BREAST WELLNESS
A FUNCTIONAL APPROACH TO CANCER

Elizabeth W. Boham MD, MS, RD
The UltraWellness Center
Lenox, MA
FUNCTIONAL MEDICINE

- Prevention
- Underlying Causes
- Science Based
- Biochemical Individuality
- Patient Centered (Not Disease Centered)
- Interconnections in our body
  - Inflammation and heart disease
  - Gut and immune system

ASKS WHY???
Not just breast cancer........
but breast cancers
Create A Healthy Terrain
Remove What Causes Imbalance
Replace What Is Needed For Balance
ESTROGEN

• As estrogen exposure increases so does our risk of breast cancer
  – Number of periods in your lifetime
  – BCPs >5 years or current use
  – HRT - 8.6% decrease in postmenopausal ER+ breast cancer since 2001
  – Endocrine Disrupters
Endocrine Disrupters -
Substances that mimic or disturb the activity or binding of our hormones

• Xenoestrogen - synthetic chemicals that act as endocrine disrupters
• Plastics -
  – BPA - Bisphenol A - #7
  – PVC - Polyvinyl chlorine - phthalates

• Pesticides
  carcinogens and endocrine disruptors
What can you do?

• Buy organic
  – Decreased pesticide exposure
  – Decreased growth hormone exposure
• Decrease animal products in general
• Use glass whenever possible
• Do not heat or microwave plastic
• Switch to non plastic reusable water bottles
• Avoid pesticides on your lawn and garden
As estrogen exposure increases so does our risk of breast cancer

- Number of periods in your lifetime
- BCPs >5 years or current use
- HRT
- Endocrine Disrupters
- Weight - % body fat
An increase in the risk of cancer is one of the consequences of obesity. The increased release of cytokines from this tissue may play a role in the inflammatory state that is associated with obesity (and cancer).

WEIGHT

- Increase weight by 22 or more pounds since age 18... 30% increase risk of breast cancer than women gained 5 or less pounds
  - JAMA. 2006. 296:193

- Women with the highest BMI had a 35 percent increase in risk of triple-negative breast cancer and a 39 percent increase in the risk of estrogen receptor-positive breast cancer.

- Women with the highest levels of physical activity had reduced risks of both triple-negative breast cancer and estrogen receptor-positive breast cancer
  - Phipps A. Cancer Epidemiology, Biomarkers, & Prevention. March 2011

- Breast cancer survivors who were overweight or obese were more likely to have their cancer recur than thinner survivors.
Adipose Tissue is an endocrine organ. Very Active.

WHY?

- Aromatase and Insulin Resistance
Decrease Aromatase

- Lower % body fat
  - Maintain healthy weight
  - Resistance exercise
- Decrease inflammation
  - Omega 3 fats
  - Avoid trans fats
  - Decrease saturated fat
  - Lower % body fat
  - inflammation made in fat
  - Turmeric
  - Aspirin ?
Decrease Aromatase

- Fiber
- Lignans – Flax seed
- Soy
- Resveratrol
- Grape Seed Extract
- Green Tea
- Brassaiopsis glomerulata
Grape Seed Extract Is an Aromatase Inhibitor and a Suppressor of Aromatase Expression

Ikuko Kijima, Sheryl Phung, Gene Hur, Sum-Ling Kwok, and Shiuun Chen
Department of Surgical Research, Beckman Research Institute of the City of Hope, Duarte, California

Abstract
Aromatase is the enzyme that converts androgen to estrogen. It is expressed at higher levels in breast cancer tissues than normal breast tissues. Grape seed extract (GSE) contains high levels of procyanidin dimers that have been shown in our laboratory to be potent inhibitors of aromatase. In this cancer cells, is thought to play a more crucial role in stimulating cancer cell growth than circulating estrogen (2). The human aromatase gene contains nine translated exons (II-X) and at least eight untranslated exon Is (I.1, I.2, I.3, I.4, I.5, I.6, I.7, and P9). The translation start site is positioned in exon II and one of the 5′-untranslated exon Is of aromatase mRNA is spliced onto a

Grape Seed Extract Is an Aromatase Inhibitor and a Suppressor of Aromatase Expression
Isolation and Characterization of Aromatase Inhibitors from

Brassaiopsis glomerulata (Araliaceae)

Marcy J. Balunas\textsuperscript{a,b,d}, Bin Su\textsuperscript{b,c,e}, Soedarsono Riswan\textsuperscript{c}, Harry H.S. Fong\textsuperscript{b}, Robert W. Brueggemeier\textsuperscript{b}, John M. Pezzuto\textsuperscript{a,f}, and A. Douglas Kinghorn\textsuperscript{b,}\textsuperscript{*}

\textsuperscript{a} Program for Collaborative Research in the Pharmaceutical Sciences, Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois 60612

\textsuperscript{b} Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University, Columbus, Ohio 43210

\textsuperscript{c} Herbarium Bogoriense, Research Center for Biology, Indonesian Institute of Science, Bogor, 16122 Indonesia

Abstract

The hexane- and ethyl acetate-soluble extracts of the leaves of Brassaiopsis glomerulata (Blume) Regell (Araliaceae), collected in Indonesia, were found to inhibit aromatase, the rate-limiting enzyme in the production of estrogens from androgens, in both enzyme- and activity-based (AI) assays. Bioassay-guided fractionation led to the isolation of six and triterpenoid classes (1–6) from the hexane extract, of which 6-La and 5 (S), was moderately active in the cell-based AI assay. Fractionation afforded seven pure isolates (7–13) of the modified peptide, fatty acid, and sterol types, including six known compounds and the new natural product, methyl ester (9). The absolute stereochemistry of 9 and the other two steroidal esters were determined by Marfey's analysis. Linoleic acid (10) was found to be inactive in the AI assay, while 9 and (−)-dehydroloiolide (12) showed activity in the aromatase inhibition assay.

Keywords

Brassaiopsis glomerulata; Araliaceae; activity-guided isolation; aromatase inhibitors; breast cancer; modified peptides; monoterpenoids; N-benzoyl-L-phenylalanine methyl ester

1. Introduction

Brassaiopsis glomerulata is a member of the Araliaceae that occurs in south and southeast Asia, including the Vietnamese peninsula (Van Kiem et al., 2003) and in Indonesia. B. glomerulata is a large shrub or small tree with thorns on the stems, palmate leaves with 5–7

\*Corresponding author. Tel: +1-614-247-8994. Fax: +1-614-247-6642. kinghorn.64@osu.edu.
\textsuperscript{e} Current address: Smithsonian Tropical Research Institute, U1344, APO, AA 34062.
\textsuperscript{f} Current address: Beckman Research Institute, City of Hope, Duarte, CA 91010.

Publisher’s Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
SHBG

- Sex Hormone Binding Globulin
- Increased level = lower free estrogen
  - Maintain a healthy weight
  - Vegetarian lower fat diet
  - Improve Insulin Sensitivity
Insulin Resistance

Normal Insulin Metabolism

Glucose

Insulin

Bloodstream

Functioning insulin receptor site

Normal Intracellular Glucose

Insulin Resistance

Glucose

Insulin

Malfunctioning insulin receptor site

Low Intracellular Glucose
Insulin Resistance

• Women with higher levels of insulin were 2.5 x more likely to have breast cancer over the next 7 years than women with the lowest insulin levels
  – 800 women without diabetes
  – not taking estrogen
Insulin Resistance

INCREASED INSULIN

INCREASED METASTASIS

INCREASED RECURRENCE

DECREASED SURVIVAL

Therefore, although two of the main causes of cell failure in type 2 diabetes are overnutrition and lack of exercise, environmental estrogens, in particular BPA, are strong candidates to exacerbate and accelerate the development of type 2 Diabetes.

Insulin Resistance

• Abdominal weight gain
• Fatigue
• Feeling tired after a meal
• Harder time losing weight
• Cravings for foods
• Hot Flashes
• Energy Swings
• Low blood sugar
Who Is At Risk?

• **Epidemic**
  – 5% of children
  – 34% of adults over age 20
  – 51% of people over age 60
  
  National Health Statistics Report, CDC. No 13, May 2009

• **Lifestyle**
  – Weight gain
  – Poor Diet
  – Lack of exercise
  – Stress
  – Sleep deprivation
  – Dysbiosis
  – Toxin
Our Genes Haven’t Changed, But Our Environment Has...
Normal blood sugar and insulin levels

BLOOD SUGAR

INSULIN

NORMAL FASTING
Insulin Resistance
Normal → Insulin Resistance → Diabetes

Insulin

Blood Sugar
METABOLIC SYNDROME
3 out of the 5

1. Impaired glucose tolerance –
   - Fasting blood sugar > 100 or high insulin
2. Elevated blood pressure
   - >130/85 or on medication
3. Central Obesity = Apple shape
   - Waist circumference > 35” women
   - Waist / Hip ratio > .80 women
4. Elevated Triglycerides > 150
5. Low HDL < 50 women
How Can I Improve Insulin Sensitivity?

• Increase **fiber** - 35 grams daily
• Protein - at each meal
• Regular Meals
• Increase omega 3 fats
• Eliminate Trans fats (partially hydrogenated fats)
• Nutrient dense foods
• 40 minutes of **exercise** daily
• Get 7-9 hours of **sleep** per night
• Manage stress
Glycemic Load Linked To Breast Cancer Risk

- 61,000 women over 17 years
- Highest Glycemic Load had about 80% increased risk of getting ER+ breast cancer

ESTROGEN METABOLISM

• 2 OH Estrone - protective
• 4 OH Estrone - promote tissue proliferation and carcinogenic
• 16 OH Estrone - promotes tissue proliferation and carcinogenic

• 2/16 ratio > 2 optimal
Improve Estrogen Metabolism

- Increase cruciferous vegetables
  I3C and DIM and Sulforaphane
- Fish oil
- Daily exercise
- Ground flax seed
- Healthy soy
Some Genes

- BRCA 1 and 2
- COMT
- CYP1B1
- GSTM1
- MTHFR
DETTOXIFICATION

- Phase I - certain people have higher risk
  - Avoid Estrogen Disrupters
  - Avoid Cigarette smoke
  - Decrease Charbroiled Meats - Heterocyclic aromatic amines
  - Limit Alcohol
ALCOHOL

- As alcohol intake increases so does our risk
  - Linear Relationship


  - For every 1 drink increase per day, a woman’s risk of getting breast cancer increased by 12%
  - >2 drinks per day = 3x increased risk


  Annals of Int Medicine 11/02.
ALCOHOL - Why?

- Liver and detox impact
- Increase free estrogen
  - by decreasing SHBG
- Associated with other unhealthy lifestyles
- Decrease B vitamins
  - important for methylation

DETOXIFICATION

• Phase II
  – Methylation
    • Need adequate folate, B12, B6
    • Alcohol increases B vitamin needs
    • Genes - MTHFR
    • Check homocysteine
    • Methylmalonic acid
  – Sulfation
    • Cysteine ---- glutathione

– Glucuronidation
  • Calcium d glucurate
  • 1000mg 2x day
Glucuronidation

- Glucuronic Acid conjugates with estrogen
- E-GA - excreted in the stool

- Beta glucuronidase - cleave E-GA and increases free estrogen
- Beta glucuronidase is elevated:
  - high meat / low fiber diets
  - Imbalanced gut flora
  - Pathogenic gut flora
Unhealthy Bacteria → Increased beta glucuronidase → Cleves estrogen from glucuronic acid → Increased free estrogen and estrogen reabsorption

Healthy gut bacteria → Soluble Fiber → Increased butyrate → Decreased inflammation and cancer
**Gut Microbiome**

**Globulin Proteins:** Proteins that may prevent unhealthy bacteria from adhering to the intestine wall.

**Lactoferrin:** A protein that helps in iron absorption and blocks its use by unhealthy bacteria, thus starving them.
Antibiotics and Breast Cancer

• 17 year period -
  – > 25 scripts -- 2 x increased risk
  – 1-25 scripts --- 1.5 x increased risk

• Immune system ?
• Damage to Gut
Heal The Gut

- Limit Antibiotic Use
- High Fiber Diet
- Decrease Red meat - <18 oz/wk (AICR)
- Probiotics
- Nutrients
- Remove inflammatory foods
- Treat infections
Increase Inflammation = Increase Cancer


Signs of Inflammation
- Increased CRP
- Increased ESR
- Water retention
- Bloating
- Joint Pain
- Asthma
- Eczema
- Digestive Distress
- Abdominal weight gain...
hsCRP

- hsCRP is a better marker than stage of disease
- < 1.0 40% alive after 3 years
- >1.0 none survived

- Associated with increased angiogenesis, invasion, metastasis
Elevated levels of CRP in cancer-free individuals are associated with increased risk of cancer of any type, of lung cancer, and possibly of colorectal cancer. Moreover, elevated levels of baseline CRP associate with early death after a diagnosis of any cancer, particularly in patients without metastases.

J Clin Oncol 27:2217-2224. © 2009 by American Society of Clinical Oncology
Recurrent or persistent inflammation may induce, promote, or influence susceptibility to carcinogenesis by causing DNA damage, inciting tissue reparative proliferation, and/or creating a stromal “soil” that is enriched with cytokines and growth factors. Future research on the complex cascade of cellular and humoral factors participating in the chronic inflammatory process will further understanding of the pathogenesis of various cancers and potentially provide a rationale for targeted chemopreventive interventions.

David Schottenfeld, MD, MSc; Jennifer Beebe-Dimmer, PhD, MPH
CA Cancer J Clin 2006;56:69–83
Initiation

Transformation

De-differentiation

Proliferation

Invasion

Angiogenesis

Metastasis

+ Damage To DNA in Cells

+ Resistance to Apoptosis

+ Induction of Angiogenesis
STOP Progression To Cancer

• 30-50% of healthy women aged 40-50 premalignant microscopic breast tumors on autopsy.

• Some tumors regress!

• Unhealthy Soil:
  – high insulin, sugar, omega 6, IGF milk and meat

• Healthy Soil
  – Phytonutrients, low inflammation, high omega 3, green tea, beta glucans
Decrease Inflammation

– Avoid refined and processed foods
– Decrease % Body Fat
– Increase Omega 3 fats
– Decrease Omega 6 and saturated fats and eliminate trans fats
– Turmeric, resveratrol, ginger and green tea
– Decrease stress and increase sleep
Effects of a Weight Loss Intervention on Body Mass, Fitness, and Inflammatory Biomarkers in Overweight or Obese Breast Cancer Survivors

Favorable changes in cytokine levels were observed in association with weight loss in this exploratory study with overweight breast cancer survivors.

Phytonutrients - plant metabolites that defend against microbes

- Increase host defense against DNA damaging molecules. Reduce oncogenic potential of carcinogens.
- Organic has more phytochemicals -- Stress
8 - 10 1/2 cups per day
Phytonutrients

- Chlorophyll – green vegetables
- Glucosinolates – cruciferous vegetables
- Xanthophyll – yellow carotenoid pigment
- Isoflavones – phytoestrogen
- Polyphenols – quercetin, lignan, flavonoids
- Flavonoids – Catechins, ECGC = epigallocatechin
- Carotenoids – yellow / orange
Chlorophyll
Glucosinolates

- Cruciferous vegetable - Give bitter taste
- Pro apoptotic activity
- Estrogen metabolism
Isoflavones

- Phytoestrogens
- Genistein
- Daidzein
- Soy
Soy Food Intake and Breast Cancer Survival

Xiao Ou Shu, MD, PhD
Ying Zheng, MD, MSc
Hui Cai, MD, PhD
Kai Gu, MD
Zhi Chen, MD, PhD
Wei Zheng, MD, PhD
Wei Lu, MD, PhD

Estrogen is believed to play a central role in breast cancer development and progression. Blocking the effect of estrogen, either by inhibiting estrogen action or by reducing estrogen production, has been widely used in breast cancer treatment as an adjuvant therapy. Soy foods are rich in phytoestrogens, mainly in the form of isoflavones, which are natural estrogen receptor modulators that possess both estrogen-like and antiestrogenic properties. Soy constituent's have also been shown to have other anticancer effects, including the inhibition of DNA topoisomerase I and II, proteases, tyrosine kinases, inositol phosphate, and angiogenesis and may also boost immune response and possess antioxidative effects.

Consumption of soy food has been inversely related to the risk of breast cancer in many epidemiological studies. However, genistein, a major form of isoflavone, has been shown to enhance the proliferation of breast cancer cells in vitro and to promote estrogen-dependent mammary tumor growth in ovariectomized rats. In addition, breast cancer treatments often lead to a decrease in the endogenous estrogen supply of survivors, and a concern has been raised as to whether soy isoflavones may exert their estrogenic effects, promote cancer recurrence, and, thus, negatively influence overall survival. Furthermore, both in vivo and in vitro studies suggested that genistein is a novel potential chemopreventive agent for breast cancer.

Context: Soy foods are rich in isoflavones, a major group of phytoestrogens that have been hypothesized to reduce the risk of breast cancer. However, the estrogen-like effect of isoflavones led to concerns about potential adverse effects. Objective: To evaluate the association between soy intake and breast cancer outcomes.

Methods: The Shanghai Breast Cancer Survival Study was a large, population-based cohort study of 5042 female breast cancer survivors in China. Women aged 20 to 75 years, with diagnoses between March 2002 and April 2006, were included. The primary outcome was breast cancer-specific death, and was reassessed after diagnosis in a linked cancer registry database with a follow-up of 11 years.

Main Outcomes: The association between soy intake and breast cancer survival was assessed within a Cox proportional hazards model.

Results: Among women with breast cancer, soy food consumption was significantly associated with a decreased risk of death and recurrence. The inverse association was evident among women with either ER-positive or ER-negative breast cancer and was present in both users and non-users of tamoxifen.

This study suggests that moderate soy food intake is safe and potentially beneficial for women with breast cancer.


©2009 American Medical Association. All rights reserved.
Flavonoids

- Anthocyanidins = Berries (Red, blue and purple)
- ECGC – Epigallocatechin – green tea
- Flavonols = onion and kale
In vitro investigations have indicated that RWPCs (red wine polyphenolic components) and GTPs (green tea polyphenols) are able to inhibit several key events of the angiogenic process.

STRESS – Increased Cortisol

• Increased insulin resistance and abdominal fat
• Increased IL-6 - inflammatory cytokine
  • Increased Inflammation = Increase Cancer Risk
• Lower NK (natural killer) cell activity
  – NK cells find and kill new cancer cells
  • Stronger a women’s NK cell activity is the higher rate of survival from breast cancer after 12 years
• Increased Social Support = Increased NK activity
Tumor rejection in rats after inescapable or escapable shock.


- Rats with cancer cells grafted to cause 50% to die
- 3 groups
- Shock and no control - 27% rejected tumor
- No electric shock - 54% rejected tumor
- Electric shock but had a lever to stop it
  - 63% rejected the tumor
Sleep
SLEEP DEPRIVATION

Cortisol and Insulin

NK cells and melatonin

Melatonin = Anticancer and antioxidant effects
Exercise and Breast Cancer

- 4 hrs per week = less risk

- 3-5 hours per week = improved survival for women who have had breast cancer

- Vigorous exercise + BMI < 25 – 20% decreased risk

JAMA – 2005
Breast Ca Research 2008
• Reduced calorie diets = reduced risk
  • Oxidative Stress
• High fiber, low fat diets = decreased estrogen in body
• High fat diet - increased reoccurrence ER- cancer

WINS - Women Intervention Nutrition Study
• Soy in adolescents = lower risk
• Green tea - ECGC - anti-angiogenesis and antioxidant
Supplements

• Vitamin D -
  – 25OH vit D > 52 = 50% decreased risk breast cancer than if vit D <12ng/dl
  – Garland etal. AACR 2006

• Probiotic

• DIM / I3C

• Sulforaphane

• Calcium d glucurate

• Fish oil – 1000mg EPA + DHA

• B vitamins
1/3rd of all cancers can be prevented...at least!

• Exercising Regularly
• Eating Healthy Foods with Increased Fruits and Vegetables
• Maintaining a Healthy Weight
  – Decrease breast cancer by 38%

Government Role

- Increase Availability of Farmer's Markets
- Increase Bike Lanes and Walking Paths
- Get Rid of Vending Machines in Schools
- End Advertising of Junk Food To Kids
- Take High Fructose Corn Syrup out of products
- Ban Trans Fats
- Decrease toxic chemicals allowed in our environment.
What Can We Do?

• Choose Whole Foods
• Get 3-5 hours of Exercise Per Week
• Increase Fiber Intake to 35gm daily
• Have Protein at Every Meal - include vegetarian options - beans, nuts as well as fish, lean poultry and eggs.
• Maintain a Healthy Weight
What Can We Do?

• Get a Good Night Sleep
• Choose Organic Foods
• Avoid Excess Toxins
• Take Probiotics
• Limit Your Alcohol Intake
  – <1 drink per day or 5 per week.
THANK YOU!

Elizabeth W. Boham MD, RD
The UltraWellness Center
45 Walker Street
Lenox, MA 01240
413-637-9991
www.ultrawellnesscenter.com