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(54) Title: NUTRIENT AND THERAPEUTIC COMPOSITIONS FOR THE TREATMENT OF CANCER

(57) Abstract

This invention relates to nutrient and therapeutic compositions for the treatment of cancer symptoms and conditions. Compositions of this invention contain a mixture of antioxidants, components that promote collagen maintenance and synthesis, components that regulate blood lipids, glucose and/or insulin, and lower homocysteine levels. Compositions also provide supplementation for nutrient (vitamin, mineral and cofactor) deficiencies to restore and maintain normal biochemical function. Cancer formulations, particularly those adapted for treatment of female cancers, can be combined with components that provide benefit in osteoporosis.

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NUTRIENT AND THERAPEUTIC COMPOSITIONS FOR THE TREATMENT OF CANCER

FIELD OF THE INVENTION

This invention relates to nutrient compositions and to therapeutic compositions for the amelioration of cancer. Cancer-protective and cancer-therapeutic compositions of this invention include antioxidants, neovascular regulators, promoters or cofactors involved in collagen synthesis, as well as vitamins and minerals to supplement nutrient deficiencies.

BACKGROUND OF THE INVENTION

Cancerous cells exhibit certain characteristics that distinguish them from normal cells. These cells exhibit aberrant metabolism and growth, often the result of genetic damage; they exhibit proliferation due to inappropriate vascularization leading to tumor development; and they can undergo metastasis leading to the spread and recurrence of cancer.

Current cancer therapies are most often directed to the removal of cancerous tissue and the direct destruction of cancerous cells. The present invention is, in contrast, designed to utilize multi-component formulations the combined ingredients of which simultaneously interfere with a variety of factors or mechanisms that promote the generation, growth and spread of cancerous cells and tissue. More specifically the formulas of the present invention contain components which inhibit the development of cancer cells, inhibit proliferation of cancer cells and inhibit metathesis. Formulas of this invention contain additional components that promote cellular repair and the restoration of collagen matrices in tissues. Further formula ingredients are provided to restore and maintain pH balance and to stimulate the immune system. Vitamins and minerals are also included to supplement deficiencies including those that can result from cachexia induced by tumor development and growth and help restore normal biochemical function to cells and tissue. Additional formula components are included to control the level and type of blood-born lipids which may be related to increased cancer risk. The control of lipoprotein (a) is of particular importance. Further, optional formula ingredients can be included to control blood glucose levels, control insulin levels and reduce homocysteine levels.

The multi-component compositions of this invention and treatment methods using them are based, at least in part, on a recognition that cancer is the result of a multi-factor etiology requiring utilization of multiple biochemical factors to successfully ameliorate or reverse conditions or symptoms of cancer. Further, the protective and therapeutic formulas of

this invention include components that are directed to simultaneously inhibit cancer at various stages, i.e., to inhibit development of cancer cells, to inhibit growth and proliferation of cancer cells and tissue and to inhibit metathesis.

Formulas provided in the present invention are useful as cancer-protective nutrient compositions that may be employed as dietary supplements and as cancer therapeutic compositions that may be combined with traditional forms of cancer treatment. Additional formulas include those directed to female cancers, including hormone-dependent cancers.

Compositions of this invention can employ a mixture of different components having the same or similar biochemical or therapeutic functionality. These functionally similar components may differ in source (e.g., extracts of different plants), differ in chemical structure, differ in specific site of action and/or differ in effective half-life on administration. Such combinations of different components with similar activities provide synergistic nonadditive benefits and improvements. Components of the compositions of this invention may themselves be multi-component mixtures with each subcomponent having one or more differing functionalities. Different composition components may have more than one biological function in the mixture and different components may have distinct, yet overlapping, biological functions. The use of functionally similar components which are structurally distinct or derived from different sources allows the inclusion of sufficiently high levels of total material to achieve a desired level of activity while avoiding the potential toxic effect that may result from use of high levels of any single component. Different but functionally similar components can have somewhat different site-specific features. Additionally, distinct but functionally similar components can have different half-lives potentially providing for extended effectiveness of the formula.

SUMMARY OF THE INVENTION

The cancer protective and therapeutic compositions of this invention combine components which control oxidative stress, provide for appropriate neovascular regulation, provide factors necessary for stimulation or promotion of collagen maintenance and synthesis and tissue restoration. Preferred combinations of antioxidants and neovascular regulators include combinations of a plant extract providing antioxidant effect comprising bioflavanoids, e.g., proanthocyanidins, with a neovascular regulator selected from the group genistein, daidzein, soy isolate (a specific source of plant isoflavones, e.g., genistein, and daidzein), cartilage or preferably chondroitin sulphate. A preferred neovascular regulator is

genistein from soy isolate. Preferred compositions can further comprise components which regulate blood lipids, glucose or insulin, decrease homocysteine levels and stimulate or promote immune response or cell differentiation. Preferred compositions can further comprise components which provide cell protection from mutation and toxins.

Without wishing to be bound by any particular theory, the antioxidant components of the present formulas are believed to protect cells from damage which may lead to mutation and the generation of cancerous cells. Antioxidant components are also believed to promote restoration of healthy cells and tissue. Neovascular regulators, i.e., angiogenesis inhibitors, are believed to prevent inappropriate vascularization, help regulate growth factors to deprive cancerous cells of a blood supply and to inhibit cancer cell proliferation. Components that promote collagen synthesis are believed to also inhibit inappropriate vascularization help restore growth factors, and to generally restore or promote healthy tissue thereby inhibiting metastasis and recurrence of cancers.

Components that regulate blood lipid levels are believed to generally inhibit cancer development, growth and recurrence. Components that control blood glucose levels are also believed to generally inhibit (directly or indirectly) cancer development, growth and recurrence. Components that stimulate the immune response are believed generally to inhibit metastasis and cancer recurrence. Components that promote pH balance are believed to provide additional protection from cell damage due to oxidative stress. Components that inhibit aberrant methylation protect cells from genetic damage and inhibit carcinogenesis. Vitamins, minerals and cofactors are generally believed to improve cell and tissue health and to help maintain and/or restore normal biochemical function to cells and tissue and thereby prevent development, growth and recurrence of cancer. Nutrient components provided in the formulas herein are also believed to protect against and/or ameliorate cachexia which may result from tumor growth.

Preferred compositions of this invention combine two or more antioxidant components, two or more neovascular regulators, a component that stimulates or enhances collagen synthesis, a component that regulates blood lipid levels, a component that stimulates the body's immune response, a component that regulates blood glucose levels and mineral, vitamin and cofactor components to supplement deficiencies and help to maintain and restore normal cell biochemistry.

In a specific embodiment, this invention provides preferred protective and therapeutic formulas for female cancers including hormone-dependent cancers and cancers that have a higher occurrence rates in women (e.g., breast cancer, ovarian cancer, colon cancer, etc.). The formulas of this invention can also be combined with components that ameliorate the symptoms and conditions associated with osteoporosis.

In another specific embodiment, this invention provides protective and therapeutic formulas for the treatment of osteoporosis. These formulas combine antioxidants, components that promote collagen synthesis, contribute bone matrix and structure and inhibit bone resorption with selected minerals vitamins and cofactors that provide particular benefit to ameliorate other symptoms and conditions associated with osteoporosis which are more likely to occur in post-menopausal women.

The formulas of this invention, for both cancer therapy and for treatment of osteoporosis, can be combined wherein indicated in a given individual with drugs and compositions for hormone replacement therapy. Formulas of this invention can be combined with male hormone supplements where appropriate in a given individual.

This invention also encompasses methods of treatment to prevent or ameliorate the symptoms and disease conditions associated with various forms of cancer. These methods comprise administration of the compositions of this invention to an individual suffering from symptoms or conditions resulting from cancer. Cancer protection methods comprise administration of the nutrient compositions of this invention to an individual desirous of obtaining such benefit. Methods of this invention can be combined with other compatible known methods for cancer treatment, known methods for hormone replacement therapy and known methods for treatment of osteoporosis.

DETAILED DESCRIPTION OF THE INVENTION

A description of various components of the formulas of the present invention follows:

Antioxidants

Antioxidants and antioxidant precursors are included in the compositions of this invention to generally combat oxidative stress and resultant genetic damage and slow the deterioration of collagen tissues. In general, antioxidants are believed to protect cells from cell damage leading to generation of cancerous cells. Further, antioxidants generally protect tissue, particularly vascular and capillary tissue, from deterioration, which is believed to inhibit metastasis and cancer recurrence. In the more preferred compositions of this invention

a complementary antioxidant strategy is employed. Different chemical types of antioxidants are combined to provide enhanced antioxidant effect. Preferred antioxidant combinations include both hydrophilic (having affinity for water or polar groups) and hydrophobic (having an affinity for lipids) antioxidants and combinations of antioxidants from different natural plant sources. In a preferred embodiment, antioxidant vitamins (vitamins C or E), the mineral zinc and potassium and different plant bioflavonoid sources are combined to achieve complementary and synergistic antioxidant effects related to cell and tissue protection and healing.

Bioflavonoids containing proanthocyanidins scavenge free radicals and chelate some minerals to prevent them from causing oxidation. These bioflavonoids are found in most plants from which they can be extracted. Commercially available proanthocyanidin-containing plant extracts include: grape seed extract (also called leucoanthocyanidin), pine bark extract (including "Pycnogenol" (Trademark, Horphag)), and bilberry extract. Ginkgo biloba and other plants which can also provide bioflavonoids, but of generally lower proanthocyanidin content, can also supplement antioxidant effect. These materials and extracts contain rather complex mixtures of catechins, tannins, oligomers and proanthocyanidins, at least some of which protect membranes from lipid peroxidation, and inhibit superoxides. They are hydrophilic antioxidants, which are many times more effective than most antioxidant nutrients at controlling free radicals, superoxides and lipid peroxides. Individual plant materials which can provide proanthocyanidins may also provide other therapeutic benefits, for example, garlic and willow bark (a source of salicylic acid) may provide additional benefit.

Oligomeric proanthocyanidins (OPCs) are polymer chains of 10 or less catechins which yield red anthocyanidin when boiled in an aqueous solution of 10% hydrochloric acid. Proanthocyanidins do not contain condensed tannins but are composed of nearly 60% catechin forms which have an extremely high affinity for collagen. Catechin binds tightly to collagen, modifies its structure by crosslinking and causes it to be resistant to enzyme degradation, such as by collagenase, or by lipid peroxidation and superoxide radicals. Proanthocyanidins inhibit capillary resistance and capillary permeability and, thus, improve vascular damage and deterioration. Collagen accumulates in vessel walls in endothelia, the connective matrix, elastin and phospholipids which helps to maintain structural integrity and protect these structures from peroxide anion damage. Plant extracts employed in this

invention as sources for proanthocyanidins contain varying levels of OPCs. Antioxidant effectiveness of an extract generally increases with increasing levels of OPCs in the extract.

Red wine extract is a source of proanthocyanidins, bioflavanoids (e.g., malvidin) and tannins. Such extracts have antioxidant effect and may function to prevent platelet aggregation.

Catechins normally protect cell membranes from lipid peroxidation. Proanthocyanidins also help to deliver and bind vitamin C to cell sites and can function to replace vitamin C at times of ascorbic acid deprivation.

Compositions of this invention can contain one or more sources of proanthocyanidins which are included as antioxidants in the formula. Proanthocyanidins also promote vascular healing and integrity by restoring the collagen matrix. Different sources of proanthocyanidins, i.e., plant extracts, can also display other therapeutically beneficial functions in compositions of this invention.

Bilberry extract may contain 5 types of anthocyanocides which account for most of its activity and 25% of its volume. While bilberry extract inhibits superoxides and lipid peroxide to some degree, it is low in oligomeric proanthocyanidins (OPCs) and therefore is less effective at controlling these free radical forms than leucoanthocyanidin (grape seed extract, for example) described below. Bilberry has an unusual anti-inflammatory effect, possibly because it can suppress leukotriene production.

Proanthocyanidins can achieve concentrations in tissue (kidney and skin) up to 5 times the level contained in the bloodstream. High tissue concentrations can remain up to 24 hours after serum concentrations have been depleted. These factors contribute to the protective effect of proanthocyanidins.

The proanthocyanidin-containing extract of grape seeds includes the material called leucoanthocyanidin. This commercially available material is obtained from white grape pips and is the most effective form of proanthocyanidin, yet discovered, for inhibiting superoxides and lipid peroxidation. This is believed to be due to the high level of oligomeric proanthocyanidins (OPCs) in the grape seed extract which strongly relates to vascular stabilization as described above. Red grape extract which is a good source of resveratrol can also be employed in this invention for antioxidant effect and other benefits.

Pine bark extract, some preparations of which are known by the trade name "Pycnogenol," is similar to leucoanthocyanidin, having relatively high OPC levels, but may possess better ability to suppress phagocytes.

Ginkgo biloba is a "middle range" proanthocyanidin possessing many of the functional characteristics of both bilberry extract and grape seed extract, but these active components are apparently present in lower concentrations. Ginkgo biloba can cause dilation of arteries, capillaries and veins and inhibit platelet aggregation. Ginkgo biloba also functions to inhibit high blood pressure and would be a preferred ingredient in formulations adapted for use by those with hypertension and related disorders.

Green tea extract, tea polyphenols, contains a small amount of 2-3% of proanthocyanidin. It nevertheless is a potent antioxidant for lipid peroxides, superoxides and hydroxyl radicals. It contains relatively high concentrations of (-) epigallocatechin gallate (EGCg), a condensed tannin polyphenol. In addition to antioxidant function, tea polyphenols also have anti-platelet, anti-cholesterolemia, anti-hypertension, anti-hyperglycemic and anti-mutagenic activities. Tea polyphenols also assist theoflavin digallate in acting as an angiotensin converting enzyme inhibitor, but do not have the undesired pro-oxidant properties of captopril.

Silymarin is an antioxidant bioflavonoid isolated from milk thistle (*Silybum marianum*). Silymarin is contains the flavonoid silybin as a major component and related compounds silydianin and silychrysin (among others) as minor components. Silymarin is typically obtained as a concentrate (80% silymarin) from milk thistle seed extract. Silymarin can also be obtained from milk thistle berries. Silymarin is reported to provide a protective effect to the liver and is believed to protect liver cells from damage due to toxins (Ferenci, P. et al. (1989) *J. Hepatol.* 9(1):105-113).

Antioxidant bioflavanoids, also include, among others, the flavanone glycosides quercitin, naringin, rutin and their aglucons, which are superoxide scavengers and inhibit oxidation of LDL. Additional antioxidant bioflavanoids include: curcumin, kaempferol, fisetin, ipriflavone, apigenein, coumadin, zingiber, malviden, galangin, robinetin, myricitin, hesperiden, taxifolin, morin, deonidin, chrysin, perlargonidin, caffeic acid any of which can be included or admixed for additional antioxidant and/or collagen-binding effect. Bioflavanoids may also be contained in plant preparations and extracts, e.g., nutgall

(containing tannins and gallic acid), ginger and cinnamon extract. In preferred antioxidant combinations, two or more antioxidant bioflavanoids are combined.

The different sources of bioflavonoids, e.g., bilberry, grape seed extract (leucoanthocyanidin), Ginkgo biloba, pine bark extract ("Pycnogenol"), green tea extract (tea polyphenols) and individual bioflavanoids described above have significant complementary and synergistic chemical function that in combination with other ingredients and antioxidants in the formulas of this invention promote cell protection and repair.

Bioflavanoids can also exhibit other beneficial activities. For example, quercitin and ipriflavone may also have benefit in treatment and prevention of osteoporosis. Supplementation with these bioflavanoids decreases bone resorption and/or effects bone development.

Vitamin C or ascorbic acid can be provided in compositions of this invention in a variety of forms. Vitamin C is available from a variety of natural sources, which may also be employed in the compositions of this invention. Vitamin C is a hydrophilic antioxidant generally found in hydrophilic environments in the body, i.e., the bloodstream, the eye, interstitial spaces between cells and within cell membranes. It not only functions as a scavenger for singlet oxygen and hydroxy radicals, but it also replenishes spent vitamin E by replacing electrons. In the bloodstream, vitamin C reduces platelet aggregation, an anti-sclerotic effect. Vitamin C, however, has a short half-life and may interfere with diabetic glucose testing. Forms of vitamin C suitable for use in the formulas of this invention include ascorbic acid, isoascorbic acid, ascorbigen, calcium, zinc, magnesium, and/or sodium ascorbate, ascorbyl palmitate, and nicotinamide ascorbate. Mixtures of ascorbate complexes are also useful in the formulas of this invention to provide a variety of half-lives, differences in collagen matrix affinity and in matrix building. In addition, combinations of vitamin C and cupric sulfate may have direct cell killing action to inhibit tumor growth. Vitamin C supplementation can increase bone mass and may have an additional benefit in osteoporosis.

Indole-3-carbinol is an antioxidant that provides functions similar to that provided by vitamin C, however, it is considered to provide protection against a broader range of biological oxidation agents.

Vitamin A or retinol or its derivatives and esters thereof are lipid-based antioxidants that can be provided in compositions of this invention in a variety of forms. Vitamin A is available from various natural sources. Vitamin A can be provided, for example, as retinol

palmitate. Vitamin A and derivatives thereof are included in the formulas of this invention for their antioxidant function. Vitamin A function can be provided for example by retinol, retinal, retinoic acid (particularly 13-cis-retinoic acid and beta-trans-retinoic acid), and aromatic retinoids.

Tocopherols (Vitamin E, d-alpha-tocopheryl salts) are hydrophobic, lipid-based compounds with antioxidant function. They are believed to have a primary role in protecting cell membranes from lipid peroxidation. Tocopherols also scavenge free radicals in the blood and help to protect Vitamin A and selenium. D-alpha tocopherol forms, the natural forms of Vitamin E, are preferred over the less bioactive d,l-tocopherol forms. Tocopherols can be provided in a variety of forms with different counterions. D-alpha-tocopheryl acetate and gamma-tocopherol are preferred for use in the compositions of this invention. Because some subjects can exhibit a slight rise in blood pressure when Vitamin E is first taken, smaller more frequent doses or a time-released form of Vitamin E may be more appropriate for those individuals having hypertension or related conditions. Different forms or derivatives of vitamin E may exhibit distinct secondary activities, in addition to antioxidant properties. For example, vitamin E succinate has been reported to exhibit inhibition of proliferation of tumor cells (Kline et al. (1990) *Nutrition and Cancer* **14**:27-41).

Lutien also called xanthophyll, a carotinoid related to beta-carotene, but not a pro-Vitamin A carotinoid, is itself a lipid peroxide scavenger and appears to promote the production of zeaxanthin, another abundant and powerful lipid-based antioxidant. Lutien is an important blood-borne carotenoid strongly related to cardiovascular health. It is found in the human retina and is believed to act, possibly in a complementary manner with zinc, to protect retinal and macular tissue from oxidative damage. Zeaxanthin, an isomer of lutein, isolated from yellow corn grits, can be employed in compositions of this invention in place of or in addition to lutien.

Beta-carotene is a lipid-based, pro-vitamin A antioxidant which quenches singlet oxygen and scavenges free radicals. It plays a role in protecting against lipid peroxidation. Beta-carotene may also have a synergistic effect with other carotenoids, including lutein or zeaxanthin, for enhanced antioxidant function. Lycopene, canthaxanthin, and apo-carotenal are other antioxidant carotenoids that are useful in the formulas herein. In preferred antioxidant combinations, two or more carotinoid antioxidants are combined.

Alpha-lipoic acid (thioctic acid), which can be provided in the acid form or as an appropriate lipoate salt, e.g., sodium lipoate, is an antioxidant and free radical scavenger that reacts with reactive oxygen species including superoxide, hydroxyl radical, hypochlorous acid, peroxyl radical, and singlet oxygen. Its reduced form, dihydrolipoate, is also an effective antioxidant. The d-form is the naturally-occurring optical isomer and preferred. The dl-form is available and can be employed in place of the d-form. Alpha-lipoic acid and its reduced dihydrolipoate form can bind to proteins including albumin which can prevent glycation reaction.

The mineral zinc, which is discussed in more detail below, is associated with protection against lipid peroxidation in retinal and epithelial vascular tissue, possibly due to its enhancement of superoxide dismutase function. The mineral potassium, also discussed below, inhibits superoxide anion.

N-Acetyl-l-cysteine and glutathione are free radical scavengers. N-Acetyl-l-cysteine is also very effective for lowering lipoprotein (a) [LP(a)] concentrations *in vivo*.

Neovascular Regulators

Normal angiogenesis regulation appears to be accomplished by a variety of means. Endogenous factors, e.g., body chemistry, genetics, as well as exogenous factors, e.g., types of food consumed, appear to play a role in this important control mechanism. A number of substances have been found to affect angiogenesis. Those substances that inhibit or moderate undesired angiogenesis are preferred for use in the compositions of this invention. Preferred compositions of this invention comprise more than one chemical type of angiogenesis regulator or more than one source of an angiogenesis regulator. Different regulators are believed to function in a complimentary manner to achieve a biochemical balance. In addition, components of the compositions, other than specifically listed neovascular agents, may also affect angiogenesis. For example, antioxidants and free-radical scavengers can control free radicals which, by various mechanisms, may destroy angiogenesis regulation. The control of oxidative stress due to antioxidants may have a significant effect on beneficial neovascular control. As discussed above regarding antioxidants, conservative doses of several angiogenic regulators are believed to be more beneficial, i.e., enhanced effectiveness with minimal potential for toxic effect, than larger doses of a single chemical.

Cartilage, an avascular tissue, is a source of angiogenesis inhibitor(s). Shark and bovine cartilage, among others, are sources of angiogenesis inhibitor and may provide collagenase inhibition as well. Chondroitin sulphate, a mucoploysaccharide found in most mammalian cartilaginous tissues and shark cartilage, is believed by many to be the most active angiogenesis regulating component of shark cartilage. The restoration of depleted chondroitin sulphates may also affect collagen stabilization which would help to normalize the collagen matrix of vascular tissue and therefore create a more stable vascular structure. Chondroitin sulphate can be provided in a number of forms with different counterions, e.g., sodium, potassium, etc. Sodium chondroitin sulphate is the form preferred for use in compositions of this invention.

Protamine sulphate is a mixture of the sulphates of basic peptides that can be prepared from the sperm or the mature testes of certain species of fish. It is an arginine rich basic protein which has been shown to be a specific inhibitor of angiogenesis, possibly due to its ability to bind to heparin. Protamine has been used in some insulin preparations to prolong the effects of insulin. Protamine is usually given as the sulphate, but the hydrochloride form may also be used.

Genistein as well as daidzein are plant-derived isoflavonoids found, for example, in soybeans, that exhibit an ability to inhibit neovascularization by controlling endothelial cell proliferation *in vitro*. Soy isolate is a natural source of genistein, daidzein or the glycoside derivatives (e.g., genistein, daidzein and sophoricoside) of these isoflavones. Soy isolate also provides nutritional benefit and may supplement depleted amino acids. Additional plant-derived isoflavonoids include kievitone. Genistein and possibly kievitone may also function as a tyrosine kinase inhibitor causing apoptosis in certain cancer cells. Certain plant derived isoflavonoids, such as genistein, exhibit estrogenic function. Such isoflavonoids can function, like estrogen, to inhibit bone loss. Phytosestrogen, particularly those isolatable from soy, can have inhibitory effects upon cancer.

Gymnema sylvestre which normalizes heparin levels is provided in the compositions of this invention, at least in part, to affect heparin levels which in turn may affect angiogenic regulation due to shark cartilage and protamine sulfate which both bind to heparin. The Gymnema sylvestre also provides for insulin/glucose stabilization which can further reduce the oxidative stress that contributes to the neovascularization factors described above.

Garlic extract (allicin), licorice extract (glyzzeryn), ginger, red wine extract, citrus pectin and/or marine tunicates can function for neovascular regulation and may provide additional therapeutic or nutritive benefit.

Collagen Factors

Maintenance and restoration of the collagen matrix in vascular and other tissue, especially as a means to stabilize and regulate growth factors, is an important aspect of the formulations of this invention. In this regard, building blocks for collagen synthesis, growth regulators related to collagen synthesis and repair, cofactors for synthesis of collagen, calcium binding and/or regulatory agents and nutrients including various minerals associated with promotion of collagen synthesis are provided in formulas of this invention. Glucosamines stimulate and provide building blocks for collagen synthesis. Chondroitin sulphate is a flucosamine that functions for growth regulation and stimulates collagen synthesis. Glucosamine sulphate is a preferred glucosamine for promoting collagen synthesis and repair.

Manganese is a cofactor which promotes collagen synthesis. Amino acids, particularly branched chain amino acids (L-leucine, L-isoleucine and L-valine), provide protein for synthesis of collagen.

Other components that affect collagen synthesis are inhibitors of mammalian collagenases and antioxidants. Inhibition of collagen breakdown by oxidative stress or by enzymatic degradation combined with stimulation and promotion of collagen synthesis is believed to result in improved collagen matrix.

Minerals

The compositions of the present invention include various minerals including zinc, chromium, calcium, magnesium, potassium, manganese, and selenium. Other minerals which may have beneficial or nutritional value for a given individual, particularly those minerals that are depleted can be provided individually or as a mineral complex. Certain minerals can have additional therapeutic value in the compositions of this invention. For example as discussed above, zinc is believed to play a significant role as an antioxidant.

In general, minerals can be provided in a variety of forms with various counterions. The choice of a given form of mineral will depend generally on the type of dosage form that is employed, whether, for example, an oral or intravenous dosage form is employed. Preferred forms of minerals are generally those that are more absorbable and those that have

lower toxicity. In addition, preferred forms will be generally compatible with the other components of a given mixture, will result in minimal irritation or other undesired side effects. Choices of form of a given mineral provided in a given composition of this invention will also depend on the other ingredients in the composition, particularly to avoid excessive levels of a given counter ion.

Zinc can be provided in a variety of forms and with various counter ions, including among others zinc citrate, zinc fumarate, zinc gluconate, zinc alpha-ketoglutarate, zinc lactate, zinc malate, zinc succinate, zinc picolinate or mixtures thereof. The preferred form of zinc in the compositions of this invention is zinc (Krebs) in which the counter ions are a mixture of the anions of the five primary organic acids of the tricarboxylic acid cycle (Krebs Cycle) i.e., a mixture of the zinc salts of citric, fumaric, malic, alpha-ketoglutaric and succinic acids. Zinc may have an indirect effect on bone resorption by inhibiting cadmium accumulation.

Chromium can be provided by a variety of dietary sources including, among others, brewer's yeast, liver, potatoes with skin, beef, fresh vegetables and cheese. Chromium exists in a dinicotino-glutathionine complex in natural foods. Such dietary and natural materials can provide sources of chromium for use in compositions of this invention. As with other minerals, there are generally a variety of forms of chromium that are useful in the compositions of this invention including, for example, chromium sulphate. Chromium nicotinate (Chromium-nicotinic acid complex) is a preferred form of chromium for use in the formulas of this invention. Chromium picolinate can be employed in the formulas of this invention, but is not generally preferred. Chromium enhances insulin activity and as a result can affect blood lipids. For example, chromium nicotinate acid complexes can lower blood triglyceride levels. Chromium also decreases calcium excretion.

Magnesium can be provided in a variety of forms and with various counter ions, including among others magnesium citrate, magnesium fumarate, magnesium gluconate, magnesium alpha-ketoglutarate, magnesium lactate, magnesium malate, magnesium succinate, magnesium picolinate, magnesium sulphate or mixtures thereof. Preferred forms of magnesium in the compositions of this invention are magnesium citrate, magnesium malate, magnesium malate-citrate, and magnesium (Krebs) in which the counter ions are a mixture of the anions of the five primary organic acids of the tricarboxylic acid cycle (Krebs

Cycle) i.e., a mixture of the magnesium salts of citric, fumaric, malic, alpha-ketoglutaric and succinic acids. Magnesium deficiency may be a risk factor in osteoporosis.

Calcium can be provided in a variety of forms and with various counter ions, including among others calcium ascorbate, calcium carbonate, calcium citrate, calcium fumarate, calcium gluconate, calcium alpha-ketoglutarate, calcium levulinate, calcium lactate, calcium malate, calcium succinate, calcium picolinate or mixtures thereof. Calcium can also be provided in a variety of natural sources including dolomite, oyster shells, and bone meal. The more preferred form of calcium in the compositions of this invention is calcium (Krebs) in which the counter ions are a mixture of the anions of the five primary organic acids of the tricarboxylic acid cycle (Krebs Cycle) i.e., a mixture of the calcium salts of citric, fumaric, malic, alpha-ketoglutaric and succinic acids. Also preferred for use in compositions of this invention are calcium carbonate, calcium citrate, and calcium malate-citrate which are noted for being highly absorbable.

Calcium is an important component of osteoporosis formulas increasing bone mass and decreasing bone fragility. Strontium, in low doses, reduces bone resorption and maintains high bone formation. Boron is included in osteoporosis formulas herein to balance in vivo potassium and calcium levels.

Potassium can be provided in a variety of forms and with various counter ions, including among others potassium citrate, potassium carbonate, potassium fumarate, potassium gluconate, potassium alpha-ketoglutarate, potassium lactate, potassium malate, potassium succinate, potassium picolinate or mixtures thereof. The preferred form of potassium in the compositions of this invention is potassium citrate which has one of the highest levels of elemental potassium.

Manganese, selenium, and strontium can be provided in a variety of forms with various counterions. Selenium is preferably supplied as an organoselenium compound, e.g., selenomethionine. Manganese aspartate is a preferred form of manganese for use in the formulas of this invention.

Ranges of zinc (Krebs), calcium (Krebs), magnesium (Krebs), chromium nicotinate, potassium citrate and other minerals in an average daily dose of a composition of this invention are provided in Table 2. The ranges given are maximum ranges which may need to be adjusted dependent upon the amount and form of other ingredients included in the

composition. These ranges can be readily adjusted by those of ordinary skill in the art of nutrient and therapeutic formulation to other forms of the minerals noted above.

A mineral complex can optionally be combined with the compositions of this invention in addition to or substituted for specific minerals in the various formulas. Preferably, the mineral complex is used to supplement nutritional minerals not already included in specific formulation. A preferred mineral complex includes absorbable salt or chelated forms of:

major mineral components: calcium, magnesium, and potassium also chloride (e.g., as potassium chloride) and sulphate (e.g., as manganese sulphate);

intermediate level components: zinc, manganese, boron and copper;

minor components: chromium, selenium, iodine, molybdenum, vanadium, lithium, rubidium, silicon (as silica), nickel, phosphorus, strontium and cadmium;

trace minerals: preferably from natural sources e.g., marine organic minerals or sea water concentrate.

The minerals may be provided in a variety of salt and complex forms, i.e., as the salts of Krebs cycle acid anions: aspartate, citrate, fumarate, malate and/or succinate salts; as salts of amino acids (e.g., arginates); as picolinate salts; as ascorbate salts, as nicotinate salts. Silicon is preferably provided as the trisillicate anion, e.g., magnesium trisillicate. Selenium is preferably provided as organoselenium compound, e.g., selenomethionine. A variety of natural sources of minerals are known to the art including plant extracts, and can be used to provide minerals in the formula of this invention. A preferred mineral complex provided in Table 1.

Minerals specifically included in a given formulation of this invention are preferably provided at the level indicated in that formulation. For an individual diagnosed with a particular mineral deficiency (e.g., iron deficiency), dosages of a given mineral may be increased as needed and additional minerals, e.g., iron, may be added to the mineral complex.

TABLE 1: MINERAL COMPLEX COMPONENTS

Calcium (Krebs) (lactate, aspartate, argininate etc.)	10 mg to 10,000 mg
Magnesium (Krebs),(aspartate, argininate, triscilicate (malate), etc.)	3 mg to 10,000 mg
Potassium (Krebs) (argininate, aspartate)	2 mg to 10,000 mg
Zinc (Krebs) (picolinate)	1 mg to 100 mg
Manganese (Krebs)	10 mcg to 100 mg
Boron (gluconate)	`0 mcg to 100 mg
Copper (Krebs)	10 mcg to 50 mg
Chromium (picolinate, nicotinate, etc.)	2 mcg to 50 mg
Selenium (1-selenomethionine)	1 mcg to 50 mg
Iodine (marine organic minerals, kelp, etc.)	1 mcg to 50 mg
Molybdenum (Krebs)	1 mcg to 50 mg
Vanadium (Krebs)	1 mcg to 50 mg
Lithium (aspartate, argininate, etc.)	1 mcg to 50 mg
Rubidium (Krebs)	1 mcg to 50 mg
Silica (sodium melasilica, magnesium trisilicate)	10 mcg to 200 mg
Trace minerals (marine organic minerals)	10 mcg to 200 mg
Cobalt	10 mcg to 200 mg
Nickel	1 mcg to 50 mg
Phosphorus (e.g., dicalcium phosphate)	1 mcg to 50 mg
Chloride (e.g., potassium chloride)	1 mg to 1,000 mg
Sulphur (manganese sulphate)	10 mcg to 100 mg
Strontium	1 mcg to 800 mg
Cadmium	1 mcg to 500 mg

Vitamins

Vitamins are included in compositions of this invention to provide supplementation for depletion and dietary deficiencies and in some cases for specific therapeutic benefits. Vitamins may also complement the activity of other components of the composition. Vitamin C, i.e., ascorbic acid, vitamin E, i.e., alpha-tocopherol, and vitamin A provide

general nutritional supplementation as well as antioxidant function, as discussed above. Vitamin B6, i.e., pyridoxine, vitamin B12, i.e., cobalamine, and folic acid (folate) provide general nutritional supplementation, and more specific benefits. Folate and vitamins B6 and B12 have antianemia properties. Folic acid decreases homocysteine levels. Vitamin B2, i.e., riboflavin, provides general nutritional supplementation. Vitamin B6 deficiency may detrimentally effect bone formation. Vitamin D can provide positive beneficial effect in protection and/or inhibition of cancer. A preferred form of vitamin D is vitamin D3.

A vitamin B complex can be employed in addition to or substituted for Vitamin B components of the formulas of this invention. A preferred Vitamin B complex includes:

Vitamin B1 (thiamine)	10μg - 100 mg	(10%))
Vitamin B2 (riboflavin)	10μg - 50 mg	(5%)
Vitamin B3 (nicotinamide or niacinamide, preferably as niacinamide ascorbate)	1 mg-1,000 mg	(53%)
Vitamin B5 (pantothenic acid)	1 mg -200 mg	(26%)
Vitamin B6 (pyridoxine HCl)	10μg - 3 mg	(5%)
Vitamin B12 (cyanocobalamin)	1μg - 200 μg	(0.03%),

where a preferred range and preferred specific relative amounts of the components are given.

Amino Acids

The formulas of this invention include amino acids that have a particular therapeutic function. Formulas of this invention may also contain additional amino acids for nutrient supplementation or for compensation for an individual's deficiency. Compositions of this invention can include any of the following: alanine, arginine, aspartic acid, cystine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, carnitive (all in the biologically active L-form) and gamma aminobutyric acid. When present in a given formula, a specifically listed amino acid is preferably provided in the amount needed to provide the desired therapeutic effect. Additional nutritional amino acids are preferably provided in an nutritionally effective amount.

Lysine

Supplementation of amino acid deficiencies is generally important to maintain normal biochemical function. Amino acid deficiencies, particularly lysine deficiency, can reduce calcium utilization. Lysine is provided in formulas herein to avoid such deficiency and enhance calcium utilization, particularly in osteoporosis formulas.

Methionine/Cysteine

Aberrant methylation can result in DNA damage, mutation and result in cancerous cells. Maintenance of normal methionine metabolism, for example by supplementation with methionine or cysteine, may avoid DNA damage and insure DNA repair. Normal methionine metabolism may also be promoted by supplementation with folic acid, choline and betaine.

Arginine may function as a non-specific immune modulator stimulating immune response.

Glutamine deficiency may occur in patients with cancerous tumors due to significant consumption of glutamine by the tumor. Glutamine is provided in formulas herein to compensate for deficiency.

Branched amino acids (leucine, isoleucine and valine) are beneficial in collagen maintenance and synthesis providing protein components for collagen synthesis.

Other components:

Sulforaphane is an isothiocyanate derived from *Cruciferae*. This material is reported to inhibit development of cancer by inducing detoxifying phase 2 enzymes (Raloff, J. (1997) *Science News* 152:183). Broccoli sprout extracts are a good source of sulforaphane.

Fenugreek (*Tigonella foenumgraecum* L. *Leguminous*) is an annual herb, the seeds of which contain a number of alkaloids, including trigonelline and coumarin, and the steroidal sapogenin, diosgenin. Fenugreek provides phytoestrogens. Fenugreek seeds reduce serum cholesterol levels in animals. In particular, the defatted fraction of fenugreek seed which is rich in fiber (about 54%) and contains about 5% of steroidal sapogenin, including diosgenin significantly lowers plasma cholesterol, blood glucose and plasma glucagon levels. Fenugreek is included in certain preferred compositions of this invention for control of blood glucose levels. The preferred form of fenugreek for formulations of this invention is the defatted, fiber-rich fraction.

Terpenes/monoterpenes and metabolites thereof can exhibit inhibition of cancer cell growth. The effect may result from inhibition of enzymes needed for cell growth. Limonene

(d-limonene), narigninen, tangeritin, nobelitin, iberene and d-carcone are exemplary monoterpenes. D-limonene is a preferred monoterpene for use in the formulas of this invention.

Source of omega-3-fatty acids

Omega-3 oils are a family of oils having relatively high concentrations of omega-3 polyunsaturated fatty acids, including eicosapentaenoic acid (EPA) and alpha-linolenic acid. These oils exhibit a hypolipidaemic action, especially a reduction in plasma triglycerides linked to a reduction in very-low density lipoproteins (VLDL). They also exhibit anti-inflammatory effects. Fish oils and other marine oils typically contain high levels of omega-3-fatty acids. In general, omega-3-fatty acids are believed to reduce blood pressure, and lower cholesterol and triglyceride levels. Omega-3 fatty acids are found in a variety of naturally-occurring sources and may be provided in their acid form or as fatty acid salts or fatty acid esters.

Chronic omega-3-fatty acid deficiency correlates with chronic nephropathic injury. EPA and DHA (docosahexanoic acid) produce an anti-inflammatory effect by reducing prostaglandin production and displacing arachidonic acid. HDL, triglycerides and fibrinogen have also been successfully reduced by omega-3-oils. Omega-3-fatty acids are included in formulas herein, at least in part, for their function in the control of blood lipid levels.

Flaxseed (also called Linseed) is a nutrient rich in omega-3-fatty acids. It is a major source of alpha-linolenic acid (an omega-3-fatty acid) and lignin. Ground flaxseed is a preferred source of omega-3-fatty acids over fish oils for use in compositions of this invention. The use of flaxseed oils, particularly in cases where the formula is being used chronically for protective or prevention benefit, avoids the potential toxicity that has been associated with long term use of fish oils. Fish and marine oils or individual omega-3-fatty acids, including EPA, and ALA (and their analogous fatty acid esters) can be used in these formulations in place of flaxseed. Omega-3 fatty acids may have a protective effect against tumorogenesis.

Essential fatty acids (EFAs) are those fatty acids that cannot be made by the body and must be supplied through the diet. Fresh, poly-unsaturated vegetable oils are a major source for EFAs (linoleic, linolenic and appropriate levels of arachidonic acids). EFAs have a variety of beneficial effects including reduction of blood pressure, lower cholesterol, and lower triglyceride levels. Linolenic acid is one essential fatty acid for formulations of this

invention. A natural source of linolenic acid is Evening Primrose Oil which also provides high levels of GLA (gamma-linoleic acid, about 9%) with minimal toxic properties. Conjugated dienoic linoleic acid is a particularly preferred derivative of linoleic acid which may provide protection from oxidation that can lead to cell damage, mutation and carcinogenesis.

Coenzyme Q_{10}, also designated ubiquinone(50) is one of a group of benzoquinones involved in electron transport. Coenzyme Q_n, where n = 1-12, has a 2,3-dimethoxy-5-methylbenzoquinone nucleus with various terpenoid side chains. Coenzyme Q with 10 isoprene units (Coenzyme Q_{10}) is the most common form in animals. Coenzyme Q_n, where n = 6-10, are naturally occurring. Coenzyme Q_{10} is a necessary component of the energy-generating process of every cell in the body. Coenzyme Q_{10} can also function as an antioxidant. Coenzyme Q_{10}, the preferred form of coenzyme Q for human nutrition and therapy, is provided in formulations of the present invention to supplement nutritional deficiencies which are believed to generally exacerbate disease conditions. Adequate tissue reserves of Coenzyme Q_{10} may also facilitate blood sugar regulation. Coenzyme Q_{10} is also believed to generally enhance an individual's energy levels. Other forms of coenzyme Q, particularly coenzyme Q_n, where n is 1-9 and 10-12 and more preferably the naturally-occurring forms where n = 6-9, can be employed along with or in place of coenzyme Q_{10} in the formulas of this invention.

Taurine is found in high concentrations in the brain, retina and kidney cortex. Taurine may have a protective effect on tissue and/or act as an antioxidant. Taurine has also been linked to inhibition of platelet aggregation and atherosclerotic lesions and has been found to help control blood pressure. Taurine can be provided from a variety of sources in different forms. Homotaurine, a taurine precursor, is a good bioavailable oral form to provide taurine. Compositions herein can contain taurine or homotaurine. Taurine appears to affect calcium levels and is included in osteoporosis formulas.

L-Carnitive is an essential co-factor of fatty acid metabolism. Faulty transport of fatty acids across mitochondrial membranes may lead to oxidative stress due to reduced lipid metabolism. Carnitive supplementation supports increases in fat utilization and oxygen uptake while decreasing plasma lactate levels and respiratory quotients. Carnitive has been shown to reduce ketones, LDL and triglycerides and increase HDL while acting as a vasodilator. L-Carnitive can be provided as N-acetyl-l-carnitive hydrochloride, the preferred

form for this invention. Carnitive can be also be provided as the l- or d,l-form as hydrochloride or other salts.

Sesamin/Sesamolin are constituents of sesame oil and/or sesame seeds. These components are believed to affect blood lipid levels.

Phytosterols, including plant sterols, which comprise beta-sitosterol, campesterol, and/or stigmasterol have been shown to reduce the absorption of the LDL cholesterol component of foods in the gut on a dose dependent basis of approximately one-to-one sterols to cholesterol, while enhancing beneficial HDL to positively effect the LDL-HDL Ratio. Plant sterols have been shown to primarily block harmful LDL cholesterol and admit beneficial HDL cholesterol, the levels of which can actually be elevated. Plant sterols can be provided in the formulas of this invention in soy oil or by addition of individual sterol components. A commercially available mixture of phytosterols, "Cholestatin III" (about 62% beta-sitosterol, about 24% campesterol and about 14% stigmasterol), produced in bacterial fermentation, is preferred for use in the formulas of this invention. Saw palmetto is another useful source of phytosterols.

Gymnema sylvestre

Gymnemic acid, the active ingredient in gymnema sylvestre, suppresses sensitivity to sugar and its absorption, thereby reducing blood glucose levels. It also restores the levels of three chondroitin sulfates which may assist in collagen repair and/or aid in angiogenesis regulation. Heparin sulphate levels are increased in diabetics while three chondroitin sulfates are decreased. Gymnema sylvestre which normalizes heparin levels could play a supporting role in the angiogenic regulation of other ingredients in this formulation, namely shark cartilage and protamine sulfate. Both are angiogenic regulators which bind to heparin. The restoration of depleted chondroitin sulfates probably plays a role in collagen stabilization which would help to normalize the collagen matrix and therefore create a more stable structure upon which angiogenesis regulation could more easily exist. The insulin/glucose stabilization effects of Gymnema sylvestre would reduce the oxidative stress that contributes to the neovascularization factors described above.

Garlic/Garlic Extract

Alicin and garlicin are active ingredients of garlic and garlic preparations that have been associated with control of blood glucose levels, cholesterol reduction and triglyceride reduction. These materials are included in the formulas herein for their general inhibitory

activity against cancer. Dried powder and extract of *Allium* species (particularly garlic) can be employed to provide these functions.

Chlorophyll is the green pigment of plants found in both higher plants and algae. Dependent upon plant/algal source chlorophyll can contain mixtures of chlorophyll a, b, c or d. A variety of commercial chlorophyll preparations are available for use in the formulas herein. Chlorophyll is employed in the formulas herein to reduce the effect of carcinogens and inhibit carcinogenesis.

Chinese Herbs. The herbs *Oldenlandia diffusa*, *Scutellaria barbata*, *Astragalus membranaceus*, and *Ligustrum lucidum* are used in traditional Chinese medicine as adjuncts to cancer therapy.

Calcitonin (Merck Index, Ninth Edition (1976) 1633 P.208) is a calcium regulating hormone secreted by mammalian thyroid gland that is employed in the treatment of bone disorders including osteoporosis. **Amylin** (see U.S. patent 5,405,831) is a peptide found in amyloid deposits of diabetics (Type 2), which may be a peptide hormone having a role in storage and disposal of food as carbohydrate and fat. Amylin increases liver output of glucose, increases lactate production in muscle and decreased insulin action. US 5,405,831 reports that amylin, variants of amylin and amylin agonists are useful, like calcitonin, for the treatment of bone disorders to prevent or inhibit bone resorption because of its role in calcium metabolism.

Fluoride/Sodium Fluoride

Calcium provided in combination with slow release sodium fluoride can inhibit development of fractures. Sodium fluoride is provided in osteoporosis formulas herein. Other forms of fluoride may provide similar benefit.

Vitamin D3 is associated with calcium transport and bone calcium resorption. 1,25-dihydroxy vitamin D3 is reported to increase calcium absorption, lower blood pressure and increase sensitivity to insulin. Certain analogs and derivatives of 1,25-dihydroxy vitamin D3 are reported to induce minimal or no hypercalcemia. (Hypercalcemia is a significant contributing factor to the toxicity of vitamin D's.) A vitamin D derivative, 22-oxa-vitamin D3, is thus indicated to have reduced toxicity compared to vitamin D3. See: Abe, J. et al. (1991)*Endrocrinology* **129**:832-837 and Mark, R. (1992) *Pediatric Nephrology* **6**:345-348. Vitamin D3 is also reported to be important in cell differentiation. The inventor includes vitamin D3, particularly lower toxicity Vitamin D3 analogs (22-oxa-Vitamin D3) in the

formulas of this invention as a calcium regulator that is a factor for promotion of collagen synthesis and more importantly for its additional function in stimulating or enhancing immune response. Vitamin D3, preferably 22-oxa-vitamin D3, is also provided in osteoporosis formulas herein.

Vitamin K

Vitamin K is a cofactor involved in blood coagulation. Vitamin K1, or phylloquinone, is a preferred form of Vitamin K for use in the formulas herein. Vitamin K is also reported to increase calcium binding affinity of certain proteins in bone formation. Vitamin K is included in formulas of this invention to supplement any vitamin or cofactor deficiency and for its calcium-binding function which indicates usefulness in tissue regeneration and benefit for osteoporosis.

Melatonin, a hormone, provides for inhibition of prolactin which is a stimulator of growth of breast cancer cells. Melatonin thus provides indirect inhibition of cancer cells.

Betaine HCl, Pepsin and Sodium Bicarbonate

Inappropriate acidity is believed to be a factor in the pathogenesis of chronic disease. Mitochondrial antagonism resulting in oxidative stress is a probable mechanism. Betaine HCl, pepsin and sodium bicarbonate have all demonstrated the ability to help regulate hyperacidity. In addition, betaine HCl and pepsin are among digestive enzymes often deficient in the elderly as well as chronic disease sufferers. Betaine may also effect methionine metabolism to provide protection from DNA damage due to aberrant methylation. Inappropriate acidity may result in bone dissolution. Factors that control acidity can provide benefit in osteoporosis and are included in osteoporosis formulas herein.

Specific cancer preventative and therapeutic formulas of this invention include:

1. Formula I which comprises:
   - (i) antioxidants selected from:
     - (a) a plant extract having antioxidant effect comprising bioflavanoids, particularly an extract providing a major source of proanthocyanidins, such as bilberry extract, grape seed extract, or pine bark extract. Bioflavanoids of lower proanthocyanidin content, for example, ginkgo biloba, can also be used to supplement major sources; combinations of plant materials and extracts can also be employed;

(b) antioxidant vitamins, e.g., vitamin C and/or vitamin E;

(ii) tea polyphenols providing for additional antioxidant benefit;

(iii) absorbable zinc, preferably zinc(Krebs) to supplement dietary deficiency; which may be provided in a mineral complex;

(iv) a neovascular regulator selected from genistein, kievitone, daidzein or a related isoflavonoid, and chondroitin sulphate or cartilage; Isoflavonid may be provided as soy isolate comprising genistein and/or daidzein; Genistein is the preferred isoflavonoid; and

2. Formula II which comprises:

(i) antioxidants including the bioflavanoids: pine bark extract (preferably high OPCs, e.g., 85% or greater oligomeric proanthocyanidins (OPCs)); and bilberry extract (preferably low OPCs, e.g., 25% oligomers OPCs); and the antioxidants: vitamin A and vitamin E;

(ii) tea polyphenols;

(iii) absorbable zinc;

(iv) genistein (optionally provided in soy isolate) and chondroitin sulphate (optionally provided in a cartilage preparation);

(v) arginine which may be provided in an amino acid complex.

3. Formula III which comprises:

(i) pine bark extract, bilberry extract, grape seed extract (leucoanthocyanidin), and ginkgo biloba;

(ii) vitamin C, vitamin E and vitamin A;

(iii) monoterpene, e.g., limonene;

(iv) antioxidant carotenoids, e.g., beta-carotene, lutein, lycopene, luteolin, zeaxanthin or apo-carotenal (beta-carotene being preferred);

(v) tea polyphenols;

(vi) absorbable zinc, calcium (e.g., calcium citrate, calcium malate or calcium maltate citrate) and magnesium (e.g., magnesium citrate, magnesium malate or magnesium malate citrate);

(vii) genistein and chondroitin sulphate;

(viii) L-arginine or amino acid complex; and

(ix) a source of omega-3 fatty acids, particularly conjugated dienoic fatty acids, e.g., linoleic acid (ALA) and/or enosapentaenoic acid (EPA), a preferred source is ground flax seed;.

4. Formula IV which comprises:

The components of Formula III; and

protamine sulphate and/or glucosamine sulphate (a preferred glycosaminoglycan and source of glycosamine, a building block for collagen synthesis);

vitamin D3, preferably derivatives thereof which induce little or substantially no hypercalcification (e.g., 22-oxa-vitamin D3); and

branched amino acids.

5. Formula V which comprises:

The components of Formula IV and

quercitin;

Saw palmetto;

vitamin B12 and folic acid (or optionally vitamin B-complex);

absorbable potassium and selenium;

alpha-lipoic acid (also called thiotic acid); and

allicin (or garlic extract);.

Formula 5A which comprises the components of Formula 5 where the antioxidant carotenoids are a mixture of beta-carotene and lutein.

Formula 5B which comprises the components of Formula 5 which contains a mixture of chondroitin sulphate, protamine sulphate and shark cartilage and where the antioxidant carotenoids are a mixture of beta-carotene and lutein.

6. Formula VI which comprises:

The components of Formula V, 5A or 5B and

silymarin;

curcumin;

niacinamide;

a source of essential fatty acids, particularly conjugated dienoic fatty acids; for example, linoleic acid and

one or more of sodium bicarbonate, betaine HCl or pepsin.

Formula 6A comprises the components of Formula 6 and contains a mixture of chondroitin sulphate, protamine sulphate, glucosamine sulphate and optionally shark or animal (e.g., bovine) cartilage.

Formula 6B comprises the components of Formula 6 and contains a mixture of the monoterpenes limonene and naringinen and a mixture of the carotenoids beta-carotene, lutein and lycopene.

7. Formula VII which comprises the components of Formulas VI, A or B and absorbable chromium;
resveratol;
kaempferol;
sesamin;
melatonin; and
coenzyme Q, particularly coenzyme Q_{10}(CoQ10).

Formula 7A comprises the components of Formula 7 and contains a mixture of chondroitin sulphate, protamine sulphate, glucosamine sulphate and a cartilage preparation (shark and/or bovine cartilage).

Formula 7B comprises the components of Formula 7 and contains a mixture of genistein and kievitone.

8. Formula VIII which comprises:
The components of Formulas VII, 7A or 7B and
Gymnema sylvestre;
biotin;
garlicin;
chlorophyll;
glutathione; and
a source of taurine.

Formula 8A comprises the components of Formula VIII and contains a mixture of carotenoids including beta-carotene, lutein, lycopene, and luteolin.

Formula 8B comprises the components of Formula VIII and contains a mixture of monterpenes including limonene, naringinen, and tangeritin.

9. Formula IX which comprises

The components of Formulas VIII, 8A or 8B and
cinnamon extract;
absorbable copper;
indole-3-carbinol;
fenugreek seed (preferably defatted powder);
N-acetylcysteine;
pectin, e.g., citrus or apple pectin;
betaine HCl and pepsin.

Formula 9A comprises the components of Formula IX containing a mixture of monoterpenes: limonene, naringenin, tangeritin and nobelitin.

10. Formula X which comprises:
The components of Formula IX or 9A and
coumarin;
zingiber;
ginger;
absorbable boron;
vitamin K1;
sesamolin; and
methionine.

Formula 10A comprises the components of Formula X and contains a mixture of monoterpenes including limonene, naringinen, tangeritin, nobiletin, and iberene.

Formula 10B comprises the components of Formula X wherein the source of omega-3 fatty acids is a fish oil.

11. Formula XI which comprises:
The components of Formula X, 10A or 10B and
nutgall; malviden; galangin; robinetin; myricitin;
absorbable manganese;
alpha-linoleic acid; and
lysine.

Formula 11A comprises the components of Formula XI and contains the mixture of carotenoids beta-carotene, lutein, lycopene, luteolin, and apo-carotenal.

Formula 11B comprises the components of Formula XI and contains a mixture of apple and citrus pectins.

12. Formula XII comprises the components of Formulas XI, 11A or 11B and:
hesperiden;
rutin;
taxifolin;
morin;
absorbable strontium;
gamma-linoleic acid;
glutamine; and
dried mushroom or mushroom extract, e.g., shitake or rieshi.

Formula 12A comprises the components of Formula X and contains a mixture of monoterpenes including limonene, naringinen, tangeritin, nobiletin, iberene, and d-carvone.

13. Formula XIII comprises the components of Formulas XII and 12A and
denonidin;
chrysin;
perlargonidin;
caffeic acid;
absorbable silicon; and
glyzzeryn (or licorice extract)

Formula 13 A comprises the components of Formula XIII and contains a mixture of genistein and daidzein.

In a specific embodiment, nutrient and therapeutic formulas for use in the treatment of female cancers, including hormone-dependent cancers are provided. Female cancers include those cancers that occur only in women or which are more prevalent in women, including breast and ovarian cancer as well as cancer of the colon.

Specific formulas for the treatment of female cancers include:

14. Formula XIV which comprises:

(i) Antioxidants:

A source of proanthocyanidins and/or bioflavanoids (e.g., pine bark extract, bilberry extract, etc.);

A neovascular regulator (e.g., genistein, cartilage, etc.);

vitamin C;

vitamin E;

vitamin A;

beta-carotene;

(ii) Vitamin D3; and

(iii) calcium.

15. Formula XV which comprises the components of formula XIV and

selenium;

folic acid;

omega-3/omega-6 fatty acids (flax seeds or fish oil); and

soy isolate containing phytoestrogens and/ or phytosterols (phytoestrogens can be replaced with soy isoflavones, such as genistein or daidzein).

16. Formula XVI which comprises the components of formula XV and

melatonin;

lycopene; and

shark or bovine cartilage.

17. Formula XVII which comprises the components of formula XVI and

limonene;

arginine; and

conjugated dienoic linoleic acid.

18. Formula XVIII which comprises the components of formula XVII and

curcumin;

niacin; and

naringenin.

The nutrient and therapeutic formulas of this invention useful in ameliorating cancer can be combined in certain applications for the treatment of cancer in females with hormone replacement formulas or drugs and or formulas or drugs for the treatment of osteoporosis.

Specific osteoporosis formula ingredients include:

Osteo I = vitamin C; quercitin; 22-oxa-vitamin D3; calcium and taurine.

Osteo II = Osteo I components with:

N-acetylcysteine, zinc, estrogenic soy components (isoflavones), soy saponins, and magnesium,

Osteo III = Oseto II with:

vitamin B6, and sodium bicarbonate.

Osteo IV = Osteo III with :

sodium fluoride, l-lysine, and vitamin K.

Osteo V= Osteo VI with:

strontium, chromium, ipriflavone, and boron.

The listed osteoporosis formulas can be combined with any of the cancer protective or therapeutic formulas.

The listed osteoporosis formulas can themselves be employed for protection from or amelioration of the symptoms and conditions of osteoporosis. Preferred osteoporosis formulas for used in the absence of the cancer formulations herein include the components listed in Osteo I-V along with a source of proanthocyanidin or bioflavonoid (pine bark extract, bilberry extract, tea polyphenols, etc.) and a source of neovascular regulatory and/or promoter of collagen synthesis (e.g., genistein, cartilage, etc.).

Formulas 1-18 (including A and B formulas) are optionally combined with aspirin or NSAIDS (non-steroid anti-inflammatories, including but not limited to acetaminophen, ibuprofen, with the priviso that recommended dosages of NSAIDS are employed) and may optionally be combined with DHEA (dehydroepiandrosterone). Red Wine Extract, a powerful proanthocyanidin-containing extract can also be employed in the above formulas in place of, or in addition to, other proanthocyanidins.

Sulforaphane, an isothiocyante that can be provided in extracts of broccoli sprouts can be combined with any of Formulas I - XVIII to provide inhibition of carcinogenesis.

Creatine phosphate and eugenol have antioxidant activity and can be employed in formulas of this invention to provide additional protection against oxidative stress and cell damage.

Phosphatidylcholine, particularly polyunsaturated phosphalidyl choline, can be added to any of the formulas herein to provide control of the blood lipid levels.

All of the above specific formulas can be combined with cellular antioxidants including glutathione peroxidase, superoxide dismutase and/or catalayze. All of the above specific formulas can be combined with fruit and/or grain fiber.

All of the above formulas can be combined with taxol, or structurally related anticancer agents as well as Juniper yew extract with the proviso that these materials can exhibit significant toxic effect. Similarly, the formulas of this invention can be combined with mistletoe extract again with the proviso that this material can exhibit toxic effect.

The formulas of this invention can optionally include nutrients, vitamins and minerals other than those specifically listed to supplement particular nutritional deficiencies of given individuals, for example, chromium, iron, or other mineral may be provided or its concentration increased to supplement a given deficiency. Similarly, a particular vitamin or amino acid deficiency can be supplemented. Analogously, a given formulation can be adapted for sensitivities or allergies of a given individual.

Specific components listed in Table 2 and in the Formulas herein which are natural isolates can be replaced or supplemented with extracts and/or powders (seeds, etc.) derived from the natural source of the component.

A number of the components of formulas herein can be obtained from natural sources. Isolated major active ingredients can be recombined with extract obtained from the natural source to provide minor components that may enhance function of the major ingredient, e.g., purified genistein can be combined with soybean extract for enhanced effect.

The formulas of this invention an also be combined with enzymes such as papain and bromelaine to aid digestion.

TABLE 2: Component Functions for Cancer Formulations

FUNCTIONS
1. Function as antioxidant to control oxidative stress 2. Function as neovascular regulators controlling angiogenesis 3. Collagen maintenance; collagen synthesis 4. Regulate blood lipid levels, regulate lipoprotein (A) 5. Decrease acidity, pH balance, digestion/absorption 6. Supplement deficiencies 7. Inhibit aberrant methylation 8. Stimulate immune response and/or differentiation 9. Regulate blood glucose and/or insulin 10. Regulate homocysteine, inhibit homocysteine 11. Anti-tumor/Anti-cancer effect

Formula Components	Functions	Average Adult Daily Dose Range (dose/day)
Pine Bark Extract (<85% OPC)	1, 2, 3	3 - 2,000 mg
Bilberry Extract (25% OPC)	1, 2, 3	5 - 1,500 mg
Grape Seed Extract Extract (95-100% OPC)	1, 2, 3	5 - 2,000 mg
Gingko Biloba (24%)	1, 2, 3	5 - 1,500 mg
Green Tea Polyphenol	1, 3, 4, 9	10 - 10,000 mg
Silymarin (80% concentrate)	1, 2	10 - 1,000 mg
Saw Palmetto	1, 4, 11	5 - 1,500 mg
Vitamin C (ascorbic acid)	1, 3, 4, 6, 10, 11	10 - 5,000 mg
Vitamin E (D-alpha-tocopheryl acetate)	1, 4, 6	5 - 800 mg
Vitamin A	1, 6, 11	1,000 IU - 25,000 IU
Antioxidant carotenoids: lutein zeaxanthin lycopene beta carotene, etc.	1, 4, 6, 10, 11	 1 - 300 mg 1 - 300 mg 1 - 300 mg 10 - 100,000 IU
Quercitin (and other antioxidant bioflavanoids)	1, 3, 11	1 - 2,000 mg
Taurine (homotaurine)	1, 6	5 - 7,000 mg
Thioctic acid (α-lipoic acid)	1	5 - 1,000 mg

TABLE 2 (CONTINUED)		
N-acetyl-L-cysteine	1, 4, 6, 7, 10	5 - 3,000 mg
L-cysteine	1, 6, 7, 10	1 - 2,000 mg
Glutathione	1	1 - 1,000 mg
CoQ10	1, 6	4 - 400 mg
Chondroitin Sulfate	2, 3	10 - 10,000 mg
Glucosamine Sulfate	2, 3	10 - 10,000 mg
Soy Isolate (e.g., genistein and other plant isoflavones)	2, 3	50 - 1,500 mg
Protamine Sulphate	2, 3, 9	10 - 900 mg
Cartilage (bovine)	2, 3	1 - 30,000 mg
Cartilage (shark)	2, 3	1 - 1,499 mg
Vitamin B5 (pantothentic)	6	1 - 200 mg
Vitamin B1 (thiamine)	6	10 µg - 100 mg
Folic Acid	6, 10	100 µg-1,500mg
Vitamin B2 (Riboflavin)	6	1 µg - 50 mg
Vitamin B6 (Pyridoxine HCl)	6, 10	1 µg - 200 mg
Vitamin B12 (Cyanocobalamin 1%)	6, 10	1 µg - 100 mg
Nicotinamide (Vitamin B3, nicotinamide ascorbate)	6	1 - 500 mg
B complex†	6, 10	1 - 500 mg
Calcium (Krebs)	4, 6, 11	10 -10,000 mg
Zinc (Krebs)	1, 6, 9	10 - 3,000 mg
Magnesium (Krebs)	6, 9	3 - 10,000 mg
Chromium nicotinate	1, 4, 6, 9	2 µg - 50 mg
Selenium (1-selenomethionine)	1, 6, 11	1 µg - 50 mg
Potassium citrate	1, 6	30 - 18,000 mg
Strontium	6	1 µg - 800 mg
Copper (cupric sulfate)	6, 11	1 µg - 500 mg
Manganese (Krebs)	3, 6	10 µg - 100 mg
Silicon (magnesium trisillicate)	6	10 µg - 200 mg

TABLE 2 (CONTINUED)		
Mineral Complex	1, 4, 6, 9, 11	1 - 50,000 mg
Sulforaphane	1, 11	1 mcg - 20 mg
Chlorophyll	1, 11	1 mg - 3,000 mg
Pectin	1, 11	1 mg - 10,000 mg
Omega-3-fatty acids (flax seed powder)	4, 6, 11	10 - 30,000 mg
Essential fatty acids (dienoic conjugated linoleic acid	1, 4, 6, 11	10 - 10,000 mg
Glyzzeryn (licorice)	3, 11	1 mcg - 20 mg
Allicin (garlic extract)	3, 11	1 mcg - 50 mg
Vitamin D3	6, 8	1 - 10,000 IU
Melatonin	11	1 - 100 mg
L-carnitine (Acetyl-L-carnitine)	1, 4	10 - 3,000 mg
Indole-3-carbinol	1	1 - 1,000 mg
Phytosterols (Cholestatin III)	1, 4, 11	10 - 3,000 mg
Creatine phosphate	1	10 - 20,000 mg
Fenugreek Seed (powder)	4, 9	10 - 30,000 mg
Gymnema sylvestre	1, 3, 9	10 - 3,000 mg
Vitamin K1	6	15 µg - 75 µg
Monoterpene (e.g., Limonene, Naringinen	11	100 mcg - 200 mg
Sesamin/Sesamolin	4	1 mcg - 40 mg
Biotin	6, 8	1 mcg - 5 mg
Dried mushroom extract	11	1 mg - 10,000 mg
Phosphatidyl choline (lecithin)	4, 6	100 mg - 50,000 mg
L-lysine	6	10 - 13,000 mg
L-arginine	6, 8	10 - 9,000 mg
L-glutamine	6	10 - 13,000 mg

TABLE 2 (CONTINUED)		
L-methionine	6, 7	10 - 300 mg
Branched Chain Amino Acids*	3, 6	10 - 70,000 mg
Betain HCl	5, 6	1 - 10,000 mg
Pepsin	5, 6	1 - 10,000 mg
Sodium Bicarbonate	5, 6	1 - 10,000 mg

† B complex = Vit. B1, Vit. B2, Vit. B3, Vit. B5, Vit. B6, and Vit. B12.
*Branched Chain Amino Acids = L-leucine, L-isoleucine, and L-valine.

Components that enhance or facilitate desirable enzyme activity, e.g., lysyl oxidase (an enzyme which participates in collagen synthesis); nitric oxide inhibitors, other antioxidant carotenoids or flavonoids, additional antihyperlipoproteinemics, including probucol and blood thinning agents, e.g., heparin can be combined with any of the formulas listed above.

Cellular antioxidants, such as the enzymes: superoxide dismutase and catalyze or thiols, including glutathione peroxidase, can be included in any of specific formulas listed above. L-carnitine (which may be in the form of L-acetyl carnitine or L-propionyl carnitive) can be combined with any of the specific formulas above.

Treatment using the compositions of this invention can be combined with hormone therapy and or hormone supplementation, including estrogenic hormone therapy or supplementation, thyroid hormone therapy or supplementation, treatment or supplementation with human growth hormone (HGH) and/or treatment or supplementation with DHEA (dehydroepiandrosterol).

The formulas of this invention can also be combined with appropriate growth factors, growth factor inhibitors and growth factor binding agents including, among others, fibroblast, epidermal, interleuken transforming and platelet-derived growth factors, agents that bind hyaluronic acid and/or collagen. The formulas of this invention can be used in combination with immune suppression of T-lymphocytes.

The formulas of this invention can also be employed in combination with therapeutic methods shown to have beneficial effect for the disorders, conditions and diseases discussed herein.

Other optional components of the formulas of this invention include antioxidants and/or preservatives, such as BHT (Butylated hydroxytoluene), BHA (Butylated hydroxyanisole), ethoxiquin and diphenyl phenylenediamine.

In general the amount of each component employed in the different compositions of this invention is sufficient to provide the desired therapeutic effect(s) or nutritive effect(s), as discussed herein, to an individual and avoid toxicity with continuing regular dosing. Because compositions of this invention can have multiple components with similar functionality, the effective amount of any given component needed to provide a given level of function in a given composition will depend on the quantities of other functionally similar or otherwise related components to be included in the composition.

Table 2 provides a summary of certain biochemical functions of components that are useful in cancer-protective and cancer-therapeutic formulas of this invention. A single component may provide more than one of the listed biological functions in a given composition. Table 2 provides a list of exemplary components of the formulas of this invention providing a preferred range of amounts of individual components that can be combined in the formulas of this invention. The amounts listed in Table 2 are average daily adult dosages. Biological functions associated with osteoporosis are not listed.

As listed in Table 2, the cancer-preventative and therapeutic formulas of this invention comprise components that (1) have antioxidant function to control oxidative stress and prevent cell damage, (2) promote and/ or stimulate collagen synthesis to provide healthy tissue and inhibit metastasis and recurrence, are (3) neovascular regulators which control angiogenesis and function to limit blood supply to cancers, (4) regulate blood lipid, particularly lipoprotein (a), levels, (5) decrease cell/tissue acidity and promote pH balance, (6) supplement dietary deficiencies, non-absorption, cachexia or nutrient spillage, (7) inhibit or prevent aberrant methylation, (8) stimulate or enhance immune response or cell differentiation, (9) control blood glucose levels, (10) lower homocysteine levels or (11) have other antitumor or anticancer activity.

One or more of the functionalities listed in Table 2 can be provided in the compositions of this invention by art-known equivalents including equivalents from natural sources and/or drug equivalents.

Compositions of this invention can be provided in a variety of nutrient and dosage forms including pills, tablets, capsules, lozenges, powders, solutions, suspensions, injection dosage forms and the like. Compositions of this invention can be administered to individuals orally, intravenously, and by various forms of injection and various forms of absorption (e.g., dermal, sublingual). Active ingredients of the formulas of this invention can be combined with excipients, fillers, buffering agents and the like to prepare desired dosage forms. Generally preferred dosage forms are those appropriate for oral administration. In cases of use for cancer therapy, the optimum mode of administration can depend upon the type of cancer.

The formulas of this invention that are useful in the treatment and prevention of the various disease conditions discussed above combine a number of related ingredients. The therapeutic and preventative compositions of this invention are based at least in part on the

inventor's recognition of similarities in etiology of the various cancers. In particular, the inventor considers that the development, growth and metastasis of malignancies, is at least in part, caused by or exacerbated by oxidative stress and tissue destruction associated with oxidative damage. Further, the inventor considers that in each of the disease conditions and symptoms, for which formulas are provided herein, that stimulating and or promoting collagen synthesis is an important factor in prevention and treatment. in this regard, the various disease conditions discussed herein also relate in part aberrant tissue growth, for example due to lack of proper growth factors or lack of growth factor inhibitors. Furthermore, individuals with cancer also suffer from the effects of deprivation of adequate nutrient, vitamin, cofactor and mineral supplies and particularly from inadequate supplies of nutrients, cofactors and the building blocks needed for restoration of the collagen matrix which is necessary for regeneration and healing of tissue in general.

The treatment methods described herein employing the formulations of this invention are believed to derive unique and unexpected benefits from complementary and synergistic interactions between the various formula components acting together upon the various symptoms and conditions associated with the various diseases and disorders discussed herein. The success of these compositions in the treatments described is, at least in part, attributable to the multi-factor strategy employed to balance nutrient and metabolic deficiencies and to control oxidative stress, while promoting or stimulating cell and tissue repair or healing and/or collagen matrix repair, and inhibiting angiogenesis.

The proposed function of components listed in the specific formulas of this invention and stated to be options herein are discussed above, are specified in Table 2 or are known to those of ordinary skill in the art.

A broad effective dose range (daily adult dose) for individual active components of the formulas of this invention. The broad dose range given in the table provides guidance regarding approximate minimal effective amounts of given components from any source and guidance for dosage of equivalents. The maximum dosages listed are estimates based generally upon what is known in the art concerning the individual components listed. The maxima listed may merely be based on an estimate of maximum amount that can be practically provided in a daily oral dosage form. Dosages can be readily adapted by those of ordinary skill in the art for use of alternate forms or sources of the components listed or for use of functional equivalents. Dosages can be readily adapted for desired dosing schedules

and to match individual needs or problems of a given patient by those of ordinary skill in the art.

U.S. Patent application 08/018,273, filed February 4, 1998, which is incorporated in its entirety by reference herein relates to nutrient and therapeutic formulations for treatment of cardiovascular disease and the complications of diabetes. The formulas therein combine antioxidants, neovascular regulators and other components having particular benefits for cardiovascular disease and diabetes complications. This patent application provides exemplary formulations including certain of the components herein and provides additional guidance for appropriate dosage. Formulas of this invention can be adapted for treatment of diabetics having cancer using components and dosages provided in this U.S. application.

Table 2 provides a summary of the general biological functions of most components that are believed to be beneficial for the treatment of cancer. This listing provides the inventor's current understanding of the functions provided by components included in the preferred composition and provides guidance for the choice of alternative components with similar functionality. The inventor, however, does not wish to be bound by the specific functional correlations listed in these tables or by proposed functionality of individual activity. The etiology of the diseases and conditions discussed herein is complex and a given component of a formula of this invention may have several different effects. In some cases, the component listed in the table is itself a mixture, for example, pine bark extract is a combination of naturally occurring compounds. In these cases, different components of the listed mixtures may contribute to different functions listed in Table 2.

The compositions of this invention specifically ameliorate cancer. The diagnosis and symptoms of various cancer conditions are understood in the medical arts and a variety of methods are known in the art to evaluate the severity and extent of the conditions.

Exemplary sources of certain components of the formulas herein are as follows: The following are sources of ingredients listed in Table 2:

Bilberry extract, as a dry hydroalcohol extract containing anthocyanosides corresponding to 25% (by weight)of anthocyanidines obtained from Indena (Milan, Italy). Grape Seed Extract (Leucocyanidins) (90-100% OPCs) can be obtained from Indena (Milan, Italy).

Pine Bark Extract (OPC 90%) can be obtained from Euromed (Barcelona, Spain).

Green tea polyphenols (95%, min. 75% catechins, low caffeine) can be obtained from TSI, International, Inc. (New York, NY).

N-Acetyl-l-cysteine (99%), L-carnitive base (Product No. 18-1870-00), CoQ10 (ubidecarenone), l-(+)-ascorbic acid, riboflavin (USP, FCC, Water CAS 7732-18-5 max 1.5%), pyridoxine hydrochloride (USP, FCC), and vitamin B12 (USP) were obtained from Schweizerhall, Inc. (Piscataway, NJ). Vitamin B12 (cyanocobalamine can be diluted in inactive filler to give a 1% by weight mixture). Acetyl-R-carnitive is available from several manufacturers.

Vitamin A acetate (T-500A) cam be obtained from Hoffmann-La Roche (Belvidere, NJ).

Taurine (98.5% min.) and folic acid (USP) were obtained from Seltzer Chemicals, Inc. (Carlsbad, CA). Homotaurine is available from several manufacturers.

Linoleic Acid (High Purity, 99% min) can be obtained from Spectrum Quality Products (Gardena, CA).

Lipoic Acid (99.8%) and protamine sulphate (USP) were obtained from Maypro Industries, Inc. (Harrison NY).

Lutein is provided in a nutrient composition "FloraGlo" Lutien (Trademark, Kemin Industries, Des Moines, IA) comprising 5% by weight lutein and 0.22% zeaxanthin. This material is in beadlet form and also comprises vegetable oil, natural vitamin E (as a preservative), rosemary, natural citric acid, gelatin, sucrose and starch. See U.S. Patent 5,382,714.

Chondroitin sulphate as the sodium salt produced by the Strandberg method from beef trachea can be obtained from Weinstein Nutritional Products (Irvine, CA).

Chromium picolinate "Chromax" can be obtained from Nutrition 21 (San Diego, CA).

Calcium (Krebs)22%, Zinc (Krebs) 30% and Magnesium (Krebs) were obtained from Monarch Nutritional Laboratories (Ogden, UT).

Potassium citrate (NF granular) complying with USP, FCC and FAO/WHO Food additive specifications can be obtained from Archer Daniels Midland.

Shark cartilage powder (100%, 200 mesh) can be obtained from Global Trading (USA) Inc. (Union, NJ).

Isolated soy protein ("Supro" HD90, Trademark) can be obtained from Protein Technologies International (St. Louis, MO). Isolate soy protein products from this source are

reported to typically contain (in mg/g protein) 0.15 to 0.72 mg daidzein, 0.48 to 1.51 mg genistein, 0.05 to 0.26 glycitein with a total isoflavone content of 0.68 to 2.49 mg (aglucone units adjusted for molecular weight).

Phytosterol complex, "Cholestatin III" can be obtained from several sources.

Vitamin E, d-alpha-tocopheryl acetate (natural source, powder) can be obtained from B&D Nutritional Ingredients, Inc. (Carlsbad, CA).

Flax seed powder containing about 23 mg of alpha-linolenic acid (omega-3-fatty acid) per 100 grams powder can be obtained from Honeyville Grain Inc. (Salt Lake City, UT).

Fenugreek seed powder can be obtained from Botanicals International (Long Beach, CA).

Ginkgo biloba L. powder extract about 26% flavonglycosides and Gymnema sylvestre powder can be obtained from Motherland International Inc. (Chino, CA).

Other components listed in Table 2 can be obtained from a variety of commercial sources.

Those of ordinary skill in the art of formulation of nutrients and therapeutic compositions will appreciate that components functionally equivalent to those specifically disclosed herein, as well as alternative forms and sources in addition to those specifically disclosed herein for individual composition ingredients are available. This invention is intended to encompass all such functional equivalents and alternatives that are readily known to the art.

I CLAIM:

1. A cancer-protective and cancer therapeutic composition which comprises:
   (a) a plant extract having antioxidant effect comprising bioflavanoids in an amount effective for providing said antioxidant effect; and
   (b) a neovascular regulator that is an inhibitor of angiogenesis in an amount effective for inhibition of angiogenesis; and
   (c) absorbable zinc in an amount effective to supplement dietary deficiency.
2. The composition of claim 1 wherein said neovascular regulator is selected from the group soy isolate, genistein and diadzein.
3. The composition of claim 1 which comprises antioxidant bioflavonoid plant extracts from at least two different plant sources.
4. The composition of claim 3 wherein said neovascular regulator is a mixture of a soy isolate and a cartilage preparation..
5. The composition of claim 3 wherein said neovascular regulator is a mixture of a soy isolate and chondroitin sulphate.
6. The composition of claim 4 which comprises Pine bark extract in an amount effective for providing an antioxidant effect.
7. The composition of claim 1 which comprises:
   (a) antioxidant components:
   Pine bark extract;
   Bilberry extract;
   Tea polyphenols;
   Vitamin C; and
   Vitamin E;
   in a combined amount effective for providing an antioxidant effect;
   (b) neurovascular regulator components soy isolate and chondroitin sulphate in an amount effective for inhibiting angiogenesis and/or stabilization of the collagen matrix; and
   (c) absorbable zinc and absorbable chromium in an amount effective for compensation of nutrient deficiency; and
   (d) L-arginine in an amount effective for compensation of nutrient deficiency.
8. The composition of claim 1 which comprises:

(a) antioxidant components

a plant extract having antioxidant effect;

an antioxidant carotinoid;

an antioxidant flavonoid;

Vitamin C;

Vitamin E; and

Vitamin A

said antioxidant components in a combined amount effective for providing an antioxidant effect and/or for stimulating collagen synthesis;

(b) neovascular regulators and/or factors for collagen synthesis:

chondroitin sulphate, and

genistein

in a combined amount effective for neovascular regulation and/or stimulating collagen synthesis;

(c) minerals:

absorbable zinc;

absorbable chromium;

absorbable magnesium; and

absorbable calcium; and

(d) L-arginine and branched amino acids

each present in an amount effective for compensating for nutritional deficiency.

9. The composition of claim 8 further comprising:

Gymnema sylvestre; Saw palmetto; Fenugreek; Ginkgo biloba; silymarin; quercitin or a mixture thereof each present in an amount effective for providing therapeutic and/or protective function.

10. The composition of claim 1 further comprising 22-oxa-vitamin D3.

11. The composition of claim 1 further comprising a composition effective for treatment of osteoporosis selected from the group of formulas Osteo I-Osteo-V.

12. The composition of claim 1 further comprising a therapeutically effective amount of sulforaphane.

13. The composition of claim 1 further comprising one or more of betaine HCl, sodium bicarbonate and pepsin each present in an amount effective for providing therapeutic and/or protective function.

14. The composition of claim 1 further comprising one or more of the following components N-acetylcysteine, absorbable copper, chlorophyll, glutathione, and melatonin each present in an amount effective for providing therapeutic and/or protective function.

15. The composition of claim 1 further comprising phosphatidyl choline in an amount effective for providing therapeutic and/or protective function.

16. A composition for the prevention or treatment of symptoms and conditions associated with osteoporosis which comprises:
antioxidant components: vitamin C, quercitin and a plant bioflavonoid present in a combined amount effective for providing antioxidant effect and/or for stimulating collagen synthesis;
neovascular regulators: soy isolate and chondroitin sulphate present in a combined amount effective for neovascular regulation and/or stimulating collagen synthesis; and
22-oxa-vitamin D3; taurine and calcium each present in an amount effective for providing therapeutic and/or protective function.

17. The composition of claim 16 further comprising one or more of the following components each of which is present in an amount effective for providing therapeutic and/or protective function:
N-acetylcysteine,
absorbable zinc,
estrogenic soy components,
soy saponins,
absorbable magnesium,
sodium fluoride,
l-lysine,
vitamin K1,
absorbable chromium,
absorbable strontium,
ipriflavone, and

absorbable boron.

18. A method for treating and/or preventing a symptom condition or disorder associated with cancer in an individual having cancer which comprises the step of administering to said individual the composition of claim 1.

19. A method for treating and/or preventing a symptom condition or disorder associated with cancer in an individual having cancer which comprises the step of administering to said individual the composition of claim 11.

20. A method for treating and/or preventing a symptom, condition or disorder associated with in an individual having osteoporosis which comprises the step of administering to said individual the composition of claim 15.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/17633

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 35/78, 31/70, 65/60
US CL :424/195.1, 641, 655, 682; 514/54,62
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/195.1, 641, 655, 682; 514/54,62

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X - Y	US 5,424,331 A (SHLYANKEVICH) 13 June 1995, see entire document.	1, 2, 18 ------ 3-17, 19, 20
X - Y	WO 96/36348 A1 (FARMILA-FARMACEUTICI MILANO S.R.L.) 21 November 1996, see entire document.	1, 3, 18 ------ 2, 4-17, 19, 20
X - Y	US 5,569,458 A (GREENBERG) 29 October 1996, see entire document.	1, 3, 18 ------ 2, 4-17, 19, 20

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 22 OCTOBER 1999	Date of mailing of the international search report 19 NOV 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer FRANCISCO C. PRATS Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/17633

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P ----- Y, P	US 5,895,652 A (GIAMPAPA) 20 April 1999, see entire document.	1, 3, 18 ------- 2, 4-17, 19 20
Y, P	US 5,840,715 A (FLORIO) 24 November 1998, see entire document.	1-20
Y	US 5,536,506 A (MAJEED et al) 16 July 1996, see entire document.	1-20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/17633

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

USPT (U.S. PATENT TEXT), EPAB (EUROPEAN PATENT ABSTRACTS), JPAB (JAPANESE PATENT ABSTRACTS), DWPI (DERWENT WORLD PATENT INDEX)
seaarch terms: pine bark, bilberry, vitamin c, vitamin e, chondroitin, soy isolate, zinc, chromium, magnesium, calcium, arginine, 22-oxa-vitamin