INTEGRATIVE INTERVENTIONS[®]

Cancer Prevention

Oxidative Stress

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Ingredients	Dosage	Rationale	Reference

Carcinogenesis is a complex process. In order to fully address cancer, one needs to consider a minimum of four functional areas: oxidative damage, immune system function, chronic inflammation, and detoxification. Hormonal balance must also be addressed for hormone-related cancers.

Coenzyme Q10 (CoQ10) (ubiquinone) Natural form High purity	Take 100 mg twice daily	 Reduced CoQ10 levels have been linked to many chronic disease states. Cancer patients demonstrate significant CoQ10 deficiency (clinical data)¹ Well-documented antioxidant and free radical scavenger Protects mitochondrial DNA, protein, and lipids from oxidative damage²⁻⁴ Slows tumor growth in cancer patients² Significantly increases levels of IgG and T4-lymphocytes (clinical study)³ To be effective, supplemental CoQ10 must cross the blood-brain barrier and increase cellular CoQ10 concentrations 	1. 2. 3.	Portakal O, et al. Coenzyme Q10 concentrations and antioxidant status in tissues of breast cancer patients. <i>Clin Biochem</i> . 2000 Jun; 33(4):279- 84. Lockwood K, et al. Partial and complete regression of breast cancer in patients in relation to dosage of coenzyme Q10. <i>Biochem Biophys Res</i> <i>Commun</i> .1994 Mar30; 199(3):1504-8. Folkers K, et al. The activities of coenzyme Q10 and vitamin B6 for immune response. <i>Biochem Biophys Res</i> <i>Commun</i> . 1993 May 28; 193(1):88-92. Folkers K, et al. Survival of cancer patients on therapy with coenzyme Q10. <i>Biochem Biophys Res Commun</i> . 1993 Apr 15; 192(1):241-5.
Clinically studied blend: Reduced Glutathione (GSH) 10% Anthocyanins Blend: Beet Bilberry Black Currant European Elder L-Cysteine	Take with water on an empty stomach, 1-3 times daily. 400 mg 200 mg 80 mg	 Reduces DNA damage due to oxidative stress and cell cycle regulation, reducing cellular mutation rate¹ Reduced glutathione is a powerful antioxidant, essential to cellular detoxification, production of coenzymes, and recycling of antioxidant vitamins E and C² Directly conjugates carcinogens and heavy metals and their bioactivated intermediates³ Also affects cell function regulators (tumor suppressor factor p53 and tumor necrosis factor (TNF-α)³ Induces apoptosis in human cancer cells without damaging healthy cells (<i>in vitro</i>)³ Anthocyanins enhance bioavailability of glutathione Also suppress tumor cell growth (<i>in vitro</i>)⁴ L-cysteine is a precursor of glutathione¹ 	1. 2. 3.	Sung JH, et al. Protective effect of glutathione in HIV-1 lytic peptide 1-induced cell death in human neuronal cells. <i>J Neurovirol.</i> 2001 Oct; 7(5):454-65. Pouillart P, et al. Therapeutic effects of GSH Cysteine Anthocyan administered by mouth in the treatment of polymetastic colon cancer. Curie Institute, Dept. of Medical Oncology, Paris, France. 1999. Bonnerstag B, et al. Reduced glutathione and S- aceylglutathione as apoptosis- inducing agents in cancer therapy. <i>Cancer Letters.</i> 1996; 110:63-70. Kamei H, et al. Suppression of tumor cell growth by anthocyanins in vitro. <i>Cancer Invest.</i> 1995; 13(6): 590-4.

Protocols

Immune System Enhancement

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Ingredients	Dosage	Rationale	Reference
Blend of: IP-6 (inositol hexaphosphate) Inositol Maitake mushroom (9 mg pure D-fraction) POA Cat's Claw (pentacyclic chemotype) (1.3% pentacyclic oxindole alkaloids (POAs))	Take twice daily. 800 mg 220 mg 30 mg 10 mg	 IP-6, inositol, maitake, and cat's claw regulate cell development and proliferation. IP-6 and Inositol Combination Reduces cell proliferation and increases cellular differentiation¹ Increases NK activity by 49.4%, more than either compound used alone (laboratory study)^{2,3} Maitake D-fraction Enhances cell-mediated immune response and inhibits carcinogenesis⁴ Supports normal lymphocyte development and proliferation, macrophage activation, and release of cytotoxic T cells^{4,5} Increases production of cancer killing substances released from macrophage; immune system enhancement was increased by 162% and the T-cell activity was increased by 173% (laboratory study)^{4,5} Inhibits tumor metastasis by 92.1% and inhibits tumor reoccurrence by 91.9% compared to control (laboratory study)⁵ Cat's Claw Increases B cell count by increasing supply of antibodies⁶ POAs have immune-modulating effect in T lymphocyte response by increasing release of CD8 and CD4 T cells⁷ 	 Prevalskaya N, et al. Ca2+ homeostasis in apoptic resistance of prostate cancer cells. <i>Biochem Biophys Res</i> <i>Commun.</i> 2004 Oct 1; 322 (4):-1326-35. Shamsuddin AM. Inositol phosphates have novel anticancer function. <i>J Nutr.</i> 1995; 125:725S-732S. Baten A, et al. Inositol- phosphate-induced enhancement of natural killer cell activity correlates with tumor suppression. <i>Carcinogenesis.</i> 1989; 10(9):1595-1598. Nanba H, et al. effect of Maitake D-fraction on cancer prevention. <i>Ann N Y Acad</i> <i>Sci.</i> 1997 Dec 29; 833:204-7. Matsui K, et al. Effects of maitake (<i>Grifola frondosa</i>) D- fraction on the carcinoma angiogenesis. <i>Cancer Lett.</i> 2000; 172:193-8. Sheng Y, et al. Enhanced DNA repair, immune function and reduced toxicity of [brand name], a novel aqueous extract from Uncaria tomentosa. <i>J Ethnopharmacology.</i> 2000; 69:115-126. Wurm M, et al. Pentacyclic oxindole alkaloids from Uncaria tomentosa induces human endothelial cells to release a lymphocyte- proliferation-regulating factor. <i>Planta Medica.</i> 1998; 65:701- 704. Wagner H, et al. The alkaloids of Uncaria tomentosa and their phagocytosis increasing effects. <i>Planta Medica.</i> 1985; 5:419-423.

$\begin{matrix} \mathbf{I} \ \mathbf{N} \ \mathbf{T} \ \mathbf{E} \ \mathbf{G} \ \mathbf{R} \ \mathbf{A} \ \mathbf{T} \ \mathbf{I} \ \mathbf{V} \ \mathbf{E} \\ \begin{matrix} \mathbf{I} \ \mathbf{N} \ \mathbf{T} \ \mathbf{E} \ \mathbf{R} \ \mathbf{V} \ \mathbf{E} \ \mathbf{N} \ \mathbf{T} \ \mathbf{I} \ \mathbf{O} \ \mathbf{N} \ \mathbf{S}^{\circ} \end{matrix}$

Cancer Prevention

Inflammation

Protocols

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Ingredients	Dosage	Rationale	Reference
Omega-3 Fatty Acids 14-18% EPA* 8.3-11.7% DHA* Pharmaceutical grade High purity Naturally stable *EPA=eicosapentaenoic acid *DHA=docosahexaenoic acid	1.5 – 5 g daily	 Possess anti-inflammatory and immunomodulatory properties¹ Regulates macrophage activity, TNF alpha and interleukin production, and induces cancer cell apoptosis^{2,3} Slows the growth of experimental cancer (laboratory study)^{2,3} Demonstrates antiproliferative effects (aliginal studiog)^{4,5} 	 Erickson KL, et al. Dietary fish oil modulation of macrophage tumoricidal activity. <i>Nutrition</i>. 1996 Jan; 12(1 Suppl):S34-8. Lo CJ, et al. Fish oil modulates macrophage P44/P42 mutagen-activated protein kinase activity induced by lipopolysaccharide. <i>JPEN J Parenter Enteral Nutr.</i> 2000 May-Jun; 24(3):159-63.
		 Reduces tumor growth and induces cell cycle arrest in cancerous cells (laboratory study)⁶ 	 Caughey GE, et al. The effect on human tumor necrosis factor alpha and interleukin beta production of diets enriched in n-3 fatty acids from vegetable oil or fish oil. Am J Clin Nutr. 1996 Jan; 63(1):116-22. Wallin R. Fish Oil Tendency to Rancidity Comparison. Unpublished data. 2004. Jho DH, et al. Role of omega-3 fatty acid supplementation in inflammation and malignancy. Integr Cancer Ther. 2004 Jun; 3(2):98-111. Hardman WE. Omega-3 fatty acids to augment cancer therapy. J Nutr. 2002 Nov; 132
Turmeric (<i>Curcuma</i> <i>longa</i>) Extract (90% curcuminoids)	Take 1.2 g twice daily	 Possesses anti-cancer, anti- inflammatory, and anti-angiogenesis properties¹ Inhibits cancer cell proliferation by arresting them at various phases of cell cycle Inhibits 70% of breast cancer cell growth (<i>in vitro</i>)² Suppresses tumor initiation, promotion and metastasis^{3,4} Helicobacter pylori is a group 1 carcinogen associated with development of gastric and colon cancer; curcumin inhibits growth of 19 H. pylori strains (<i>in vitro</i>)⁵ 	 (11Suppl):3508S-3512S. Somasundaram S, et al. Dietary curcumin inhibits chemotherapy-induced apoptosis in models of human breast cancer. <i>Cancer Res.</i> 2002 Jul 1; 62(13):3868-75. Baatout S, et al. Increased radiation sensitivity of an eosinophilic cell line following treatment with epigallocatechin-gallate, Resveratrol and curcuma. <i>Int J</i> <i>Mol Med.</i> 2005 Feb; 15(2):337- 52. Gao C, et al. [Study of the effects of curcumin on angiogenesis] <i>Zhong Yao Cai.</i> 2003 Jul; 26(7):499-502. Aggarwal BB, et al. Anticancer potential of curcumin: preclinical and clinical studies. <i>Anticancer Res.</i> 2003 Jan-Feb; 23(1A):363-98. Mahady GB, et al. Turmeric (Curcuma longa) and curcumin inhibit the growth of Helicobacter pylori, a group 1 carcinogen. <i>Anticancer Res.</i> 2002 Nov-Dec; 22(6C):4179- 81.

I N T E G R A T I V EI N T E R V E N T I O N S[®]

Cancer Prevention

Detoxification

Protocols

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Ingredients	Dosage	Rationale	Reference
Dietary fiber Fiber blend containing: Psyllium husk Oat bran Guar gum Pectin (from citrus fruit) Marshmallow root	2 g daily 1727 mg daily	 General Detoxification Support Absorbs toxins and carcinogens, such as secondary bile acids and diacylclycerol, while in the intestinal tract¹ Augments immune system by enhancing natural killer cell activity¹ To be effective, encapsulated fiber products must adequately disperse following ingestion (<i>in vitro</i>)² 	 Reddy BS. Prevention of colon carcinogenesis by components of dietary fiber. <i>Anticancer</i> <i>Res.</i> 1999 Sep- Oct;19(5A):3681-3. Study on the comparative dispersion of encapsulated fiber blends. Unpublished data. June 2003.
Stable, Gastric- Protected Probiotic Blend of: <i>Lactobacillus acidophilus</i> <i>and Bifidobacterium</i> <i>longum</i>	Take 1 billion CFU daily	 Restoration of Healthy Intestinal Flora Acid-stable probiotics balance the intestinal flora in immune compromised individuals Enhance detoxification of DNA-toxic substances in intestines; associated with anti-carcinogenic effects^{1,2} To provide full health benefits, supplement must survive gastric conditions and be released in the intestine (<i>in vitro</i>)³ 	 Goossens D, et al. Probiotics in gastroenterology: indications and future perspectives. <i>Scand</i> <i>J Gastroenterol Suppl.</i> 2003(239):15-23. Wollowski I, et al. Protective role of probiotics and prebiotics in colon cancer. <i>Am</i> <i>J Clin Nutr.</i> 2001 Feb;73(2 Suppl_:451S-455S. Probiotic Comparison Testing. Unpublished data. June 3, 2002

INTEGRATIVE INTERVENTIONS[®]

Cancer Prevention

Hormonal Balance

Protocols

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Ingredients	Dosage	Rationale	Reference
Stable, Bioavailable Diindolylmethane (DIM), co-solubilized with vitamin E and phosphatidylcholine, for enhanced absorption and bioavailability	Take 120 mg blend (30 mg DIM) daily	 Increases ratio of desirable 2-OH estrogen metabolites over undesirable 16-hydroxyestrone (16-OH) estrogen metabolites¹ Also regulates level of dihydrotestosterone (DHT), a potent androgen² Documented anti-proliferative effects against prostate, breast, and cervical cancer cells²⁻⁴ Selectively induces apoptosis in leukemia cells through modulation of extracellular signal-regulated kinase and proliferators-activated receptor gamma (PPAR-γ) signaling pathway (<i>in vitro</i>)^{2,5} Strongly inhibits development of human breast tumor in experimental cancers by up to 64% (laboratory study)^{1,6} Possesses antiangiogenic properties; neovasculation was inhibited up to 76% (laboratory study)^{1,6} 	 McDougal A, et al. Methyl- substituted diindolylmethanes as inhibitors of estrogen- induces growth of T47D cells and mammary tumors in rats. <i>Breast Cancer Res Treat.</i> 2001 mar; 66(2):147-57. Le HT, et al. Plant-derived 3, 3'-Diindolylmethane is a strong androgen antagonist in human prostate cancer cells. <i>J Biol Chem.</i> 2003; 278(23):21146- 45. Vanderlaag K, et al. Inhibition of breast cancer cell growth and induction of cell death by 1, 1-bis (3'-indolyl) methane (DIM) and 5, 5'-dibromoDIM. <i>Cancer Lett.</i> 2005 Jul 25; [Epub ahead of print]. Contractor R, et al. Anovel ring-substituted diindolylmethane, 1, 1-bis [3'-(5-methoxyindolyl)]-1-(p-t- butylphenyl) methane, inhibits extracellular signal-regulated kinase activation and induces apoptosis in acute myelogenous leukemia. <i>Cancer Res.</i> 2005 Apr 1; 65(7):2890-8. Chang X, et al. 3, 3'- diindolylmethane inhibits angiogenesis and the growth of transplantable human breast carcinoma in athymic mice. <i>Carcinigenesis.</i> 2005 Apr; 26(4):771-6. Epub 2005 Jan 20. Li'Y, et al. selective growth regulatory and pro-apoptotic effects of DIM is mediated by AKT and NF-kappaB pathways in prostate cancer cells. <i>Front Biosci.</i> 2005 Jan 1; 10:236-43.

Cancer Prevention

Prostate Cancer

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Ingredients	Dosage	Rationale	Reference	
Zinc Saw Palmetto (<i>Serenoa</i> <i>repens</i>) Stinging Nettle (<i>Urtica</i> <i>dioica</i>) Beta-sitosterol Lycopene	Take daily with food. 30 mg 600 mg 300 mg 60 mg 1 mg	 Zinc is critical for proper cell growth, proliferation, metabolism and migration¹ Saw palmetto inhibits prostate cell growth by up to 20-25% and cancer cell growth by up to 50% (<i>in vitro</i>); also reduces inflammation (COX-2)² Stinging nettle improved lower urinary tract symptoms for 81% of patients; peak flow rate increased 2.5 times that of placebo³ Beta-sitosterol inhibits growth of prostate cancer cells by 70%, inhibits invasion of prostate cancer cells by 78%, and reduced migration of tumor cells by 60-93%⁴ Research suggests lycopene may decrease growth of prostate cancer⁵ 	 Costello LC, et al. The clinical relevance of the metabolism of prostate cancer; zinc and tumor suppression: connecting the dots. <i>Mol</i> <i>Cancer</i>. 2006 May 15;5(1):17 [Epub ahead of print] Goldmann WH, et al. Saw palmetto berry extract inhibits cell growth and Cox-2 expression in prostatic cancer cells. <i>Cell Biol Int</i>. 2001;25(11):1117-24. Safarinejad MR. Urtica dioica for Treatment of Benign Prostatic HyperplasiaA Prospective, Randomized, Double-Blind, Placebo- Controlled, Crossover Study. <i>J Herb Pharmacother</i>. 2005;5(4):1-11. Awad AB, et al. In vitro and in vivo (ACID mice) effects of phytosterols on the growth and dissemination of human prostate cancer PC-3 cells. <i>Eur J Cancer Prev</i>. 2001 Dec;10(6):507-13. Kucuk O, et al. Phase II randomized clinical trial of lycopene supplementation before radical prostatectomy. <i>Cancer Epidemiol Biomarkers Prev</i>. 2001;10:861-868. 	
Calcium D-Glucarate Green Tea (<i>Camellia</i> <i>sinensis</i>) Maitake (<i>Grifola</i> <i>frondosa</i>) Mushroom Lycopene	Take twice daily with meals. 200 mg 50 mg 55 mg 2.5 mg	 Calcium D-glucarate Elevated beta-glucuronidase activity has been associated with an increased risk for various cancers, particularly hormone- dependent cancers such as breast, prostate, and colon cancers. Calcium D-glucarate inhibits activity of β- glucuronidase^{1,2} Green tea inhibits prostate cancer development, progression, and metastasis^{3,4} Maitake mushroom activates immune cells and possesses anti-tumor activities⁵ 	 Walaszek Z, et al. Metabolism, uptake, and excretion of a Dglucaric acid salt and its potential use in cancer prevention. <i>Cancer</i> <i>Detect Prev</i>.1997;21:178- 190. Walaszek Z. Potential use of D-glucaric acid derivatives in cancer prevention. <i>Cancer</i> <i>Lett</i> 1990;54:1–8. Gupta S, et al. Inhibition of prostate carcinogenesis in TRAMP mice by oral infusion of green tea polyphenols. <i>Proc Natl Acad Sci U S A</i>. 2001;98:10350-10355. Chung LY, et al. Induction of apoptosis by green tea catechins in human prostate cancer DU145 cells. <i>Life Sci</i>. 2001;68:1207-1214. Matsui K, et al. Effects of maitake (Grifola frondosa) D- Fraction on the carcinoma angiogenesis. <i>Cancer Lett</i>. 2001;172:193-198. 	

Cancer Prevention

Prostate Cancer

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Ingredients	Ingredients Dosage Rationale		Reference

ADDITIONAL SUPPORT FOR PROSTATE CANCER PREVENTION OR ESTROGEN DOMINANCE					
Stable, Bioavailable Diindolylmethane (DIM), co-solubilized with vitamin E and phosphatidylcholine, for enhanced absorption and bioavailability	30 mg daily	 Estrogen Balance Shifts estrogen metabolism to C-2 pathway in liver, which increases ratio of 2-hydroxy and 2-methoxy estrogen metabolites over 16-hydroxyestrone estrogen metabolites¹ Exhibits potent antiproliferative and antiandrogenic properties in androgen- dependent human prostate cancer cells² Also reduces intracellular and secreted PSA levels² 	 Zeligs MA. Safer estrogen with phytonutrition. <i>Towns Lett.</i> 1999;189:83-88. Le HT, et al Plant-derived 3,3'- Diindolylmethane is a strong androgen antagonist in human prostate cancer cells. <i>J Biol Chem.</i> 2003 Jun 6;278(23):21136-45. 		
Calcium D-Glucarate	0.5 - 1.5 g three times daily with meals	 Estrogen Detoxification Detoxifies estrogen and xenoestrogen by inhibiting beta-glucuronidase and preventing hydrolysis of their glucuronides¹ 	 Walaszek Z, et al. Metabolism, uptake, and excretion of a D-glucaric acid salt and its potential use in cancer prevention. <i>Cancer Detect Prev</i>. 1997;21(2):178-90. 		

This Integrative Interventions protocol is sponsored by Integrative Therapeutics, Inc., Green Bay, WI, 54311 <u>www.integrativeinc.com</u> 1-800-931-1709