FUNCTIONAL FOODS TO ENHANCE HEALTH

Wayne R. Bidlack and Wei Wang

College of Agriculture California State Polytechnic University, Pomona

> Presented at the 2005 CSL/JIFSAN Joint Symposium Food Safety



Hippocrates: The Father Of Medicine (ca. 400 BC)



Nutritional Value: Diet and Disease Prevention

- Historical Identification of Deficiency Disease
 - infectious agent
 - nutrient identification
- Dietary Guidelines
- Food Guide Pyramid







Parcelsus: Father of Toxicology and Pharmacology (1493-1541)





The Dose Makes The Poison



Ethnobotany: Folk Medicine

- Identification by population (human and animal) use
- Varied chemistry within plant species
- Active components depend on plant cycle, ecology, soil and climate

Therapeutic plants were identified, the active components isolated, and new pharmaceuticals designed to treat specific diseases.



Physiologically Active Food Components Identified by Mechanism of Action

- antioxidants, superoxide quencher; modifiers of oxidative damage and detoxification mechanisms related to oxidative stress; NO Synthetase inducer; enhanced DNA repair; decreased DNA damage/modification
- antimutagens, anticarcinogens, and inducers of enzymes of xenobiotic phase II metabolism; inhibits tumor promotion; antimetastatic agent; inhibits cell proliferation; inhibits angiogenesis.
- ♦ antimicrobial, antiviral bioactive substances
- enhancers of GI function, and colonic microflora; decreased risk for cancer and cardiovascular disease
- immunomodulators; stimulates immune function
- anti-inflammatory agents

Physiologically Active Food Components Identified by Mechanism of Action

- Neuroregulatory substances: improve psychological condition, memory enhancement
- Modulation of hormones: relieves symptoms of menopause
- Antihypertensives: control of BP
- Hypocholesterolemic agents: lowers serum cholesterol, reduces CHD
- diminishes allergenicity
- Decreases platelet aggregation: reduces stroke
- Stimulates bone repair: reduces osteoporosis
 - inhibits macular degeneration

Cancer Protection Pyramid



Caragay, A. 1992. Cancer-Preventive Foods and Ingredients. Food Technology 46(4) 65-68.

Anticancer Activity of Phytochemicals



1. Modification of carcinogen activation

- a. Polyphenols b. Alkyl
- c. Sulfide d. Isothiocyanates;
- e. Monoterpenes f. Flavonoids

2. Modification of carcinogen detoxification

a. Alkyl cysteines b. Isothiocyanates

3. Blocks initiation

- a. Polyphenols b. Indole c. Sulfides
- d. Flavonoids e. Protease inhibitors

4. Blocks DNA reactive species

- a. Carotenoids b. Polyphenols c. Flavonoids
- d. Terpenes e. Protease inhibitors
- f. Sulfides g. Indoles

5. Blocks cell proliferation

- a. Monoterpenes
- b. Vitamin A, precursors and metabolites

Functional Foods Definition (IFT Panel)

- Functional foods are foods and food components that provide a health benefit beyond basic nutrition (for the intended population).
 - Examples may include conventional foods; fortified, enriched or enhanced foods; and dietary supplements.
- Functional foods provide essential nutrients often beyond quantities necessary for normal maintenance, growth, and development, and/or other biologically active components that impart health benefits or desirable physiological effects.





HISTORICAL FUNCTIONAL FOODS

- yogurt
 - * anti-aging (Metchnikoff)
 - intestinal enhancement
 - * live culture
- fiber
 - bulk (regularity)
 - soluble fiber (viscosity)



Functional Foods

Food that imparts a physiological benefit

through crop selection, breeding enhancement, biotechnology, added ingredients, or processing modification.



Design of the Functional Tomato





Selection for Bioactive Agents



CLASSIFICATION OF BIOACTIVE FOOD COMPONENTS

- A. Isoprenoids
 - Carotenoids, Saponins, Tocotrienols, Tocopherols & Simple terpenes
- B. Phenolic Compounds
 - Coumarin, Tannins, Lignin, Anthrocyanins, Isoflavones & Flavonols
- C. Protein/Amino Acid Based
 - Amino acids, Allyl-S-compounds, Capsaicinoids, Isothiocyanates, Indoles, Folate & Choline; Lactoferrin
- D. Complex Carbohydrate
 - Oligosaccharides, Non-starch polysaccharide
- E. Fatty Acid Lipids
 - ✤ W-3 PUFA, CLA, MUFA, Sphingolipids & Lecithin

F. Microbial

Probiotics & Prebiotics

A. ISOPRENOIDS

Carotenoids – Lycopene, Carotene, Lutein/Zeaxanthin

Food Source

Potential Health Benefit

Tomatoes, carrots, yams, cantaloupe, spinach, sweet potatoes, citrus fruit, apricots, mango, pumpkin, kale Reduction of cancer and heart disease; reduction the risk of macular degeneration. **Possible Mechanisms and Functions**

Antioxidant activity; Free radical scavenger;

Singlet oxygen scavenger;

Induction of cell-cell communication, and growth control;

Inhibition of the proliferation of acute myeloblastic leukemia;

Modulation of mutagenesis, cell differentiation, and proliferation;

Differentiation and growth control of epithelial cells.

Carotenoids



Lycopene content of various foods

	Food	Content	Food	Content
♦	Tomatoes, fresh	0.88-4.20	Ketchup	9.90-13.44
	Tomatoes, cooked	3.70	Apricot	< 0.01
	Tomato sauce	6.20	Apricot, canned	0.06
	Tomato paste	5.40-150	Apricot, dried	0.86
♦	Tomato soup, condensed	7.99	Grapefruit, raw pink	3.36
	Tomato powder	112-126	Guava, fresh	5.40
	Tomato juice	5.00-11.60	Guava juice	3.34
	Sun-dried tomato in oil	46.50	Watermelon, fresh	2.30-7.20
	Pizza sauce, canned	12.71	Papaya, fresh	2.00-5.30

A. ISOPRENOIDS Tocopherols & Tocotrienols

Food Source

Potential Health Benefit **Possible Mechanisms and Functions**

Green leaf vegetables

nuts

grains

vegetable oil

Antioxidant Anticancer Hypocholesterolemic effects Lowering free radical;

inhibition of lipid peroxidation;

Inhibition of proliferation of cancer cells;

Inhibition of HMG-CoA reductase (tocotrienols)





Fig. 2.1. Molecular structures of tetretocopherol and tetretocomenol

- α-Tocopherol is the unit standard for vitamin activity, based on E-deficiency fetal resorption
- All tocopherols and tocotrienols have antioxidant activities: ranking depends on oxidative model used.
- Tocopherols, tocotrienols and metabolites have activities separate from their antioxidant effect

other: α -tocopherol quinone, γ -tocopherol metabolites (γ -CHEC, LLU- γ)



- Anti-inflammatory
 - LPS-stimulated macrophage PGE2 synthesis: α-tocopherol inhibits macrophage but not epithelial cell
 - COX2 activity: I by γ-tocopherol & γ-CEHC -- not antioxidant effect
- Naturiuretic (regulates cellular fluids related to HT and CVD)
 - LLU-α is an endogenous natriuretic factor; may I 70pSK channel in apical membrane of kidney
 - * α -tocotrienol increases LLU- α (mechanism unknown)
- Signal transduction
 - * tocopherols and tocotrienols I Protein Kinase C (α -toc> β -, γ -, δ -toc and α -tocotrienol)
 - α-and γ-tocopherol increase NO generation, NO Synthetase (cNOS); only γ-tocopherol increase cNOS protein expression and I NO₂ formation

Platelet adhesion

* γ -tocopherol> α -tocopherol and quinone, but all decrease adhesion

- Cholesterol synthesis
 - * γ-tocotrienol I HMG-CoA Reductase in vitro and in animal models
 - tocotrienols decrease apoB levels in hypercholesterolemic patients, mixed impact on cholesterol levels.
- Cancer cells
 - * γ -tocopherol> α -tocopherol I prostate cancer cells in vivo and reduces ras p21 oncogenes in colonocytes
 - * γ -tocotrienol I growth of breast, leukemia and melanoma cells
 - * α -, γ -, and δ -tocotrienols and α -tocopherol induce apoptosis in cells



B. Phenolics *F*lavonoid Family of Compounds

Anthocyanidins

(oenin, cyanidin)

*Flavonols

(quercetin, kaempferol)

Flavones

(rutin, luteolin, chrysin, apigenin)

*Flavanols

(catechins)

Flavanones (hesperetin, naringin, taxifolin)

*Isoflavones

(genestein, diazein)

Hydroxycinnamate

(ferulic acid, caffeic acid, chlorogenic acid, p-coumaric acid) •Black grapes, red wine, raspberries, strawberries

 onion, apple skin, berries, black grapes, tea, broccoli

lemon, olive, celery, red pepper, fruit skin, parsley

black grapes, red wine, teas

citrus fruit, citrus peel

soybeans, soy foods, legumes

grain, tomatoes, spinach, cabbage, asparagus, white grapes, olives, apples, pears, cherries, plums, peaches





Principal Polyphenolic Components in Tea

Components	Green Tea	Black Tea
Catechins	30-42	3-10
Flavones	5-10	6-8
Other Flavonoids	2-4	-
Theogallin	2-3	-
Gallic acid	0.5	-
Quinic acid	2.0	-
Theanine	4-6	-
Methylxanthines	7-9	8-11
Theaflavins	-	3-6
Thearubigens	_	12-18
Source: Katiyar and Mukhtar (1996)		

Flavonols: Quercetin and Myricetin Contents of Wines and Fruit Juices

Beverage	Quercetin (mg/L)	Myricetin (mg/L)
Wine		
Red chianti	16	8
Red Rioja Otoual	4	9
White Bordeaux	<0.5	<0.5
Fruit Juice		
Apple	2.5	<0.5
Grape	4.4	6.2
Tomato	13	< 0.5
Lemon	7.4	<0.5
Orange	5.7	< 0.5

B. Phenolics

Active Compound	Food Source	Potential Health Benefit	Possible Mechanisms & Functions
Coumarins	Vegetables, Citrus fruits	Reduction in blood clotting; Anticarcinogenic activity	Anticoagulants; Inhibitors and inactivators of carcinogen and mutagen; Scavengers of superoxide anion
Tannins	Sorghum Hazelnuts Certain berries Grape seed (dry)	Cancer prevention; Reduction of heart disease; Antimicrobial	Antioxidant; Inhibitors of superoxide radicals production and tumor promotion
Lignan	Oilseeds whole-grain cereals legumes vegetables & fruit	Reduction of heart disease Reduction of breast cancer risks	Inhibition of the production of oxygen free radicals by PMN leukocytes in hypercholesterolemia; Decrease in serum cholesterol, LDL-C, and lipid peroxidation product and increase in HDL-C and antioxidant reserve; Inhibition of endogenous estrogens for premenopausal women.
Resveratrol	Grapes Red wine	Anticarcinogenic activity; Cardiovascular protective effects	Antioxidant; Anti-proliferative effect; Induction of growth inhibition and apoptosis; Stimulation of eNOS expression and activity; Phytoestrogen.

C. Protein/Amino Acid Derived

- Amino acids
- Allyl-S-compounds
- Capsaicinoids
- Isothiocyanates
- Indoles
- Folate & Choline
- Lactoferrin



C. Animal Derived Protein Lactoferrin

alth

Food	Potential He
Source	Benefit

Milk

Stimulation of immune system; Antimicrobial agent; Healing gastrointestinal wound

Possible Mechanisms and Functions

Stimulation of a beneficial gut microflora;

Increase in the production and release of cytokines, which may affect the immune system;

T-cell dependent augmentation of NK cell activity;

Inhibition of the cell migration of certain gastrointestinal cell lines.

D. Complex Carbohydrate

Oligosaccharides

Non-starch polysaccharides



E. Fatty Acids *Conjugated linoleic acid (CLA)*

Food	Potential Health
Source	Benefit

DairyReduction of cancer;productsatherosclerosis; andCheesesobesity.

Meat

Possible Mechanisms and Functions

Reduction of cell proliferation, alteration in the components of the cell cycle and induction of apoptosis;

Reduction of the LDL cholesterol to HDL cholesterol ratio and total cholesterol to HDL cholesterol ratio in rabbits;

Decrease in preadipocyte proliferation and differentiation into mature adipocytes, decrease in fatty acid and triglyceride synthesis, and increase in energy expenditure, lipolysis, and fatty acid oxidation.



Conjugated Linoleic Acid



Dietary Source

dairy foods, ruminant foods; 4-6 mg/g lipid

Dietary Intake

- US 70-120 mg/da greatest
 - in teen and young adults, M>W
- German 250-450 mg/da

Conjugated Linoleic Acid

Impact on Disease

- Cancer
 - mice and rats, decrease chemically induced tumors
 - MCF-7 breast cancer cell line
- Atherosclerosis
 - rabbit, 1% cholesterol diet decrease Tot-C, LDL/HDL, TG
 - decreased severity of pre-induced lesion (abdominal aorta plaque)
- Diabetes Mellitus (type 2)
 - Zucker diabetic rats decrease plasma glucose, insulin, TG & FA
- Adipose reduction
 - growing animals vs adult humans
 - animal dose (1% of diet) vs 2-3 g human

• Side Effects

✤ GI disturbance

Yurawecz, Mossoba, Kramer, Pariza and Nelson, AOCS Press, 1999

E. Fatty Acids

Omega-3 fatty acids: docosahexaenoic acid /eicosapentaenoic acid

Food Source Potential Health Benefit

SalmonReduction in plasmaTunatriacylglycerol;

Other ocean fish

Algae

Reduction of heart disease;

Prevention of sudden cardiac death or fatal arrhythmias;

Anti-inflammatory activity

Possible Mechanisms and Functions

Reduction in the total and LDLcholesterol: HDL-cholesterol ratios;

Increase in serum HDL-cholesterol;

Reduction in endogenous production of TG-rich lipoproteins and increase in elimination of TG-rich lipoproteins;

Blockage of excessive sodium and calcium current in the heart;

Antithrombotic effect;

Decrease in monocyte and neutrophil chemotaxis and decreases in production of proinflammatory cytokines.

EPA and DHA Content in Fish

Fish	(g/100g)
Atlantic Mackerel	2.5
Atlantic Salmon	1.8
Pacific Herring	1.7
Atlantic Herring	1.6
Lake Trout	1.6
Bluefin Tuna	1.6
Sturgeon	1.5
Anchovy	1.4
Sprat	1.3
Sardines (canned/trained)	1.1

JADA 91: 331-337 (1991)

Fatty Acid (% Total Fat)

	α Linoleic (18:3n-3)	Eicosapentaenoic (20:5n-3)	Docosahexaenoic (22:5n-3)
Freshwater fish	1-6	5-13	1-5
Marine fish	1		
Pacific Anchovy		18	11
Mackerel		8	8
Cod fish		9	3
Herring		3-5	2-3
Sardine		3	9-13
Linseed	45-60		
Rapeseed	10-11		
Green Leaves	56		

Modified from Canadian J. Physiol & Pharmacol. 72:945-953, 1994

F. MICROBIAL

Prebiotics: nondigestible but fermentable oligosaccharides

Food Source

Potential Health Benefit

Possible Mechanisms and Functions

Garlic Asparagus Chicory Barley Oatmeal Intestinal fortification; Stimulation of immune function; Anticarcinogenic effects; Hypolipidemia Supporting the growth of lactobacilli and bifidobacteria, which are found in the large intestine and are generally considered to be beneficial by stimulating the immune system and protecting body from infection; modulation of lipid metabolism.



Nondigestible Fermentable Oligosaccharides

- Fructooligosaccharide (FOS), as example
- Physiological Actions
 - enhances intestinal bacteria
 - lower hepatic glucose production; no effect on fasting plasma glucose or insulin
 - lowered serum cholesterol
 - animal decreased plasma TG
- Side Effects
 - ✤ flatus (>30 g FOS/da)
 - abdominal cramps and diarrhea (>50 g FOS/da)



F. MICROBIAL *Probiotics: lactobacilli, bifidobacteria*

Food Source

Potential Health Benefit **Possible Mechanisms and Functions**

Fermented	dairy
foods:	
Yogurt	
Kefir	

Enhancement of immune function; Prevention of diarrhea; Anticarcinogenic effects Alter the intestinal microflora balance, inhibition the growth of harmful bacteria



Functional Food Products

- The examples of functional food products provided here are only representative of a larger effort to provide a healthy and safe diet.
- Some of the functional products identified here are already available in the marketplace, while others are being developed and some indicate opportunities for future project development.
- Designing of new delivery systems enables benefits from the use of each active functional food ingredient to be provided to a broader consumer population.

However, the new food products must taste good!



- Tofu and other soy products are prepared using calcium coagulation of the protein, providing the food products with a ready source of calcium, high quality protein, and phytoestrogens.
- Flavoring of soy milk to enhance consumption.
- Textured soy protein can be formulated into a variety of new products, including meat substitutes.
- Roasted soy nuts (soybeans) as a healthy snack food.
- Soy butter, a substitute for peanut butter.





milk, cheese, yogurt and protein (casein and whey) isolates

- Phospho-peptides produced by partial hydrolysis of casein enhance calcium absorption
- A milk based product has been developed, replacing fat with β-glucan + Oatrim (USDA) to lower cholesterol.
- Plant sterols can be added to milk and yogurt beverages to aid lowering of cholesterol.
- Prebiotic oligosaccharides can be added to milk or yogurt; even though not digested, calcium absorption increased an additional 18%.
- The dairy cow can be challenged with specific microorganisms, producing specific gamma globulins
 - isolated from the milk they can be used in therapeutic situations for calves (currently) and perhaps humans (in the future).



*O***-3 Fatty Acids**

may reduce the risk of CHD, ocean fish, algae, in their diet.

- Designer oils containing eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA) can be created and blended with other oils as ingredients to create specialty products, such as salad dressing, cooking oils or margarine.
- Growth incubators have been designed to promote the continuous production of the algae, allowing recovery and extraction of pure ω -3 fatty acids.
- The algae can be incorporated into feed products for egg laying poultry and for fish grown by aquaculture on fish farms.

Delivery Mechanisms for Bioactive Agents

Functional Foods Designer Food Products



Cereal

- Ready to eat breakfast cereals are one of the early functional foods, delivering the fiber, and nutrient value, in a palatable form.
- RTE cereal is coated with vitamins and some minerals acting as a convenient nutrient delivery system, and should provide a delivery system for functional food ingredients.





a nutritionally sound product in a self contained package

- Addition of cholestyramine to the chicken diet reduces the cholesterol content of eggs. Natural nutraceutical compounds may produce the same effect.
- Chickens fed marigolds or dietary carotenoids, incorporate greater ß-carotene levels into their egg yolks (bright redorange color). Similar feeding of other phytochemicals could transform eggs into a functional food.
- Chickens fed ω-3 fatty acids or algae incorporate the ω-3 fatty acids into the egg yolk, a rapidly growing consumer health product.



Margarines/spreads/cooking oils

- Phytosterols, stanols and sterols have esters that are GRAS approved, food grade ingredients
 - commercially available in margarine.
- Phytosterols can be incorporated into other foods, such as chocolate candy, yogurt and smoothies
 - health stores have added phytochemicals and herbs to smoothies for years.
- Esters of the phytosterols can be created using CLA, DHA or EPA to enhance the delivery of multiple phytochemicals in a single product.
 - The esters are hydrolyzed during digestion releasing the fatty acid ester.

Orange juice

- Calcium fortification of beverages, such as orange juice, and snack foods is not new, but can contribute to bone repair and prevention of osteoporosis.
- Nano-dispersion of phytosterols, imbedded in a lecithin liposome, into orange juice enables more people to benefit from the cholesterol lowering effects of the plant nutraceutical.
- Addition of other phytochemicals could be delivered by a similar mechanism.





CENIC illevilli

Plus

TRUS

Calcium

Most people love orange juice and most people need more calcium in their diet. But nature put almost no calcium in ordinary orange juice. That's why Citrus Hill has fortified 100% pure orange juice with calcium. So now there are three reasons to serve Citrus Hill Plus Calcium to your family every day.

Qne. Citrus Hill Plus Calcium starts with naturally delicious juice, squeezed from the heart of the orange. Two. Citrus Hill Plus Calcium is a better source of calcium because it

Two. Citrus Hill Plus Calcium is a better source of calcium because it has a unique calcium delivery system, CCM, that's even more absorbable than milk. In fact, Citrus Hill Plus Calcium is the first calcium

product accepted by the AMERICAN MEDICAL WOMEN'S ASSOCIATION, a national organization of 10,000 leading women physicians.

Which leads to three, why would you want ordinary orange juice on your family's breakfast table?

Citrus Hill Plus Calcium. Treat yourself to a better source of calcium.



"Casta Hill Plan Calsions has been observed to be a well-adsorbed source of distancy radiance which, as part of a Subserved dark, and accompanied by organize water has a tenhelp-bailed and maintains observed "every" "American Made al Primar's darm inform

Also available in 60% grapefruit juice beverage. Available in limited areas. © 1967 Proces & Gamble

Chewing gum

- Inclusion of zinc allows coating of the throat and possibly decreases colds.
- Inclusion of cinnamic aldehyde was added to provide a cinnamon flavor, but was determined to act as an antimicrobial agent and prevent bad breadth.
- Inclusion of oligosaccharides (in Japan) as a prebiotic to promote beneficial bacteria in the gastrointestinal tract.
- Inclusion of vitamins in a chewable form; other functional ingredients could be used as well.



The Value of Efficacious Functional Foods

To date, the average consumer has been willing to pay a higher price for health foods and nutritional and herbal supplement products.

What price the consumer will consistently pay for these and future value added products remains unknown?

But if the manufacturer can assure the consumer of an efficacious product that will provide an identifiable health benefit, they will spend more of their disposable income on "healthy" functional foods.



In Closing....

Functional Foods Hold Great Promise

- The criterion for efficacy must be based on the mechanism of action of the specific compound and the lowest possible safe exposure level
- Over promotion of functional foods before efficacy is established could damage the credibility of the whole category of compounds and their food products, and deter delivery of their potential health benefits

