This article originally appeared in the Canadian Association of Naturopathic Doctors' Vital Link Journal, Fall-Winter 2014 Issue. Opinions expressed in this article are not necessarily those of the editors, the CAND nor its board of directors.

Natural Health Products Commonly Used in Cancer Management

Dr. Mark Fontes, ND, **Dr. Kimberley Ramberan,** ND

Naturopathic oncology is the application of the art and science of naturopathic medicine in the field of cancer care and treatment.[1] Given the complexity of cancer and the potential limitations of treatment, it is understood that no single therapy is sufficient to treat a patient with cancer.[2] The evolving practice of naturopathic oncology should be incorporated into the integrative model of patient-centered cancer care.

The goals of naturopathic oncology are to improve overall survival, minimize the side effects of chemotherapy and radiation therapy safely and effectively, and improve quality of life for patients living with cancer. Naturopathic oncology is a vital component of a comprehensive, whole-person approach to cancer care that spans from prevention through treatment and into survivorship.[1]

In order to achieve these goals, naturopathic oncology focuses on specific dietary interventions, lifestyle changes, exercise recommendations, nutritional supplementation and addressing the mental-emotional impact of the process.

This article focuses on the clinical application, efficacy, and safety of key nutritional and botanical supplements that have been found to be effective in the treatment and management of patients living with cancer. This paper will discuss *Astragalus membranaceus* (astragalus), *Curcuma longa* (turmeric), EGCG, fish oil, melatonin, modified citrus pectin, medicinal mushrooms, and vitamin D.

Astragalus (*Astragalus membranaceus*)

The dried root of the herb *Astragalus membranaceus* (astragalus) is a widely used agent in herbal medicine. The use of astragalus in cancer care came about due to its historical reputation as an immune-modulating agent. Studies have identified that the immune-modulating effects are mostly from the polysaccharide (astragalan) component of the dried root.[3] Although human trials are currently limited, *in vivo* and *in vitro* studies are showing promising results that correlate with clinical findings; in particular, improvements in increasing white blood cell counts.

Astragalus has been found to produce profound immunological effects by stimulating macrophage and NK cell activity.[4] Human studies have demonstrated that when given with chemotherapy, Astragalus improves overall survival, and stabilizes or improves Karnofsky performance status (a quality of life assessment).[5] It also has been shown to protect white blood cells counts during chemotherapy with cyclophosphamide, platinum agents, and other myelosuppressive chemotherapies.[6]

Dosage: 2000 mg qd cc.

Safety: Avoid in acute infections and use with caution with immunosuppressive medications and in patients with autoimmune disease.[4]

Turmeric (*Curcuma longa*)

Curcumin is a polyphenolic derivative extracted from turmeric (*Curcuma longa*) root. It has been used traditionally for centuries in medicine for a variety of ailments, and in particular inflammatory conditions.[7] Curcumin has been shown to exhibit a variety of pharmacological effects in cancer cells by inhibiting enzymes generating reactive oxygen species and inflammatory lipids (e.g., COX, LOX), pro-inflammatory transcription factors (e.g., NF-κβ, STAT3) and kinases (e.g., PKC, EGFR tyrosine kinase). Through these mechanisms, curcumin may provide a direct anti-cancer effect and substantially alleviate the side effects associated with chemotherapy and radiation therapy.[8] Curcumin has been widely studied as an adjunctive treatment with several cancers including colorectal, hepatocellular, kidney, gastric, lung, ovarian and hematological malignancies.[8] For a list of additional studies on curcumin refer to Table 1.

A significant problem to curcumin's therapeutic effect is its poor oral bioavailability. Several studies have looked at different formulations in order to improve absorption and utilization of curcumin. Further research is required in order to ascertain which type of curcumin preparation is the most appropriate to use in cancer care.

Overall safety of curcumin in combination with chemotherapy and radiation therapy has been studied. A randomized controlled trial of 30 breast cancer patients undergoing radiation therapy took 2 grams of curcumin three times per day. At the end of treatment, the group treated with curcumin had fewer side effects, including less severe radiation dermatitis.[9] Curcumin has been demonstrated to be safe in patients receiving various chemotherapy agents including gemcitabine, erlotinib, doxorubicin, 5-FU, paclitaxel, cisplatin, oxaliplatin, and docetaxel.[7,10]

Dosage: 2,000 mg to 6,000 mg *Curcuma longa* qd cc.

Safety: Evidence from *in vitro* and *in vivo* studies suggests curcumin

may interact with drugs that are substrates of P-glycoprotein or cytochrome P450 enzymes[11]. Curcumin should only be used under the supervision of a practitioner trained in naturopathic oncology by patients receiving chemotherapy, as there are some chemotherapeutics with which curcumin is contraindicated.

TABLE 1. Selected Research Studies on Turmeric

Study	Cancer or cell type	Results
Yin 2014. In vivo.[12]	Ovarian cancer	Induces apoptosis in dose-dependent manner.
Carroll 2011. Phase II trial.[13]	Colorectal cancer	Prevents colorectal neoplasia.
Dhillon 2008. Phase II trial.[14]	Pancreatic cancer	Reductions in inflammatory markers.

Epigallocatechin-3-gallate *(EGCG)*

EGCG is the major polyphenol with pharmacological activity found in green tea (*Camellia sinensis*) leaf.[15] Studies have demonstrated anti-carcinogenic and anti-mutagenic activities, which suggest that it can reduce tumour progression, and provide preventative effects.

The cancer preventative effects of EGCG are supported by results from epidemiological, *in vitro*, animal and clinical studies. Multiple studies have demonstrated that treatment with EGCG inhibits tumour incidence in different organ sites such as skin (UV radiation and chemically induced), lung, liver, breast, prostate, stomach, mammary gland and colon based on preclinical, observational, and clinical trial data.[16] EGCG functions as a powerful anti-oxidant and can suppress inflammatory processes that lead to transformation, hyper-proliferation, and the initiation of carcinogenesis.[17]

In vitro, EGCG has shown to cause growth inhibition, apoptosis and cell cycle arrest in various human cancer cell lines including leukemia, melanoma, breast cancer, lung cancer, and colorectal cancer.[15] The ability of EGCG to inhibit angiogenesis, initiate apoptosis in cancer cells and suppress oncogenic transcription factors has also been proven by research.[18] EGCG promotes cytotoxic T-cell activities in a tumour microenvironment, thereby improving the immune status in a patient undergoing treatment.[19] For a list of additional studies on EGCG refer to Table 2.

EGCG is currently being researched *in vivo* for its synergistic effects with chemotherapy.[20] The combination of EGCG and doxorubicin has been shown to facilitate anti-tumour effects in hepatocellular carcinoma and metastatic prostate cancer.[21,22]

Dosage: 1000-1500mg qd cc of 95% polyphenol extract.[23]

Safety: May cause nausea and GI upset if not taken with food.[24] *In vitro* and *in vivo* evidence suggests EGCG may interact with drugs that are substrates of cytochrome P450 enzymes.[25] EGCG should only be used under the supervision of a practitioner trained in naturopathic oncology by patients receiving chemotherapy, as there are some chemotherapeutics where it is contraindicated.

TABLE 2. Selected Research Studies on EGCG

Study	Cancer or cell type	Results
D'Arena 2013. Clinical trial.[26]	Chronic lymphocytic leukemia	EGCG controlled lymphocytosis and prevented disease progression.
Seely 2005. Meta-analysis.[27]	Breast cancer	Five or more cups of green tea daily demonstrates a trend towards prevention of breast cancer.

Fish Oil (Omega-3 Fatty Acids)

Dietary fish oil has been shown to have beneficial effects in several chronic degenerative and inflammatory diseases such as cardiovascular disease, diabetes and cancer. These beneficial effects appear to be due to the high content of the omega-3 polyunsaturated fatty acids, docosahexanoic acid (DHA) and eicosapentanoic acid (EPA). Neither can be synthesized by mammals and must be obtained from dietary sources.

Researchers have established the capability of omega-3 fatty acids to influence cancer cell proliferation and differentiation, while reducing inflammation and chemotherapy related side effects. DHA in particular has been shown to improve tumour cell cytotoxicity and to inhibit angiogenesis and metastasis. The majority of current literature supports the use of omega-3 fatty acids for the prevention and treatment of breast cancer, colorectal cancer and prostate cancer.[28]

Human studies have demonstrated that at doses over two grams of combined EPA and DHA per day, fish oil can prevent loss of muscle mass and decrease overall weight loss.[29] In non-small cell lung cancer patients who were supplemented with EPA and DHA, CRP and IL-6 levels decreased over the course of two months, supporting the anti-inflammatory mechanism of action of fish oil.[30] Other trials have demonstrated similar findings,[31] including the ability of fish oil supplementation to reduce cachexia and improve albumin levels.[32] These findings are significant as inflammation is a critical component of tumour progression, in that it fosters proliferation, survival and migration of cancer cells.[33] For a list of additional studies on fish oil refer to Table 3.

Dosage: 2,000 + mg combined EPA and DHA qd cc.

Safety and drug interactions: Omega-3 fatty acids are thought to have anticoagulant effects and impair bleeding time. However, studies have shown they do not affect platelet function after surgery.[34] Some patients may experience belching, nausea and diarrhea, although studies show these adverse effects are reported with low incidence.[32]

TABLE 3. Selected Research Studies on Fish Oil

Study	Cancer or cell type	Results
Kim 2009. Case-control study.[35]	Breast cancer	High consumption of fatty fish is associated with a reduced risk of breast cancer, especially postmenopausal breast cancer.
Hutchins-Wiese 2014. RCT.[36]	Postmenopausal breast cancer survivors	At 4g of EPA and DHA per day for 3 months, reduces bone resorption associated with aromatase inhibitor use.
Singh 2014. Review.[37]	Hepatocellular carcinoma	May be associated with reduced risk of hepatocellular carcinoma
Yeh 2013. RCT.[38]	Head and neck cancer	Improved body weight and serum albumin levels in patients with cachexia.

Melatonin

Melatonin is a pleiotropic hormone that was initially believed to be synthesized solely in the pineal gland, however, it has been recently recognized that it has multiple actions and is produced in a variety of tissues, including locally in the GI tract.[39] Melatonin is a natural oncostatic agent that has been researched for its diverse and profound effects in a cancer care setting, including: inflammation, apoptosis, angiogenesis, immune stimulation, reduction in treatment related side-effects, and improvements in tolerance to chemotherapy and radiation therapy. Additionally, melatonin has evidence to suggest it improves overall survival and progression free survival in patients with cancer.[40]

Melatonin has been studied in conjunction with radiation therapy and a variety of chemotherapeutic agents, including anthracylines, anti-estrogens and antiaromatases,[41] etoposide, cisplatin, gemcitabine, oxalipatin, and 5-Fluorouracil.[40] Melatonin may improve treatment response and decrease side effects including thrombocytopenia, neurotoxicity and fatigue.[42, 43]

Melatonin has been shown to significantly modulate the effects of chemotherapy by enhancing its therapeutic effect and reducing its toxicity. This effect is believed to be due in part to melatonin's antioxidant effect and prevention of chemo-induced lymphocytic damage.[44] Lissoni *et al.* assessed the 5-year survival results in 100 metastatic non-small cell lung cancer patients undergoing cisplatin and etoposide, with or without melatonin (20mg qd hs). Overall tumour regression rate and 5-year survival results were higher in patients concomitantly treated with melatonin.[45]

In a systematic review and meta-analysis of randomized trials, melatonin was assessed in conjunction with chemotherapy, radiotherapy, supportive care and in a palliative care setting. 1-year survival, complete response (CR), partial response (PR), stable disease (SD) and chemotherapy-associated toxicities were all assessed. Pooled relative risk for 1-year mortality was 0.63. Improved effect was found for CR, PR, and SD. Melatonin also significantly reduced asthenia, leukopenia, nausea and vomiting, hypotension and thrombocytopenia.[43] For a list of additional studies on melatonin refer to Table 4.

Dosage: 20mg qd hs.

Safety: Melatonin may cause drowsiness, altered sleep patterns and vivid dreams, although these side effects are reported with a low incidence.[45]

TABLE 4. Selected Research Studies on Melatonin

Study	Cancer or cell type	Results
Schernhammer 2012. Clinical trial.[46]	Breast cancer	Melatonin was well-tolerated without any grade 3/4 toxicity.
Lissoni 2007. RCT.[47]	Advanced solid cancers (non-small cell lung cancer, colorectal cancer, gastric cancer)	2-year study survival rate was significantly higher in patients concomitantly treated with melatonin (20mg qd orally).
Persson 2005. RCT.[48]	Advanced gastrointestinal cancer	Melatonin provided a weight stabilizing effect.
Yan 2002. Prospective study.[49]	Hepatocellular carcinoma	Melatonin protected liver function and improved the effect of transcatheter arterial chemoembolization.

Modified Citrus Pectin (MCP)

MCP is a complex polysaccharide that is the water soluble component of plant fiber derived from citrus fruit and modified by means of high pH and temperature treatment.[50] It is used in naturopathic oncology in order to decrease risk of metastasis and induce cancer cell apoptosis.

A significant mechanism of action of MCP is antagonizing the binding protein, Galectin-3 (Gal-3). Gal-3 is a carbohydrate-binding

protein that is involved in many physiological and pathological processes, such as cell growth and differentiation, cell-cell and cell-extracellular matrix adhesions, metastasis, and regulation of apoptosis.[51] Gal-3 has also been shown to enhance tumour cell sensitivity to chemotherapy through the regulation of apoptotic responses to cytotoxic drugs.[52] Gal-3 is expressed in a variety of cancers, including bladder,[53] breast,[54] colorectal,[55] and thyroid[56] cancers. By inhibiting Gal-3, MCP is able to exhibit beneficial anti-adhesive properties and increases apoptotic responses of tumour cells to chemotherapy.

Dosage: The typical adult dosage for the powder is 5g tid, mixed with water or juice. For capsules, the suggested dose is 800mg tid cc.

Safety: May cause mild abdominal cramps and diarrhea, which resolve after stopping MCP.[57]

Medicinal Mushrooms

Mushrooms have an established history of use in traditional Chinese medicine especially in the treatment of cancer, which has led to investigative research into their anti-tumour properties.

Currently there are over 700 published studies demonstrating anti-cancer (cytotoxic and immune enhancing) properties of medicinal mushrooms with large scale clinical trials of *Trametes versicolor* and *Lentinus edodes*, and on a smaller scale, *Grifola frondosa*, *Ganoderma lucidum* and *Agaricus brasiliensis*.[58] Mushrooms contain a diverse variety of compounds with physiological activity. Most clinical trials have studied the polysaccharide portions of the mushrooms (beta-glucans, proteoglycans, and related compounds).[59] Polysaccharides are long-chain polymers of glucose found in the cell walls of fungi. They are minimally orally available in the raw biomass form. It is important to note that hot water extraction is a necessary processing step in making these polysaccharides bioavailable. The level of anti-cancer activity appears to be related to the degree of branching of the polysaccharides and their solubility in water.[58]

Mushrooms have been most thoroughly studied in gastrointestinal cancers (esophageal, gastric, colorectal), hepatocellular carcinomas and breast cancer. However, it is clear that mushrooms have additional benefits through their biological activity in improving immunological parameters, such as white blood cell counts and platelets, in patients with cancer undergoing chemotherapy and/or radiotherapy.

Agaricus has immunological effects on the complement and innate immune systems, which could potentially lead to pro-apoptotic and anti-angiogenic effects.[60] *Coriolus* contains two polysaccharides, Polysaccharide peptide (PSP) and Polysaccharide-K (PSK), that improve overall survival rates in patients with multiple cancers, including gastric, colorectal, and breast carcinomas.[61] *Grifolia* stimulates the function of various immune cells and may improve overall quality of life, reduce tumour burden and act synergistically with chemotherapy, especially in patients with hepatocellular, breast and lung cancer.[62] *Ganoderma* may reduce tumour burden and stimulate immunity in various cancer types.[63] For a list of additional studies on medicinal mushrooms refer to Table 5.

Dosage: Therapeutic dose varies depending on which species of mushroom is used. 3-6 grams qd in divided doses is generally recommended.

Safety: Caution with patients diagnosed with an autoimmune condition, and/or using immunosuppressive medications.[58]

TABLE 5. Selected Research Studies on Medicinal Mushrooms

Study	Cancer or cell type	Results
Tanaka 2012. RCT.[64] Mushroom: *Coriolus*	Gastric cancer	In patients with early tumour recurrence, overall survival was significantly better in the PSK group. In patients with lymph node metastasis, median overall survival was better in the PSK group compared with the control group.
Shibata 2011. RCT.[65] Mushroom: *Coriolus*	Metastatic colorectal cancer	PSK + FOLFOX chemotherapy resulted in lower frequencies of adverse effects (nausea, peripheral neuropathy, neutropenia).
Oka 2010. RCT.[66] Mushroom: *Ganoderma*	Colorectal adenomas	Inhibits development of precancerous colorectal adenomas vs. control.
Kodama 2003. Human trial.[67] Mushroom: *Maitake*	Colorectal adenomas	D-Fraction modestly increased CD4+ and CD8+ cell numbers, and significantly increased NK cell numbers after administration

Vitamin D

Vitamin D, a sterol nutrient, is unique in that it can be obtained either from the diet or endogenous synthesis. Vitamin D undergoes hydroxylation reactions mostly in the liver, to form 25-hydroxyvitamin D (25(OH)D), and then in the kidney where 25(OH)D is converted to 1,25-dihydroxyvitamin D ($1,25(OH)_2D$).[68] The most commonly measured vitamin D metabolite is serum 25(OH)D due to its longer half-life and higher serum levels compared with the $1,25(OH)_2D$ metabolite. Studies have demonstrated that low 25(OH)D levels are associated with an increase in all-cause mortality, cardiovascular mortality, and cancer-related mortality (particularly in patients with a history of cancer).[69] It has been projected that raising serum 25(OH)D levels to 100-150nmol/L would prevent approximately 58,000 new cases of breast cancer and 49,000 new cases of colorectal cancer each year in North America.[70] This is significant because 32% of Canadians are estimated to have vitamin D levels below 50 nmol/L.[71]

	Serum 25(OH)D
Deficient	< 25nmol/L
Insufficient	25-75nmol/L
Optimal	75-250nmol/L

The anti-cancer effects of vitamin D result from its role as a nuclear transcription factor that regulates cell growth, differentiation, apoptosis and a wide range of cellular mechanisms central to the development of cancer. 25(OH)D levels have been found to be associated with a reduction in occurrence of aggressive prostate cancer,[72] breast cancer,[73] lymphoma[74] and colorectal cancer.[75] Improved survival has also been reported for early stage non-small cell lung cancer patients,[76,77] likely due in part to the effect of vitamin D on anti-inflammatory processes in the lung.[78] Preliminary data has demonstrated an anti-proliferative effect of vitamin D on hepatocellular carcinoma cell lines.[79] Evidence is currently limited and inconclusive for esophageal cancer, gastric cancer, and pancreatic cancer. Although studies have focused on the ability of vitamin D to prevent cancer, studies suggest that the effects of vitamin D may be more significant for cancer mortality than for incidence.[80] For a list of additional studies on vitamin D, refer to Table 6.

Further study is required to ascertain the precise benefit regarding vitamin D supplementation in cancer. In particular, the dose and serum levels required to impact outcomes like incidence, prognosis, quality of life and immunological parameters in patients with cancer.

Dosage: 1,000 + IU qd cc depending on 25(OH)D serum levels.

Safety: Close monitoring of vitamin D levels advised in patients with kidney disease, high blood calcium levels, liver disease, or other diseases associated with impaired calcium metabolism. Although rare, case studies of acute toxicity resulting in hypercalcemia have been reported.[81] Discontinue vitamin D immediately until levels return to normal range and symptoms resolve.

TABLE 6. Selected Research Studies on Vitamin D

Study	Cancer or cell type	Results
Maalmi 2014. Meta-analysis.[82]	Colorectal and breast cancer	Higher 25(OH)D levels (>75nmol/L) associated with significantly reduced mortality.
Mohr 2014. Meta-analysis.[83]	Breast cancer	Higher 25(OH)D levels associated with lower mortality. Target levels should be at least 80nmol/L.
Zeicher 2014. Retrospective.[83]	HER2+ non-meta static breast cancer	Improved disease free survival.
Li 2014. Meta-analysis.[84]	Colorectal cancer, breast cancer, lymphoma.	Improved overall survival in patients with higher circulating 25(OH)D levels at or near the time of diagnosis.

Conclusion

The art and science of naturopathic oncology strives to use the best of current available evidence and clinical experience to provide safe, comprehensive and efficacious strategies for patients living with cancer. Studies have demonstrated that over 80% of patients diagnosed with cancer report using vitamin or mineral supplementation.[85] It is imperative that these recommendations are made by a licensed naturopathic doctor in order to provide proper patient care and avoid any interactions with conventional treatment. An integrative patient-centered approach involves the incorporation of naturopathic medicine modalities with conventional therapies. As healthcare professionals providing patient centered healthcare, naturopathic doctors and medical doctors working together will provide patients with the best care and outcome. The field of naturopathic oncology continues to evolve in its awareness among the medical community, research groups and among patients seeking integrative care. Clinical evidence and studies demonstrate that naturopathic treatments can provide significant and profound improvements in quality of life, treatment tolerance and overall prognosis for patients living with cancer.

About the Authors

Dr. Mark Fontes, ND is a graduate from the Canadian College of Naturopathic Medicine (CCNM) in Toronto, Ontario, Canada. He received additional training in naturopathic oncology and intravenous therapies during his clinical residency at CCNM. Dr. Fontes currently practices at Restore Integrative Health on Queen Street East in Toronto, where he strives to work alongside medical doctors and oncologists in order to provide patients with the best possible care. He is also part-time faculty at CCNM where he supervises fourth-year interns and the intravenous therapy shift in the student teaching clinic. Dr. Fontes is the Ontario board member for the Canadian Association of Naturopathic Doctors and maintains an active membership with the Ontario Association of Naturopathic Doctors and the Oncology Association of Naturopathic Physicians.

Dr. Kimberley Ramberan, ND has been in practice since 2010 and has had a major clinical focus in integrative oncology and cancer care support. She is intravenous therapy board certified which allows her to provide comprehensive naturopathic care. She practices at Naturopathic Foundations Health Clinic in Markham, Ontario. Dr. Ramberan is a graduate of the Canadian College of Naturopathic Medicine (CCNM) and a recipient of the Naturopathic Grassroots award for excelling in the field of woman's health and compassionate care. She is a member of the Canadian Association of Naturopathic Doctors, Ontario Association of Naturopathic Doctors, and the Oncology Association of Naturopathic Physicians.

References

1. Oncology Association of Naturopathic Physicians. 2014.
2. Kirkwood J, Tarhini A, Sparano J, et al. Comparative clinical benefits of systemic adjuvant therapy for paradigm solid tumors. *Cancer Treatment Reviews*. 2012;39:27-43.
3. Fu J, Wang Z, Huang L, et al. Review of the botanical characteristics, phytochemistry, and pharmacology of Astragalus membranaceus (Huangqi). *Phytother Res*. 2014 Sep;28(9):1275-83.

4. Mills S, Bone K. *Principles and Practice of Phytotherapy*. Edinburgh, Scotland: Churchill Livingstone, 2000. p 14-15.
5. McCulloch M, See C, Shu XJ, et al. Astragalus-based Chinese herbs and platinum-based chemotherapy for advanced non-small cell lung cancer: meta-analysis of randomized trials. *J Clin Oncol*. 2006;24(3):419-30.
6. Stargrove M, Treasure J, McKee D. *Herb, Nutrient and Drug Interactions: Clinical Implications and Therapeutic Strategies*. 2008. p 5-9.
7. Bayet-Robert M, Kwiatkowski F, Leheurteur M, et al. Phase I dose escalation trial of docetaxel plus curcumin in patients with advanced and metastatic breast cancer. *Cancer Biology and Therapy*. 2010;9(1):8-14.
8. Belcaro G, Hosoi M, Pellegrini L, et al. A Controlled Study of Lecithinized Delivery System of Curcumin (Meriva) to Alleviate the Adverse Effects of Cancer Treatment. *Phytotherapy Research*. 2014;28:444-450.
9. Ryan JL, Heckler CE, Ling M, et al. Curcumin for radiation dermatitis: a randomized, double-blind, placebo-controlled clinical trial of thirty breast cancer patients. *Radiat Res*. 2013;180(1):34-43.
10. Kanai M, Otsuka Y, Otsuka K, et al. A phase I study investigating the safety and pharmacokinetics of highly bioavailable curcumin in cancer patients. *Cancer Chemother Pharmacol*. 2013;71(6):1521-30.
11. Zhang W, Tan TM, Lim LY. Impact of curcumin-induced changes in P-glycoprotein and CYP3A expression on the pharmacokinetics or peroral ciliprolo and midazolam in rats. *Drug Metab Dispos*. 2007;35(1):110-5.
12. Yin Z, Sun J. Curcumin induces human SKOV3 cell apoptosis via the activation of Rho-kinase. *Eur J Gynaecol Oncol*. 2014;35(4):433-7.
13. Carroll RE, Benya RV, Turgeon DK, et al. Phase II clinical trial of curcumin for the prevention of colorectal neoplasia. *Cancer Prev Res*. 2011;4(3):354-64.
14. Dhillon N, Aggarwal BB, Newman RA, et al. Phase II trial of curcumin in patients with advanced pancreatic cancer. *Clin Cancer Res*. 2008;14(14):4491-9.
15. Brahma N. Singh, Sharmila Shankar, and Rakesh K. Srivastava. Green tea catechin, epigallocatechin-3-gallate (EGCG): mechanisms, perspectives and clinical applications. *Biochem Pharmacol*. Dec 15, 2011; 82(12): 1807–21.
16. Mukhtar H, Ahmad N. Tea polyphenols: prevention of cancer and optimizing health. *AJCN*. 2000;71:1698S–702S.
17. Thawonsuwan J, Kiron V, Satoh S, Panigrahi A, Verlhac V. Epigallocatechin-3-gallate (EGCG) affects the antioxidant and immune defense of the rainbow trout, Oncorhynchus mykiss. *Fish physiology and biochemistry*. 2010;36:687–97.
18. Khan N, Afaq F, Saleem M, Ahmad N, Mukhtar H. Targeting multiple signaling pathways by green tea polyphenol (-)-epigallocatechin-3-gallate. *Cancer Research*. 2006;66:2500–5.
19. Chen D, Milacic V, Chen MS, et al. Tea polyphenols, their biological effects and potential molecular targets. *Histol Histopathol*. 2008;23(4):487-96.
20. Butt MS1, Sultan MT. Green tea: nature's defense against malignancies. *Crit Rev Food Sci Nutr*. 2009 May;49(5):463-73.

21. Li C, Hui-Lan Y, Guo Z, Wen-Min Y, Xing-Zhou C, Fa-Can Z, and Gang L. Autophagy Inhibition Contributes to the Synergistic Interaction between EGCG and Doxorubicin to Kill the Hepatoma Hep3B Cells. *PLoS One*. 2014;9(1):1-10.
22. Stearns ME, Amatangelo MD, Varma D, Sell C, Goodyear SM. Combination therapy with epigallocatechin-3-gallate and doxorubicin in human prostate tumor modeling studies: inhibition of metastatic tumor growth in severe combined immunodeficiency mice. *Am J Pathol*. 2010 Dec; 177(6):3169-79.
23. Pizzorno Joseph E, Murray Michael T. *Textbook of Natural Medicine*, Elsevier. 1999.
24. McKinney Neil. *Naturopathic Oncology - An Encyclopedia Guide for Patients and Physicians*, Second Edition. Liaison Press, Vancouver, BC, Canada. 2012.
25. Wanwimolruk S, Wong K, Wanwimolruk P. Variable inhibitory effect of different brands of commercial herbal supplements on human cytochrome P-450 CYP3A4. *Drug Metabol Drug Interact*. 2009;24(1):17-35.
26. D'Arena G, Simeon V, De Martino L, et al. Regulatory T-cell modulation by green tea in chronic lymphocytic leukemia. *Int J Immunopathol Pharmacol*. 2013;26(1):117-25.
27. Seely D, Fritz H, Kennedy D, et al. Green Tea and Lung Cancer. *Int Can Ther*. 2012;12(1):7-24.
28. Merendino N, Costantini L, Manzi L, et al. Dietary omega-3 Polyunsaturated Fatty Acid DHA: A Potential Adjuvant in the Treatment of Cancer. *BioMed Research International*. 2013.
29. Murphy RS, Mourtzakis M, Chu QS, et al. Nutritional intervention with fish oil provides a benefit over standard of care for weight and skeletal muscle mass in patients with nonsmall cell lung cancer receiving chemotherapy. *Cancer*. 2011;117(8):1775-82.
30. Finocchiaro C, Segre O, Fadda M, et al. Effect of n-3 fatty acids on patients with advanced lung cancer: a double-blind, placebo-controlled study. *Br J Nutr*. 2011;25:1-7.
31. Weiss G, Meyer F, Matthies B, et al. Immunomodulation by perioperative administration of n-3 fatty acids. *Br J Nutr*. 2002;87:89-94.
32. Mocellin MC, Pastore SJ, Camargo C, et al. Fish oil decreases C-reactive protein/albumin ratio improving nutritional prognosis and plasma fatty acid profile in colorectal cancer patients. *Lipids*. 2013;48(9):879-88.
33. Coussens, L and Werb Z. Inflammation and cancer. *Nature* 2003;4(20)860-867.
34. Ries A, Trottenberg P, Elsner F, et al. A systematic review on the role of fish oil for the treatment of cachexia in advanced cancer: an EPCRC cachexia guidelines project. *Palliat Med*. 2012;26(4):294-304.
35. Kim J, Lim SY, Shin A, et al. Fatty fish and fish omega-3 fatty acid intakes decrease breast cancer risk. *BMC Cancer*. 2009;9:216.
36. Hutchins-Wiese HL, Picho K, Watkins BA, et al. High-dose eicosapentanoic acid and docosahexaenoic acid supplementation reduces bone resorption in postmenopausal breast cancer survivors on aromatase inhibitors: a pilot study. *Nutr Cancer*. 2014;66(1):68-76.
37. Singh S, Singh PP, Roberts LR, Sanchez W. Chemopreventive strategies in hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol*. 2014;11(1):45-54.
38. Yeh KY, Wang HM, Chang JW, et al. Omega-3 fatty acid, micronutrient, and probiotic enriched nutrition helps body weight stabilization in head and neck cancer patients. *Oral Surg*. 2013;116(1):41-8
39. Del Fabbro E, Dev R, Hui D, Palmer L, Bruera E. Effects of Melatonin on Appetite and Other Symptoms on Patients with Advanced Cancer and Cachexia: a double-blind placebo-controlled trial. *J Clin Oncol*. 2013;31(10):1271-1276
40. Lissoni P. Biochemotherapy with standard chemotherapies plus the pineal hormone melatonin in the treatment of advanced solid neoplasms. *Pathol Biol*. 2007;55(3-4):201-4.
41. Sanchez-Barcelo EJ, Mediavilal MD, Alonso-Gonzalez C, et al. Melatonin uses in oncology: breast cancer prevention and reduction of the side effects of chemotherapy and radiation. *Expert Opin Investig Drugs*. 2012;21(6):819-31.
42. Wang YM, Jin BZ, Ai F, et al. The efficacy and safety of melatonin in concurrent chemotherapy or radiotherapy for solid tumours: a meta-analysis of randomized controlled trials. *Cancer Chemother Pharmacol*. 2012;69(5):1213-20.
43. Seeley D, Wu P, Fritz H, et al. Melatonin as adjuvant cancer care with and without chemotherapy: a systematic review and meta-analysis of randomized trials. *Integr Cancer Ther*. 2012;11(4):293-303.
44. Lissoni P, Chilelli M, Villa S, et al. Five year survival in metastatic non-small cell lung cancer patients treated with chemotherapy alone or chemotherapy and melatonin: a randomized trial. *J Pineal Res*. 2003;35(1):12-5.
45. Avery D, Lenz M, Landis C. Guidelines for prescribing melatonin. *Ann Med*. 1998;30(1):122-30.
46. Schernhammer ES, Globbie-Hurder A, Gantman K, et al. A randomized controlled trial of oral melatonin supplementation and breast cancer biomarkers. *Cancer Causes Control*. 2012;23(4):609-16.
47. Lissoni P, Paolorossi F, Tancini G. A phase II study of tamoxifen plus melatonin in metastatic solid tumour patients. *Br J Cancer*. 1996;74(9):1466-8.
48. Persson C, Glimelius B, Ronnelid J, et al. Impact of fish oil and melatonin on cachexia in patients with advanced gastrointestinal cancer: a randomized pilot study. *Nutrition*. 2005;21(2):170-8.
49. Yan JJ, Shen F, Wang K, et al. Patiehts with a dvanced primary hepatocellular carcinoma treated by melatonin and transcatheter arterial chemoembolization: a prospective study. *Hepatobiliary Pancreat Dis Int*. 2002;1(2):183-6.
50. Brinker F. *Herbal Contraindications and Drug Interactions: Plus Herbal Adjuncts With Medicines*, 4th Edition. Eclectic Medical Publications. 2010.
51. Yang RY, Liu FT. Galectins in cell growth and apoptosis. *Cell Mol Life Sci*. 2003;60:267–276.
52. Kim J, Olga V, et al. Galectin-3 as a Potential Therapeutic Target in Tumors Arising from Malignant Endothelia. *Neoplasia*. 2007; 9(8): 662–670.

53. Cindolo L, Benvenuto G, Salvatore P, et al. Galectin-1 and galectin-3 expression in human bladder transitional-cell carcinomas. *Int J Cancer*. 1999;84:39–43.
54. Shekhar MP, Nangia-Makker P, Tait L, et al. Alterations in galectin-3 expression and distribution correlate with breast cancer progression: functional analysis of galectin-3 in breast epithelial-endothelial interactions. *Am J Pathol*. 2004;165:1931–1941.
55. Miyazaki J, Hokari R, Kato S, et al. Increased expression of galectin-3 in primary gastric cancer and the metastatic lymph nodes. *Oncol Rep*. 2002;9:1307–1312.
56. Feilchenfeldt J, Totsch M, Sheu SY, et al. Expression of galectin-3 in normal and malignant thyroid tissue by quantitative PCR and immunohistochemistry. *Mod Pathol*. 2003;16:1117–1123.
57. Guess BW, Scholz MC, Strum SB, et al. Modified citrus pectin (MCP) increases the prostate-specific antigen doubling time in men with prostate cancer: a phase II pilot study. *Prostate Cancer Prostatic Dis*. 2003;6(4):301-4.
58. Martin Powell (2010) *Medicinal Mushrooms A Clinical Guide*. Mycology Press.
59. Wasser SP. Medicinal mushrooms as a source of antitumor and immunomodulating polysaccharides. *Appl Microbiol Biotechnol*. 2002 Nov;60(3):258-74.
60. Lima C, Cordova C, Nobrega O, Funghetto S, Karnikowski M. Does the Agaricus blazei Murill Mushroom Have Properties That Affect the Immune System? *Journal of Medicinal Food*. 2011 March;14(1/2):2-8.
61. Wong E, Fai C, Chung L. Efficacy of Yun Zhi (Coriolus versicolor) on Survival in Cancer Patients: Systematic Review and Meta-Analysis. *Recent Patents on Inflammation and Allergy Drug Discovery*. 2012;6:78-87.
62. Kodama N, Komuta K, Nanba H. Can Maitake MD-Fraction Aid Cancer Patients? *Alternative Medicine Review*. 2002;7(3):236-9.
63. Jin X, Ruiz J, Sze DMY, Chan GCF. Ganoderma lucidum (Reishi mushroom) for cancer treatment (Review). *The Cochrane Collaboration*. 2012;6:1-38.
64. Tanaka H, Muguruma K, Ohira M, et al. Impact of adjuvant immunochemotherapy using protein-bound polysaccharide-K on overall survival of patients with gastric cancer. *Anticancer Res*. 2012 Aug;32(8):3427-33.
65. Shibata M, Shimura T, Nishina Y, et al. PSK decreased FOLFOX4-induced peripheral neuropathy and bone marrow suppression in patients with metastatic colorectal cancer. *Gan To Kagaku Ryoho*. 2011 May;38(5):797-801.
66. Oka S, Tanaka S, Yoshida S, et al. A water-soluble extract from culture medium of Ganoderma lucidum mycelia suppresses the development of colorectal adenomas. *Hiroshima J Med Sci*. 2010 Mar;59(1):1-6.
67. Kodama N, Komuta K, Nanba H. Effect of Maitake (Grifola frondosa) D-Fraction on the Activation of NK cells in Cancer Patients. *J Med Food*. 2003;6(4):371-77
68. Feldman D, Krishnan AV, Swami S, et al. The role of vitamin D in reducing cancer risk and progression. *Nat Rev Cancer*. 2014;14(5):342-57.
69. Mena JM, Brenner, H. Vitamin D and Cancer: An Overview on Epidemiological Studies. Chapter 2 of *Sunlight, Vitamin D and Skin Cancer*. 2014.
70. Garland CF, Gorham ED, Mohn SB, Garland FC. Vitamin D for cancer prevention: global perspective. *Ann Epidemiol*. 2009;19(7):468-83.
71. http://www.statcan.gc.ca/pub/82-624-x/2013001/article/11727-eng.htm
72. Gilbert R, Metcalfe C, Fraser WD, et al. Associations of circulating 25-hydroxyvitamin D with prostate cancer diagnosis, stage and grade. *Int J Cancer*. 2012;131(5):1187-96.
73. Yin l, Grandi N, Raum E, et al. Meta-analysis: serum vitamin D and breast cancer risk. *Eur J Cancer*. 2010;46(12):2196-205.
74. Drake MT, Maurer MJ, Link BK, et al. Vitamin D insufficiency and prognosis in non-Hodgkin's lymphoma. *J Clin Oncol*. 2010;28(27):4191-8.
75. Maalmi H, Ordonez-Mena JM, Schottker B, Brenner H. Serum 25-hydroxyvitamin D levels and survival in colorectal and breast cancer patients: systematic review and meta-analysis of prospective cohort studies. *Eur J Cancer*. 2014;50(8):1510-21.
76. Zhou W, Suk R, Liu G, et al. Vitamin D is associated with improved survival in early-stage non-small cell lung cancer patients. *Cancer Epidemiol Biomarkers Prev*. 2005;14(10):2303-9.
77. Zhou W, Heist RS, Liu G, et al. Circulating 25-hydroxyvitamin D levels predict survival in early-stage non-small cell lung cancer patients. *J Clin Oncol*. 2007;25(5):479-85.
78. Herr C, Greulich T, Koczulla RA, et al. The role of vitamin D in pulmonary disease: COPD, asthma, infection and cancer. *Respir Res*. 2011.
79. Grant WB. Ecological studies of the UVB-vitamin D-cancer hypothesis. *Anticancer Res*. 2012;32(1):223-36.
80. Keum N, Giovanucci E. Vitamin D supplements and cancer incidence and mortality: a meta-analysis. *Br J Cancer*. 2014 Jun; 111(5):976-80.
81. Genzen JR. Hypercalcemic crisis due to vitamin D toxicity. *Lab Med*. 2014;45(2):147-50.
82. Mohr SB, Gorham ED, Kim J, et al. Meta-analysis of vitamin D sufficiency for improving survival of patients with breast cancer. *Anticancer Res*. 2014;34(3):1163-6.
83. Zeichner S, Koru-Sengal T, Shah N, et al. Improved Clinical Outcomes Associated with Vitamin D Supplementation During Adjuvant Chemotherapy in Patients with Her-2+ Nonmetastatic Breast Cancer. *San Antonio Breast Cancer Symposium*. 2013.
84. Li M, Chen P, Li J, et al. Review: the impacts of circulating 25-hydroxyvitamin D levels on cancer patient outcomes: a systematic review and meta-analsysis. *J Clin Endocrinol Metab*. 2014;99(7):2327-36.
85. Velicer CM, Ulrich CM. Vitamin and mineral supplement use among US adults after cancer diagnosis: a systematic review. *J Clin Oncol*. 2008;26(4):665-73.