American Institute of Integrative Oncology
RESEARCH & EDUCATION

Foundations of Integrative Oncology
COURSE

GRAND ROUNDS CALL
With Dr. Nalini Chilkov
July 18th, 2018
Second Wednesday of Every Month
5:30 PM Pacific / 6:30 PM Mountain / 7:30 PM Central / 8:30 PM Eastern

Clinical Pearl: Protecting the Blood Brain Barrier in Cancer Patients
Managing Inflammation and Cognitive Impairment

Reference the attached slides.

- Astragalus 3-6 grams per day: *BBB*
- Melatonin 20 mg hs: *BBB*
- Curcumin 2-6 g/d:*CNS Inflammation*
- Omega 3 Fatty Acids 2-6g/day: *CNS Inflammation*
- Probiotics (Klaire Target gbx) 1 sachet per day: *CNS Inflammation*

Questions & Answers

PHOTODYNAMIC THERAPY
Corey Deacon: **Do you have any experience with Photodynamic Immunotherapy for breast cancer?**

Dr. Chilkov:
This is typically not practiced in the US. It is not standard of care, but the subject of much research. PDT is used in Europe in some integrative cancer clinics. I am not aware of current use WITH immunotherapy drugs (mostly it is cost prohibitive if there is no insurance coverage).

Some studies on PDT therapy in the context of cancer are referenced here.

PDT does itself induce an immune response, but it ALSO can induce angiogenesis due to the fact that it increases hypoxia, the trigger for angiogenesis. There are also issues with collateral damage to healthy cells. More recent studies show that combining PDT with other therapies CT, RT, IT and even hyperthermia can increase efficacy. PDT has only been done on tumors near the surface as light does not penetrate deep into the body. The use of lasers, fiberoptics and nanotechnologies is expanding the potential use of PDT.

Photodynamic Therapy: Amercian Cancer Society Summary Overview
https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/photodynamic-therapy.html#references

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REVIEW: Oncologic Photodynamic Therapy: Basic Principles, Current Clinical Status and Future Directions
van Straten, D., Mashayekhi, V., de Bruijn, H. S., Oliveira, S., & Robinson, D. J. (2017). Oncologic photodynamic therapy: basic principles, current clinical status and future directions. Cancers, 9(2), 19.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5332942/

Abstract

Photodynamic therapy (PDT) is a clinically approved cancer therapy, based on a photochemical reaction between a light activatable molecule or photosensitizer, light, and molecular oxygen. When these three harmless components are present together, reactive oxygen species are formed. These can directly damage cells and/or vasculature, and induce inflammatory and immune responses. PDT is a two-stage procedure, which starts with photosensitizer administration followed by a locally directed light exposure, with the aim of confined tumor destruction. Since its regulatory approval, over 30 years ago, PDT has been the subject of numerous studies and has proven to be an effective form of cancer therapy. **This review provides an overview of the clinical trials conducted over the last 10 years,** illustrating how PDT is applied in the clinic today. Furthermore, examples from ongoing clinical trials and the most recent preclinical studies are presented, to show the directions, in which PDT is headed, in the near and distant future. Despite the clinical success reported, PDT is still currently underutilized in the clinic. We also discuss the factors that hamper the exploration of this effective therapy and what should be changed to render it a more effective and more widely available option for patients.

REVIEW Photodynamic combinational therapy in cancer treatment.

Zhang, Q., & Li, L. (2018). Photodynamic combinational therapy in cancer treatment. Journal of BU ON.: official journal of the Balkan Union of Oncology, 23(3), 561-567.
https://www.ncbi.nlm.nih.gov/pubmed/30003719

Abstract

Photodynamic therapy (PDT) has attracted widespread attention in recent years as a non-invasive and highly selective approach for cancer treatment. PDT involves the activation of a photosensitizer by an appropriate wavelength of light, generating transient levels of reactive oxygen species (ROS). However, the **utilization of PDT against deep tumors has been greatly limited by insufficient luminous flux and the occurrence of peripheral tissue damage.** Therefore, experts have begun to explore whether the combination of PDT with other treatments can improve its efficacy. In this review, we have collected articles about experiments (in vitro and in vivo) and **clinical research on photodynamic combination therapies in recent years, roughly divided into four parts corresponding to PDT combined with chemotherapy, radiotherapy, immunotherapy and other therapies, to compare the therapeutic effects of the combination therapy and monotherapy. The results showed that photodynamic combination treatments, in general, perform better than single treatment modalities. Thus, the increased therapeutic effects, reduced side effects and coordination treatment effects of PDT are worth of further exploration.**

MURINE CELL STUDY 2010

Targeted Therapy of Cancer Using Photodynamic Therapy in Combination with Multi-faceted Anti-Tumor Modalities.

Olivo, M., Bhuvaneswari, R., Lucky, S. S., Dendukuri, N., & Soo-Ping Thong, P. (2010). Targeted therapy of cancer using photodynamic therapy in combination with multi-faceted anti-tumor modalities. Pharmaceuticals, 3(5), 1507-1529.
https://www.ncbi.nlm.nih.gov/pubmed/27713315

Abstract

Photodynamic therapy (PDT) has emerged as one of the important therapeutic options in the management of cancer and other diseases. PDT involves a tumor-localized photosensitizer (PS), which when appropriately illuminated by visible light converts oxygen into cytotoxic reactive oxygen species (ROS), that attack key structural entities within the targeted cells, ultimately resulting in

necrosis or apoptosis. Though PDT is a selective modality, it can be further enhanced by combining other targeted therapeutic strategies that include the use of synthetic peptides and nanoparticles for selective delivery of photosensitizers. Another potentially promising strategy is the application of targeted therapeutics that exploit a myriad of critical pathways involved in tumorigenesis and metastasis. Vascular disrupting agents that eradicate tumor vasculature during PDT and anti-angiogenic agents that targets specific molecular pathways and prevent the formation of new blood vessels are novel therapeutic approaches that have been shown to improve treatment outcome. **In addition to the well-documented mechanisms of direct cell killing and damage to the tumor vasculature, PDT can also activate the body's immune response against tumors**. Numerous pre-clinical studies and clinical observations have demonstrated the **immuno-stimulatory capability of PDT**. **Herein, we aim to integrate the most important findings with regard to the combination of PDT and other novel targeted therapy approaches, detailing its potential in cancer photomedicine.**

MURINE STUDY 2013

Immune Stimulating Photoactive Hybrid Nanoparticles for Metastatic Breast Cancer

Marrache, S., Choi, J. H., Tundup, S., Zaver, D., Harn, D. A., & Dhar, S. (2013). Immune stimulating photoactive hybrid nanoparticles for metastatic breast cancer. Integrative Biology, 5(1), 215-223.

Abstract

A therapeutic technology that combines the phototoxic and immune-stimulating ability of photodynamic therapy (PDT) with the widespread effectiveness of the immune system can be very promising to treat metastatic breast cancer. We speculated that the knowledge of molecular mechanisms of existing multi-component therapies could provide clues to aid the discovery of new combinations of an immunostimulant with a photosensitizer (PS) using a nanoparticle (NP) delivery platform. Therapeutic challenges when administering therapeutic combinations include the choice of dosages to reduce side effects, the definitive delivery of the correct drug ratio, and exposure to the targets of interest. These factors are very difficult to achieve when drugs are individually administered. By combining controlled release polymer-based NP drug delivery approaches, we were able to differentially deliver zinc phthalocyanine (ZnPc) based PS to metastatic breast cancer cells along with CpG-ODN, a single-stranded DNA that is a known immunostimulant to manage the distant tumors in a temporally regulated manner resulting in more effective management of deadly metastatic breast cancer. We encapsulated ZnPc which is a long-wavelength absorbing PS within a polymeric NP core made up of poly(D,L-lactic-co-glycolic acid)-b-poly(ethylene glycol) (PLGA-b-PEG). After coating the outside of the polymeric core with gold NPs (AuNPs), we further modified the AuNP surface with CpG-ODN. In vitro cytotoxicity using 4T1 metastatic mouse breast carcinoma cells shows significant photocytotoxicity of the hybrid NPs containing both ZnPc and CpG-ODN after irradiation with a 660 nm LASER light and this activity was remarkably better than either treatment alone**. Treatment of mouse bone marrow derived dendritic cells with the PDT-killed 4T1 cell lysate shows that the combination of PDT with a synergistic immunostimulant in a single NP system results in significant immune response, which can be used for the treatment of metastatic cancer.**

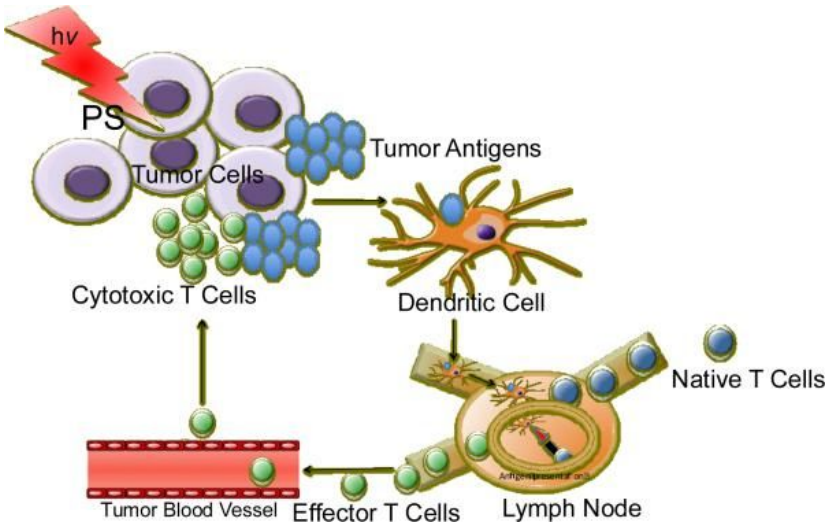
Introduction

The management of metastatic breast cancer remains a therapeutic challenge. An ideal cancer treatment should not only cause tumor regression and eradication but also induce a systemic antitumor immunity for control of metastatic tumors and long-term tumor resistance. This can be achieved by using the immune system as a weapon to recognize the tumor antigen so that once the primary tumor is eliminated, metastases will also be destroyed. Earlier success in applying the immune system to metastatic cancer, as well as the limited contributions from conventional chemo or radiation therapy makes metastatic cancer a focus for contemporary development of novel treatment options.2 The main pillars of cancer treatment chemotherapy, surgery, and radiation therapy are known to suppress the immune system. **The only cancer**

treatment that stimulates anti-tumor immunity is photodynamic therapy (PDT). **PDT involves administration of a photosensitizer (PS) followed by illumination of the tumor with a long wavelength (600-800 nm) light producing reactive oxygen species (ROS) resulting in vascular shutdown, cancer cell apoptosis, and the induction of a host immune response.**

The exact mechanism involved in the PDT-mediated induction of anti-tumor immunity is not yet understood. Possible mechanisms include alterations in the tumor microenvironment by stimulating pro-inflammatory cytokines and direct effects of PDT on the tumor that increases immunogenicity.

PDT can increase dendritic cells (DC) maturation and differentiation, which leads to the generation of tumor specific cytotoxic CD8 T cells, that can destroy distant deposits of untreated tumor



Assessing CARNITINE Status
Stacy D'Andre: **How do you know if your patient is carnitine deficient? Is there a specific lab test?**

(Refer to Slides on Carnitine in Foundations of Integrative Oncology Course MODULE 4.2)

There is a lab test for CARNITINE. This measures ONLY "**Free Carnitine"** in the serum.

Quest Laboratories reports the **reference range** of total **carnitine** as follows :
Men: 30-70 µmol/L. Women: 25-58 µmol/L.

Serum carnitine is an essential cofactor for the transport of free fatty acids into the mitochondria.

Carnitine status is linked to geriatric frailty, cancer related fatigue, cachexia and sarcopenia.

Remember that the body can synthesize carnitine and MOST of the carnitine is found in muscle and in the mitochondria, therefore in tissues where there are more mitochondria (skeletal muscle, cardiac muscle, neurons, esp CNS and the liver).

Primary S&S of Deficiency: fatigue, sarcopenia, hypoglycemia, mitochondropathies

SUPPLEMENT with L Carnitine, Carnitine Tartrate (muscle) or Acetyl L Carnitine (PNS, CNS)

DOSE 1.5-3.0 grams/day

FOOD SOURCES OF CARNITINE Animal products like **meat**, **fish**, **poultry**, and **milk** are the best sources. In general, the redder the **meat**, the higher its carnitine content. **Dairy products** contain carnitine primarily in the **whey** fraction.

CAUTION: In Congestive Heart Failure and cardiomyopathy serum, carnitine increases as the myocardium deteriorates and is prognostic of disease progression and mortality...not of carnitine repletion or adequacy.

Selected References:

Matsui, H., Einama, T., Shichi, S., Kanazawa, R., Shibuya, K., Suzuki, T., ... & Taketomi, A. (2018). ***L-Carnitine supplementation reduces the general fatigue of cancer patients during chemotherapy****. Molecular and Clinical Oncology, 8(3), 413-416.* **(1500 mg/d)**

Ringseis, R., Keller, J., & Eder, K. (2013). ***Mechanisms underlying the anti-wasting effect of L-carnitine supplementation under pathologic conditions: evidence from experimental and clinical studies.*** *European journal of nutrition, 52(5), 1421-1442.*

Cruciani, R. A., Dvorkin, E., Homel, P., Malamud, S., Culliney, B., Lapin, J., ... & Esteban-Cruciani, N. (2006). ***Safety, tolerability and symptom outcomes associated with L-carnitine supplementation in patients with cancer, fatigue, and carnitine deficiency: a phase I/II study.*** *Journal of pain and symptom management, 32(6), 551-559.*

QUERCETIN AND ESTROGEN RECEPTOR POSITIVE BREAST CANCER

Stacy D'Andre: Is there any updated data on quercetin safety data in breast cancer? In rats it exacerbated estrogen induced breast tumors.

Given its interaction with CYP liver enzymes do we have to worry about giving this along with chemotherapy?

Quercetin is a bioflavinoid and a phyto-estrogen found in many food plants, especially red apples and purple onions and many medicinal therapeutic plants. It is not readily absorbed orally and it is difficult to achieve high serum levels by oral administration when used as a supplement. Most studies are murine studies.

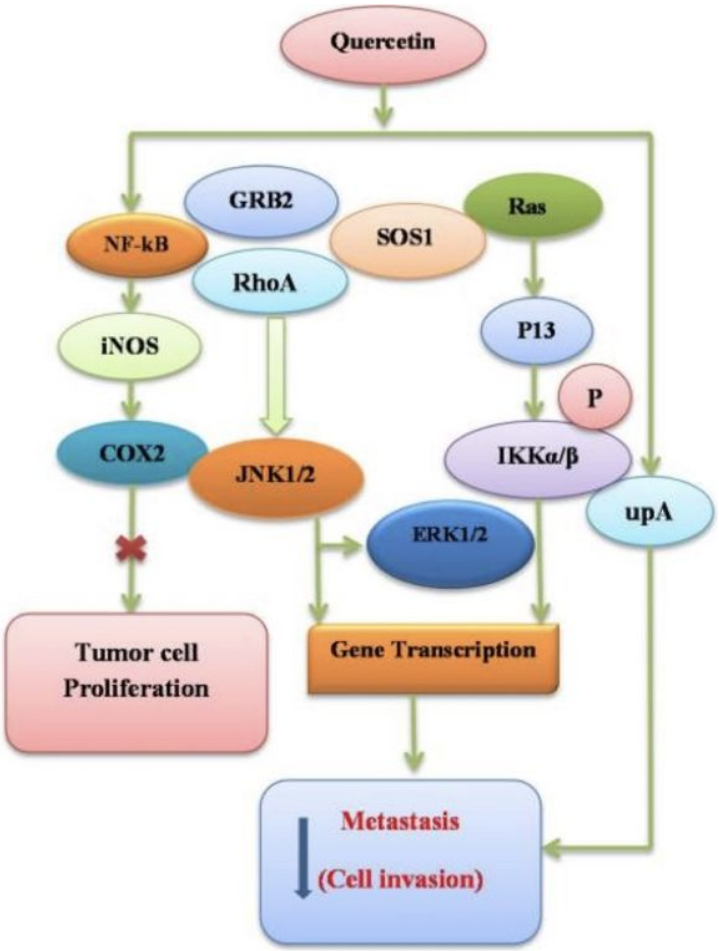
Quercetin can be administered IV and is used in high doses to treat advanced cancers by Dr. Mohammed Nezami MD http://www.allcancercare.com/

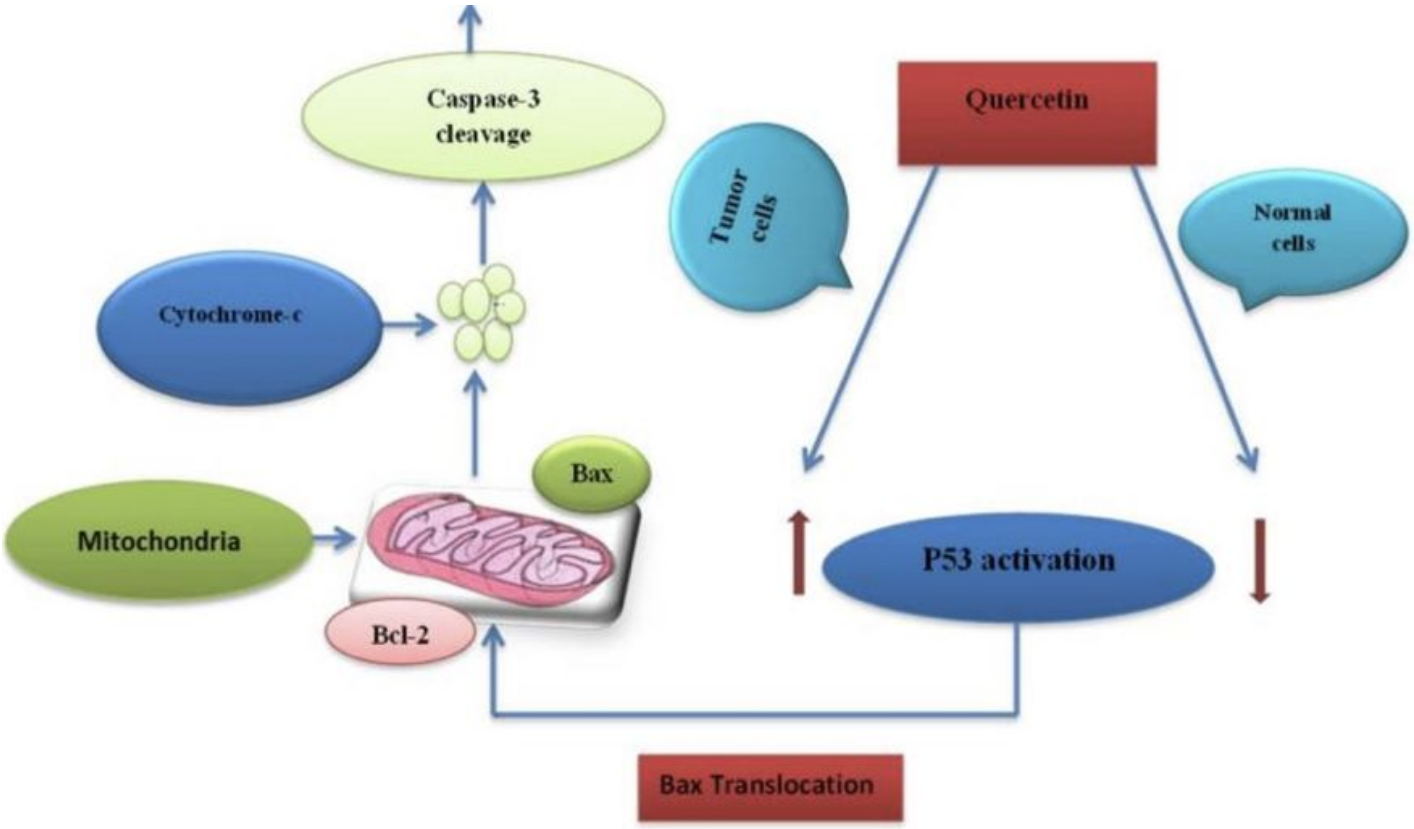
Most studies point to Quercetin inhibiting tumor proliferation and metastasis and promoting apoptosis and cell cycle arrest.

QUERCETIN AND TUMOR INHIBITION
(From Module 4.3 in Foundations of Integrative Oncology Course)

- Estrogen Receptor regulation: down-regulates estrogen binding
- Direct Antioxidant (Redox recycling)
- Modulates inflammation COX 2, LOX5
- Inhibits cancer-related angiogenesis
- Downreg tumor growth factors EGF & Her2neu
- Down regulates NFkB
- Activates PTEN (tumor suppressor)
- Down regulates mutant p53 (tumor suppressor)
- Down regulates TNF-alpha
- Promotes Apoptosis
- Downregulates PARP, Bcl2,

- Activates caspase-3, Bax, and Bak
- Elevates p21 and p27 (tumor suppressors)
- Inhibits angiogenesis in TAM resistant Breast CA
- Reduces circulating IGF, increasing IGF-BP
- Down regulates MMP-2 and 9
- Inhibits VEGF-2 (Angiogenesis)
- Inhibits HIF-1alpha (Hypoxia Inducable Factor)
- Down regulates cyclin D and E
- Upregulates Caspase 3 and Apoptosis
- Inhibits BRAF and MEK protein
- Down regulates heat shock protein 70 (migration)
- Inhibits Chemo Resistance
- Chemosensitizer
- Radiosensitizer





Hashemzaei, M., Delarami Far, A., Yari, A., Heravi, R. E., Tabrizian, K., Taghdisi, S. M., ... & Nikitovic, D. (2017). Anticancer and apoptosis-inducing effects of quercetin in vitro and in vivo. Oncology reports, 38(2), 819-828.

Bak, M. J., Gupta, S. D., Wahler, J., & Suh, N. (2016, October). Role of dietary bioactive natural products in estrogen receptor-positive breast cancer. In Seminars in cancer biology (Vol. 40, pp. 170-191). Academic Press.

Case Study: 54yo M Prostate Cancer Stage 4 Recurrence
Submitted by: Kamron Keep
Overview: Prostate cancer, diagnosed 2012. Currently stage 4, recurrence. High grade, gleason 9. Mets to bone, with multiple nodal mets.
Core Question**:** ***I'd appreciate your thoughts and suggestions on the health plan I've devised, what you may change or add. Also what your priorities would be, I'd love to do more, but need to be mindful of expenses for the client.***
Dr. Chilkov Recommendations: *See attached Case Study with Recommendations from Dr. Chilkov*
PRIOR RADIATION EXPOSURE Core Question: ***Given the patient's history of uranium and radioisotope exposure, is there anything you would add given this?***

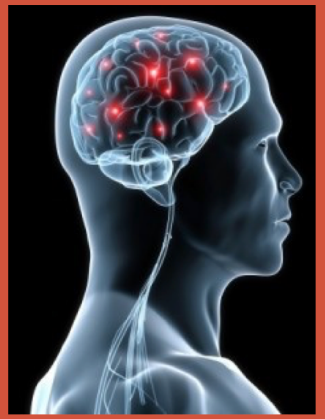
Dr. Chilkov:
Exposure to radiation has already damaged the mitochondria and nuclear DNA which likely was an initiating factor. This helps us to understand that DNA damage, strand breaks and oxidative stress were contributors in the past. This amount of radiation overwhelms cellular repair and recovery mechanisms. The current cells are no longer being exposed to this insult, but were transformed by the exposure in the past.

Follow-up**: How long would you have the client take the cytotoxic supplements for?**

Dr. Chilkov:

- Take toxic supplements with food in stomach
- Artemesinin is more active when taken with something that contains iron
- Reevaluate supplements in health plan every 3 months

CLINICAL PEARL
RESOLVING CANCER RELATED COGNITIVE IMPAIRMENT



REPAIRING THE BLOOD BRAIN BARRIER

Nalini Chilkov, L.Ac., O.M.D., Founder
American Institute of Integrative Oncology Research and Education

“Not Just Chemobrain”

CRCI
Cancer Related Cognitive Impairment

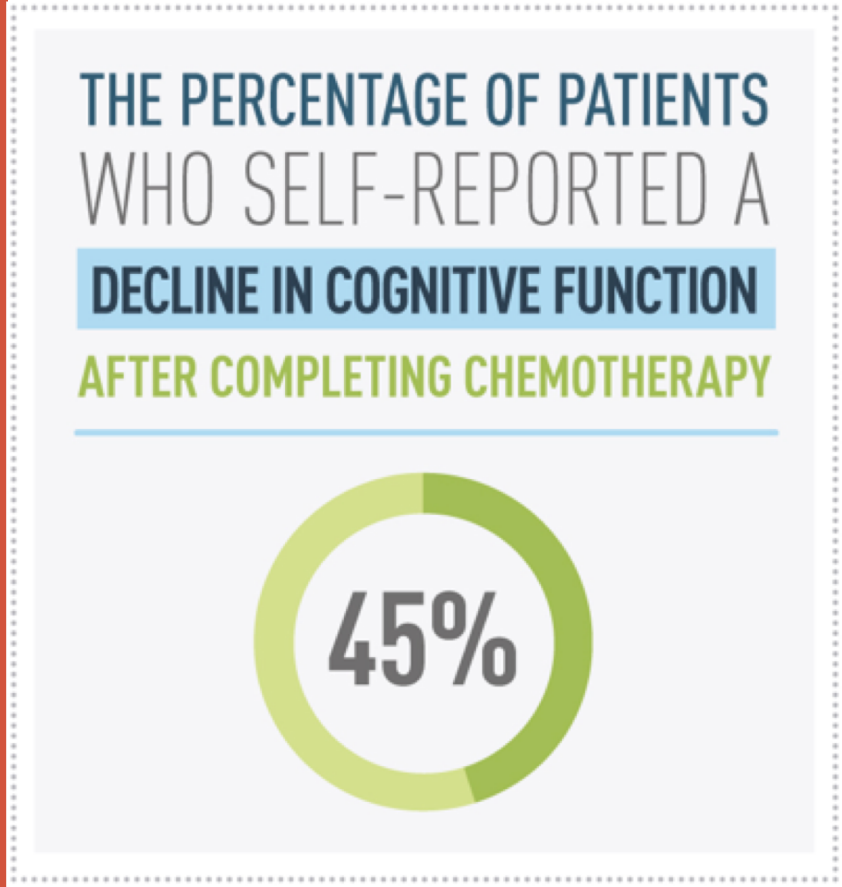
CICI
Chemotherapy Induced Cognitive Impairment

Affected cognitive domains:
Attention, Memory, and Executive Functions

Impairments **attributed to Chemotherapy, Fatigue, and THE CANCER ITSELF**

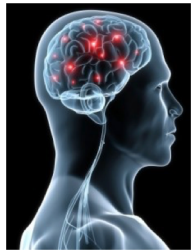
Cognitive deficits occur independently from treatment and can already be **PRESENT BEFORE initiation of therapy.**

Ahles TA, Root JC, Ryan EL (2012) Cancer- and cancer treatment associated cognitive change: an update on the state of the science.J Clin Oncol 30:3675–3686.



CHANGES in STRUCTURE and FUNCTION

Persistent/Long-term 15-35%



Impairments in Cognitive Function
both at diagnosis & after treatment

- Executive Function
- Processing Speed
- Memory
- Attention-Concentration
- Spatial Learning
- Neurogenesis

Accelerated Brain Aging

Clin Adv Hematol Oncol. 2015 Jul;13(7):441-50Asher A, Myers JS. .**The effect of cancer treatment on cognitive function.**

BLOOD BRAIN BARRIER

HYPERPERMEABILITY & LOSS of TIGHT JUNCTIONS

BLOOD BRAIN BARRIER HYPERPERMEABILTY

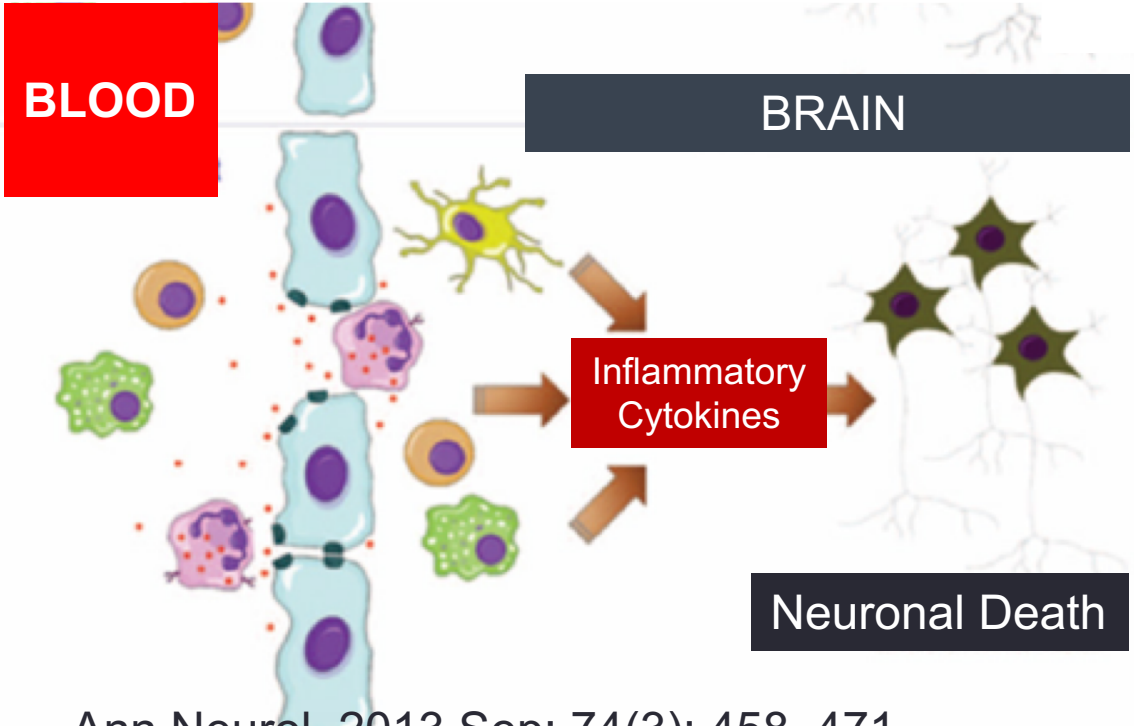
Loss of Tight Junctions in Epithelium Mediated by

- Inflammatory Cytokine IL-1B
- Matrix Metalloproteinase 9 (MMP-9)
- Proteolytic Enzymes

Ann Neurol. 2013 Sep; 74(3): 458–471.

BBB HYPERPERMEABILITY
LOSS of TIGHT JUNCTIONS

↑Neuronal Death
↓Neurogenesis

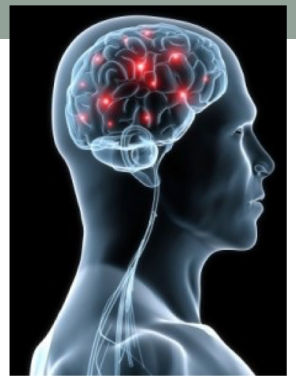


Loss of Tight Junctions in Epithelium Mediated by:

- **Inflammatory Cytokine IL-1B**
- **Matrix Metalloproteinase 9**
- **Proteolytic Enzymes**

Ann Neurol. 2013 Sep; 74(3): 458–471.

BLOOD BRAIN BARRIER HYPERPERMEABILITY: A Function of CNS Malignant Cell Infiltration



PLoS One. 2011;6(8):e20599.

Matrix metalloproteinase-2 and -9 secreted by **leukemic cells increase the permeability of blood-brain barrier** by disrupting tight junction proteins.

Feng S1, Cen J, Huang Y, Shen H, Yao L, Wang Y, Chen Z. © 2018 Dr. Nalini Chilkov AIIORE

Melatonin Maintains BBB Integrity

a pineal neurohormone

10-20mg hs

anti-inflammatory and anti-oxidant properties

PLoS One. 2016 May 6;11(5):e0154427. doi: 10.1371/journal.pone.0154427. eCollection Alluri, H, Wilson RL et al

Melatonin Preserves Blood-Brain Barrier Integrity and Permeability via Matrix Metalloproteinase-9 Inhibition

Melatonin: Maintains BBB Integrity 10-20 mg hs

Front Aging Neurosci. 2017 May 24;9:165 Liu WC, Wang X, et al

Melatonin Supplementation, a Strategy to Prevent Neurological Diseases through Maintaining Integrity of Blood Brain Barrier in Old People.

Inhibits Matrix Metalloproteinase-9 (MMP-9)
Inhibits NADPH oxidase-2
Activates SIRT1 Silent Information Regulator 1
Activates AMP Activated Protein Kinase (AMPK)

ASTRAGALUS Promotes

1-6g/day

- **Decreased BBB Permeability**
- **Inhibition of MMP-9**
- Neuro-Immuno-regulation
- Control of Oxidative Stress
- Control of Neuro-inflammation
- Regulation of Neuro-apoptosis
- Inhibition of p53
- Modulation of the Bcl-2/Bax

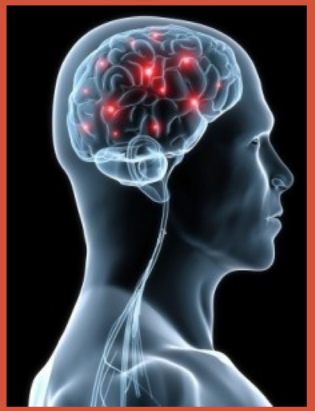
J BMC Complementary and Alternative Medicine 2014 **14**:313 Jun Cai, et al

Journal of Ethnopharmacology Vol 158, Part A, 2 Dec 2014, pp 301-309

European Journal of Pharmacology Vol715, Issues 1–3, 5 Sep 2013, pp 189-195

Understanding the mechanisms of the cytokines as mediators in chemotherapy-induced cognitive impairment will improve our knowledge of the clinical implications of 'chemobrain"

Cytokines as Mediators of Chemotherapy-Associated Cognitive Changes:. Yin Ting Cheung, et al 2013 PLOSone



NEURO-INFLAMMATION

- ↑ NEUROTOXICITY
- ↑ NEURONAL DEATH
- ↓ NEUROGENESIS

A Systematic Review of the Association between Immunogenomic Markers and Cancer-Related Fatigue Brain Behav Immun. 2012 Aug; 26(6): 830–848.
LN Saligan, HS Kim

NEURO TOXICITY

↑Neuronal Death
↓Neurogenesis

Brain

Brain

Cancer Treatment
↓
INFLAMMATION
↕
Cancer Progression

Pro-inflammatory cytokines interact with brain structures altering behavior (Fung et al., 2010)

↑ IL-6 ↑ IL-1β

Increased cytokine movement and leukocyte migration across altered BBB (Strey et al., 2002)

MICROGLIAL ACTIVATION Inflammation

APOE4

Pro-inflammatory Cytokines Cross Blood Brain Barrier

↓Brain Metabolism
↓Brain Volume

BBB disruption

BLOOD

NEURO-ONCO-INFLAMMATION 2-4g/day

H. Green Tea Catechins	NFkB,TNFa,IL1B,COX-2
Rz. Curcuma longa	COX 2, NFkB, TNFa, IL6, IL1
Curcuminoids	LOX5, CRP, IL8
O-3 FA EPA DHA	COX 2, LOX5, PGE2, IL1, IL6, TNFa, CRP
Probiotics	TNFa, IL6, IL 10, NFkB
Rx. Scutellaria baicalensis	TNFa IL-6 IL-1 NFkB
Baicalein polyphenol	COX-2
Berberine alkaloid	IL-6 TNFa IL1
Ganoderma polysaccharide	TNFa, IL1B1,IL6
Resveratrol stilbene	COX1, COX2, NFkB, IL1, IL6, IL8
Boswellia serrata-AKBA	IL1, IL2, IL6,IFN,TNFa, NFkB, IL10,PGE2







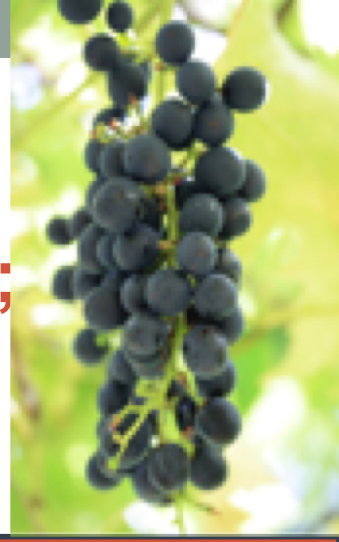
RESVERATROL

1000mg bid x 52 weeks

DBPCT: Resveratrol regulates neuro-inflammation and induces adaptive immunity in Alzheimer's disease

(BBB permeability)

Resveratrol decreases CSF MMP9, modulates neuro-inflammation, and induces adaptive immunity and SIRT1 activation



Nutrients. 2017 Jan 3;9(1). **Effects of Resveratrol on Cognitive Performance, Mood and Cerebro Vascular Function in Post-Menopausal Women; A 14-Week Randomised Placebo-Controlled Intervention Trial. (75 mg bid)**

Significant improvements in the **performance of cognitive tasks : verbal memory** (p = 0.041),**overall cognitive performance** (p = 0.020), which correlated with **increase in CerebroVascular Responsiveness** (r = 0.327; p = 0.048).

PTEROBSTILBENE crosses BBB

- Inhibitory effect on microglia activation
- Protective effect on neuronal injury
- Decreases production of NO, TNF-α and IL-6 in microglial cells.
- More lipophilic than Resveratrol

50-100 mg/d

Pterostilbene attenuates learning and memory impairment possibly via inhibiting microglia activation and protecting neuronal injury in mice. Prog Neuropsychopharmacol Biol Psychiatry. 2014 Oct 3;54:92-102

Relationships between diet-related changes in the Gut Microbiome and Cognitive Flexibility

- Altering the **microbiome can influence the brain and behavior**
- Changes in the **microbiome may contribute to cognitive changes** including **short term and long term memory**
- Higher percentages of Clostridiales and lower expression of Bacteroidales in high-energy diets were related to the poorer **cognitive flexibility** (in mice). 

Neuroscience. 2015 Aug 6;300:128-40. Magnusson KR et al

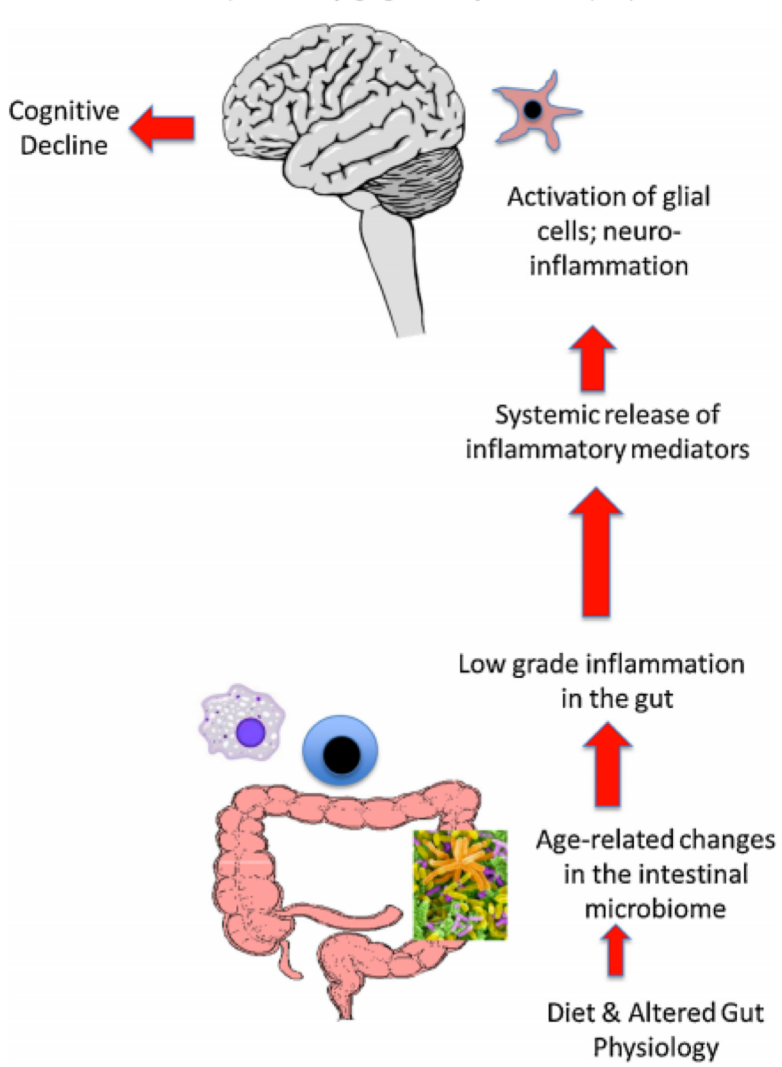
Cognitive decline, dietary factors and gut–brain interactions

Barbara Caracciolo et al

Mechanisms of Ageing and Development
136-137 (2014) 59–69

RX

PROBIOTICS
PREBIOTICS
POLYPHENOLS
Soluble + Insoluble Fibers



KLAIRE Target gb-X
Targeted Probiotic Blend 1 packet/day

Specifically designed to influence the gut-brain axis through defined mechanisms

- Strengthening of the gut barrier function
- Modulation of cytokines and inflammatory response
- Production of potentially neuroprotective metabolites

KLAIRE Target gb-X
Targeted Probiotic Blend 1 packet/day

Specifically designed to influence the gut-brain axis through defined mechanisms

- Shift away from macrophage-produced cytokines to T-lymphocyte-produced cytokines
- Reduction in circulating lipopolysaccharide endotoxins
- Marked reduction in transcription of hippocampal genes related to HPA regulation

KLAIRE Target gb-X 1 packet
Targeted Probiotic Blend 2 grams

Lactobacillus casei W56
Lactobacillus acidophilus W37
Lactobacillus salivarius W24
Lactobacillus brevis W63
Lactococcus lactis ssp. *lactis* W58
Lactococcus lactis ssp. *lactis* W19
Bifidobacterium animalis ssp. *lactis* W52
Bifidobacterium lactis W51
Bifidobacterium bifidum W23

REFERENCES –GUT_BRAIN

1.Steenbergen L, Sellaro R, van Hemert S, Bosch JA, Colzato LS. A randomized, controlled trial to test the effect of multispecies probiotics on cognitive reactivity to sad mood. Brain Behav Immun. 2015 Aug;48:258-64.

2.Abildgaard A, Elfving B, Hokland M, Wegener G, Lund S. Probiotic treatment reduces depressive-like behaviour in rats independently of diet. Psychoneuroendocrinology. 2017 May;79:40-48.

3.Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Ann Gastroenterol. 2015 Apr-Jun; 28(2): 203–209.

Curcumin and Cognition 3-6g/day

- Crosses Blood Brain Barrier
- Supports Axonal Regeneration
- Increases Brain Derived Neurotrophic Factor
- Reduces NeuroInflammation
  - linked to mood dysregulation and cognitive function
- Stimulates Clearance of beta amyloid plaques

Genet Mol Res. 2014 Mar 24;13(1):2039-47. **Effects of curcumin on hippocampal expression of NgR and axonal regeneration in Aβ-induced cognitive disorder rats.** Yin HL, et al

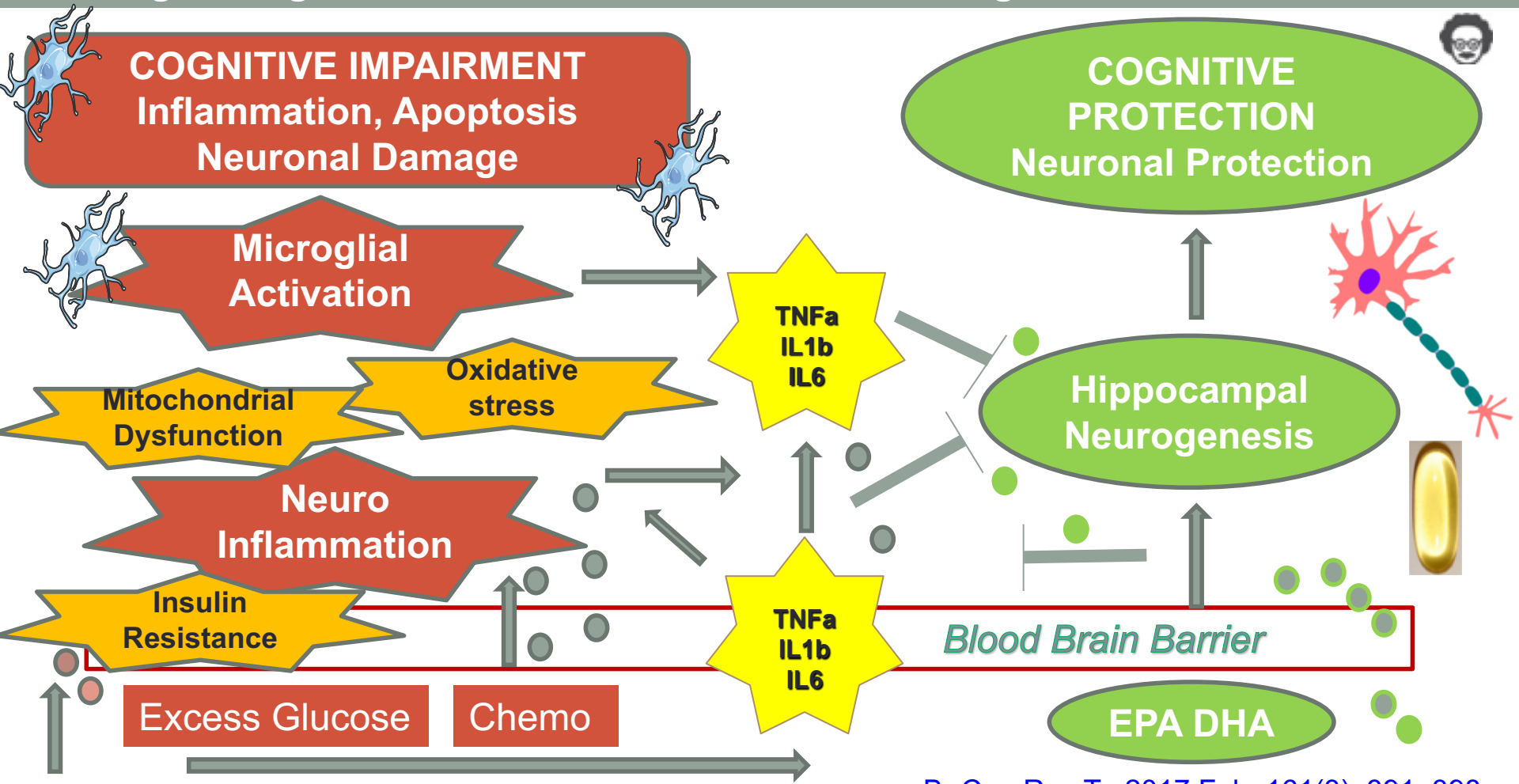
Breast Cancer Research and Treatment Feb 2017, Vol 161, Iss 3, pp 391–398|

Clearing the fog: a review of the effects of dietary omega-3 fatty acids & added sugars on chemotherapy-induced cognitive deficits 1.8g/d

-Opposing actions of omega-3 fatty acids and added sugars on cognitive function, neuroinflammation, and adult hippocampal neurogenesis

-A diet rich in long-chain, marine-derived omega-3 fatty acids and low in added sugars may be an ideal pattern for preventing or alleviating neuroinflammation and oxidative stress, thereby protecting neurons from the toxic effects of chemotherapy.

Clearing the fog: a review of the effects of O3FA & Sugar on CICI



Br Can Res Tr. 2017 Feb; 161(3): 391–398.

LION'S MANE MUSHROOM
Hericium eranaceus (Yamabushitake)

- Strengthens Memory and Concentration
- Enhances Cognition
- Stimulates the synthesis of Nerve Growth Factor
  Promotes and Accelerate Myelination
- Immune Modulation

3-5 g/day

Phytother Res. 2009 Mar;23(3):367-72

American Institute of Integrative Oncology
RESEARCH & EDUCATION

CASE STUDY SUBMISSION

Important: In observance of HIPAA and the sacred trust between care giver and patient, absolutely no patient names or identifying information is to be disclosed. Patient privacy is to be preserved. If you attach any medical records, pathology, surgical or laboratory reports, all names are to be removed.

Date	6/30/18
Clinician Name & Credentials	Kamron Keep, BSN, RN
Email	kamronkeep@yahoo.com

Describe Your Patient (Please SUMMARIZE and use economy of words. You will have 15 minutes to present)

Age, Gender & Ethnicity	54, Male, Caucasian
Body Type	Slim build and stature
Values *What is most important to this patient? (Quality of Life, Decision Making, Side Effects?)*	Primary goals are longevity and to ideally wean himself from pharmaceutical treatment. Hormonal balance. He's very worried about being a burden to others. Secondarily, he mentioned he'd like to regain a feeling of intimacy with his wife. There are barriers here with ED and loss of libido. They've tried various ways to connect, but he feels 'numb' when it comes to any intimacy.
Stress Resilience	Very high stress levels due to work, seems to detach and push through, rather than cope.
Other	Exposed to medical radioisotopes and uranium in his early 20's through work. He's a software developer/engineer.
Primary Diagnosis & Date *(ex. Breast Cancer L, T3 N1 M0, BRCA1 positive, grade 3, Ki67 > 45%)*	Prostate cancer, diagnosed 2012. Currently stage 4, recurrence. High grade, gleason 9. Mets to bone, with multiple nodal mets. At the time of his diagnosis he was having a lot of stress at work, was changing jobs, working remotely from home, it was during the recession and he had two kids in college.
Secondary Diagnosis *(ex. Diabetes Type 2, Obesity)*	Healthy otherwise, previous history of elevated cholesterol

Patient Status

☐ New Diagnosis ☑ Recurrence ☑ In Treatment ☐ In Recovery ☐ In Remission ☐ At Risk

Concomitant and/or Complicating Factors *(ex: poorly controlled diabetes, insomnia, poor support system)*	High stress levels, travels frequently for work, insomnia, has almost developed an eating disorder related to following a strict keto diet and monitoring his ketones/BG.
Adverse Effects of Cancer or Cancer Treatments *(ex. anxiety-depression, diarrhea, peripheral neuropathy)*	Notes low energy, decreased libido, erectile dysfunction
Relevant Laboratory, Pathology & Medical Reports *(attach a PDF with patient identifying information removed or summarize)*	NLR calculated at 5.2 (Neutrophil #1.67; lymphocyte 0.32)- the patient had a significant jump in this number at the time he started to obsessively track his values for the keto diet he's been following. PSA, total <0.09, PSA, Free <0.07, PSA Free PCT: Outside measurement range, unable to calculate. Testosterone, Total <20, Vitamin D 22. No other abnormal lab results. These results were from June 2018. Osteopenic, at lumbar spine (dexa scan).

Brief Summary of Recent History

Diagnosed in 2012 at age 50, prostatectomy in 2013. Recently recurred with bone & nodal mets. Exercises 2-3 times per week, he doesn't feel this is enough. He used to run up to 100 miles per month, now doing about 10 miles per week if that. Consumes 1 beer and 1 wine per month. Reports daily stressors highest around job and health. Poor sleep, wakes nightly about 3-4 am. Able to get to sleep okay. The patient enjoys doing ice baths twice a day. He feels this helps quiet his nerves and relieve his stress (I'm not sure this is a good idea, given his advanced cancer). As mentioned, he has a lot of stress due to work. He does not feel he properly deals with his emotions, or has even really processed his diagnosis. He can be very driven, pushing through things, and has a hard time focusing on one task. He gets distracted easily, which he's trying to work on. I observed him to be quite intense in his focus. Very kind, highly intelligent man.

Brief Summary of Additional Relevant Health, Medical, Psycho-Social and/or Family History

Healthy as a child, rarely/if ever gets sick. No childhood trauma. States he had a happy, 'normal' childhood. Mom had severe "GI issues", died from liver failure r/t the meds she took to help manage her bowel concerns. Father had heart disease, low grade prostate cancer. Sister sarcoid disease. He's married, reports a happy marriage. Two grown children. No current or past history of smoking/drugs.

Other Relevant Information

Such as Chinese or Ayurvedic diagnosis, Naturopathic/Homeopathic Information, etc. *(ex. Liver Qi Stagnation, Dysbiosis)*

Brief Summary of Relevant Past Oncology or Medical Treatments

(ex. surgery, radiotherapy, chemotherapy, immunotherapy, hormone therapy, drug therapy)

Prostatectomy in 2013, radiation 2014, chemotherapy/hormone therapy

Summary of Recent and Current Treatments

Medical Oncology Care *(surgery, radiotherapy, chemotherapy, immunotherapy, hormone therapy, drug therapy)*

Currently on prolia 60 mg/ml every 6 months for bone health, lupron 22.5 mg every 3 months, prednisone 5 mg daily, Zytiga 250 mg daily

Integrative Oncology Care *(nutraceutical, botanical, phytochemical, acupuncture, energy medicine, other)*

Currently receives regular massage and acupuncture, which help his sleep and stress for a few days

Your 2 Core Questions (stated clearly and succinctly)

1. I'd appreciate your thoughts and suggestions on the health plan I've devised, what you may change or add. Also what your priorities would be, I'd love to do more, but need to be mindful of expenses for the client.
2. Given the patient's history of uranium and radioisotope exposure, is there anything you would add given this?

Attached Medical Records for Reference (with patient identifying information removed)

PROPOSED TREATMENT PLAN Your case will not be reviewed without a completed proposed treatment plan

Nutriceutical, Phytochemical and Botanical Supplements (name of supplement, dosing)

Foundation Nutrition Supplements:

DFH Osteoben 2 tab BID (bone support with bone mets)
DFH Vitamin D complex 2 tab daily (increase vitamin D from 22 to functional range)
DFH Metabolic Synergy 3 tab BID (quality multi-vitamin, specially with patient's limited nutritional intake)
DFH OmegAvail 2 tab daily (immune support, anti-cancer & anti-inflammatory support, anticoagulant support)

Targeted Supplements:

VN Melatonin 20 mg q hs (anti-cancer support)
EcoNugenics Modified Citrus Pectin 20-25 gm daily (metastatic support, Full Script doesn't carry Clinical Synergy, this is the equivalent)
EcoNugenics MycoPhyto Complex powder 1-2 scoops BID (mushroom complex for immune & anti-cancer support, help shift NLR)

Functional Foods and/or Therapeutic Shake

DFH Pea Protein, DFH Green Powder for supplement additions to shake. I'm strongly encouraging the therapeutic shake with the patient, increasing his nutrients and protein. He has lost about 20 lbs in the last year, which doesn't bother him. He feels this is positive. He is smaller in stature and weight already, appears cachexic with dull complexion and dark circles under his eyes. Would also like to add creatinine, if his budget will allow it.

Dietary Guidelines

I"m focusing a lot on nutrition with him right now. Goal to shift from full ketogenic diet and obsessively tracking his numbers to a more low carb, high protein, whole food diet. I am working with the patient on enjoying and finding pleasure from food, instead of seeing everything as 'bad'. The patient also eats very small amounts of food per day. He does intermittent fasting in the morning, only eats greens with some coconut oil for lunch and dinner. Very little, if any protein. He's almost anorexic given the limited amount of food he eats. He's seems afraid to eat, worried it will 'feed his cancer'. He used to enjoy, and still does enjoy, food but restricts himself.

Lifestyle Guidelines

Focus on stress management, encouraging client to spend time outdoors, which is a big stress reliever for him. Recommending the client play music/sound therapy during the day at work, such as Wholetones, to help decrease and manage his stress levels. Recommending guided imagery, since the client is very focused and intense, this may give him something positive to direct his energy towards. Breathing practices, something the client is starting to do now, to help with stress, centering and relaxation.

Recommended Diagnostics

Referrals to specialists

Other Notes (please do not include additional notes in your email – notate them here within the case study)

CASE STUDY SUBMISSION

By Kamron Keep, BSN, RN kamronkeep@yahoo.com 6/30/18

ADVANCED PROSTATE CANCER Stage 4

Recurrence with Bone and Lymph Node Metastasis

Patient Status

54, Male, Caucasian

Slim build and stature

Primary goals are longevity and to ideally wean himself from pharmaceutical treatment. Hormonal balance.

He's very worried about being a burden to others. Secondarily, he mentioned he'd like to **regain a feeling of intimacy** with his wife. There are barriers here with **ED and loss of libido.** They've tried various ways to connect, but he feels 'numb' when it comes to any intimacy.

Very high stress levels due to work, seems to detach and push through, rather than cope.

Exposed to medical radioisotopes and uranium in his early 20's through work. He's a software developer/engineer.

Prostate cancer, diagnosed 2012. Currently stage 4, recurrence. High grade, gleason 9. Mets to bone, with multiple nodal mets. At the time of his diagnosis he was having a lot of stress at work, was changing jobs, working remotely from home, it was during the recession and he had two kids in college.

Healthy otherwise, previous history of elevated cholesterol

High stress levels, travels frequently for work, insomnia, has almost developed an eating disorder related to following a strict keto diet and monitoring his ketones/BG.

Notes low energy, decreased libido, erectile dysfunction

NLR calculated at 5.2 (Neutrophil #1.67; lymphocyte 0.32)- the patient had a significant jump in this number at the time he started to obsessively track his values for the keto diet he's been following. PSA, total <0.09, PSA, Free <0.07, PSA Free PCT: Outside measurement range, unable to calculate. Testosterone, Total <20, Vitamin D 22. No other abnormal lab results. These results were from June 2018. **Osteopenic, at lumbar**

spine (dexa scan).

RECOMMEND ADDITIONAL BIOMARKERS D Dimer, Fibrinogen activity, hs CRP, ESR, HgbA1c, IGF-1, Selenium, Zinc, Copper, Ceruloplasmin , RBC Magnesium, Ferritin, Iron, IBC, Saturation, OMEGA 3:6 Ratio, Estradiol, DHEA Sulfate, **LDH, GGPT, URINE Ntx**

Brief Summary of Recent History

Diagnosed in 2012 at age 50, prostatectomy in 2013. Recently recurred with bone & nodal mets. Exercises 2-3 times per week, he doesn't feel this is enough. He used to run up to 100 miles per month, now doing about 10 miles per week if that. Consumes 1 beer and 1 wine per month. Reports daily stressors highest around job and health. Poor sleep, wakes nightly about 3-4 am. Able to get to sleep okay. The patient enjoys doing ice baths twice a day. He feels this helps quiet his nerves and relieve his stress (I'm not sure this is a good idea, given his advanced cancer). As mentioned, he has a lot of stress due to work. He does not feel he properly deals with his emotions, or has even really processed his diagnosis. He can be very driven, pushing through things, and has a hard time focusing on one task. He gets distracted easily, which he's trying to work on. I observed him to be quite intense in his focus. Very kind, highly intelligent man.

Brief Summary of Additional Relevant Health, Medical, Psycho-Social and/or Family History

Healthy as a child, rarely/if ever gets sick. No childhood trauma. States he had a happy, 'normal' childhood. Mom had severe "GI issues", died from liver failure r/t the meds she took to help manage her bowel concerns. **Father had heart disease, low grade prostate cancer. Sister sarcoid disease**. He's married, reports a happy marriage. Two grown children. No current or past history of smoking/drugs.

Other Relevant Information Such as Chinese or Ayurvedic diagnosis, Naturopathic/Homeopathic Information, etc. (ex. Liver Qi Stagnation, Dysbiosis)

Brief Summary of Relevant Past Oncology or Medical Treatments

Prostatectomy in 2013, radiation 2014, chemotherapy/hormone therapy TREATMENT RESISTANT

CURRENT THERAPY

Currently on **Prolia** 60 mg/ml every 6 months for bone health, **lupron** 22.5 mg every 3 months, **prednisone** 5 mg daily, **Zytiga** 250 mg daily

Integrative Oncology Care

Currently receives regular massage and acupuncture, which help his sleep and stress for a few days

Your 2 Core Questions

1. I'd appreciate your thoughts and suggestions on the health plan I've devised, what you may change or add. Also what your priorities would be, I'd love to do more, but need to be mindful of expenses for the client.

   Priorities: QOL, Peace, Relaxation, Intimacy, Nutrient Density, Add CytoToxic and Adaptogenic Support

2. Given the patient's history of uranium and radioisotope exposure, is there anything you would add given this? This insult and damage occurred long ago. The damage is already done. Can look at his current levels of oxidative stress.

Attached Medical Records for Reference (with patient identifying information removed)

No Medcial Records Attached

PATIENT PROPOSED TREATMENT PLAN

Nutriceutical, Phytochemical and Botanical Supplements (name of supplement, dosing)

Foundation Nutrition Supplements:

DFH Osteoben 2 tab BID (bone support with bone mets)

DFH Vitamin D complex 2 tab daily (increase vitamin D from 22 to functional range) goal 75 ng/ml

DFH Metabolic Synergy 3 tab BID (quality multi-vitamin, specially with patient's limited nutritional intake) ‘

DFH OmegAvail 2 tab daily (immune support, anti-cancer & anti-inflammatory support, anticoagulant support) increase to 2 tid (6 g/day)

ADD

Buffered Magnesium Glycinate 300 mg bid

Adaptogens Adrenotone or Power Adapt 2 tid

Probiotics Klaire Therbiotic Complete 2 caps daily

Prebiotics DFH Paleofiber 2 tsp or DFH Saccharomyces boulardii 2 caps daily

Targeted Supplements:

VN Melatonin 20 mg q hs (anti-cancer support)

EcoNugenics Modified Citrus Pectin 20-25 gm daily (metastatic support, Full Script doesn't carry Clinical Synergy, this is the equivalent)

EcoNugenics MycoPhyto Complex powder 1-2 scoops BID (mushroom complex for

immune & anti-cancer support, help shift NLR)

ADDITIONS

ALTERNATE WEEKS

Natura Health Products PHYTOCYTO 60 drops 3 times daily Week One. cytotoxic

Allergy Research Group Super Artemesinin 2 caps 3 times daily Week Two (cytotoxic)

DAILY

DFH Curucumevail 2 tid

Allergy Research Vascustatin 2 caps 2x/day Convolvulis arvensis- (support angiogenesis control)

Chi's Enterprise AngioStop. 2 caps daily Sea Cucumber extract (Philinopside A: angiogenesis control)

See Custom Botanicals Sample Plan Below

focussing on Cytoxic Botanicals and Adaptogens

Functional Foods and/or Therapeutic Shake

DFH Pea Protein, 30 grams protein per shake + Digestive Enzymes

DFH Green Powder for supplement additions to shake.

DFH PaleoFiber 2 tsp prebiotics

DFH Carnitine Tartrate Powder ½ tsp

(Can add MycoPhyto Powder to shake)

GOAL 60-80 g protein daily

I'm strongly encouraging the therapeutic shake with the patient, increasing his nutrients and protein. He has lost about 20 lbs in the last year, which doesn't bother him. He feels this is positive. He is smaller in stature and weight already, appears cachexic with dull complexion and dark circles under his eyes. Would also like to add creatinine, if his budget will allow it.

Dietary Guidelines

I"m focusing a lot on nutrition with him right now. **Goal to shift from full ketogenic diet and obsessively tracking his numbers to a more low carb, high protein, whole food diet.** I am working with the patient on enjoying and finding pleasure from food, instead of seeing everything as 'bad'. The patient also eats very small amounts of food per day. He does intermittent fasting in the morning, only eats greens with some

coconut oil for lunch and dinner. Very little, if any protein. **He's almost anorexic** given the limited amount of food he eats. **He's seems afraid to eat, worried it will 'feed his cancer'**. He used to enjoy, and still does enjoy, food but restricts himself.

Lifestyle Guidelines Focus on **stress managemen**t, encouraging client to **spend time outdoors**, which is a big stress reliever for him. Recommending the client play **music/sound therapy** during the day at work, such as Wholetones, to help decrease and manage his stress levels. Recommending **guided imagery**, since the client is very focused and intense, this may give him something positive to direct his energy towards. **Breathing** practices, something the client is starting to do now, to **help with stress, centering and relaxation.**

Recommended Diagnostics **see above**

Referrals to specialists

Naturopathic Oncologist: High Dose IVC, IV Mistletoe,

Consider Oral Cu Chelation (Tetrathuomolybdate) compounding pharmacy/RX

20mg tid with meals, 60mg empty stomach before bed

Other Notes (please do not include additional notes in your email – notate them here within the case study)

RX Consider Metformin , 500-1000mg bid

AIIORE CASE STUDY Advanced Prostate Cancer: CUSTOM BOTANICALS

SAMPLE PLAN

Custom Tonic: Tumor Control + Adaptogenic Formula

16oz	8 oz	
480 ml	240 ml	
CYTOTOXIC-TUMOR CONTROL		
60	30	Scutellaria baicalensis
60	30	Red Sage Dan Shen Salvia milt
40.	20	Rabdosia
40	20	Polygonatum Solomon's Seal
40	20	Green Tea

40	20	Oldenlandia
30	15	Milk Thistle
30	15	Feverfew

ADAPTOGENS-Tonics—Harmonizers

30	15	Ashwaganda (also anti proliferative)
30	15	Rhodiola
30	15	Red Ginseng
20	10	Astragalus (immune support)
20	10	Chen Pi Tangerine Peel
10	05	Licorice Root

ALTERNATE PLAN If unable to mix a custom tonic: COMBINE

Freeze-Dried granules: Brion-Sun Ten, Evergreen , Min Tong, TCMZone

OR Liquid Extracts: Heron Botanicals, Golden Lotus Herbs Wise Woman Herbals, Kan Herbs

Tumor Control-Immune Support

Minor Bupleurum Formula	2000mg
Astragalus and Ganoderma Formula	2000mg
Pinellia and Magnolia Formula.	2000mg
Dan Shen (Salvia milthirrhiza).	3000mg
Huang Qin Scutellaria baicalensis	3000mg
Red Ginseng	1000 mg

Adaptogenic Support

DFH Adrenotone 3 bid.

OR Natura Health Products Power Adapt 3 bid