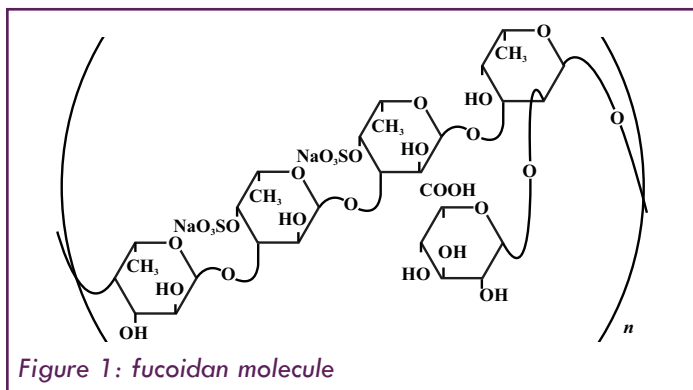


Far too many are reluctant to treat cancer naturally. This is understandable. Outrageous claims have been made in the past with regards to nutritional supplements used for those suffering from cancer. Unfortunately, this has led to distrust and skepticism. Although more research is needed, there is no doubt that nutrients can be powerful allies in the fight against cancer.

Nutrients can be used to prevent^{1,2} and treat^{3,4} neoplasia. Nutrients can also be used to support radiation and chemotherapy.^{5,6} It is also important to realize that prescription medications are a leading cause of death in North America⁷ and that chemotherapy, although proven effective for the treatment of cancer, is also a frequent cause of death in cancer patients.⁸ Nutritional strategies that can support the body while patients are undergoing chemotherapy or radiation treatments should not be discounted.

Plants have long been used for their health benefits. Many plant's first documented use dates back thousands of years. Seaweed has not only been used as a food source but also as a medicine for thousands of years. Fucoidans are one important constituent of seaweed, first mentioned in the medical literature in 1970. Fucoidans are sulfated polysaccharides extracted from brown algae and contain fucose, uronic acid and sulphate. Fucoidans are responsible for the characteristic slippery texture of seaweed.



If you only know algae as the dark stuff that is wrapped around your raw fish at the sushi bar, you are missing out on one of the greatest health resources available to date. Humans and animals rely on their immune systems to combat disease. Plants however do not have immune systems and must produce chemicals that prevent and take care of infections and parasites - those chemicals are responsible for the medicinal properties of plants. Oceans contain most of the living space on earth and their potential as sources of health-promoting nutrients remain largely unknown.⁹ Nonetheless, fucoidans have emerged from the sea and have been the subject of over 600 medical papers.¹⁰ Research has shown that fucoidans possess potent antiproliferative properties,¹¹ are effective antithrombotic agents,¹² reduce inflammation,¹³ and prevent tumor growth and metastasis.¹⁴

Knotted Wrack, also known as *Ascophyllum Nodosum*, is an edible seaweed found in the Northern Atlantic Ocean that has been used as a fertilizer because of its rich nutrient content. Knotted Wrack is an excellent source of fucoidan and the fucoidans specific to this seaweed have been researched extensively.



Picture 1: *Ascophyllum Nodosum*

Preliminary research in cancer cell lines showed that fucoidans extracted from the seaweed *Ascophyllum Nodosum* possess anti-tumor properties. Initial studies looked at the effect of the seaweed extract in non-small-cell human bronchopulmonary carcinoma, a cancer that is difficult to treat.¹⁵ It was found that the addition of fucoidan to the cellular culture prevents the proliferation of the cancer cells and blocks the G1 phase of the cell cycle. This phase of the cell cycle is a period of major cellular growth (see sidebar). The same researchers then proceeded to animal studies in which fucoidan exhibited antitumor properties. This led them to conclude that the extract is a potent antitumor agent.¹⁶

Mitosis is the cellular process responsible for cellular replication. Mitosis involves the division of a mother cell into two daughter cells. The genetic material from the mother cell must be copied and transferred to the daughter cells. In animals and humans, the daughter cells are created through the "pinching off" of the mother cell.

Mitosis is a 4-stage process:

- **Interphase-** during this initial stage, the cell prepares for replication. The chromosomes are duplicated so that a copy of the genetic information is available for each of the daughter cells. DNA is only synthesized during this phase. It is this phase that is inhibited by fucoidans.
- **Prophase** - the nucleus (the part of the cell where the chromosomes are found) breaks apart.
- **Metaphase** - the chromosomes collect where the cell will divide once the nucleus divides.
- **Anaphase** - the chromatid (daughter chromosomes) separate and in Telophase, a new nucleus envelope surrounds the two new groups of chromosomes. This is followed by the division of the cellular membrane into two new daughter cells.

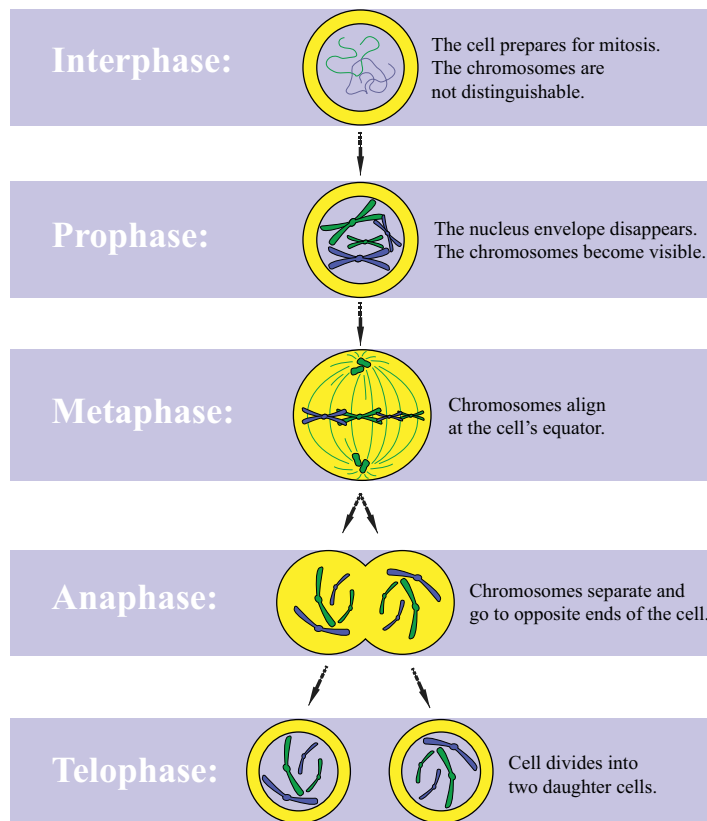


Figure 2: Cellular proliferation through mitosis

The structure of fucoidan is similar to that of heparin.^{17,18}

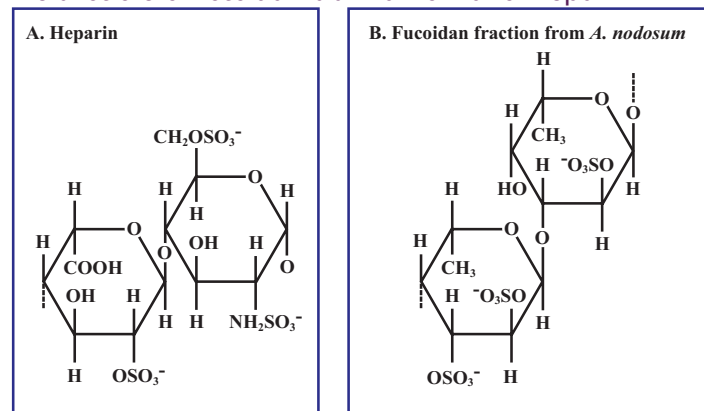


Figure 3: Structures of heparin and fucoidan fraction from *A. Nodosum*

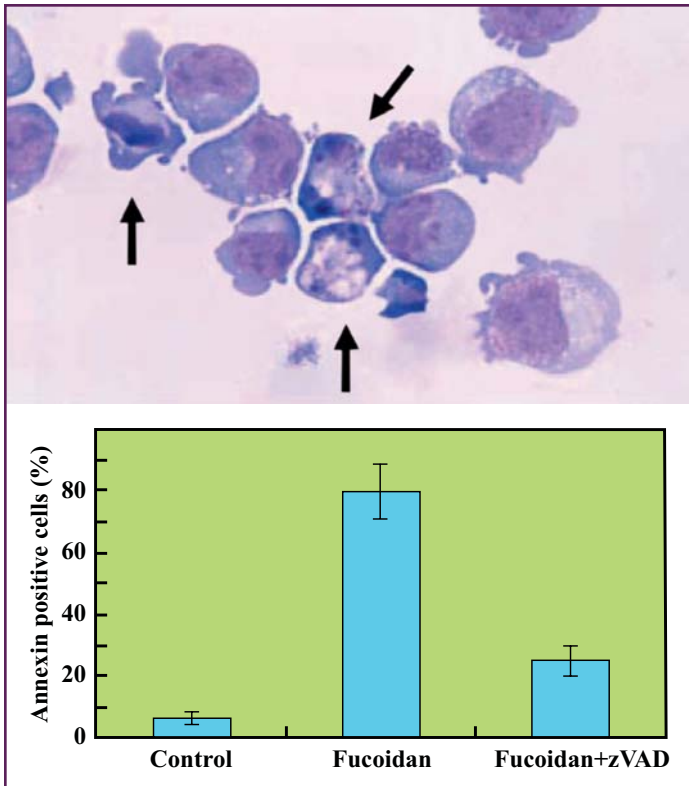
Heparin has been shown to possess anti-cancer activity.^{19,20} It appears that heparin is an anti-metastatic agent capable of preventing cell-to-cell interactions.^{21,22} Heparin interferes with the interaction of cancer cells with other cells - preventing attachment and metastasis through isolation. Like heparin, fucoidans possess antiproliferative activity.²³

The effects of fucoidans do not end there; the seaweed extract also stimulates the immune system. Recent studies in cell lines have shown that exposure to fucoidans activates macrophages and lymphocytes (two types of immune cells).²⁴ In vitro studies have also shown that fucoidans can lead to the cellular death (apoptosis) of cancer cells. The

study revealed that fucoidans inhibit the proliferation of cancer cells in a dose dependant manner. Seventy nine percent of the cancer cells exposed to fucoidans scored positive on the annexin-V assay (a test designed to identify apoptotic cells) whereas only 6.3% of the controls tested positive.²⁵

When the same cancer cells were pretreated with a caspase inhibitor, the efficacy of the fucoidans dropped to 25%, implying that caspases are involved in fucoidan-induced cellular apoptosis (caspases digest cells from the inside out leading to their demise - a process known as apoptosis). Further testing led to the discovery that

fucoidans influence cellular signaling and promote apoptosis in cancer cells by down-regulating extracellular signals such as GSK and ERK.²⁶ These two cellular pathways have previously been linked to the initiation of apoptosis.^{27,28}



Graph 1: Detection of apoptosis by annexin-V staining. Redrawn from (29)

The activity of fucoidans appears to be related to their molecular weight, charge and degree of sulfation.³⁰ For instance, studies on low molecular weight fucoidans have demonstrated that the molecule influences cellular processes important for angiogenesis, endothelial cell tube formation and cell migration. Low molecular weight fucoidans may prove to be invaluable to patients with atherosclerosis and cardiovascular disease. Studies have also shown that low molecular weight fucoidans prevent cellular proliferation.³¹ Cellular proliferation is the increase in cell number engendered through cellular division - a process that is central to cancer.

Meanwhile, other researchers have shown that fucoidans can prevent angiogenesis by altering the binding of growth factors to cellular receptors.³² This apparent dichotomy can be explained by the molecular weight of the fucoidan fraction studied. Previous in vitro studies have shown that a high molecular weight hyaluronan is antiangiogenic whereas the smaller but otherwise similar hyaluronan oligosaccharides stimulate the formation of new blood vessels.³³ Such divergence may also apply to fucoidans, with low molecular weight fractions promoting angiogenesis

and larger molecules preventing it.³⁴ Studies have also demonstrated that sulfated polysaccharides such as fucoidans prevent the metastasis of cancer cells. This activity is attributable to an interference with cellular receptors, which is mediated by fucoidans. This prevents the passage of the cancerous cell through the capillary wall, thereby discouraging metastasis.³⁵

Studies show that the ability of fucoidan to inhibit cellular proliferation is also dependant on the degree of sulfation - more sulfated fucoidans being more effective at preventing angiogenesis.^{36,37}

Fucoidans possess several other health benefits, which include the reduction of inflammation through the inactivation of the complement pathway and by inhibiting the release of nitric oxide from macrophages.^{38,39} Fucoidans are also anticoagulants with antithrombotic activity,^{40,41} and can modulate cellular adhesion and growth factor release.⁴²

Epidemiological evidence speaks loudly to the health benefits associated with the consumption of seaweed. The traditional Japanese diet is comprised of roughly 10-25% seaweed.⁴³ On the other hand, Western nations have a very low consumption of seaweed. Chronic disease rates in nations consuming greater amounts of seaweed suggest a beneficial influence of seaweed on health. For example, breast cancer rates in Japan are 42.2 per 100,000 and represent roughly a third of the North American rate of 125.9 per 100,000.⁴⁴ Granted that several other factors are important in explaining this difference, but given the weight of the scientific evidence supporting the value of seaweed, there is little doubt that fucoidans and other phytonutrients go a long way towards explaining this disparity.

References

- 1 Waters, D.J., S. Shen, D.M. Cooley, et al. 2003. Effects of dietary Se supplementation on DNA damage and apoptosis in canine prostate. *J. Natl. Cancer Inst.* 95: 237-241.
- 2 Flanagan JN, Young MV, Persons KS, Wang L, Mathieu JS, Whitlatch LW, Holick MF, Chen TC. Vitamin D metabolism in human prostate cells: implications for prostate cancer chemoprevention by vitamin D. *Anticancer Res.* 2006 Jul-Aug;26(4A):2567-72.
- 3 Buletic Z, Soprano KJ, Soprano DR. Retinoid targets for the treatment of cancer. *Crit Rev Eukaryot Gene Expr.* 2006;16(3):193-210.
- 4 Ferah Y, Ayse K, Mustafa C, Ugur S, Murat G, Lale AI. Possible therapeutic role of vitamin D3 in aggressive fibromatosis. *Jpn J Clin Oncol.* 2004 Aug;34(8):472-5.
- 5 Basu P, Biswas J, Mandal R, Choudhury P. Is interferon-alpha and retinoic acid combination along with radiation superior to chemo-radiation in the treatment of advanced carcinoma of cervix? *Indian J Cancer.* 2006 Apr-Jun;43(2):54-9.
- 6 Kassouf W, Highshaw R, Nelkin GM, Dinney CP, Kamat AM. Vitamins C and K3 sensitize human urothelial tumors to gemcitabine. *J Urol.* 2006 Oct;176(4 Pt 1):1642-7.
- 7 Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA.* 1998 Apr 15;279(15):1200-5.
- 8 Ohe Y, Yamamoto S, Suzuki K, Hojo F, Kakinuma R, Matsumoto T, Ohmatsu H, Nishiwaki Y. Risk factors of treatment-related death in chemotherapy and thoracic radiotherapy for lung cancer. *Eur J Cancer.* 2001 Jan;37(1):54-63.

9 Benchley P, Gradwohl J. Ocean Planet: Writings and Images of the Sea. Harry N. Abrams Inc

10 Tanaka K, Sorai S. Hydrolysis of fucoidan by abalone liver alpha-L-fucosidase. *FEBS Lett.* 1970 Jul 15;9(1):45-48.

11 McCaffrey TA, Falcone DJ, Borth W, Brayton CF, Weksler BB. Fucoidan is a non-anticoagulant inhibitor of intimal hyperplasia. *Biochem Biophys Res Commun.* 1992 Apr 30;184(2):773-81.

12 Thorlacius H, Vollmar B, Seyfert UT, Vestweber D, Menger MD. The polysaccharide fucoidan inhibits microvascular thrombus formation independently from P- and L-selectin function in vivo. *Eur J Clin Invest.* 2000 Sep;30(9):804-10.

13 Yang JW, Yoon SY, Oh SJ, Kim SK, Kang KW. Bifunctional effects of fucoidan on the expression of inducible nitric oxide synthase. *Biochem Biophys Res Commun.* 2006 Jul 21;346(1):345-50.

14 Riou D, Collic-Jouault S, Pinczon du Sel D, Bosch S, Siavoshian S, Le Bert V, Tomasoni C, Sinquin C, Durand P, Roussakis C. Antitumor and antiproliferative effects of a fucan extracted from ascophyllum nodosum against a non-small-cell bronchopulmonary carcinoma line. *Anticancer Res.* 1996 May-Jun;16(3A):1213-8.

15 Riou D, Collic-Jouault S, Pinczon du Sel D, Bosch S, Siavoshian S, Le Bert V, Tomasoni C, Sinquin C, Durand P, Roussakis C. Antitumor and antiproliferative effects of a fucan extracted from ascophyllum nodosum against a non-small-cell bronchopulmonary carcinoma line. *Anticancer Res.* 1996 May-Jun;16(3A):1213-8.

16 Riou D, Collic-Jouault S, Pinczon du Sel D, Bosch S, Siavoshian S, Le Bert V, Tomasoni C, Sinquin C, Durand P, Roussakis C. Antitumor and antiproliferative effects of a fucan extracted from ascophyllum nodosum against a non-small-cell bronchopulmonary carcinoma line. *Anticancer Res.* 1996 May-Jun;16(3A):1213-8.

17 Logeart D, Prigent-Richard S, Jozefonvicz J, Letourneur D. Fucans, sulfated polysaccharides extracted from brown seaweeds, inhibit vascular smooth muscle cell proliferation. I. Comparison with heparin for antiproliferative activity, binding and internalization. *Eur J Cell Biol.* 1997 Dec;74(4):376-84.

18 Giroux JL, Matou S, Bros A, Tapon-Bretaudiere J, Letourneur D, Fischer AM. Modulation of human endothelial cell proliferation and migration by fucoidan and heparin. *Eur J Cell Biol.* 1998 Dec;77(4):352-9.

19 Niers TM, Klerk CP, Dinisio M, Van Noorden CJ, Buller HR, Reitsma PH, Richel DJ. Mechanisms of heparin induced anti-cancer activity in experimental cancer models. *Crit Rev Oncol Hematol.* 2006 Oct 28

20 Kragh M, Loechel F. Non-anti-coagulant heparins: a promising approach for prevention of tumor metastasis (review). *Int J Oncol.* 2005 Oct;27(4):1159-67.

21 Kragh M, Loechel F. Non-anti-coagulant heparins: a promising approach for prevention of tumor metastasis (review). *Int J Oncol.* 2005 Oct;27(4):1159-67.

22 Niers TM, Klerk CP, Dinisio M, Van Noorden CJ, Buller HR, Reitsma PH, Richel DJ. Mechanisms of heparin induced anti-cancer activity in experimental cancer models. *Crit Rev Oncol Hematol.* 2006 Oct 28

23 Logeart D, Prigent-Richard S, Boisson-Vidal C, Chaubet F, Durand P, Jozefonvicz J, Letourneur D. Fucans, sulfated polysaccharides extracted from brown seaweeds, inhibit vascular smooth muscle cell proliferation. II. Degradation and molecular weight effect. *Eur J Cell Biol.* 1997 Dec;74(4):385-90.

24 Choi EM, Kim AJ, Kim YO, Hwang JK. Immunomodulating activity of arabinogalactan and fucoidan in vitro. *J Med Food.* 2005 Winter;8(4):446-53.

25 Aisa Y, Miyakawa Y, Nakazato T, Shibata H, Saito K, Ikeda Y, Kizaki M. Fucoidan induces apoptosis of human HS-sultan cells accompanied by activation of caspase-3 and down-regulation of ERK pathways. *Am J Hematol.* 2005 Jan;78(1):7-14.

26 Aisa Y, Miyakawa Y, Nakazato T, Shibata H, Saito K, Ikeda Y, Kizaki M. Fucoidan induces apoptosis of human HS-sultan cells accompanied by activation of caspase-3 and down-regulation of ERK pathways. *Am J Hematol.* 2005 Jan;78(1):7-14.

27 Song L, De Sarno P, Jope RS. Central role of glycogen synthase kinase-3beta in endoplasmic reticulum stress-induced caspase-3 activation. *J Biol Chem.* 2002 Nov 22;277(47):44701-8.

28 Loberg RD, Vesely E, Brosius FC 3rd. Enhanced glycogen synthase kinase-3beta activity mediates hypoxia-induced apoptosis of vascular smooth muscle cells and is prevented by glucose transport and metabolism. *J Biol Chem.* 2002 Nov 1;277(44):41667-73.

29 Aisa Y, Miyakawa Y, Nakazato T, Shibata H, Saito K, Ikeda Y, Kizaki M. Fucoidan induces apoptosis of human HS-sultan cells accompanied by activation of caspase-3 and down-regulation of ERK pathways. *Am J Hematol.* 2005 Jan;78(1):7-14.

30 Boisson-Vidal V, Zemani F, Caligiuri G, Galy-Fauroux, Collic-Jouault S, Helley D, Fischer AM. Neovascularization Induced by Progenitor Endothelial Cells: Effect of Fucoidan from Marine Algae. *Cardiovascular & Hematological Agents in Medicinal Chemistry*, 2007, 5.

31 Koyanagi S, Tanigawa N, Nakagawa H, Soeda S, Shimeno H. Oversulfation of fucoidan enhances its anti-angiogenic and antitumor activities. *Biochem Pharmacol.* 2003 Jan 15;65(2):173-9.

32 Koyanagi S, Tanigawa N, Nakagawa H, Soeda S, Shimeno H. Oversulfation of fucoidan enhances its anti-angiogenic and antitumor activities. *Biochem Pharmacol.* 2003 Jan 15;65(2):173-9.

33 Rahmanian M, Pertoff H, Kanda S, Christofferson R, Claesson-Welsh L, Heldin P. Hyaluronan oligosaccharides induce tube formation of a brain endothelial cell line in vitro. *Exp Cell Res.* 1997 Nov 25;237(1):223-30.

34 Matou S, Helley D, Chabut D, Bros A, Fischer AM. Effect of fucoidan on fibroblast growth factor-2-induced angiogenesis in vitro. *Thromb Res.* 2002 May 15;106(4-5):213-21.

35 Coombe DR, Parish CR, Ramshaw IA, Snowden JM. Analysis of the inhibition of tumour metastasis by sulphated polysaccharides. *Int J Cancer.* 1987 Jan 15;39(1):82-8.

36 Koyanagi S, Tanigawa N, Nakagawa H, Soeda S, Shimeno H. Oversulfation of fucoidan enhances its anti-angiogenic and antitumor activities. *Biochem Pharmacol.* 2003 Jan 15;65(2):173-9.

37 Riou D, Collic-Jouault S, Pinczon du Sel D, Bosch S, Siavoshian S, Le Bert V, Tomasoni C, Sinquin C, Durand P, Roussakis C. Antitumor and antiproliferative effects of a fucan extracted from ascophyllum nodosum against a non-small-cell bronchopulmonary carcinoma line. *Anticancer Res.* 1996 May-Jun;16(3A):1213-8.

38 Tissot B, Montdargent B, Chevotot L, Varenne A, Descroix S, Gareil P, Daniel R. Interaction of fucoidan with the proteins of the complement classical pathway. *Biochim Biophys Acta.* 2003 Sep 23;1651(1-2):5-16.

39 Yang JW, Yoon SY, Oh SJ, Kim SK, Kang KW. Bifunctional effects of fucoidan on the expression of inducible nitric oxide synthase. *Biochem Biophys Res Commun.* 2006 Jul 21;346(1):345-50.

40 Nardella A, Chaubet F, Boisson-Vidal C, Blondin C, Durand P, Jozefonvicz J. Anticoagulant low molecular weight fucans produced by radical process and ion exchange chromatography of high molecular weight fucans extracted from the brown seaweed *Ascophyllum nodosum*. *Carbohydr Res.* 1996 Aug 19;289:201-8.

41 Marais MF, Joseleau JP. A fucoidan fraction from *Ascophyllum nodosum*. *Carbohydr Res.* 2001 Nov 8;336(2):155-9.

42 Nardella A, Chaubet F, Boisson-Vidal C, Blondin C, Durand P, Jozefonvicz J. Anticoagulant low molecular weight fucans produced by radical process and ion exchange chromatography of high molecular weight fucans extracted from the brown seaweed *Ascophyllum nodosum*. *Carbohydr Res.* 1996 Aug 19;289:201-8.

43 Skibola CF. The effect of *Fucus vesiculosus*, an edible brown seaweed, upon menstrual cycle length and hormonal status in three pre-menopausal women: a case report. *BMC Complement Altern Med.* 2004 Aug 4;4:10.

44 Pisani P, Bray F, Parkin DM. Estimates of the world-wide prevalence of cancer for 25 sites in the adult population. *Int J Cancer.* 2002 Jan 1;97(1):72-81.

SeMC

Simply Selenium



SeMC stands alone as a 200 microgram selenium supplement, distinguished by the use of the best selenium available: Se-methylselenocysteine.

SeMC is backed by research as being the most potent and least toxic form of selenium available.

EGCG MAX™

Green Tea perfected!

We have all heard of the health benefits associated with green tea. Unlike black tea, which is fermented, green tea undergoes little processing which leaves the natural antioxidants found in green tea intact.

EGCG MAX is a high-potency standardized extract of green tea, high in epigallocatechin gallate (EgCG), believed to be the key phytonutrient in green tea, responsible for its health benefits.

Studies most consistently report health benefits in persons drinking ten cups a day of high-EgCG sencha-style Japanese green tea; each cup of this tea contains 150 milligrams of EgCG.

The labels of most green tea extracts exaggerate the number of cups of tea represented in their capsules by comparing the product to poor-quality teas. **EGCG MAX** allows you to more fully enjoy the healthy properties of a sencha-rich lifestyle without consuming large volumes of tea.



Harness the power of green tea with EGCG MAX.

www.aor.ca