showing the results from a negative control cell growth inhibition assay showing combinations of fucoidan and dried red grape extract.

[0017] Figure 6 is an illustrative graphical diagram showing the results from an apoptosis attenuation assay demonstrating a reduction in apoptosis with fucoidan.

[0018] Figure 7 is an illustrative graphical diagram showing the results from an apoptosis attenuation assay demonstrating a reduction in apoptosis with a natural antioxidant.

[0019] Figure 8 is an illustrative graphical diagram showing the results from an apoptosis attenuation assay demonstrating synergistic activity with fucoidan and green tea extract.

[0020] Figure 9 is an illustrative graphical diagram showing the results from an apoptosis attenuation assay demonstrating synergistic activity with fucoidan and green tea extract.

DETAILED DESCRIPTION OF THE INVENTION

[0021] Fucoidan is a natural product that is obtained as an extract from brown algae such as nemacystus, undaria seaweeds, and sea tangles. Structurally, fucoidan is a sulfated polysaccharide whose primary constituent sugar is fucose. Fucoidan has become a desirable additive for food, cosmetic, and pharmaceutical preparations based on reports of the various pharmacologic properties of fucoidan. For example, fucoidan has been reported to have antitumor effects (Maruyama, F. et al. *Kitasato Arch. Of Exp. Med.,* 60:105-121 (1987), Ellouali, M. et al., *Anticancer Res.,* 13:2011-2019 (1993)), antiulcer effects (Japanese Patent

Publication Nos. 7 (1995)-138166 and 10 (1998)-59860), antivirus effect (Bana, M. et al, *Antimicrob. Agents Chemother.*, 32:1742-1745 (1988), Bana, et al., *Antiviral. Res.* 9:335-343 (1988), and Clark, G.F. et al, *FASEB J.*, 6:233 (1992)); anti-inflammatory effects (Japanese Patent Publication No. 8 (1996J-92103, Heinzelmann, M. et al., *Infect. Immun.*, 66:5842-5847 (1998), Gan, L. et al., *Invest. Ophthalmol. Vis. Sci.*, 40:575-581 (1999)); anticoagulant effects (CoUiec, S. et al., *Phytochemistry*, 35:697-700 (1994), Millet, J. et al., *Thrombo, Haemost.*, 81:391-395 (1999)); immunopotentiating effects (Japanese Patent Publication No. 11 (1999J-228602); Type I antiallergic effects (Japanese Patent Publication No. 10 (1998J-72362); and antihyperlipernic effects.

[0022] There is, therefore, a need for new methods and compositions for treating cellular proliferative disorders such as cancer. In particular, there is a need for treatment compositions and methods capable of inhibiting unregulated growth and differentiation of cancer cells.

[0023] Described herein are formulations and methods of treating a variety of cellular proliferative disorders such as cancer. Described herein are methods for inhibiting growth of hyperproliferative cells, stimulating growth of hypoproliferative cells, and treating such disorders related thereto. Also provided are compositions of fucoidan and a natural antioxidant extract.

[0024] As used in this specification and the appended claims, the singular forms "a", "an", and "the" include plural references unless the context clearly dictates otherwise. Thus, for example, references to "the method" includes one or more methods, and/or steps of the type described herein which will become apparent to those persons skilled in the art upon reading this disclosure and so forth.

[0025] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art.

[0026] Fucoidan is a sulfated polysaccharide, which is found in abundance in the slippery texture of Brown Algae. The first isolation of fucoidan from marine algae was reported by Dr. Killing in 1913. Algal fucoidan was found to be present in several orders of brown algae (Phaeophyceae), mainly Fucales and Laminariales, but also in Chordariales, Dictyotales, Dictyosiphonales, Ectocarpales and Scytosiphonales. Fucoidan, often called fucans, is composed mainly of sulfated L-fucose, but is also made of various proportions of different sugar residues such as fucose, galactose, xylose and uronic acids. As used herein, the term "fucoidan" is used to describe a sulfated complex polysaccharide (fucan) extracted from brown algae containing 20% to 60% of L-fucose. Fucoidan is found in various species of brown seaweed including and not limited to kombu, limu moui, bladderwrack, wakame, mozuku, hijiki, Rhodophyceae such as common laver (Porphyra tenera), Gelidium

cartiliagimeum and Gracilaria confervoides; Chlorophyceae such as Ulva lactuca; and Phaeophyceae such as Ecklonia cava, Eisenia arboria var. bicyclis, Nemacystus dicipiens, Hizikia fusiforme, undaria seaweeds (e.g., Undaria pinnatifida), Kjellmaniella crassifolia, sea tangles (e.g., Laminaria japonica), and animal forms including, but not limited to, sea cucumber. The term includes F-fucoidan, which is >95% composed of sulfated esters of fucose, and U-fucoidan, which is approximately 20% glucuronic acid. Methods of extracting fucoidan from the cell wall of brown algae are described in, for example, Japanese Patent Publication Nos. 10 (1998)-195105; 2002-220402; 2002-262788, and in U.S. Publication No. 20070087996, incorporated herein by reference in its entirety.

[0027] As used herein, the term "algae" refers to any of an organism classified into the Protista kingdom and is a chlorophyll-bearing organism that can survive in both salt- and freshwater, reproduce from a unicellular spore, and ranges in size from a single cell to giant kelp, including most kinds of seaweed. The term "brown algae" refers to any organism classified into the Protista kingdom and further into the Phaeophyta division.

[0028] Although fucoidans have been known for some time to act as modulators of coagulation, as have other algal polysaccharides, fucoidans from brown algae were regarded only as a potential source of L-fucose for many years. Recently, a search for new biological modifiers has raised interest in sulfated polysaccharides. Fucoidans have been proposed as alternatives to the anti-coagulant Heparin, which is prepared from mammalian mucosa because, being of vegetable origin, fucoidans are less likely to contain infectious agents, such as viruses or prions. Like heparin, however, it has been shown that fucoidans affect many cellular-biological and biochemical activities, such as anti-inflammation, anti-virus/parasites infection, anti-obesity, anti-cancer, immune enhancement, antithrombogenic, anti-complement effect, protection of vascular system, anti-helicobacter pylori, anti-ulcer, anti-renal stone formation, protection of liver function, beneficial for wound healing, anti-oxidative activities, anti-neuropathy, etc. In addition, fucoidan has recently been demonstrated to mobilize hematopoetic stem cells, which contributes to regenerative medicine.

[0029] Accordingly, in one aspect, provided herein are methods of treating a cellular proliferative disorder in a subject. The method includes administering to the subject in need of such treatment a combination of fucoidan and one or more natural antioxidant extracts. In some embodiments, a combination of fucoidan and one or more natural antioxidant extracts provides improved therapeutic benefit (e.g., greater or more rapid reduction in cell proliferation) compared to the administration of fucoidan alone or one or more antioxidant extracts alone. In some embodiments, a combination of fucoidan and one or more natural antioxidant extracts provides improved therapeutic benefit (e.g., enhanced anti-apoptotic

activity) compared to the administration of fucoidan alone or one or more antioxidant extracts alone. In some embodiments, a combination of fucoidan and one or more natural antioxidant extracts provides improved therapeutic benefit (e.g., increased apoptosis) compared to the administration of fucoidan alone or one or more antioxidant extracts alone.

[0030] In some embodiments, administration of a combination of fucoidan and one or more natural antioxidant extracts produces a synergistic effect (e.g.., a more potent therapeutic effect) compared to treatment with one of the components alone. For example, as shown in Example II, acai berry extract enhances the activity of fucoidan on cancer cells by inhibiting cell growth and inducing apoptosis. In some embodiments, administration of a combination of fucoidan and one or more natural antioxidant extracts produces a synergistic effect (e.g., a more potent therapeutic effect) at lower doses of each component compared to treatment with one of the components alone.

[0031] In some embodiments, a cell proliferative disorder described herein is caused by oxidative stress to a cell and/or tissue. In some instances, oxidative stress contributes to generation of free radicals (e.g., reactive oxygen species including and not limited to peroxide, superoxide or the like) that cause cellular and/or tissue injury including, for example, apoptosis and/or hyperproliferation. In some instances, apoptosis that is induced by oxidative stress triggers a cascade of reactions in cells and/or tissues that lead to symptoms of neurodegenerative disorders including and not limited to Lou Gehrig's disease (aka MND or ALS), Parkinson's disease, Alzheimer's disease, Huntington's disease or any other neurodegenerative disorders described herein. In some instances, apoptosis that is induced by oxidative stress triggers a cascade of reactions in cells and/or tissues that lead to symptoms of certain cardiovascular disease. In some instances, oxidation of Low Density Lipids in the vascular endothelium is a precursor to plaque formation and subsequent manifestation of disorders of the vasculature, including defective angiogenesis, neovascular and/or cardiovascular disorders. In some instances, apoptosis that is induced by oxidative stress triggers a cascade of reactions in cells and/or tissues and plays a role in the ischemic cascade. In some instances, apoptosis that is induced by oxidative stress triggers a cascade of reactions in cells and/or tissues and leads to symptoms of chronic fatigue syndrome. In some instances, hyperproliferation that is induced by oxidative stress triggers a cascade of reactions in cells and/or tissues and leads to cancers including and not limited to melanoma, leukemia, or any other cancers described herein. Thus oxidative stress-induced and/or free radical-induced apoptosis and/or hyperproliferation of cells underlies the etiology of a wide range of disorders including any disorders described herein.

[0032] In some embodiments, administration of a combination of fucoidan and one or more antioxidant extracts produces a synergistic effect that reduces cellular oxidative stress and/or

generation of free radicals. Advantageously, in some embodiments, administration of a combination of fucoidan and one or more antioxidant extracts produces a synergistic effect that reduces or delays the progression of cell proliferative disorders. In some other embodiments, administration of a combination of fucoidan and one or more antioxidant extracts produces a synergistic anti-apoptotic effect.

[0033] As used herein, the term "cell proliferative disorder" refers to a hyperproliferative disorder or a hypoproliferative disorder. As used herein, a "hyperproliferative disorder" refers to any state or condition that results in an abnormal increase in the number of cells as a result of cell growth and cell division, as compared to the number of cells resulting from cell growth or cell division of a corresponding normal cell. As used herein, a "hypoproliferative disorder" refers to any state or condition that results in the destruction, shedding, or inadequate growth/proliferation or excessive cell death (*e.g.*, apoptosis or necrosis) of a particular cell type, as compared to the number of cells resulting from cell growth, cell division, or cell death of a corresponding normal cell. As such, a "hyperproliferative cell" refers to any cell that undergoes an abnormal increase in the number of cells as a result of cell growth and cell division, as compared to the number of cells resulting from cell growth or cell division of a corresponding normal cell. Likewise, a "hypoproliferative cell" refers to any cell that undergoes increased destruction, increased shedding, decreased growth/proliferation, or excessive cell death, as compared to a corresponding normal cell.

[0034] In one embodiment, a cell proliferative disorder as described herein is a neoplasm. Such neoplasms are either benign or malignant. The term "neoplasm" refers to a new, abnormal growth of cells or a growth of abnormal cells that reproduce more aggressively than normal. A neoplasm creates an unstructured mass (a tumor) which can be either benign or malignant. The term "benign" refers to a tumor that is noncancerous, *e.g.*, its cells do not invade surrounding tissues or metastasize to distant sites. The term "malignant" refers to a tumor that is cancerous, metastastic, invades contiguous tissue or is no longer under normal cellular growth control. As such, in one embodiment, the cell proliferative disorder is cancer. Exemplary cancers that can be treated by the methods and compositions described herein include, but are not limited to, melanoma, glioma, teratoma, medulloblastoma, seminoma, prostate cancer, esophageal cancer, lung cancer, breast cancer, ovarian cancer, testicular cancer, liver cancer, kidney/renal cancer, cervical cancer, pancreatic cancer, gall bladder cancer, stomach cancer, spleen cancer, bladder cancer, colorectal cancer and/or colon cancer, head and neck cancer, heart cancer, carcinoma, sarcoma, hepatoma, lymphoma, mycosis fungoides, leukemia, and brain tumors. Also included as an exemplary cancer is Li-Fraumeni syndrome, which is linked to germline mutations of the p53 tumor

suppressor gene that normally helps control cell growth, thereby increasing a subject's susceptibility to cancer.

[0035] In another embodiment, a cell proliferative disorder as described herein is a neurodegenerative disorder. The term "neurodegenerative disorder" as used herein includes any disorder in which cells of the retina, brain and spinal cord are lost. Exemplary neurodegenerative disorders that can be treated by the methods and compositions described herein include, but are not limited to, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, Parkinson's disease, Schizophrenia, alcoholism, Alexander's disease, Alper's disease, Ataxia telangiectasia, Batten disease, bovine spongiform encephalopathy (BSE), canavan disease, cockayne syndrome, corticobasal degeneration, Creutzfelft-Jakob disease, HIV-associated dementia, ischemia, Kennedy's disease, Krabbe's disease, Lewy body dementia, spinocerebeliar ataxia, multiple sclerosis, multiple system atrophy, narcolepsy, neuroborreliosis, palizaeus-merzbacher disease, Pick's disease, primary lateral sclerosis, Prion diseases, Refsum's disease, Schildr's disease, Sanhoff's disease, subacute combined degeneration of spinal cord secondary to pernicios aneamia, spinocerebellar ataxia, spinal muscular atrophy, Steele-Richardson-Oliszewski disease, tabes dorsalis, geographic atrophy and retinary pigmentary degeneration.

[0036] Angiogenesis or the formation of new vasculature is a fundamental process by which new blood vessels are formed. It participates in essential physiological events, such as reproduction development and wound healing. Under normal conditions, angiogenesis is highly regulated. However, many diseases are driven by persistent unregulated angiogenesis. In rheumatoid arthritis, for example, new capillary blood vessels invade the joints and destroy the cartilage. In diabetic retinopathy, new capillaries in the retina invade the vitreous, bleed, and cause blindness. As such, in another embodiment, a cell proliferative disorder as described herein is a neovascular disorder and/or a neovascularization-associated disorder. The term "neovascular disorder" refers to any disorder characterized by the formation of functional microvascular networks with red blood cell perfusion. Exemplary neovascular disorders that can be treated by the methods and compositions described herein include, but are not limited to, solid tumors, diabetic retinopathy, age-related macular degeneration, rheumatoid arthritis, osteoarthritis, glaucoma, keloids, corneal graft rejection, wound granularization, angiofibroma, Osler-Webber Syndrome, myocardial angiogenesis, Ataxia Telangiectasia, vasoagglutination, vascular deformation, endotheioma, hypertrophy, progeria, psoriasis, sarcoma, calorification, arthritis, emphysema, bronchitis, obesity, and cataracts.

[0037] In another embodiment, a cell proliferative disorder as described herein is a hypoproliferative disorder. Exemplary hypoproliferative disorders include, but are not limited to, anemia and ischemia.

[0038] As used herein the term "corresponding normal cells" or "corresponding normal sample" refers to cells, or a sample from a subject that is free of the cell proliferative disorder being treated and is from the same organ and of the same type as the cells being examined. In one embodiment, the corresponding normal cells comprise a sample of cells obtained from a healthy individual that does not have a cell proliferative disorder. Such corresponding normal cells can, but need not be, from an individual that is age-matched and/or of the same sex as the individual providing the cells being examined.

[0039] As used herein the term "administration" or "administering" are defined to include an act of providing a compound or composition described herein to a subject in need of treatment. The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually orally or by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticulare, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion. The phrases "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" as used herein mean the administration of a compound, drug or other material other than directly into the central nervous system, such that it enters the subject's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

[0040] The term "therapeutically effective amount" or "effective amount" means the amount of a compound or composition that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

[0041] As used herein, the term "ameliorating" or "treating" means that the clinical signs and/or the symptoms associated with a particular cell proliferative disorder are lessened as a result of the actions performed. The signs or symptoms to be monitored will be characteristic of a particular cell proliferative disorder and will be well known to the skilled clinician, as will the methods for monitoring the signs and conditions.

[0042] As used herein, the terms "reduce" and "inhibit" are used interchangeably.

[0043] The term "subject" as used herein refers to any individual or patient to which the subject methods are performed. Generally the subject is human, although as will be appreciated by those in the art, the subject is an animal. Thus other animals, including mammals such as rodents (including mice, rats, hamsters and guinea pigs), cats, dogs, rabbits, farm animals

including cows, horses, goats, sheep, pigs, etc., and primates (including monkeys, chimpanzees, orangutans and gorillas) are included within the definition of subject.

[0044] In another aspect, provided herein are methods of inhibiting growth of a hyperproliferative cell. The method includes contacting the cell with fucoidan in combination with one or more natural antioxidant extracts. In another aspect, provided herein are methods of ameliorating hyperproliferative cells in a subject. The method includes administering to the subject in need of such treatment a therapeutically effective dosage of fucoidan in combination with one or more natural antioxidant extracts.

[0045] In another aspect, provided herein are methods of stimulating growth of a hypoproliferative cell. The method includes contacting the cell with fucoidan in combination with one or more natural antioxidant extracts. In another aspect, provided herein are methods of ameliorating hypoproliferative cells in a subject. The method includes administering to the subject in need of such treatment a therapeutically effective dosage of fucoidan in combination with one or more natural antioxidant extracts.

[0046] As used herein, a "natural antioxidant extract" refers to the extract of any organic substance that is capable of counteracting the damaging effects of oxidation in animal tissues. Exemplary natural antioxidant extracts include, but are not limited to, acai berry extract, green tea extract, coffee bean extract, and blueberry extract. Additional organic substances that provide an extract useful in the methods and compositions described herein include, but are not limited to, oranges, apples, tomatoes, pomegranates, lemons, pears, grapes, blueberries, cherries, blackberries, cranberries, raspberries, strawberries, huckleberries, lemons, melons, kiwis, grapefruits, oranges, apricots, prunes, watermelons, mangosteens, plums, dates, bananas, broccoli, green barley leaves, red chili, carrot, tumeric and safran.

[0047] In some embodiments, one or more of the natural antioxidant extracts contain catechins. Catechins are polyphenolic antioxidant plant metabolites. They belong to the family of flavonoids and, to be more specific, flavan-3-ols. These compounds are abundant in teas derived from the tea-plant *Camellia sinensis* as well as in some cocoas and chocolates (made from the seeds of *Theobroma cacao*). The health benefits of catechins have been studied extensively in humans and in animal models. Reduction in atherosclerotic plaques was seen in animal models, as was reduction in carcinogenesis *in vitro*. As such, the methods described herein are also compatible with using catechins in addition to, or in place of the natural antioxidant extract.

[0048] All methods further include the step of bringing the active ingredient(s) (*e.g.*, fucoidan alone or in combination with one or more natural antioxidant extracts) into association with a pharmaceutically and/or neutraceutically acceptable carrier, which constitutes one or more accessory ingredients. As such, also provided herein are compositions for use in treating

subjects having one or more cell proliferative disorders. In one embodiment, the composition includes as the active constituent a therapeutically effective amount of fucoidan in combination with one or more natural antioxidant extracts together with a pharmaceutically and/or neutraceutically acceptable carrier, diluent of excipients.

[0049] Pharmaceutically and/or neutraceutically acceptable carriers useful for formulating a composition for administration to a subject are well known in the art and include, for example, aqueous solutions such as water or physiologically buffered saline or other solvents or vehicles such as glycols, glycerol, oils such as olive oil or injectable organic esters. A pharmaceutically and/or neutraceutically acceptable carrier can contain physiologically acceptable compounds that act, for example, to stabilize or to increase the absorption of the conjugate. Such physiologically acceptable compounds include, for example, carbohydrates, such as glucose, sucrose or dextrans, antioxidants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins or other stabilizers or excipients. One skilled in the art would know that the choice of a pharmaceutically and/or neutraceutically acceptable carrier, including a physiologically acceptable compound, depends, for example, on the physico-chemical characteristics of the therapeutic agent and on the route of administration of the composition, which can be, for example, orally or parenterally such as intravenously, and by injection, intubation, or other such method known in the art. The composition also can contain a second (or more) compound(s) such as a diagnostic reagent, nutritional substance, toxin, or therapeutic agent, for example, a cancer chemotherapeutic agent and/or vitamin(s).

[0050] As such, in certain embodiments, fucoidan is administered in powder, liquid, or solid form. Likewise, the natural antioxidant extract is administered in powder, liquid, or solid form. In one embodiment, the fucoidan and the natural antioxidant extract are administered in identical forms (*e.g.*, powder form). In another embodiment, the fucoidan and the natural antioxidant extract are administered in different forms. For example, the fucoidan is administered as a tablet or a capsule containing a powdered form thereof, and the natural antioxidant extract is administered in liquid form (*e.g.*, in juice or mixed in water).

[0051] Formulations described herein that are suitable for oral administration are presented as discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of the active compound in the form of a powder or granules; or as a suspension of the active compound in an aqueous liquid or non-aqueous liquid such as a syrup, an elixir, an emulsion or a draught.

[0052] Accordingly, in another aspect, provided herein is the use of fucoidan in combination with one or more natural antioxidant extracts, as herein defined, for the manufacture of a medicament useful in human medicine for treating cell proliferative disorders. Such a

medicament is also useful for inhibiting growth of hyperproliferative cells and/or ameliorating symptoms associated with hyperproliferative cells in a subject. Similarly, such a medicament is also useful for stimulating growth of hypoproliferative cells and/or ameliorating symptoms associated with hypoproliferative cells in a subject. Thus, in another aspect, the methods described herein are further combined with other compounds, compositions or therapeutic regimens that are known to inhibit angiogenesis, neovascularization or excessive cellular proliferation such as that which occurs in cancer. Such therapies include, but are not limited to chemotherapy, radiation therapy and the administration of anti-angiogenic compounds.

[0053] The total amount of a compound or composition to be administered in practicing a method described herein is administered to a subject as a single dose, either as a bolus or by infusion over a relatively short period of time, or can be administered using a fractionated treatment protocol, in which multiple doses are administered over a prolonged period of time (*e.g.*, once daily, twice daily, etc.). One skilled in the art would know that the amount of fucoidan and the amount of natural antioxidant extract to treat cell proliferative disorders as herein defined depends on many factors including the age and general health of the subject as well as the route of administration and the number of treatments to be administered. In view of these factors, the skilled artisan would adjust the particular doses and concentrations as necessary. In general, the formulation of the composition and the routes and frequency of administration are determined, initially, using Phase I and Phase II clinical trials.

[0054] Accordingly, in certain embodiments, the methods described herein include an intervalled or sequential treatment regimen. It was observed that accumulation of fucoidan in a subject allows for administration of fucoidan followed by administration of the natural antioxidant extract within 2-5 days of administering the fucoidan. As such, in one embodiment, the fucoidan and the natural antioxidant extract are administered sequentially. For example, in one embodiment, the fucoidan is administered up to three days prior to administering the natural antioxidant extract. In another exemplary embodiment, the fucoidan is administered one or two days prior to administering the natural antioxidant extract. In another embodiment, the fucoidan and the natural antioxidant extract are administered simultaneously.

[0055] The ratio of fucoidan to natural antioxidant extract is anywhere from 5:1 to 1:5. For example, in one embodiment, the ratio of fucoidan to natural antioxidant extract is 2:1, 1:2, or 1:1.

[0056] In another aspect, provided herein are methods of identifying hyperproliferative cells (*e.g.*, cancer cells) and/or hypoproliferative cells (*e.g.*, anemic cells) that are amenable to the treatments described herein. The method can be performed, for example, by contacting a

sample of cells to be treated with a composition described herein and determining a change in the total cell number as a result of the contact, as compared to the total cell number of an untreated cell. Detection of decreased cell number (*i.e.*, inhibition of cell proliferation) in the hyperproliferative cells as compared to the untreated cells indicates that the cells can benefit from treatment. Likewise, detection of increased cell number (*i.e.*, stimulation of cell proliferation) in the hypoproliferative cells as compared to the untreated cells indicates that the cells can benefit from treatment. As such, the methods described herein are useful for providing a means for practicing personalized medicine, wherein treatment is tailored to a subject based on the particular characteristics of the hyperproliferative or hypoproliferative cells in the subject.

[0057] The sample of cells examined according to the present method can be obtained from the subject to be treated, or can be cells of an established cancer cell line or known hyperproliferative and/or hypoproliferative cells of the same type as that of the subject. In one embodiment, the established cell line can be one of a panel of such cell lines, wherein the panel can include different cell lines of the same type of disease and/or different cell lines of different diseases associated with hyperproliferation or hypoproliferation. Such a panel of cell lines can be useful, for example, to practice the present method when only a small number of cells can be obtained from the subject to be treated, thus providing a surrogate sample of the subject's cells, and also can be useful to include as control samples in practicing the present methods.

[0058] Once disease is established and a treatment protocol is initiated, the methods described herein are repeated on a regular basis to evaluate whether the hyperproliferative or hypoproliferative cells in the subject begin to show resistance to the therapy. The results obtained from successive assays are used to show the efficacy of treatment over a period ranging from several days to months. Accordingly, the invention is also directed to methods for monitoring a therapeutic regimen for treating a subject having a cell proliferative disorder. A comparison of the total cell number prior to and during therapy indicates the efficacy of the therapy. Therefore, one skilled in the art will be able to recognize and adjust the therapeutic approach as needed.

[0059] The methods described herein are adaptable to a high throughput format, thus allowing the examination of a plurality (*i.e.*, 2, 3, 4, or more) of cell samples and/or compositions, which independently can be the same or different, in parallel. A high throughput format provides numerous advantages, including that various compositions can be tested on several samples of cells from a single subject, thus allowing, for example, for the identification of a particularly effective concentration of a particular ingredient of the composition to be administered to the subject, or for the identification of a particularly effective natural

antioxidant extract, or combination thereof, to be administered to the subject in combination with fucoidan. As such, a high throughput format allows for the examination of two, three, four, etc., different extracts, alone or in combination, on the hyperproliferative cells of a subject such that the best (most effective) extract or combination of extracts can be used for a therapeutic procedure. Further, a high throughput format allows, for example, control samples (positive controls and or negative controls) to be run in parallel with test samples, including, for example, samples of cells known to be effectively treated with an extract being tested.

[0060] When performed in a high throughput (or ultra-high throughput) format, the methods can be performed on a solid support (*e.g.*, a microtiter plate, a silicon wafer, or a glass slide), wherein samples to be contacted with an extract or combination thereof are positioned such that each is delineated from each other (*e.g.*, in wells). Any number of samples (*e.g.*, 96, 1024, 10,000, 100,000, or more) can be examined in parallel using such a method, depending on the particular support used. Where samples are positioned in an array (*i.e.*, a defined pattern), each sample in the array can be defined by its position (*e.g.*, using an x-y axis), thus providing an "address" for each sample. An advantage of using an addressable array format is that the method can be automated, in whole or in part, such that cell samples, reagents, test agents, and the like, can be dispensed to (or removed from) specified positions at desired times, and samples (or aliquots) can be monitored, for example, for decreased cell number.

EXAMPLES

Example I Tumor Suppressive and Apoptosis Activity of Acai and Fucoidan

[0061] *Cell line and culture.* The human lymphoma, HS-Sultan was purchased from the ATCC. HS-Sultan was cultured in RPMI1640 medium (Mediatech Inc.) supplemented with 10% fetal bovine serum (FBS, Invitrogen) and Penicillin-Streptomycine solution (Mediatech Inc.) in a humidified atmosphere with 5% CO_2.

[0062] *Preparation of fucoidan samples.* Fucoidan samples are dissolved in PBS (Mediatech Inc.) at a concentration of 50 mg/mL by incubating at 50°C for 2 hrs. If the solutions contained insoluble substances, the solutions were subjected to centrifugation at 12,000 rpm for 10 min to remove such insoluble substances. The sample solutions were then sterilized by 0.2 or 0.45 μm syringe filters (VWR).

[0063] *Cell viability assay.* The effects of fucoidan samples on cell growth of HS-Sultan were examined by use of the cell proliferation reagent water soluble tetrazolium (WST)-8, tetrazolium salt (Wako Chemicals USA). Cells ($1x10^5$ cells/mL) were incubated in a 48-well microculture plate in the presence or absence of various concentrations of fucoidan. After 72 hrs of culture, WST-8 (20 μL) is added for the last 4 hrs of incubation, and the

absorbance at 450nm is measured using an automated microplate reader. Measuring the mitochondrial dehydrogenase cleavage of WST-8 to formazan dye indicates the level of proliferation.

[0064] *Apoptosis assay (Caspase-3 assay).* Cells were suspended at a final concentration of $1x10^5$ cells/mL in RPMI1640 with 10% FBS and Penicillin-Streptomycin solution in a 96-well microculture plate in triplicate. Fucoidan was then added to each well at various concentrations, and incubated for 24 hrs. The activation of caspase-3 was analyzed using a caspase-3 assay kit according to the manufacturer's instructions.

[0065] Individual cell inhibition activities of sample solutions on HS-Sultan cells were compared with each other. As shown in Table 1, acai berry extract (water soluble fraction) has a stronger cell growth inhibition activity on HS-Sultan cells than those of the fucoidan samples (*Cladosiphon okamuranus*). Fucoidan induced complete apoptosis at the higher concentrations (Figure 1).

Table 1 – Cell number remaining following treatment with Fucoidan and Acai berry

	Concentrations of Sample solution					
	1 mg/mL	2 mg/mL	3 mg/mL	4 mg/mL	5 mg/mL	6 mg/mL
Fucoidan *(Cladosiphon okamuranus)*	300 $x10^3$ cells/mL	88 $x10^3$ cells/mL	4 $x10^3$ cells/mL	0	0	0
Acai berry	30 $x10^3$ cells/mL	0	0	0	0	0

The cell number of Control (added PBS only) was $590x10^3$ cells/mL.

Example II Synergistic effects of Fucoidan and Acai berry extract

[0066] This example demonstrates the synergistic tumor suppressive activity and apoptosis enhancing activity of fucoidan (*Cladosiphon okamuranus*) in combination with acai berry extract. HS-Sultan cells were contacted with different concentrations (*i.e.*, 0-2 mg/mL) of acai berry extract alone and in the presence of 1-3 mg/mL fucoidan.

[0067] As shown in Table 2, fucoidan at a concentration of 1.0 mg/ml did not exhibit any cell growth inhibitory activity on HS-Sultan cells alone. However, a synergistic effect was observed when fucoidan is added to acai berry extract (Figure 2). These results suggest that acai berry extract enhances the activity of fucoidan on cancer cells by inhibiting cell growth and inducing apoptosis.

Table 2 – Synergistic effect of Acai berry extract and Fucoidan

	Fucoidan Concentrations (mg/mL)			
	0	1.0	2.0	3.0
0	530 $x10^3$ cells/mL	490 $x10^3$ cells/mL	98 $x10^3$ cells/mL	6 $x10^3$ cells/mL

Acai berry extract (mg/mL)	0.5	190 x10^3 cells/mL	0	0	0
	1.0	85 x10^3 cells/mL	0	0	0
	1.5	3 x10^3 cells/mL	0	0	0
	2.0	0	0	0	0

EXAMPLE III – Partial identification of the tumor suppressive fraction in Acai berry extract

[0068] Acai berry powder (5.0 g) was suspended in PBS (Mediatech Inc.), and extracted by incubating at 50°C for 9 hrs. Insoluble substance was eliminated by centrifugation at 12,000 rpm for 10 min. The solution was fractionated into two fractions, Fraction I (>3,000 daltons) and Fraction II (<3,000 daltons), by ultrafiltration using a Macrosep Centrifugal Device 3K (PALL Life Sciences) with a molecular cutoff for bio-molecules of 3,000. The two fractionated solutions were sterilized by 0.45 μm syringe filters (VWR). On the other hand, Acai berry solution (100 mg/mL) was heated at 95°C for 1 hr. The heat-treated Extract was sterilized by 0.45 μm syringe filters (VWR). Using these three solutions, the tumor suppressive activities of Acai berry Extract (water-soluble fraction – WSF) was compared on HS-Sultan cells. These results are shown in Table 3.

[0069] Surprisingly, heat-treated extract has a stronger tumor suppressive activity than that of the original extract (WSF), and induces apoptosis in HS-Sultan cells at concentrations of more than 1 mg/mL. This phenomenon indicates that the biologically active molecules in Acai berry Extract that have tumor suppressive activity are activated by heat-treatment (*e.g.*, 95°C, 1 hr). As shown in Table 3, Fraction I exhibits lesser tumor suppressive activity than that of the original extract (WSF), but stronger activity than that of Fraction II, suggesting that the biologically active molecules are heat-activated, and mostly contained in Fraction I (>3,000 daltons). Moreover, which fraction has synergistic activities on the tumor suppressive effects of fucoidan, and which fraction is activated by heat-treating was determined.

Table 3 –Tumor suppressive activity of Acai solutions

	Concentrations of Sample solutions				
	1 mg/mL	2 mg/mL	4 mg/mL	6 mg/mL	8 mg/mL
Acai berry Extract (WSF)	400 x10^{3}cells/mL	84 x10^{3}cells/mL	0.5 x10^{3}cells/mL	0	0
Heat-treated Extract	240 x10^{3}cells/mL	20 x10^{3}cells/mL	0	0	0
Fraction I	370 x10^{3}cells/mL	340 x10^{3}cells/mL	38 x10^{3}cells/mL	0	0
Fraction II	710 x10^{3}cells/mL	430 x10^{3}cells/mL	210 x10^{3}cells/mL	95 x10^{3}cells/mL	22 x10^{3}cells/mL

The cell number of Control (added PBS only) was $710x10^3$ cells/mL.

[0070] Both Fraction I and II exhibited the synergistic activities on the tumor suppressive effects of fucoidan. At low concentration (1 mg/mL), Fraction II (<3,000 daltons) was relatively higher synergistic activity than that of Fraction I (>3,000 daltons). However, at the concentration of 4 mg/mL, Fraction II could not show the synergistic effect. The synergistic effects of Acai Extracts could derive from the activities of both Fraction I and Fraction II.

[0071] It was observed that heat-activation of Fraction I has an effect on the tumor suppressive activity on HS-Sultan cells. The heat-activation of Fraction I contributes to the activity that is observed in Table 3.

EXAMPLE IV – Synergistic effects of Fucoidan and other extracts

[0072] This example demonstrates the synergistic tumor suppressive activity and apoptosis enhancing activity of fucoidan in combination with extracts from other natural antioxidant containing substances. As shown in Figure 3, HS-Sultan cells were contacted with various concentrations of green tea extract, coffee bean extract, and 1 mg/mL fucoidan in combination with each of those substances. In each instance, the addition of 1 mg/mL fucoidan showed a significant synergistic activity in cell growth inhibition. As shown in Figure 4, HS-Sultan cells were contacted with various concentrations of blueberry extract to determine concentrations that inhibit cell growth and induce apoptosis. The addition of 1 mg/mL fucoidan showed a significant synergistic activity in cell growth inhibition. As shown in Figure 5, dried red grape was used as a negative control in the cell growth inhibition assay on HS-Sultan. The addition of 1 mg/mL fucoidan showed no significant synergistic activity in cell growth inhibition over dried red grape extract alone.

EXAMPLE V – Synergistic effects of Fucoidan and Natural Antioxidant for Apoptosis Attenuation

[0073] This example demonstrates the apoptosis attenuation activity of Fucoidan (*Cladosiphon okamurae*) on ethanol-induced apoptosis of HS-Sultan cells. HS-Sultan was obtained and prepared as described in Example I.

[0074] *Apoptosis Attenuation Assay* – The attenuation effects of fucoidan (*Cladosiphon okamuranus*) on ethanol (EtOH)-induced apoptosis of HS-Sultan cells were examined. Cells (1x105 cells/mL) were incubated in a 48-well microculture plate in the absence or presence of EtOH (1 μL/well), with various concentrations of fucoidan solution. After 72 hrs of culture, the cells of each well were harvested by centrifugation at 5,000 rpm for 2 min, and suspended in PBS. The cells without staining with Trypan Blue dye (0.4%, Sigma-Aldrich) were counted under the microscope.

[0075] *Induction of apoptosis by EtOH on HS-Sultan cells and attenuation of the apoptosis by fucoidan* – Addition of EtOH (1 μL/well) to the culture of HS-Sultan cells induced cell growth inhibition and apoptosis on the cells (Table 4). However, the combination of various concentrations of fucoidan attenuated EtOH-induced apoptosis on the cells, resulting in recovery of cell growth at the concentrations of 10 and 25 μg/mL (Figure 6). It was also observed that the natural antioxidant obtained from green tea extract also has the activity (Table 5; see Figure 7).

Table 4 – Apoptosis Attenuation Assay (Fucoidan)

	Concentrations of fucoidan				
	0 μg/mL	10 μg/mL	25 μg/mL	50 μg/mL	100 μg/mL
Control (0 μL/well EtOH)	865 x10^3 cells/mL	648 x10^3 cells/mL	730 x10^3 cells/mL	258 x10^3 cells/mL	40 x10^3 cells/mL
EtOH (1 μL/well)	94 x10^3 cells/mL	154 x10^3 cells/mL	193 x10^3 cells/mL	91 x10^3 cells/mL	41 x10^3 cells/mL

Initial cell number was 100x10^3 cells/mL.

Table 5 – Apoptosis Attenuation Assay (Natural Antioxidant)

	Green tea extract concentrations (equal to the initial materials)					
	0 μg/mL	5 μg/mL	10 μg/mL	20 μg/mL	30 μg/mL	40 μg/mL
Control (0 μL/well EtOH)	933 x10^3 cells/mL	965 x10^3 cells/mL	483 x10^3 cells/mL	14 x10^3 cells/mL	13 x10^3 cells/mL	8 x10^3 cells/mL
EtOH (1 μL/well)	19 x10^3 cells/mL	25 x10^3 cells/mL	341 x10^3 cells/mL	10 x10^3 cells/mL	0	0

Initial cell number was 100x10^3 cells/mL.

[0076] As shown in Table 6, a synergistic effect was observed when fucoidan was added to a natural antioxidant extract (Figures 8 and 9). These results suggest that natural antioxidant extracts enhance the activity of fucoidan on hypoproliferative cells by inhibiting apoptosis.

Table 6 – Synergistic effects of Natural Antioxidant Extract and Fucoidan

		Concentration of fucoidan (μg/mL)					
		0	5	10	20	30	40
Green tea extract (μg/mL)	0	68 x10^3 cells/mL	115 x10^3 cells/mL	60 x10^3 cells/mL	57 x10^3 cells/mL	21 x10^3 cells/mL	3 x10^3 cells/mL
	5	164 x10^3 cells/mL	339 x10^3 cells/mL	253 x10^3 cells/mL	180 x10^3 cells/mL	185 x10^3 cells/mL	6 x10^3 cells/mL
	10	340 x10^3 cells/mL	395 x10^3 cells/mL	294 x10^3 cells/mL	237 x10^3 cells/mL	92 x10^3 cells/mL	58 x10^3 cells/mL
	20	164 x10^3 cells/mL	171 x10^3 cells/mL	100 x10^3 cells/mL	45 x10^3 cells/mL	68 x10^3 cells/mL	16 x10^3 cells/mL

Initial cell number was 100x10^3 cells/mL.
The cell number of Control (added PBS only) was 675x10^3 cells/mL.

[0077] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by

way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating a cellular proliferative disorder in a subject comprising administering to the subject a combination of fucoidan and a natural antioxidant extract.

2. The method of claim 1, wherein the cellular proliferative disorder is a neurodegenerative disorder, neovascular disorder, or cancer.

3. The method of claim 2, wherein the cancer is lymphoma, leukemia, melanoma, prostate cancer, breast cancer, renal cancer, cervical carcinoma, colon cancer, pancreatic cancer, gall bladder cancer, stomach cancer, lung cancer, head and neck cancer, hepatoma, or a brain tumor.

4. The method of claim 2, wherein the neurodegenerative disorder is amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, Parkinson's disease, and Schizophrenia.

5. The method of claim 2, wherein the neovascular disorder is diabetic retinopathy, age-related macular degeneration, rheumatoid arthritis, osteoarthritis, glaucoma, keloids, corneal graft rejection, wound granularization, angiofibroma, Osler-Webber Syndrome, and myocardial angiogenesis.

6. The method of claim 1, wherein the natural antioxidant extract is a combination of two or more natural antioxidant extracts.

7. The method of claim 1, wherein the natural antioxidant extract is selected from the group consisting of acai berry extract, green tea extract, and coffee bean extract.

8. The method of claim 1, wherein the natural antioxidant extract is an extract selected from the group consisting of blueberry, grape, cherry, blackberry, cranberry, raspberry, strawberry, huckleberry, lemon, melon, kiwi, grapefruit, orange, apple, apricot, prune, watermelon, mangosteen, plum, date, and banana.

9. The method of claim 1, wherein the fucoidan and the natural antioxidant extract are administered simultaneously.

10. The method of claim 1, wherein the fucoidan and the natural antioxidant extract are administered sequentially.

11. The method of claim 10, wherein the fucoidan is administered up to 3 days prior to administration of the natural antioxidant extract.

12. The method of claim 11, wherein the fucoidan is administered 1 or 2 days prior to administration of the natural antioxidant extract.

13. The method of claim 1, wherein the subject is a human.

14. A method of ameliorating hyperproliferative cells in a subject comprising administering to the subject a combination of fucoidan and a natural antioxidant extract, thereby ameliorating the hyperproliferative cells in the subject.

15. The method of claim 14, wherein the hyperproliferative cells are lymphoma cells, leukemia cells, melanoma cells, prostate cancer cells, breast cancer cells, renal cancer cells, cervical carcinoma cells, colon cancer cells, pancreatic cancer cells, gall bladder cancer cells, stomach cancer cells, lung cancer cells, head and neck cancer cells, hepatoma cells, or brain tumor cells.

16. The method of claim 14, wherein the natural antioxidant extract is a combination of two or more natural antioxidant extracts

17. The method of claim 14, wherein the natural antioxidant extract is selected from the group consisting of acai berry extract, green tea extract, coffee bean extract, blueberry extract, and grape extract.

18. The method of claim 14, wherein the natural antioxidant extract is an extract selected from the group consisting of blueberry, grape, cherry, blackberry, cranberry, raspberry, strawberry, huckleberry, lemon, melon, kiwi, grapefruit, orange, apple, apricot, prune, watermelon, mangosteen, plum, date, and banana.

19. The method of claim 14, wherein the subject is a human or another mammal.

20. A method of inhibiting growth of a hyperproliferative cell comprising contacting the cell with a combination of fucoidan and a natural antioxidant extract.

21. The method of claim 20, wherein the natural antioxidant extract is a combination of two or more natural antioxidant extracts.

22. The method of claim 20, wherein the natural antioxidant extract is selected from the group consisting of acai berry extract, green tea extract, coffee bean extract, blueberry extract, and grape extract.

23. The method of claim 20, wherein the natural antioxidant extract is an extract selected from the group consisting of blueberry, grape, cherry, blackberry, cranberry, raspberry, strawberry, huckleberry, lemon, melon, kiwi, grapefruit, orange, apple, apricot, prune, watermelon, mangosteen, plum, date, and banana.

24. The method of claim 20, wherein the hyperproliferative cell is selected from the group consisting of a lymphoma cell, a leukemia cell, a melanoma cell, a prostate cancer cell, a breast cancer cell, a renal cancer cell, a cervical carcinoma cell, a colon cancer cell, a pancreatic cancer cell, a gall bladder cancer cell, a stomach cancer cell, a lung cancer cell, a head and neck cancer cell, a hepatoma cell, or a brain tumor cell.

25. The method of claim 20, wherein the contacting is performed *in vivo*.

26. The method of claim 20, wherein the contacting is performed *in vitro*.

27. A composition comprising fucoidan and one or more natural antioxidant extracts.

28. The composition of claim 27, wherein the natural antioxidant extract is selected from the group consisting of acai berry extract, green tea extract, coffee bean extract, blueberry extract, and grape extract.

29. A method of identifying a cell proliferative disorder amenable to treatment with fucoidan in combination with a natural antioxidant extract comprising detecting inhibited cell proliferation in a sample of cells as compared to cell proliferation in a corresponding untreated sample, thereby identifying a cell proliferative disorder amenable to treatment with fucoidan in combination with a natural antioxidant extract.

30. The method of claim 29, wherein the natural antioxidant extract is a combination of two or more natural antioxidant extracts.

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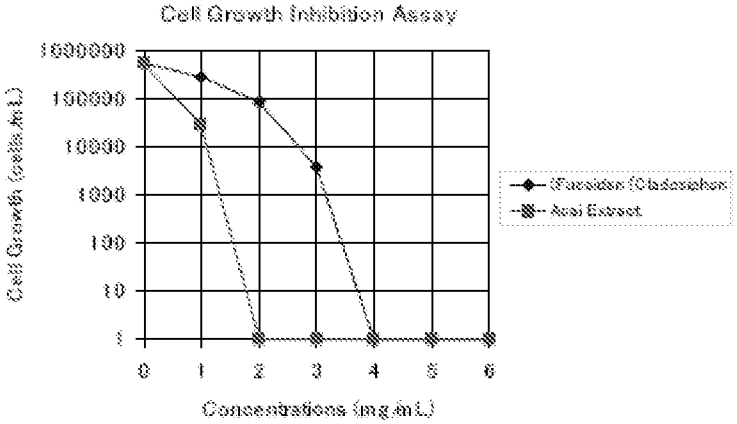
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Concentrations (mg/mL)
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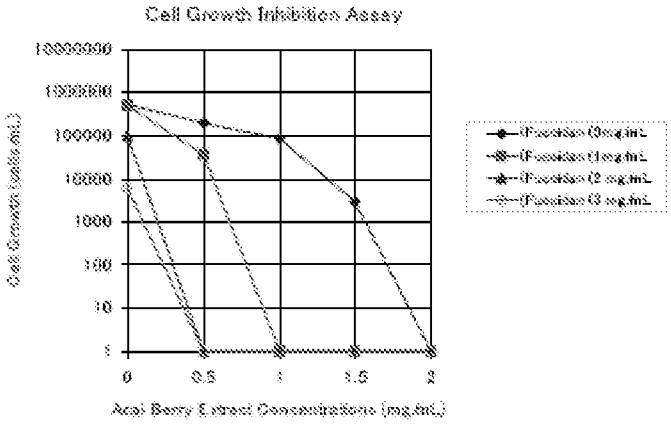
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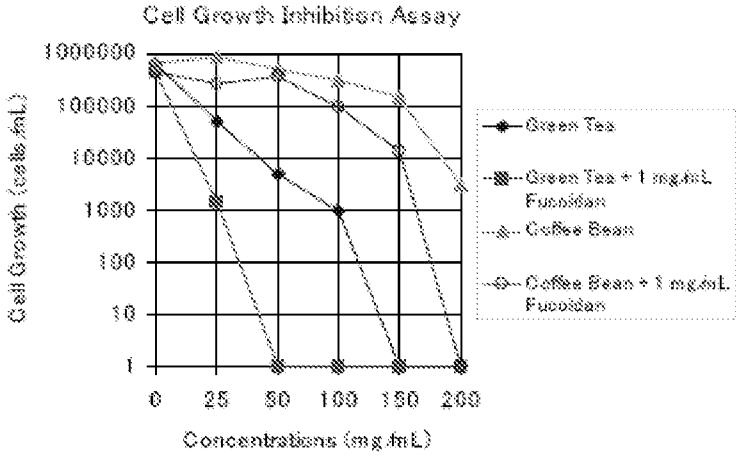
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Cell Growth (cells/mL)
0
25
50
100
150
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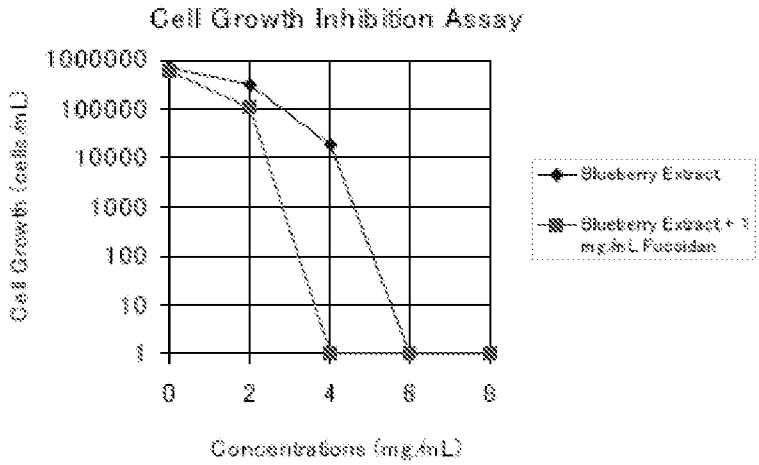
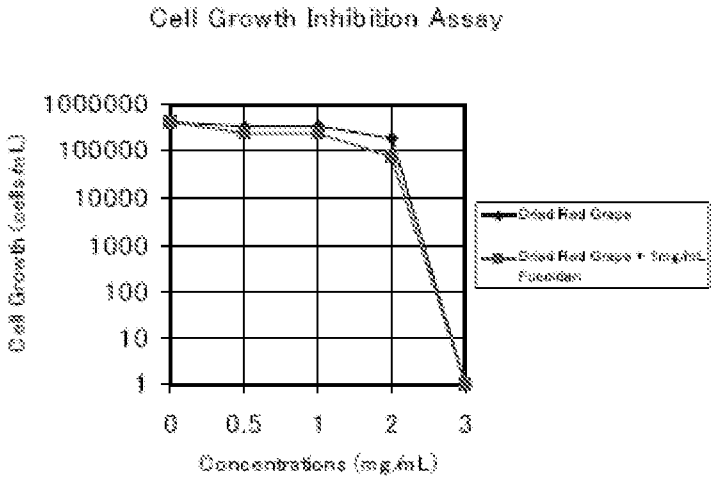
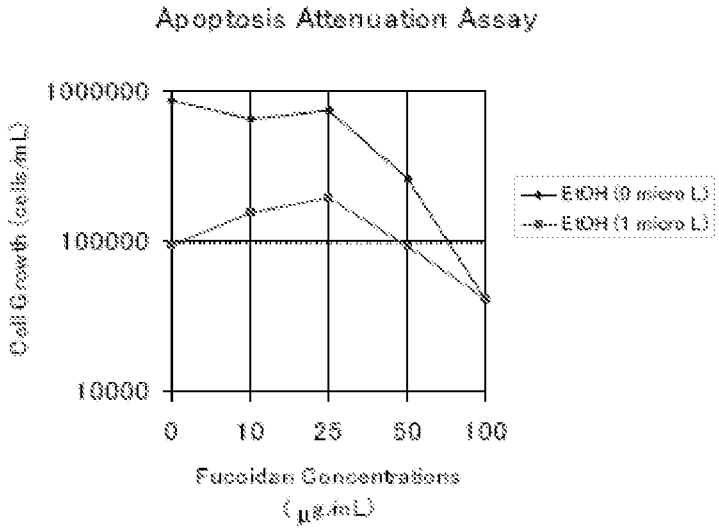
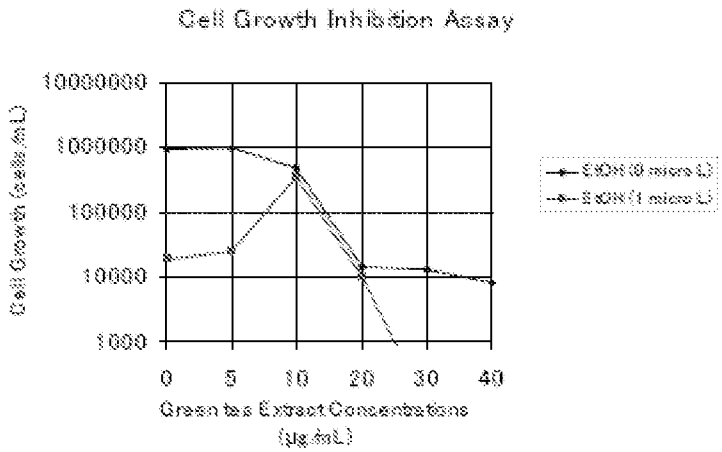
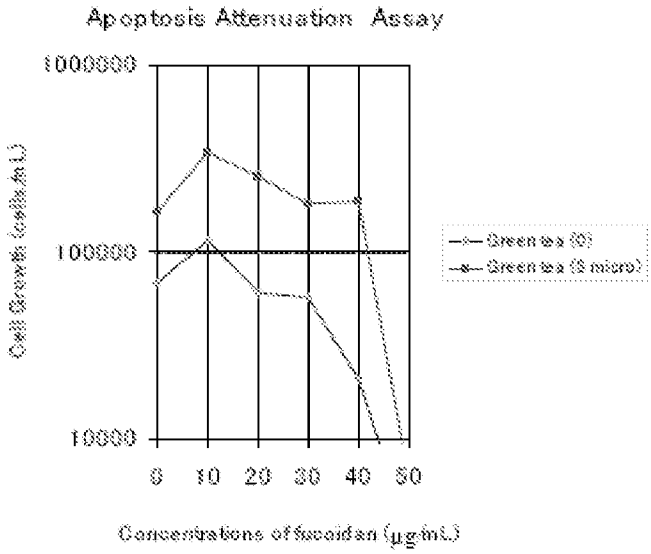
Concentrations (mg/mL)
Green Tea
Green Tea + 1 mg/mL Fucoidan
Coffee Bean
Coffee Bean + 1 mg/mL Fucoidan

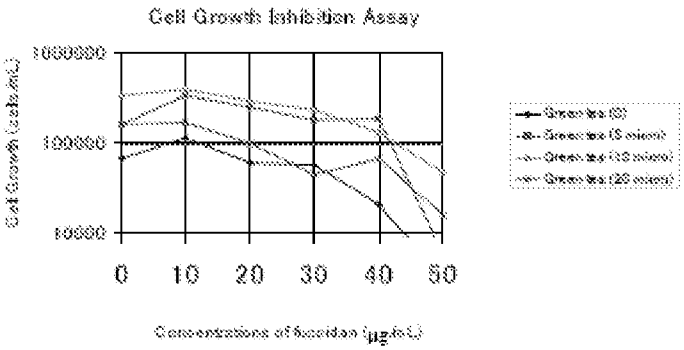

Cell Growth Inhibition Assay
1000000
100000
10000
1000
100
10
1
0
2
4
6
8
Concentrations (mg/mL)
Blueberry Extract
Blueberry Extract + 1 mg/mL Fucoidan


Cell Growth Inhibition Assay
1000000
100000
10000
1000
100
10
1
0
0.5
1
2
3
Concentrations (mg/mL)


Apoptosis Attenuation Assay
1000000
100000
10000
Cell Growth (cells/mL)
0
10
25
50
100
Fucoidan Concentrations
(µg/mL)
EtOH (0 micro L)
EtOH (1 micro L)


Cell Growth Inhibition Assay
10000000
1000000
100000
10000
1000
0
5
10
20
30
40
Green tea Extract Concentrations
(µg/mL)


Apoptosis Attenuation Assay
1000000
100000
10000
0
10
20
30
40
50
Concentrations of fucoidan (μg/mL)
Green tea (0)
Green tea (3 micro)


Cell Growth Inhibition Assay
1000000
100000
10000
0
10
20
30
40
50