Overview

- Introduction to ETMS toolboxes: Botanical, Nutritional, Dietary, Lifestyle, Pharmaceutical
- Prevalence, causes, and connection between Insulin Resistance (IR) and Cancer
- Compounding factors that cause IR
- How IR causes and promotes cancer
- Molecular pathways relative to IR and cancer
- The ETMS assessment of host, microenvironment and tumor
- Application of five ETMS toolboxes
7 out of 10 deaths among Americans each year are from chronic diseases.

Heart disease, cancer and stroke account for more than 50% of all deaths each year.

In 2005, 133 million Americans—almost 1 out of every 2 adults—had at least one chronic illness.

69% of the U.S. are either overweight or obese (>BMI)


Insulin Resistance Causes & Promotes Cancer

A substantial body of epidemiological evidence over recent decades has demonstrated a positive link between excess bodyweight, type 2 diabetes mellitus (DM), insulin resistance and many types of cancer, as well as cancer recurrence and poor outcome.1

High serum levels of IGF-1 and the IGF-1/IGFBP-3 ratio are associated with increased risk of all-cause mortality in women with breast cancer and colon cancer.2

IR Doubles the risk of Breast Cancer Risk Incidence.3


Breast Cancer recurrence score (Oncotype DX) skewed by Metabolic Syndrome Skews

- IR is a potent independent risk factor for breast cancer recurrence in patients who would otherwise be considered low risk, based on a widely used 21-gene Oncotype DX recurrence score assay.
- Breast cancer recurred in 62% of the woman with IR, that otherwise scored low on Oncotype.
- The impact of IR on recurrence score was independent of tumor grade, size, HER2/neu status, and Ki67, as well as patient age and menopausal status.
- Also, Oncotype DX’s HER2/neu assessment is not reliable: Of 24 unequivocally HER2-positive cases by IHC/FISH, only 10 shown to be unequivocally positive by Oncotype DX.


Obesity has become a major health concern. 1 in every 3 adults is obese.


Four contributing causes to IR

- Diet: what you eat and don’t eat
- Sedentary Life-style
- Stress, including Environmental
- Genes: Many SNP’s predispose one to IR (rs61 r2943634)

Cardiovascular Diabetology 2012, 11:133

Problem: Diet rich in refined sweeteners, grains, and fats

- Foods are not only “fast” foods but “fast release” foods
  - American diet is high in calorie-dense, insulin-provoking refined carbohydrates (e.g., flour, sugar, corn syrup etc.)
  - Loss of nutrients and fiber
  - 98% of grain products consumed in the US are refined and contain GMOs (wheat, corn, soy etc.)
  - Refined grains: blood sugar and insulin responses 2-3 times greater than whole grains or coarse-milled products
  - Endocrine-disrupting-chemicals (EDCs) also called Xenohormones (PCBs, BPA, Alkylphenols etc).
- Loss of micronutrients involved in glucose regulation
  - vanadium, zinc, chromium, copper, iron, and nickel
Major endocrine organs are vulnerable to endocrine disruption, including the HPA axis, reproductive organs, the pancreas, and the thyroid gland. EDCs are also known to impact hormone-dependent metabolic systems and brain function.

Model of the endocrine systems targeted by EDCs.

EDCs major cause to endocrine dysfunction, male infertility, reducing sperm morphology%

Solutions for EDCs

- Isothiocyanates, DIM
- Phenolic compounds, Lignans
- Thiol compounds, Trace elements
- Adaptogens, Endocrine modulators

Nrf2

Regulation of the Nrf2-mediated pathways by natural phytochemicals, providing multiple modes of resistance to EDC and other chemical induced carcinogens.
Isothiocyanates potent anti-cancer compounds

- Inhibit Cancer
  - Potent cell and hepatic detoxifiers, promote the elimination of potential carcinogens
  - Redox regulators of GSH
  - Normalizes gene behavior and expression
  - Selectively induces cancer cell apoptosis
  - Regulates histones, down-regulate cancer cell HDAC

Organic broccoli seeds & sprouts are exceptionally rich sources of Sulfuraphane

Chronic Stress & Anxiety can cause Insulin Resistance (IR)

- Stress can definitely cause insulin resistance and cancer.
- Stress includes trauma, acute illness, surgery, chemotherapy, working night-shits, or sleep deprivation; as well as the environment (EDC)
- The most notable and intriguing may be that relative sleep deprivation can cause insulin resistance and cancer.

Sleep deprivation = IR = Oxidative stress/inflammation = Cancer

Multiple ways that stress-induced immune dysregulation can impact cancer

- Repeated Social Defeat
- HPA activation: GC
- SNS activation: NE/EPI
- Immune Dysregulation
- Potential Effects on Cancer Biology
  - Inflammatory mediators/immune cells in tumor microenvironment
  - Tumor growth
  - Migration and invasion of tumor cells
  - Angiogenesis/pro-angiogenic cytokines (IL-6)
Insulin Growth Factors (IGFs)

- The IGF system is highly complex & exerts a multitude of effects on the growth & differentiation of both normal & malignant cells.
- It consists of two IGFs (IGF-I and IGF-II), specific cell-surface receptors (the type I receptor – which is similar to the insulin receptor, and the type II receptor).
- At least 80% of circulating IGF1 is produced in the liver.
- Insulin regulates liver IGF-1 production, both directly and indirectly, by upregulating IGF receptors.
- Insulin also increases IGF-1 bioavailability (unbound) by cancer cells by down-regulating IGFBP1 and 3.
- SNPs in IGF-I pathway have been associated with elevated circulating levels of IGF-I.
GLUT-4 and Insulin Resistance

- GLUT4 is a glucose transporter in fat and muscle cells.
- When an insulin receptor is activated, it induces the GLUT4 protein to move from reserves (inside cells) to active (outside cells).
- Deficient GLUT-4 translocation to plasma membranes in response to insulin can cause a glucose/insulin traffic jam, leading to insulin resistance.
- In insulin resistance GLUT4 transporter no longer moves to the cell membrane to let in insulin,
- However cancer cells up-regulate GLUT-4 and other GLUT transporter letting in larger amounts of insulin and glucose to feed the proliferation and growth.

Cancer Cells Contain a Range of distinguishing mutations and characteristics

- Drivers – Promote cancer
- Passengers
  - Some assist the driver
  - Others are just with the driver
- Example: c-MYC drives glutamine into the cancer cells (glutamine is not the problem), mutated PTEN is likely “driver” that activates NF-kB

Vitamin D is a potent down regulator of c-MYC and is a key nutrient for the suppression of cancer.

IGF-1 & IGFBP-3

- Premenopausal women with a relatively high circulating concentration of IGF-1 and low IGFBP-3 are at significant increased risk of developing breast cancer.
- The majority of HER II+ breast cancer patients who achieve an initial therapeutic response to Herceptin will show disease progression within 1 year.
- HER-2 interacts with IGF-IR and activation of IGF-1R is a major cause for Herceptin resistance.
General mechanisms of resistance of Herceptin

Botanicals & Herceptin

Multi-Targeted Botanical Compounds

Targeting HER II Neu
Metabolic and Hormonal Changes with Insulin Resistance

- **↑Leptin** → +↓ adiponectin
  - +↑Pro-inflammatory Cytokines
  - +↑Angiogenic switch (HIF-1a, IL-8)
- **↑Insulin** → cell proliferation
- **Hyperinsulinemia** → J-AMPK, → ↑mTOR/PI3-K, ↓IGF-1 & III binding protein→ ↑free IGF-1
- **↑c-MYC, p53 mutation**
- **↑Estrogen (Aromastase)** → cell proliferation
- ↓Sex hormone binding globulin → ↑free sex hormone
- Thyroid Hormone dysfunction (resistance) as well as a host of other endocrine imbalances, some induced from Endocrine disruptor chemicals.

AMP-activated protein kinase (AMPK)

- Master regulator and enhancer of cellular ‘catabolic’ energy.
- Enhances both the transcription and translocation of GLUT4, resulting in an increase in insulin-stimulated glucose uptake and cell glucose and fatty acid (oxidation) utilization.
- A key therapeutic target for the treatment of obesity, type II diabetes mellitus, and cancer.
- Acts to inhibit cancer through regulation of cell growth, cell proliferation, autophagy, stress responses and cell polarity.
- Is a critical modulator of aging through its interactions with mTOR, SirT1 and the sestrins.
Aerobic glycolysis (Warburg effect) is only one piece of the puzzle of anabolic metabolism in tumor cells. The Amino acid Glutamine is an alternative fuel source, collected by tumor cells, through the over-expression of c-MYC, RAS, & the mutation of p53. Enhanced c-Myc is the driver of glutamine metabolism within cancer cells.

Insulin • Inflammation • Aromatase

Estrogen receptors act as cofactors of HIF and enhance HIF-dependent transcription of glycolytic genes under hypoxia.

Enhanced c-Myc is the driver of glutamine metabolism within cancer cells. Oncogene (2013) 32, 2079–2086

Aromatase Inhibitors and ER+ Cancer

- Aromatase inhibitors (AIs) have proven to be more effective than Tamoxifen in treating ER+ breast cancer
- However, AIs cause major side effects such as bone loss, joint pain, weight gain, and abnormal lipid metabolism.
- BMI effects AI dosage and response. Low BMI = poor response
- Combining an AI with Metformin, an insulin sensitizer, is more effective than an AI alone at inhibiting breast cancer recurrence.
- Also, combining an AI with mTOR or a COX-2 inhibitor can be much more effective than an AI alone.
Natural Aromatase Inhibitors/Modulators

- Lignans and flavonoids are naturally-occurring diphenolic compounds found in high concentrations in whole grains, legumes, fruits, and vegetables.
  - Chrysin, Grape seed OPC, EGCG, RES, ellagic acid, luteolin, kaempferol, Ursolic acid and apigenin
  - Medicinal and common mushrooms
  - Isoflavones biochanin A, genistein, and coumestrol
  - The lignan agent enterolactone (flax seeds)
  - Coptis (Berberine), also EGFR, HER II, COX-2
- Insulin and Leptin-trophic compounds also reduce ER, via aromatase pathways

Chrysin from Passiflora spp. & Bee Propolis

- Significantly inhibits cancer and cancer related angiogenesis by decreasing the expression of:
  - HIF-1α (Hypoxia), International Journal of Molecular Sciences, vol. 11, no. 5, pp. 2168–2188, 2010

Thyroid hormones influences Insulin, Leptin, Estrogens, Mitochondrial Energy, and Hepatic Detoxification

- Dysfunctional thyroid (low T-3), contributes to general endocrine imbalances, and resistant hormones including insulin, leptin, and estrogen.
- Leptin resistance, which is strongly associated with breast and other cancers, is a link between obesity and alterations of thyroid hormones.
- Leptin concentrations influence TSH release.
- Low T-3 also causes low cellular energy production and mitochondrial weakness.
- Hyperthyroidism is associated with breast and other cancers and poor outcome in breast cancer.

Sherlock’s Corner

Host • Microenvironment • Tumor

- Most-conducive to optimal health
- Least hospitable for cancer

Blood test

Pathology

Branch I & II assessment
Etiology

- Age
- Genetics / Ancestry
- Weight (birth weight too)
- Eyes, tongue etc.
- Stress/dis-stress
  - Emotional, mental and physical
  - Excessive production of stress hormones
  - Sleep
- Life Style
  - Diet
  - Exercise
  - Smoking

Blood Factors
- HGB A1C
- C-peptide
- Leptin/Adiponectin
- Insulin/pro-insulin
- IGF-1 and II
- IGFBP-III
- Testosterone (total/free)
- DHEA sulfate
- CRP
- Vitamin D (25 OH & 125 diOH)
- Fibrinogen/PAI-1/ADMA
- Lipid panel
- Thyroid panel
- SNP's (CYP 19, 1B1, Apo E-4)

The Micro-Environment, a tug-of-war between the Host and the Tumor

How do we approach this problem with our toolboxes?
Hemoglobin A1C (A1C) (Glycosylated hemoglobin)

- Maintaining normal Hemoglobin A1C (glycated hemoglobin) overall, and good glycemic control can help reduce the burden of cancer. Range <5.8, but lower is better.
  - Multiple studies have shown that elevated A1C is associated with an increase risk of all-cause mortality.
  - Vitamin D 25-OH levels >50 & <80 is associated with a significant reduced risk of all-cause mortality.

Prostate cancer recurrence in men treated for localized prostate cancer

- The study group comprised 1734 men treated with radical prostatectomy (RP) or radiation therapy (RT) for localized PCs between 2001–2010.
- Recurrence was identified in 16% of men over a mean follow-up period of 41 months (range 1–121 months). Those with elevated glucose had a 50% increased risk of recurrence compared with those with a normal glucose level.

IR related biomarkers associated with increased cancer risk

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Risk of associated cancer &amp; mortality</th>
<th>Reference</th>
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</table>
Adipose tissue (AT): 2 types

- **Type I:** White adipose tissue (WAT) is specialized in the storage of energy in periods of positive energy balance and mobilization of this chemical energy when needed to meet the body energy demand.
- WAT has an enormous capacity of expansion, which can be viewed as an adaptive mechanism for the periods of food shortage.
- The energy is stored as triglycerides made up of fatty acids (FA) esterified on a glycerol backbone.
- Breakdown of triglycerides releases glycerol and FA into the bloodstream, a process called lipolysis.
- **Type II:** Brown adipose tissue (BAT) main function is to burn lipids through fatty acid oxidation to produce heat.

Uncoupling Protein 1 (UPC1)

- Transgenic mice expressing UCP1 in WAT are protected against genetic and dietary obesity, and have an increase in WAT oxygen consumption.
- Treatment with cAMP-elevating agents or PPARα agonist have been shown to increase UCP1 and transform WAT into fat-burning cells (The “Browning” of WAT)
- Forskolin & Fucoxanthin activate cAMP and UCP1.

Adipocyte Products

**ADIPOKINES ASSOCIATED WITH INSULIN SENSITIVITY**
ADIPONECTIN (ACRP)

**ADIPOKINES ASSOCIATED WITH INSULIN RESISTANCE**
RESISTIN (FOR RESISTANCE TO INSULIN)
LEPTIN (RESISTANCE)
TUMOR NECROSIS FACTOR (TNF)
INTERLEUKIN –6 (IL-6)

Leptin & Leptin Resistance

- An adipose hormone that aids in storing energy as fat
- The balance between leptin and adiponectin is a major factor in the control of cancer
- Leptin resistance, similar to insulin resistance
  - Occurs when communication between the hypothalamus & the adipose tissue becomes dysfunctional
  - Leads to more fat accumulation and less-efficient fat being burned for energy
  - Pro-angiogenic: Activates a cascade of growth factors including MAPK, HER II, IL-1, -6 and -8.
  - Associated with an increased risk of several common cancers: breast, prostate, colon, bladder, and pancreatic
IR related biomarkers associated with increased cancer risk

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Risk of associated cancer &amp; mortality</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Leptin &lt;15</td>
<td>Increased</td>
<td>1 Immuno 2007; 179:1290-1302, Cellular Signaling Volume 20, Issue 6, August 2008, Pages 1678-1688</td>
</tr>
<tr>
<td>All cancers</td>
<td></td>
<td>BJI Int. 101 (2008) 1137x1322, Journal of Oncology Volume 2012, Article ID 280386, 8 pages</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td></td>
<td></td>
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<tr>
<td>Breast</td>
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**Peroxisome Proliferator-Activated Receptor (PPAR) Alpha & Gamma Ligands**

**Inhibit the Growth of Cancer**

- Receptor/transcriptional factors that influence the activity of gene-regulating factors
- Activation of PPARs reduces the expression of AP-1, which is a transcriptional regulator of COX-2, & VEGF
- Stimulation of PPARgamma interrupts the PDGF & EGF signaling pathways
- PPAR gamma activation also results in significant protection not only from cancer but also CVDs

**Natural Compounds that Activate PPAR A & G**

- Resveratrol (Nutricon, VitaKem & Cardiovascular Diseases (2007) 17, 247x256)
- Grape seed extract (Rescence, Biotechnology and Biochemistry, Vol. 68 (2004), No. 11 pp 2853-2859)
- Guggulsterones (Journal of Nutritional Biochemistry; 10: 1016), (purebio. 2005-07 020)
- Pterostilbene (J Agric Food Chem. 2005 May 4;53(9):3403-7)
- Astragalus Polyaccharides (Plu. 505: 7(2010): e45541)
- Carnosic acid, carnosol, ursolic acid (phenolic diterpene compounds from rosemary & sage), Methformin-like effect (Br J Nutr. 2006 Aug;96(2): 326-33.
- Quercetin - Decreases IGf levels, improves signaling and IGBP-3 (J Carcinog. 2006 Apr 6(5):10)
- CLA (Also targets Leptin resistance) (Wei Sheng Yan Ju. 2004 May;33(5):307-9)

**Botanicals Solutions that Target IR and Suppress Cancer**

- Primary • Secondary • Companion
- Target Endocrine system [Adrenal/Pancrease/Thyroid etc.]
- Insulin sensitizer & signal transduction /AMPK/ Mitochondria/ glucose & fatty acid utilization
- Spleen Tonics/Hepatics/Lymphatics/Immune system modulators
- Remove toxins/cytotoxic
Adaptogenic Plants with Insulintrophic effects & Main Compounds

<table>
<thead>
<tr>
<th>Adaptogenic Plant</th>
<th>Main Compound</th>
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<tbody>
<tr>
<td><em>Panax ginseng</em> (ginseng) &amp; <em>Panax qu.</em>**</td>
<td>Ginsenosides</td>
</tr>
<tr>
<td><em>Withania somniferum</em> (ashwagandha)</td>
<td>Withanolides</td>
</tr>
<tr>
<td><em>Eleutherococcus senticosus</em></td>
<td>Eleutherosides</td>
</tr>
<tr>
<td><em>Astrogalus membranaceus</em></td>
<td>Astragalosides</td>
</tr>
<tr>
<td><em>Ocimum sanctum</em> (holy basil)</td>
<td>Triterpenic acids</td>
</tr>
<tr>
<td><em>Rhodiola rosea</em> (rose crown)</td>
<td>Flavonoids</td>
</tr>
<tr>
<td><em>Schisandra chinensis</em> (5 spice)</td>
<td>Lignans</td>
</tr>
<tr>
<td><em>Oplopanax</em> (Devil’s club)</td>
<td>Saponins</td>
</tr>
<tr>
<td><em>Cordyceps sinensis</em></td>
<td>Rich in Vanadium,*</td>
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Ginseng

*Panax ginseng* (Asian) or *Panax quinquefolius* (American)

- Hypoglycemic effects:
  - Decreasing rate of carbohydrate absorption
  - Increasing blood sugar transport and storage
  - Improves insulin signaling
  - Activates AMPK
  - Anti-fatigue and Thermogenic
  - Improves insulin resistance/inhibits cancer
  - Down regulates IGF-1/Akt in cancer
- American ginseng cooling & overall well-suited type-A people that tend to run hot.

*Oplopanax elatus* & *horridum* (*Echinopanax elatus*)

- Common name: Devil’s club

- Known in the Northwest of North America as a Adaptogen with profound insulintrophic effects, and cancer inhibiting.
- Contains triterpene saponins, coumarins, flavonoids, alcaloid aralin, and cardiac glycosides
- Native Americans have long used its root for controlling diabetes
- Anti-microbial effects

Aralia manchurica/elata

*(Manchurian Thorn Tree / Spikenard)*

- Grows in Far East of Russia
- Builds ‘Vital Force’ Spleen
- Officially approved for therapeutic use in the USSR since 1958 as a tonic / adaptogen (before Eleuthero)
- Active Constituents: Triterpenoid saponins - aralosides A, B, C, and elatosides E and F, tannins, volatile oils, resins, lectins, flavonoids, anthocyanins, alkaloids, etc.
Insulin-sensitizing Actions of Aralia

- **Lowers blood lipids**: decreases total lipids, triglycerides, cholesterol level and increases beneficial phospholipids
- **Anti-diabetic/obesity**: decrease in total body weight and fat weight, reduced perilipin content in adipocytes and plasma triglyceride content, and stimulated activity of hormone-sensitive lipase
- **Immune enhancing/Anti-cancer** lectin compound ‘Aralin’ exhibits potent cytotoxic activity against various types of human cancer cell lines; cervical carcinoma cells (HeLa) proved the most sensitive


Top Companion Adaptogens for IR & Cancer

<table>
<thead>
<tr>
<th>Latin Binomial</th>
<th>Common Name</th>
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<tbody>
<tr>
<td>Curcuma longa</td>
<td>Turmeric (Curcumin)</td>
</tr>
<tr>
<td>Camellia sinensis</td>
<td>Green tea (EGCG)</td>
</tr>
<tr>
<td>Polygonum cuspidatum</td>
<td>Japanese knotweed (Resveratrol)</td>
</tr>
<tr>
<td>Vaccinium myrtillus</td>
<td>Bilberry (wild Blueberry)</td>
</tr>
</tbody>
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Rich in Anthocyanidines


Botanicals with Insulinotrophic, Anti-Inflammatory & Anti-Cancer Effects

- Pterocarpus (Pterocarpus spp.)
- Green tea (Camellia sinensis)
- Holy Basil (Ocimum sanctum) “Tulsi”
- Japanese Knotweed (Polygonum cuspidatum) “resveratrol”
- Chapparal (Larrea divaricata) - *Nordihydroguaiaretic acid (NDGA)*, is a selective compound against IGF-1R & HER II neu, that has shown to suppress cancer
- Turmeric (Curcuma longa) “Curcumin” decreased the secretion of IGF-1 while increasing IGFBP-3
- Cinnamon (Cinnamomum zeylanicum) VEGF
- Goldenseal (Hydrastis c.) - Berberine – potent insulintrophic, cancer-suppressing effects – also inhibits MDR
Botanicals with Insulinotrophic, Anti-Inflammatory
Anti-obesity & Anti-Cancer Effects (continued)

- Bitter melon (*Momordica charantia*)
- Black cumin (*Nigella sativa*)
- Fenugreek (*Trigonella foenum graecum*)
- Coleus (*Coleus forskohlii*)
- Goat’s rue (*Galega officinalis*)
- Mucuna (*Mucuna pruriens*)
- Salacia (*Salacia reticulata*)
- Gymnema Leaf (*Gymnema sylvestre*)
- Jambul seed (*Syzygium jambolanum*)
- Cinnamon (*Cinnamomum aromaticum*)

Bitter melon (*Momordica charantia*)

Main actions on the anti-diabetic effects

- "vegetable insulin"
- Increase glucose utilization by the liver,
- Decrease gluconeogenesis via inhibition of two key enzymes (glucose-6-phosphatase and fructose-1,6-bisphosphatase),
- Improve glucose oxidation through the shunt pathway by activating glucose-6-phosphate dehydrogenase,
- Enhance cellular uptake of glucose, promote insulin release and potentiate its effect,
- Increase the number of insulin-producing beta cells in the pancreas of diabetic animals.

Momordica extract (ME) possesses profound anti-tumor effects

- Induces cycle arrest and apoptosis without affecting normal cell growth.¹
- Chemopreventive effect against DMBA induced skin tumorigenesis, melanoma tumor & cytogenicity.²
- Modulates signal transduction pathways for inhibition of breast cancer cell growth.³
- IV of ME to nude mice resulted in a 100% survival compared with 80% in the controls.
- Anti-metastatic effect, both in vitro and in vivo.

Momordica extract inhibits migration of lung cancer by reducing the expression and activation of Src decreasing the downstream Akt, β-catenin, and MMP 2 & 9.

Nigella sativa seeds
- Generally enhances immunity and cancer inhibiting.
- Has specifically been used traditionally for treating diabetes. Journal of Endocrinology and Metabolism, Vol. 1, No. 1, Apr 2011
- A human study indicated that a dose of 2 gm/day of is beneficial in type 2 diabetic patients. Journal of Endocrinology and Metabolism, ISSN 1923-2861, 1923-287, April, 2011
- I use the CO2 supercritical extract (2-5 mls daily)

Insulin-trophic-Anti-obesity-Thermogenic and Anti-cancer effects of EGCG rich Green tea extract
- Stimulation adipose tissue – increased glucose metabolism in adipocytes Experimental and Molecular Medicine 2003; 35(2): 136-139
- EGCG, inhibits IGF-1 and interacts specifically with a component of a leptin-independent appetite control pathway. Cancer Res. 2004 Dec 15;64(23):9365-72
- Improves muscle health by reducing necrosis and oxidative damage.

EGCG decreases activity of multiple cancer cell receptors EGFR, HER2, HER3, & IGF-1R
- Cysteine rich domain
- Tyrosine kinase domain
- Proliferation / Survival / Metastasis

TK oncogene family & biomarker for dasatinib (along with c-KIT & PDGF)
**Pterocarpus (Pterocarpus marsupium)**
- The heart-wood of pterocarpus has been used traditionally in Ayurveda for diabetes and inflammation
- Active compounds: Silbenes, pterostilbene and epicatechin
- Anti-diabetic:
  - Reverse and/or regenerate damaged pancreatic beta cells
  - Pterocarpus extract, (5% pterostilbene), can reverse damaged beta cells and actually repopulate the islets; and almost complete restoration of normal insulin secretion.
- Anti-diabetic effects comparable to Metformin

**Guggul (Commiphora Mukul)**
- Guggul extract - from the mukul myrrh tree (India)
- Traditionally used for arthritis
- Contains a group of compounds known as guggulsterones that account for the lipid-lowering action.
- Six randomized clinical trials concluded that Guggulsterones (Guggul extract 7.5%) lower serum cholesterol by 10-27%
- Has an overall protective effect against CVD and Cancer
  - Three distinctive mechanisms:
    - Improves the liver’s ability to process, metabolize and excrete cholesterol, in particular LDL cholesterol
    - Improves thyroid function by increasing T4 to T3 conversion
    - Improves insulin efficiency & glucose utilization (PPARgamma)
- Aids in weight loss
- Recently shown to suppress cancer

**Aloe Vera**
- Widely used in India and on the Arabian peninsula to treat diabetes.
- Ancient Egypt referred to as the “Sanctuary of immortality”
- Reduces blood sugar, makes cells more sensitive to insulin.
- #1 herbal food for healing and protecting the GI tract.
- Acemannan (18% of BiAloe powder) potent immune-modulating, cancer-suppressing & anti-viral/fungal and bacterial effects
- Also contains Aloe-emodin anthraquinone
- I often add 1/8 to 1/4 tsp. of BiAloe to smoothie, also can use the juice.

**Cinnamon**
Cinnamon – two plant sources, one cassia (Cinnamomum cassia) from southeast Asia, and the other the higher quality cinnamon (Cinnamomum zeylandicum or aromatica) native to India and Sri Lanka.
- Insulin sensitizers: improve fasting blood glucose & lowers HGB A1C, decreases plasma C-peptide, serum triglyceride, and total cholesterol (raises HDL).
- Lowers blood pressure
- Procyanidin type A present in cinnamon inhibited cancer related VEGFR2 and VEGFR2 signaling
Fenugreek Seed (Trigonella foenum-graecum)

- Member of pea family.
- Traditionally used to treat diabetes – insulin like effect.
- Soothes mucous membranes of the sinuses, lungs, and digestive tract. Externally used as drawing agent.
- Improves glucose, insulin & lipids and decreases insulin resistance in type-2 diabetics,
- Protodioscin, purified from fenugreek seed inhibits leukemia through an induction of apoptosis
- Intra-peritoneal administration of the alcohol extract in mice produced more than 70% inhibition of tumor cell growth.

**Nutritional Supplementation that targets IR and suppresses cancer**

- **Macro-nutrition**
  - Protein (AAs)
  - Fats (FAs)
  - Carbo’s
- **Micro-nutrition**
  - Vitamins and Minerals (ReNatured)
- **Trace**
  - Vital trace elements (R-lipoic/ALA)

**Vitamin D**

- An estimated 1 billion people world-wide have insufficient vitamin D,
- Vitamin D is useful for the prevention and possible treatment of breast, prostate, thyroid, colon, melanoma, pancreatic, and lung,
- There are vitamin D receptors in over thirty areas of the body.
- Over 95% of breast cancer patients D deficient, normalizing 25-OH D can help prevent cancer,
- D Deficiency promotes human breast cancer growth of bone metastasis,
- Vitamin D interacts with estrogen, androgen, IGF-1 and insulin,
- Vitamin D reduces risk of Parkinson’s and Alzheimer’s disease, fragility syndrome, heart disease, autoimmune disease, and even acute infections such as colds and the flu.

**A xanthophyll carotenoid** antioxidant found in the brown seaweed, wakame. In animal studies Fucoxanthin burned fat, prompting them to lose stored fat. It works to promote fat burning in white adipose tissue (WAT) by increasing the expression of thermogenin, through the uncoupling protein 1 (UCP1) expression.

Fucoxanthin improves insulin resistance & decreases blood glucose levels regulating of cytokine secretions from WAT.
Adequate 25-OH vitamin D

• The data show a positive correlation of 25-hydroxyD3 with insulin sensitivity and a negative effect of hypovitaminosis D on beta cell function.


• “The recommended adequate intakes for vitamin D is inadequate, and, in the absence of exposure to sunlight”. (25-OH D levels should be between 50-80) Am J Clin Nutrition 2004; 39; 362-71.

Stabilized R-lipoic acid (RALA)

• BioEnhanced™ Na-RALA is a stabilized form of RALA that won’t degrade at high temperatures, is more bioavailable than regular RLA, and has no solvent residues.

RALA has demonstrated superior effects to LA

• Lowers glucose, insulin, HGB A1C and lactate

• Reduces age-related mitochondria oxidative damage

• Improves metabolic activity, lowers oxidative stress, glucose and insulin metabolism, and glucose disposal.

• The most important cell protective and restorative agent

• Demonstrated anti-tumor effects

Improving vitamin D status can help lower risk of cancer (colon) associated with higher IGF-1/IGFBP-3 ratio or C-peptide levels.


Vanadium
Best in low dosage together with other harmonious insulin-regulating cofactors, and amino acid chelates

• Enhances both insulin and IGF sensitivity (more effective binding to IGFBPs I and II

• Ergogenic

• Cancer preventive Inhibits cellular tyrosine kinases, regulating signal transduction pathways, and plays a role in apoptosis

• Involved in gene stability

... Cofactors

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Comments</th>
<th>Functions or Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boron</strong></td>
<td>ReNatured, or Albion lab amino acid chelate</td>
<td>Best in low dosage together with other harmonious insulin-regulating cofactors, and</td>
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<tr>
<td></td>
<td></td>
<td>amino acid chelates</td>
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<tr>
<td></td>
<td></td>
<td>• Enhances both insulin and IFG, insulin and leptin sensitivity</td>
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<td></td>
<td></td>
<td>• Anabolic and Ergogenic</td>
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<td></td>
<td></td>
<td>• Shown to inhibit prostate cancer, via IGF1 down-regulation within cancer cells.</td>
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<td></td>
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<td>Toxicol Ind Health. 2013 Jan-4, Toxicol Pathol. 2004 Jan-Feb 32:1-73-8,</td>
</tr>
<tr>
<td><strong>Zinc</strong></td>
<td>Vitamin D &amp; K, and several B-vitamins including</td>
<td>are also important for proper glucose and insulin control, Co-enzyme Q 10 a</td>
</tr>
<tr>
<td></td>
<td>Vitamin B-1, 3, 6, 12,</td>
<td>mitochondrial specific nutrient is also useful as well</td>
</tr>
</tbody>
</table>

Nutrigenomics and Nutrigenetics

- Junction between health, diet and genomics
- Molecular nutrition + genomics
- Modifies gene expression
- Prevents and repairs cellular damage at the genetic and epigenetic levels
- Induces apoptosis
- Different Genetic-types response differentially to the same food and food compound

Ideal diet

Physical Activity in Cancer Survivors Associated With Better Health Outcomes

45 studies analyzed were published between 1950 and 2011, with the majority from 2005 and later.

27 observational studies showed evidence that **physical activity is linked to a reduced all-cause, and cancer mortality**;

11 randomized studies analyzing specific biomarkers suggest that **exercise can benefit the insulin levels of survivors, reduce inflammation, and could even improve immune function**;

Pre-diabetic patients who engage in regular aerobic exercise reduce their risk of cancer & heart disease even if no weight loss occurs. Moderate-intensity physical activity ameliorates breast cancer risk in diabetic women.

Gene expression changes in adipose tissue with diet- and/or exercise program

- Weight-loss can cause positive changes in adipose-tissue gene expression after 6 months,
- Two relative pathways that link obesity and cancer:
  - steroid-hormone metabolism ( ↑17β-hydroxysteroid dehydrogenase-1),
- Regular physical activity, sun exposure, sufficient sleep, low chronic stress, and significant dietary changes, together with botanical and nutritional medicine can significantly improve health, inhibit cancer and all chronic disease, promoting a long and fruitful life.

• Healing above all else involves an exchange of love
• We may have inoperable cancer, but we also can love, ask for forgiveness, try new things, and learn that our lives are part of a larger reality than our personal mortality (for we have already survived).