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An Evidence-Based Systematic Review of Slimple®
By the Natural Standard Research Collaboration

SYNONYMS/COMMON NAMES/RELATED SUBSTANCES

Slimple®:

- Achiote leaf, *Cassia nomame*, chuchuhuasi, citrus bioflavonoids, MaCoca™, glycomacropeptide (GMP), green tea, guggulsterones, lotus leaf extract.

Achiote leaf (*Bixa orellana* L.):

- Acetate, acetone, achiot (Spanish - Colombia), achiote (Spanish - Peru), achiote seeds, achiotillo, achiotin, arnotta, arnotto (Native American), annatto, annatto extract, annatto tree, annotta, aploppas, apocarotenoids, azo dyes, biche, bija, *Bixa acuminata*, *Bixa acuminata* Bojer., *Bixa americana*, *Bixa americana* Poiret, *Bixa katangensis* Delpierre, *Bixa odorata*, *Bixa odorata* Ruiz & Pav. ex G. Don., *Bixa orellana*, *Bixa platycarpa*, *Bixa platycarpa* Ruiz & Pav. ex G. Don., *Bixa purpurea*, *Bixa purpurea* Hort., *Bixa tinctoria*, *Bixa tinctoria* Salixb., *Bixa upatensis*, *Bixa upatensis* Grosscurdy, *Bixa urucurana*, *Bixa urucurana* Willd., Bixaceae (family), bixin, brickdust, butter color, BXN, carotenoids, calcium sulfate, chalk, changuarica (Spanish - Mexico), colcothar, E160b, E number E160b, eroya, essential oil, false damiana, farinaceous matter, fat-soluble color, fatty acid, fiber, flag annotta, gypsum, ishwarane, jafara, kasujmba-kelling, kham thai, k'u-zub (Spanish - Mexico), lipstick tree, natural color, natural food color, norbixin, occidentalol, occidentalol acetate, ochre, onoto (Spanish - Venezuela), orellana, *Orellana americana*, *Orellana americana* Kuntze, *Orellana orellana*, *Orellana orellana* (L.) Kuntze, orellin, orleana, Orleanstrauch (German), orucu-axiote, phosphoric acid, potassa, powdered bricks, pumacua (Mexico), red ochre, rocou (Dutch, French), roucou (French - Dominica and the French West Indies), roucouyer, ruku (Hungarian), sand, sand gypsum, silica, spathulenol, starchy bodies, sulfuric acid, terebinthinous body, tomentosic acid, Ultrabix™, unane, urucu (Portuguese - Brazil), urucum (Portuguese), urucu-üva, uruku, water-soluble color, (Z,E)-farnesyl acetate.

***Cassia nomame*:**

- Anthraquinoids, anthraquinones, cássia de empingem (Portuguese (Brazil)), *Cassia mimosoides*, *Cassia mimosoides* var. nomame, *Cassia nomame*, catechins, *Chamaecrista mimosoides* L., chichani (Marathi), emodic acid, emodin, emodin glycosides, Fabaceae (family), feather-leaved cassia, fish-bone cassia, fiveleaf cassia, glucosides, guaiacol peroxidase, hama cha (Japanese), Japanese tea, kawara-ketumei (Japanese), kita, Leguminosae (family), luteolin, luteolin glucosides, mateloi, mateloi lalahi, mimosoides tea, mountain flat-bean, nemucha (Japanese), nomame, nomame herba, patwa ghas (Hindi), phenols, physcion, sensitiva (Portuguese (Brazil)), Slimple™, tea senna, ukellela chedip (Palauan).

Chuchuhuasi (*Maytenus krukovii, Maytenus macrocarpa, Maytenus laevis*):

- 3-oxofriedelan-28-oic acid, 3-oxofriedelan-29-oic acid, 4'-methyl-(-)-epigallocatechin, 6-benzoyl-6-deacetylmayteine, 7,8-dihydro-B alpha, 7,8-dihydro-C alpha, 7,8-dihydro-C beta, 7,8-dihydro-D alpha, 7,8-dihydro-D beta, 15-alpha-hydroxy-21-keto-pristimerine, 22-hydroxytingenone, 24(Z)-3-oxodammara20(21),24-dien-27-oic acid, 28,29-dihydroxyfriedelan-3-one, agarofuran sesquiterpenes, canophyllol, catechin tannins, Celastraceae (family), *Celastrus macrocarpus*, chocha huasha (shipibo-conibo), chu chu huasu, chucchu huashu, chuchasha, chuchuasi, chuchuhuasha, chuchuhuasi, chuchuwasha, chuchuwasha blanca, dammarane-type terpeines, dulcitol, ebenifoline alkaloids, euojaponine alkaloids,

friedelane-type triterpenes, *Haenkea macrocarpa*, *Haenkea multiflora*, isoxuxuarines B alpha, isoxuxuarines B beta, krukovine A, krukovine B, krukovine triterpenes, laevisine alkaloids, macrocarpin triterpenes, macrocarpins, makrocarpine, maytansine, mayteine, maytenin, maytenoic acid, *Maytenus boaria*, *Maytenus chuchuhuasca*, *Maytenus colasii*, *Maytenus diversifolia*, *Maytenus ebenifolia*, *Maytenus guyanensis*, Maytenus *krukovii*, *Maytenus laevis*, *Maytenus macrocarpa*, *Maytenus multiflora*, *Maytenus terapotensis*, mebeverine, octa-nor-13-hydroxydammara-1-en-3,17-dione, ouratea-proanthocyanidin A, ouratea-proanthocyanidin B, phenoldienones, pristimeran, pristimerin, proanthocyanidins, sesquiterpenes, Slimple™, tingenone, triterpenes, xuxuá, xuxuasin A, xuxuasin B.

- **Note**: The name "catuaba" may be used for the infusions of the bark of several trees that are native to Brazil. The most widely used barks are derived from the trees *Trichilia catigua* and *Erythroxylum vacciniifolium*; however, "catuaba" may also refer to the bark of *Maytenus* species. Catuaba is a remedy common in Brazilian folk medicine.
- *Maytenus* spp. may be found around the world and may be used in a variety of traditional medicine systems. This monograph, however, will focus on *Maytenus* spp. from South America that are more commonly associated with chuchuhuasi. According to review, several different species may be referred to as "chuchuhuasi," which may cause a modicum of confusion {Gonzalez, 2000, No pmid}. In addition to *Maytenus macrocarpa*, *Maytenus* species that are generally used as chuchuhuasi may also include, but may not be limited to, *Maytenus krukovii* (*Maytenus chuchuhuasha*) and *Maytenus laevis*, and occasionally *Maytenus colasii* (*Salacia colasii*) {Gonzalez, 2000, No pmid}. Other species that have been associated with chuchuhuasi include *Maytenus ebenifolia*, *Maytenus boaria*, and *Maytenus guyanensis* (secondary sources). Typically, however, *Maytenus macrocarpa*, *Maytenus krukovii* (*Maytenus chuchuhuasha*), and *Maytenus laevis* are the more widely accepted species for chuchuhuasi. Some secondary sources cite that *Maytenus ilicifolia* is used as chuchuhuasi; however, expert opinion indicates that this species should not be associated with chuchuhuasi. This monograph focuses on *Maytenus macrocarpa*, *Maytenus krukovii* (*Maytenus chuchuhuasha*), and *Maytenus laevis*, in addition to *Maytenus ebenifolia*, *Maytenus boaria*, *Maytenus guyanensis*, and to a lesser extent, *Maytenus colasii*.

Citrus bioflavonoids (hesperidin):

- 3',5,7-trihydroxy-4-methoxyflavanone 7-rhamnoglucoside, 3',5,7-trihydroxy-4'-methoxyflavanone 7-rhamnoglucoside, 3',5,7-trihydroxyflavanone 7-rhamnoglucoside, 3',5,9-dihydroxy-4'-methoxy-7-O-rutinosyl flavanone, 5,7, 3'-trihydroxy-4'-methoxy-flavanone 7-rhamnoglucoside, α-glucosylhesperidin**,** bioflavonoid, citrus flavonoids, Dangyooja (*Citrus grandis* Osbeck), flavanone, flavonoid glycosides, flavonoids, G-hesperidin, glucosyl hesperidin, hesperidin, hesperidin-7-O-rutinoside, hesperidin-7-rhamnoglucoside, hesperidin-7-rutinose, hesperidin-7-rutinoside, hesperidin glycoside, hesperidin methyl chalcone (HMC), hesperidine methylchalcone, Kjool (*Citrus unshiu* Marcow), micronized purified flavonoid fraction, MPFF, neohesperidin, vitamin P, trimethyl-hesperidin-chalkon, yuza (*Citrus junos* Sieb ex Tanaka).
- 5682 SE, Alvenor®, Ardium®, Arvenum 500®, Capiven®, Daflon® 500mg, Detralex®, Elatec®, S 5682, Venotec®, Rikkunshito, Slimple™,Venitol®: micronized purified flavonoid fraction that contains diosmin and flavonoids (hesperidin, isorhoifolin, linarin, disometin) expressed as hesperidin; Cyclo 3 Fort®, Great Legs: Ruscus aculeatus root extract + hesperidin methyl chalcone, and <ref id="vitaminc">ascorbic acid</ref>.

Glycomacropeptide (GMP):

- Acetyl galactosamine, branched chain amino acids (BCAAs), carbohydrate, casein-derived peptide (CDP), casein glycomacropeptide (cGMP), casein glycopeptide (CGP), casein macropeptide (CMP), caseinglycopeptide, caseinmacropeptide, caseinoglycomacropeptide, cheese, cholecystokinin (CCK),

galactosamine, galactose, glucosamine, isoleucine, kappa-casein, milk, phosphorus, sialic acid (*N*-acetylneuraminic acid), Slimple™, sweet whey, valine, whey.

Green tea (*Camellia sinensis*):

- (-)-epigallocatechin, anthocyanins, Árbol del té (Spanish), arbre à thé (French), caffeine, čaj (Czech, Russian, Slovenian), čaje zelené (Czech), čajnoe derevo (Russian), čajovník čínský (Czech), camellia, *Camellia assamica*, *Camellia sinensis*, *Camellia sinensis* (L.) Kuntze, camellia tea, *Camellia thea*, *Camellia theifera*, catechins, çay (Turkish), cha (Chinese, Thai, Japanese, Korean, Sinhalese, Urdu), chá (Portuguese - Brazil), cha no ki (Japanese), chaa (Hindi), chaay (Hindi, Sinhalese), chá-da-Índia (Portuguese), chaha (Kannada), chai (Hindi, Russian), Chainoe derevo (Russian), chá-preto (Brazilian), chay (Persian, Urdu), chaya (Tamil), Chinese rea, Chinesischer Thee (German), chiya (Nepali), EGC, EGCG, epicatechin gallate, epicatechins, epigallocatechin, epigallocatechin-3-gallate, green tea extract, GTE, herbata chińska (Polish), hiina teepõõsas (Estonian), ichibi (Japanese), Japanese tea, kamelia (Polish), lignin, lotus-f3, L-theanine, matcha, matcha green tea, matsu-cha tea, methylxanthine, nok cha (Korean), O-methylated catechin, organic acids, phenolic acids, phytochemicals, pianta del tè (Italian), planta del té (Spanish), Poly E, polyphenols, Polyphenon E®, proanthocyanidins, shay (Arabic), sinecatechins, te (Danish, Kannada, Norwegian, Sinhalese, Swedish), Slimple™, tannins, té (Spanish), tea (Hungarian), tea green, tebusk (Danish), tebuske (Swedish), tee (Finnish, German), teekameelia (Estonian), teepensas (Finnish), teestrauch (German), teestruik (Dutch), teh (Hebrew, Malay), teyaku (Telugu), thayilai (Tamil), the (French), *Thea bohea*, *Thea sinensis*, *Thea viridis*, Theaceae (family), theanine, theesoortt (Dutch), theestrauch (German), theestruik (Dutch), théier (French), theifers, theobromine, theophylline, VeregenT®, vitamins.
- **Combination product examples**: AR25®, Exolise®, FertilityBlend (chasteberry extract, green tea extracts, L-arginine, vitamins and minerals), LipoKinetix® (norephedrine, caffeine, yohimbine, diiodothyronine, and sodium usnate), Metabolife 356 (caffeine, plus extracts of green tea, *Garcinia cambogia*, and yerba mate), Nature's Bounty® Green Tea Extract, PhosphoLEAN™ (85mg N-oleyl-phosphatidylethanolamine extracted from soya lecithin and 121mg of a dry green tea extract), Puritan's Pride® Green Tea Extract.

Guggul (*Commiphora mukul*):

- African myrrh, Arabian myrrh, *Balsamodendrum mukul* (Hook. ex Stocks), *Balsamodendrum wightii* Arn., bdellium (Greek, Hebrew, Latin), bdellium gum, bdellium tree, Burseraceae (family), *Commifora mukul*, *Commiphora erlangeriana*, *Commiphora mukul*, *Commiphora mukul* (Hook. ex Stocks), *Commiphora opobalsamum*, *Commiphora whightii*, *Commiphora wightii* (Arn.) Bhandari, E-guggulsterone, false myrrh (as *C. mukul*), fraction A, guggal, guggul (Hindi), guggul oleoresin, guggulipid, guggulipid C+, guggulsterone, guggulsterone (4,17(20)-pregnadiene-3,16-dione), guggulu (Sanskrit), guglip, gugul, gugulimax, gugulipid, Gugulmax®, gum guggul, gum guggulu, gum myrrh, Indian bdellium (as *C. mukul*), Indian bdellium tree (as *C. mukul*), Indian myrrh, mo ku er mo yao (as *C. mukul*) (Chinese), mo yao, myrrha, myrrhe des Indes (French), sesquiterpenoids, Vitamin World® Select Herbals Standardized Extract Guggul Plex 340mg, Z-guggulsterone.
- **Combination products:** Sunthi guggulu, sunthi-guggulu (combination with <ref id="ginger">*Zingiber officinale*</ref>), Slimple™.
- **Note**: Mirazid® is a commercial preparation of an extract of <ref id="myrrh">*Commiphora molmol*</ref> (<ref id="myrrh">myrrh</ref>) manufactured by Pharco Pharmaceuticals. It is marketed as an anthelmintic for the treatment of schistosomiasis and fascioliasis. This monograph is primarily concerned with *Commiphora mukul* and does not grade the safety or efficacy of <ref id="myrrh">*Commiphora molmol*</ref>*;* however, examples of current research using Mirazid® are listed {Soliman, 2004,

15587320; Abo-Madyan, 2004, 15587309; Hassan, 2004, 15587312; Massoud, 2004, 15125536; El Baz, 2003, 14708852; Allam, 2002, 12512828; Hegab, 2003, 14964667; Fathy, 2005, 16333909}.

Lotus (*Nelumbo nucifera*):

- 2,6-dihexadecanoate, adenine, alkaloids, aporphine, arbutin, ascorbic acid, asimilobine, astragalin, bean of India, benzylisoquinoline, beta-ionone, beta-sitosterol glucopyranoside, bisbenzylisoquinoline alkaloids, carbohydrates, catechin, chungyang, coclaurine, flavone, flavonoids, gallic acid, garam, geranyl acetone, hexahydrofarnesyl acetone, hyperin, hyperoside, inchisa, Indian lotus, isoliensinine, isoquercetin, isoquercitrin, isorhamnetin glycosides, kaempferol, kaempferol 3-O-alpha-L-rhamnopyranosyl-(1-->6)-beta-D-glucopyranoside, kaempferol 3-O-beta-D-galactopyranoside, kaempferol 3-O-beta-D-glucopyranoside, kaempferol 3-O-beta-D-glucuronopyranosyl methylester, kaempferol-3-O-glucopyranoside, lian fang, lian xu, lian zi, liensinine, lirinidine, lotus leaf extract, lotusine, methyl gallate, muan, myo-inositol, myricetin 3',5'-dimethylether 3-O-beta-D-glucopyranoside, myricetin-3-O-glucopyranoside N-nornuciferine, neferine, negferine, *Nelumbium nelumbo* (L.) Druce, *Nelumbium speciosum* Willd., *Nelumbo nucifera*, *Nelumbo nucifera* Gaertn., *Nelumbo nucifera* Gaertn. 'Tielian', Nelumbonaceae (family), NN-9, NNSE, norcoclaurine, nuciferine, nuciferone, O-nornuciferine, pentadecyl acrylate, phenolics, procyanidins, pronuciferine, quercetin, quercetin 3-O-alpha-arabinopyranosyl-(1-->2)-beta-galactopyranoside, quercetin 3-O-beta-D-glucopyranoside, quercetin 3-O-beta-D-glucuronide, quercetin-3-O-beta-D-glucoside, quercetin-3-O-beta-galactoside, quercetin-3-O-glucopyranoside, quercetin-3-O-glucuronide, quercetin-3-O-rutinose, red lotus, rutin, sacred lotus, sacred water-lily, saponins, (S)-armepavine procyanidin B-3, *trans*-phytol, Slimple™, triterpenoids, tryptophan, vitamins.
- **Note**: This monograph does not include plants from the *Lotus* or *Nymphaea* genera, as these are distantly related plants from other botanical families.

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CLINICAL BOTTOM LINE

Brief Background:

Slimple®

- Slimple® is a proprietary weight-loss blend of herbs and amino acids. This product aims to suppress hunger while stimulating the body to burn more calories. It contains achiote leaf (*Bixa orellana* L.), *Cassia nomame*, chuchuhuasi (*Maytenus krukovii*, *Maytenus macrocarpa*, *Maytenus laevis*), citrus bioflavonoids (such as hesperidin), MaCoca™, glycomacropeptide (GMP), green tea (*Camellia sinensis*), guggulsterones (*Commiphora mukul*), and lotus (*Nelumbo nucifera*).

Achiote leaf (*Bixa orellana* L.)

- Achiote (*Bixa orellana*) is a tree or shrub native to the tropics of North and South America, the Caribbean, and the East Indies. It is most abundant from Mexico to Ecuador, as well as Brazil, Bolivia, Venezuela, and several other South American countries. *Bixa orellana* is cultivated in South America and also in southeastern Asia, where it was introduced by Spaniards in the 17th Century.
- Annatto is a pigment produced from the seed of the achiote tree (*Bixa orellana*). Annatto is commonly used as a coloring agent for pharmaceutical ointments and plasters. It contains the pigment bixin, which is commonly used in the food and cosmetics industries to add yellow or red colors {Rodrigues, 2007, 17952668}. Annatto has also long been a staple in Latin American cooking and Caribbean cuisine as a coloring agent and flavoring, and it is sometimes used as a substitute for saffron. Annatto adds a slightly sweet and peppery taste.
- *Bixa orellana* has traditionally been used for diabetes and snakebites. It has recently been used as an ingredient in weight-loss products. At this time, there is insufficient available evidence in humans to support the use of *Bixa orellana* for any indication.

Cassia nomame:

- Nomame (*Cassia nomame*), while native to China, also grows wild in Africa, the Pacific Islands, Australia, and tropical and temperate areas of Asia.
- Nomame is a medicinal herb that is typically marketed in weight-loss formulations. According to secondary sources, it is thought to act as a lipase inhibitor {McCarty, 2005, 15533633}, thereby reducing fat breakdown in the intestinal tract, resulting in less fat absorption and a reduction in total caloric intake and blood triglyceride levels. In animal study, an extract of nomame reduced weight and prevented obesity {Yamamoto, 2000, 10878683}. However, there is a lack of clinical or basic science research regarding the effects of nomame on body weight, body composition, or fat metabolism in humans. According to secondary sources, nomame may also have diuretic and thermogenic properties, believed to play a role in its purported weight loss effects.
- According to secondary sources, there are some claims that nomame is also effective for the treatment of diabetes; however, with a lack of data from clinical trials supporting these claims, this herb cannot be safely recommended for the treatment of any medical condition.

Chuchuhuasi (*Maytenus krukovii, Maytenus macrocarpa, Maytenus laevis*)

- Chuchuhuasi may refer to several different species of the *Maytenus* genus, including but not limited to *Maytenus macrocarpa*, *Maytenus krukovii* (*Maytenus chuchuhuasha*), *Maytenus laevis*, and occasionally *Maytenus colasii* (*Salacia colasii*) {Gonzalez, 2000, No pmid}. Other species that have been associated with chuchuhuasi include *Maytenus ebenifolia*, *Maytenus boaria*, and *Maytenus guyanensis* (secondary sources). Typically, however, *Maytenus macrocarpa*, *Maytenus krukovii* (*Maytenus chuchuhuasha*), and *Maytenus laevis* are the more widely accepted species for chuchuhuasi. *Maytenus* spp. native to South

America may be found in the tropical rainforests of Bolivia, Brazil, Colombia, Ecuador, Peru, and Venezuela. The trees may grow up to 30 meters in height, with large leaves, small, white flowers, and tough, heavy, reddish-brown bark. Chuchuhuasi may contain a variety of active substances including alkaloids and terpenes.

- The bark, roots, and leaves of various species referred to as "chuchuhuasi" have been used in ethnomedicine for many purposes, including the treatment of rheumatism, due to their purported anti-inflammatory and analgesic properties. Chuchuhuasi has also been used for tuberculosis, bronchitis, stomachache, and fever. Chuchuhuasi bark may be bitter and is therefore often ingested as an alcoholic decoction mixed with honey. According to secondary sources, in Peru and Colombia, *Maytenus ebenifolia* is often soaked in aguardiente or rum and ingested as a tonic or aphrodisiac. Chewing the bark of the chuchuhuasi is considered by traditional medicine experts to be effective for the treatment of diarrhea, arthritis, and menstrual problems. Secondary sources cite that it also has been used as a muscle relaxant, to break up and disperse lactic acid, and to enhance virility.

Citrus bioflavonoids (hesperidin)

- Hesperidin is a flavanone diglycoside that is principally found in unripe citrus fruit. Hesperidin is available as a dietary supplement with reputedly beneficial effects through action on veins and capillaries. Relevant uses of hesperidin are based on clinical trials that appeared in medical literature in the late 1980s. However, hesperidin lacks evidence of therapeutic effect as a dietary supplement by itself. Available studies have used preparations that contain hesperidin (e.g., *Ruscus aculeatus* root extract (150mg) plus hesperidin methyl chalcone (150mg), and <ref id="vitaminc">ascorbic acid</ref> (100mg); micronized purified flavonoid fraction consisting of 90% (450mg) diosmin and 10% (50mg) flavonoids as hesperidin. Nutratech's Diosmin Complex® is a micronized mixture of 90% diosmin and 10% hesperidin that has been used in various clinical trials, and has been deemed qualitatively and quantitatively identical to other branded diosmin/hesperidin formulations available outside the United States including Arvenum 500®, Capiven®, Daflon® 500mg, Detralex®, and Venotec®.

Glycomacropeptide (GMP)

- Purified glycomacropeptide (GMP) has been used in dietary supplements, as well as in functional foods and beverages that provide some health benefit beyond basic nutrition. When milk is treated with an enzyme called chymosin (also known as rennin) during cheese making, the milk protein kappa-casein is hydrolyzed into para-kappa-casein and glycomacropeptide (GMP). Para-kappa-casein becomes part of the cheese curd. The GMP peptide becomes part of the whey. GMP exists as a mixture of different glycoforms due to the carbohydrate residues (sialic acid, galactose, galactosamine, and glucosamine) attached by O-glycosidic linkages {Keogh, 2010, 20205966}. GMP is also formed during digestion by pepsin hydrolysis in the stomach {Stan, 1974, 4601210}. GMP may also be called casein glycomacropeptide (cGMP), casein macropeptide (CMP), casein-derived peptide (CDP), or casein glycopeptide (CGP). GMP is different from other whey proteins due to low levels of aromatic amino acids (phenylalanine, tryptophan, and tyrosine).
- GMP also has relatively high amounts of the branched-chain amino acids (BCAAs) isoleucine and valine. BCAAs are believed to stimulate the production of cholecystokinin (CCK), a peptide that is released after eating and may act as an appetite suppressant by providing a sense of satiety. The effects of GMP supplementation have not been consistent in clinical trials. Some studies reported that GMP increased satiety over a short-term period but did not affect the amount of food eaten at a subsequent meal {Keogh, 2010, 20205966; Lam, 2009, 18948128}. Other studies have reported that GMP did not have an effect on satiety {Veldhorst, 2009, 19185957; Veldhorst, 2009, 19101599; Veldhorst, 2007, NO PMID; Burton-Freeman, 2008, 17964616; Keogh, 2010, 20205966} or weight loss {Keogh, 2008, 18541546}. Although one human study found that GMP stimulated the release of cholecystokinin (thereby promoting satiety) {Burton-Freeman, 2008, 17964616}, another study reported conflicting results {Keogh, 2010, 20205966}.

Based on clinical research, the satiety effects may be more pronounced in females than males {Burton-Freeman, 2008, 17964616}.

- Clinical studies have used GMP in infant formulas {Andersson, 2009, 19734215; Sandstrom, 2008, 18400715; Bruck, 2006, 17130747} and weight loss {Keogh, 2010, 20205966; Keogh, 2008, 18541546; Lam, 2009, 18948128; Burton-Freeman, 2008, 17964616; Veldhorst, 2009, 19101599; Veldhorst, 2009, 19185957} supplements, although GMP has been associated with causing hyperthreoninemia (high threonine levels) in premature babies fed a formula containing GMP {Rigo, 2001, 11321379}. The low level of phenylalanine, however, makes it a potential protein source in patients with phenylketonuria (PKU), and it has been shown to be an effective substitute for synthetic amino acids in the diets of PKU patients {van Calcar, 2009, 19244369; MacLeod, 2010, 20466571}.
- According to secondary sources, GMP may also have athletic performance and muscle mass / strength enhancing effects.
- Better-designed clinical trials are needed before recommendations can be made regarding the use of GMP for any health condition.

Green tea (*Camellia sinensis*)

- Green tea is made from the dried leaves of *Camellia sinensis*, a perennial evergreen shrub. Green tea, black tea, and oolong tea are all derived from the same plant. Green tea is produced by lightly steaming the freshly cut leaf, thus not allowing oxidation of the enzymes within the leaf to take place. Green tea is produced and consumed primarily in China, Japan, and countries in North Africa and the Middle East.
- Recent research has shown that plant-derived polyphenolic compounds are promising nutraceuticals for control of various disorders such as cardiovascular, neurological, and neoplastic disease {Ullah, 2008, 18712957}. Similar to wine, curcumin, purple sweet potato leaves, and cocoa, green tea is high in polyphenols (catechins, anthocyanins, phenolic acids) {Jalil, 2008, 18830150; Walzem, 2008, 19109750; Strimpakos, 2008, 18370854; Chen, 2008, 18818160}. Unlike leaves used for black or oolong teas, leaves used to prepare green tea do not undergo a fermentation process. Therefore, green tea retains higher levels of catechins, which are highly antioxidant polyphenolic compounds. Many of the potential cancer preventive effects of green tea are thought to be mediated by its most abundant catechin, epigallocatechin gallate (EGCG) {Khan, 2008, 18501505}. Tea also contains tannins, trace elements, and vitamins.
- Green tea is a source of caffeine, a methylxanthine, which stimulates the central nervous system, relaxes smooth muscle in the airways to the lungs (bronchioles), stimulates the heart, and acts on the kidney as a diuretic (increasing urine). One cup of tea contains approximately 50mg of caffeine, depending on the strength and size of the cup (as compared to coffee, which contains 65-175mg of caffeine per cup).
- Green tea is used as an antioxidant for chronic disease prevention. It has been studied for genital warts, anxiety, arthritis, cancer, cardiovascular conditions, common cold, liver disease, prevention of dental caries, diabetes, infertility, human T-cell lymphocytic virus, hypercholesterolemia, hypertension, hypertriglyceridemia, menopausal symptoms, mental performance, obesity, photoprotection, and weight loss. Future well-designed clinical trials are required in these areas before recommendations regarding the health benefits of green tea can be made.

Guggul (*Commiphora mukul*)

- Guggul (gum guggul) is the resin produced by, as well as the common name for, *Commiphora mukul* (also known as *Commiphora wightii*), or the mukul myrrh tree. Guggulipid, which is extracted from guggul, contains the plant sterols guggulsterone E and guggulsterone Z, which are believed to be its bioactive compounds. Based on secondary sources, guggulsterones are a mixture of several compounds isolated from the plant sources.
- Prior to 2003, the majority of scientific evidence suggested that guggulipid elicits significant reductions in serum total cholesterol, low-density lipoprotein (LDL), and triglycerides, as well as elevations in high-

density lipoprotein (HDL) (1-11). However, most published studies were small and not well-designed or reported. In August 2003, a well-designed trial reported small, statistically significant increases in serum low-density lipoprotein cholesterol (LDL-C) levels associated with the use of guggul extract (1000-2000mg, three times per day) compared to placebo (12). No significant changes in total cholesterol, high-density lipoprotein (HDL), or triglycerides were measured. These results were consistent with two prior published case reports (13;14). Although this evidence provides preliminary evidence against the efficacy of guggul for hypercholesterolemia, due to the precedent of prior research and historical use, further study is necessary before a definitive conclusion can be reached.

- While most well-known for its purported anti-hyperlipidemic effects, guggul has also been investigated for possible therapeutic benefit in a number of other indications and health conditions including acne, obesity, and both osteoarthritis and rheumatoid arthritis. Despite an increasing body of research, guggul has yet to garner sufficient evidence of efficacy in any human indication.

Lotus (*Nelumbo nucifera*):

- *Nelumbo nucifera* has reportedly been used throughout Egypt, the Middle East, India, Japan, and China since ancient times, primarily as a food. The flowers, seeds, leaves, and rhizomes of lotus are all edible. The petals of the flower are used as a wrap for foods in Asia, and the rhizome is a common ingredient in soups and stir-fried foods.
- Based on secondary sources, all parts of the lotus plant, but primarily the flower, have been used medicinally for over 1,000 years. Primary uses mentioned in secondary texts include gastrointestinal and bleeding disorders and fever. In preliminary research, lotus and its constituents had inhibitory activity on platelet aggregation {Yu, 1997, 11243209}, reduced blood glucose and fasting blood insulin {Mukherjee, 1997, 9421256; Pan, 2009, 19527823}, and may have antihypertensive effects {Yang, 2004, 15386549}. In animal and *in vitro* studies, lotus leaf has been shown to have antibacterial {Li, 2008, 18481022; Li, 2007, 17992914}, antilipemic {Kulkarni, 2008, 20046740; Lin, 2009, 19499892; Pan, 2009, 19527823; Ono, 2006, 16495025}, antiobesity {Ono, 2006, 16495025; Ohkoshi, 2007, 17893829}, and hepatoprotective {Lin, 2009, 19499892; Sohn, 2003, 12725571} effects.
- Scientific evidence supporting the clinical uses of lotus is lacking at this time. Further study is warranted.

Expert Opinion and Historic/Folkloric Precedent:

Slimple®

- The formulation of Slimple® is based on traditional use of its constituents: achiote leaf, *Cassia nomame*, chuchuhuasi, citrus bioflavonoids, glycomacropeptide (GMP), green tea, guggulsterones, and lotus leaf extract.

Achiote leaf (*Bixa orellana* L.)

- *Bixa orellana* has traditionally been used for a variety of ailments and conditions worldwide, most prominently in South America, Mexico, and the Caribbean. All parts of the plant have been used, including the dried pulp of the fruit, roots, leaves, and seeds.
- *Bixa orellana* has been used in the Caribbean as a folk remedy and as part of West Indian folk medicine to treat diabetes mellitus {Morrison, 1991 65 /id;Russell, 2005 15 /id;Russell, 2008, 18773125}. In a survey of ethnomedicines used in Trinidad and Tobago, annatto was reportedly used to treat diabetes, jaundice, and hypertension {Lans, 2006, 17040567}.
- *Bixa orellana* products are often marketed as herbal treatments for liver conditions, urinary conditions, heartburn, digestive and prostate problems, internal inflammation, arterial hypertension, high cholesterol,

cystitis, obesity, and renal insufficiency, and to strengthen the immune system. *Bixa orellana* is also used in multi-ingredient weight-loss products.

- According to the U.S. Food and Drug Administration (FDA), the toxicology profile of annatto seeds and extract has been fully investigated for annatto's use as a food additive. Annatto is specified in the Food Chemical Codex (No. 73.30, 73.1030 & 73.2030) and is Generally Recognized as Safe (GRAS) for human consumption in food products. There is a lack of available information about the GRAS status for the medicinal use of annatto. The European Union uses "E numbers" to identify food additives. E stands for "Europe." Annatto food coloring has the E number E160b {Scotter, 2009, No PMID}.

Cassia nomame

- Hama-cha, an aqueous extract of leaves, stems, and pods of nomame, is a popular tea in Japan. Nomame is also reportedly used as a raw material for a diuretic or antidote in folk remedies.
- Nomame is not listed in the U.S. Food and Drug Administration (FDA) Generally Recognized as Safe (GRAS) database.

Chuchuhuasi (*Maytenus krukovii, Maytenus macrocarpa, Maytenus laevis*)

- Chuchuhuasi may stimulate the adrenal glands to produce enzymes to treat adrenal fatigue. Once the adrenals become depleted, adrenal exhaustion may occur as a result of chronic increased release of cortisol, which may increase hunger and calorie intake. The adrenal medulla makes epinephrine (adrenaline) and norepinephrine (noradrenaline). As one of its functions, epinephrine is secreted in response to low blood levels of glucose as well as exercise and stress; it causes the breakdown of the storage product glycogen to sugar glucose in the liver and facilitates the release of fatty acids from fat tissue.
- A survey on medicinal plants used in the Peruvian Amazonian district of Chazuta showed that plant remedies were used to treat musculoskeletal disorders (29.7% of all the medicinal-use reports), gastrointestinal complaints (13.4%), and skin conditions (12.9%) {Sanz-Biset, 2009, 19146943}. *Maytenus macrocarpa* was employed most often. Because of its popularity, there is concern about the rate at which *Maytenus macrocarpa* is being harvested in Chazuta.
- Indigenous tribes in Colombia and Peru may add chuchuhuasi bark (typically from *Maytenus ebenifolia*) to rum or aguardiente, an alcoholic beverage made from sugarcane. The bark is allowed to steep for up to seven days. This popular "jungle drink" is served in bars and to tourists. It is often called "go-juice" because it purportedly relieves pain and muscle aches and helps drinkers to "keep going" during long treks in the rainforest. It is also considered to be an aphrodisiac.
- The Quijos Quichua people of Ecuador chew or decoct the inner bark of *Maytenus krukovii*. Typically this is given as a tonic to patients recovering from various illnesses, including tuberculosis, bronchitis, fever, and stomach upset. An indigenous ethnic group, the Siona people of Colombia, decocts the bark and uses this as a stimulant.
- Chuchuhuasi is not listed in the U.S. Food and Drug Administration (FDA) Generally Recognized as Safe (GRAS) list. The FDA required LifePlus International to verify information claimed by the company on the effects of some of their products, including some that contained chuchuhuasi (e.g., Berry'd Treasure™, Cat's Claw Plus).

Citrus bioflavonoids (hesperidin)

- Hesperidin, a citrus flavonoid, may be found in fruits such as lemons, oranges, and tangelos {Gonzalez-Molina, 2010, 19748198; Kanaze, 2009, 18823075}. It may be beneficial as an antioxidant, antimicrobial, immunomodulatory, and chemopreventive agent {Hardin, 2010, no PMID; Kanaze, 2009, 18823075}. Secondary sources suggest that it may also be beneficial for cardiovascular disease and has been linked to lowering cholesterol and blood pressure. Other secondary sources suggest that hesperidins and other flavonoids may also be useful in stimulating the metabolism and reducing bone loss.

- It has been reported that hesperidin methyl chalcone, the methylated derivative, may be the more beneficial form of hesperidin. Hesperidin has been found to increase capillary resistance, decrease capillary permeability, and enhance venous motility/tone and blood vessel dilation ability. It may be useful in reducing edema related to chronic venous diseases in both early and advanced stages {Sapelkin, 2008, 19791434}.
- Rikkunshi-to (TJ-43) is a combination herbal product that contains hesperidin (along with *Atractylodis Lanceae* Rhizoma, <ref id="ginseng">*Ginseng* radix</ref>, Pinelliae tuber, Hoelen, *Zizyphi fructus*, *Aurantii nobilis* Pericarpium, <ref id="licorice">*Glycyrrhizae* radix</ref> and <ref id="ginger">*Zingiberis* rhizoma</ref>) that is used as a gastroprotective agent {Kito, 2010, 20167876}.
- Detralex®, a product that contains hesperidin, diosmin, and rutin, has been found to be useful in reducing arthritis-related swelling and inflammation, particularly in combination with methotrexate {Rovensky, 2009, 19758231}.
- Hydrophylic preservatives are reportedly best in maintaining the physical stability during storage of hesperidin nanosuspensions; aggregations were noticed after adding caprylyl glycol, MultiEx naturotics™, and Phenonip® {Al Shaal, 2010, 20225649}. In experiments evaluating suitable delivery methods of hesperidin, cellulose acetate phthalate (CAP) was found to be an adequate polymeric carrier to protect hesperidin in the gastric medium. Enhancers such as sodium carboxymethylcellulose crosslinked (CMC), sodium dodecylbenzene sulfonate (SDBS), and Tween85™ were beneficial in obtaining complete drug release in intestinal fluid {Sansone, 2009, 19381835}. Stablizers, Inutec® and Plantacare®, stabilized nanosuspensions with no change in photon correlation spectroscopy (PCS) diameter and LD diameter 99%; other stabilizers, Poloxamer and Tween™, were also found to stabilize nanosuspensions without impairing the use of hesperidin in dermal formulations {Mishra, 2009, 19162147}.
- A diet of 0.05% hesperidin, 0.05% naringenin, or 0.5% pectin fed to chickens resulted in reduced egg yolk cholesterol levels, increased yolk weight and ratio of yolk weight/egg weight, and elevated blood serum superoxide dismutase (SOD) activity and antioxidant capacity {Lien, 2008, 18341078}.
- Hesperidin is not included in the U.S. Food and Drug Administration (FDA) Generally Recognized As Safe (GRAS) list.

Glycomacropeptide (GMP)

- Highly purified glycomacropeptide (GMP) and other purified dairy protein fractions may be used for individuals with special nutritional needs (diabetes, obesity, and hypercholesterolemia) to expand their dietary options and increase compliance with restricted diets {Etzel, 2004, 15051860; LaBell, 1998, NO PMID}.
- It has been reported that milk whey protein concentrates has a higher GMP content than milk serum protein concentrate {Evans, 2009, 19762792}.
- Many methods for quantification, detection, or purification of GMP have been described, such as detection of sialylated phosphorylated kappa-casein GMP {Nakano, 2007, 17348671}, purification of GMP from caseinate hydrolysate {Nakano, 2000, NO PMID}, isolation of kappa-casein GMP from sweet whey for industrial scale production of GMP {Nakano, 2004, 15675803}, analysis of the molecular weight of GMP in whey protein products {Wang, 2003, 14594226}, and quantification of the amount of GMP in skimmed milk powder {Miyamoto, 2009, 19734671}.
- GMP is not listed in the U.S. Food and Drug Administration (FDA) Generally Recognized as Safe (GRAS) list.

Green tea (*Camellia sinensis*)

- Tea ranks second only to water as a major component of fluid intake worldwide and has been considered a health-promoting beverage since ancient times {Khan, 2008, 18501505}. Green tea is the fourth most commonly used dietary supplement in the United States {Sarma, 2008, 18484782}.

- Traditional health claims for green tea include: improving blood and urine flow, assisting in the elimination of alcohol and toxins, relieving joint pain, and improving resistance to diseases {Balentine, 1997 181 /id}. Green tea is an accepted cancer preventive agent in Japan and Fiji {Fujiki, 1999 93 /id}. In a study to determine total polyphenol consumption from beverages in Japanese people, it was determined that total consumption of beverages in a Japanese population was 1.11 ± 0.51L daily, and total polyphenol contents from beverages was 853 ± 512mg daily {Fukushima, 2009, 19187022}. Coffee and green tea shared 50% and 34% of total polyphenol consumption in beverages, respectively.
- Traditional Chinese medicine uses green tea as an astringent, cardiotonic, central nervous system stimulant, and diuretic. It may be used for treating flatulence, regulating body temperature, promoting digestion, and improving mental processes. In India, the leaf infusion of green tea has additionally been used to treat fungal infections {McKenna, 2000 1019 /id}. It has been suggested that green tea is more cardioprotective in women than in men {Cheng, 2007 3038 /id}. Based on secondary sources, some experts recommend that iced tea should be avoided if maximal benefits are desired, because the catechins in the tea bind to the ice and, thus, are diminished in the tea, although it is possible that when the ice melts, the catechins would disperse throughout the liquid. Catechins from green tea have been proposed to expand the lifespan and reduce age-associated diseases {Rockenfeller, 2010, 20079384}.
- Historically, green tea bags have been used topically to soothe sunburn, headache, tired eyes, and to stop bleeding of the gums or tooth sockets.
- Historically, tea has been served as a part of various ceremonies, and has been used to stay alert during long meditations. A legend in India describes the story of Prince Siddhartha Gautama, the founder of Buddhism, who tore off his eyelids in frustration at his inability to stay awake during meditation while journeying through China. A tea plant is said to have sprouted from the spot where his eyelids fell, providing him with the ability to stay awake, meditate, and reach enlightenment. Turkish traders reportedly introduced tea to Western cultures in the 6th Century.
- Green tea was identified as a source of complementary and alternative therapy in women before and after breast cancer diagnosis {Greenlee, 2009, 19184414}. Moiseeva et al. have suggested that it is necessary to regulate the *in vitro* experimental conditions under which dietary phytochemicals, including epigallocatechin-3-gallate, are investigated for their protective effects against cancer in order to improve clinical relevance {Moiseeva, 2009, 19584074}. In one study, it was determined that among patients with cancer, green tea was included as an herbal remedy most often used that had potential interactions with the chemotherapy they were also receiving due to similar metabolism via the cytochrome P-450 metabolizing enzymes (CYPs) and/or the P-glycoprotein (P-gp) transporter {Engdal, 2009, 19174505}.
- The general health benefits of green tea have been reviewed {Schneider, 2009, 19378876}. Potential drug-botanical interactions, including those involving green tea, have also served as a topic of review {Shord, 2009, 19815591}.
- In 2006, the proprietary partially purified water extract of green tea, called VeregenT (Polyphenon E®), was approved for external topical use as a prescription for genital warts caused by human papilloma virus, in the United States by the U.S. Food and Drug Administration (FDA) {Wu, 2008, 18614266}. This marked the first prescription botanical drug approved by FDA under the drug amendments of 1962 that required drugs to be proven both safe and effective prior to being marketed in the United States.
- Catechins from green tea extract are currently pending approval as a Generally Recognized as Safe (GRAS) product by the FDA.

Guggul (*Commiphora mukul*)

- Guggul has been used medicinally since at least 600 B.C., having been prescribed in ancient healing traditions for weight loss, heart conditions, and numerous other ailments. In Ayurveda, gum resin from guggul has been used to treat tumors, obesity, liver disorders, malignant sores and ulcers, urinary complaints, intestinal worms, leucoderma (vitiligo), sinuses, edema, and sudden paralytic seizures

{Shishodia, 2008, 19189646}. Although widely used in India, guggul and its preparations are less well known in the United States. Reviews of the literature have noted the potential benefits of guggul in the treatment of lipid disorders, but have cautioned that more extensive clinical research is required to evaluate safety and efficacy (18;19) {Cuzzolin, 2009, 19140118; Tweed, 2009, No PMID}.

- Guggul is not listed on the U.S. Generally Recognized as Safe (GRAS) list.

Lotus (*Nelumbo nucifera*)

- Based on secondary sources, the lotus plant has been used medicinally for generations in Asia. Lotus leaf juices are used for diarrhea and sunstroke when mixed with licorice. The flower is used for abdominal cramps, bloody discharges, bleeding gastric ulcers, excessive menstruation, and postpartum hemorrhage. The flower stamens are used for urinary frequency, premature ejaculation, hemolysis, epistasis, and uterine bleeding. The fruit is used for agitation and fever. Lotus seed has also been shown to lower cholesterol levels and to relax the smooth muscle of the uterus. It has also been used for poor digestion, enteritis, chronic diarrhea, insomnia, and palpitations. Mukherjee et al. published a general review on traditional uses, phytochemistry, and therapeutic reports of lotus {Mukherjee, 2009, 19298686}.
- Genetics of the lotus plant {Pan, 2007, No PMID; Pan, 2010, 19666746} and characteristics of lotus flower {Grant, 2008, 18252702} and leaf {Guo, 2008, No PMID; Tang, 2008, 18571664; Evans, 2006, No PMID; Drahl, 2007, No PMID; Balani, 2009, 19584417; Vartan, 2006, No PMID; Bhushan, 2009, 19239196, No author, 2009, No PMID} have been investigated.
- Lotus is not listed in the U.S. Food and Drug Administration (FDA) Generally Recognized as Safe (GRAS) list.

Brief Safety Summary:

Slimple®:

- **Likely safe**: When used orally and short-term in recommended dosages by healthy adults who are not pregnant or nursing.
- **Possibly safe**: When used under medical supervision by adults taking medications with no known interactions with the components of Slimple®.

Achiote leaf (*Bixa orellana* L.)

- **Likely Safe**: When used orally in food amounts in nonsensitive individuals.
- **Possibly Safe**: When used medicinally in small dosages of 10-20mg of powdered *Bixa orellana* leaf tablet daily for up to two weeks, based on expert opinion and animal study {Agner, 2004 25 /id}.
- **Possibly Unsafe**: When used in patients with bleeding disorders or those using anticoagulants (secondary sources). When used in patients with impaired kidney function {Bautista, 2004 29 /id}. When used in patients taking mutagenic agents, such as cyclophosphamide {Alves de Lima, 2003 39 /id}. When used in patients taking diuretics (anecdote). When used in patients taking antihypertensive agents (theoretical). When used in patients using cytochrome P450 1A or 2B substrates {De Oliveira, 2003 38 /id}. When used in patients with a history of constipation or those who are using laxatives {Shilpi, 2006 9 /id}. When used in patients with diabetes or those using antidiabetic agents {Morrison, 1991 65 /id;Fernandes, 2002 41 /id;Russell, 2005 15 /id; Russell, 2008, 18773125}. When used in patients using CNS depressants {Shilpi, 2006 9 /id}. A methanol extract of *Bixa orellana* leaves reduced gastrointestinal motility {Shilpi, 2006 9 /id} and theoretically may alter the absorption of concomitantly administered drugs.
- **Likely Unsafe**: When used by individuals who may be or are allergic or hypersensitive to *Bixa orellana*, *Bixa orellana* seeds, constituents of *Bixa orellana*, or any member of the Bixaceae family {Nish, 1991 6 /id;Taylor, 2001 48 /id;Lucas, 2001 49 /id}.

***Cassia nomame*:**

- **Possibly unsafe**: When used in patients with gastrointestinal conditions or malabsorptive syndromes due to the risk of laxative effects, according to secondary sources. When used in patients taking weight loss supplements, orlistat, or those on restricted diets, as nomame may act as a lipase inhibitor, according to secondary sources {McCarty, 2005, 15533633}, and may have weight-loss effects, according to preliminary study {Yamamoto, 2000, 10878683;McCarty, 2005, 15533633}.
- **Likely unsafe**: When used in individuals with a known allergy/hypersensitivity to nomame, its constituents, or plants of the Fabaceae (Leguminosae) family. When used in pregnancy and lactation, due to insufficient evidence.
- **Note**: Safety is based on traditional health practice patterns and expert opinion; there is a lack of available reliable human trials demonstrating safety or efficacy of nomame.

Chuchuhuasi (*Maytenus krukovii, Maytenus macrocarpa, Maytenus laevis*):

- **Possibly unsafe**: When used in persons operating heavy machinery or while driving, since chuchuhuasi may increase drowsiness and promote relaxation, according to anecdotal sources. In pregnant women, as *Maytenus macrocarpa* has been used traditionally as an abortifacient and contraceptive {Sanz-Biset, 2009, 19146943}.
- **Likely unsafe**: When used in individuals with known allergy/hypersensitivity to chuchuhuasi, its constituents, or members of the Celastraceae family.
- **Note**: Safety is based on traditional health practice patterns and expert opinion; there are no available reliable human trials demonstrating safety or efficacy of chuchuhuasi.

Citrus bioflavonoids (hesperidin):

- **Likely safe**: When used orally for less than one year.
- **Possibly Unsafe**: When used in patients using anticoagulants and antiplatelets {Jin, 2007, 17092506}. When used in patients using antihypertensives {Yamamoto, 2008, 18329851}. When used in patients using antilipemic agents {Rizk, 2009, no PMID;Jung, 2006, 16427799; Chiba, 2003, 12771335; Akiyama, 2009, 19966469}. When used in patients using anticonvulsants {Dimpfel, 2006, 16536905}. When used in patients using cardiovascular agents {Liu, 2008, 18197618; Chiou, 2008, 18430059}. When used in patients who are using CNS depressants {Fernandez, 2005, 15840404; Loscalzo, 2008, 18048026}. When used in patients with diabetes or those taking antidiabetic agents {Rizk, 2009, no PMID; Akiyama, 2009, 19966469; Jung, 2004, 15465737}. When used in patients with blood disorders or those using anticoagulants or antiplatelets {Jin, 2007, 17092506}. When used in patients using celiprolol, a beta-blocker {Uesawa, 2008, 18344215}. When used in patients using calcium channel blockers {Choa, 2009, 19505375; Piao, 2008, 18449511}. When used in patients using agents metabolized by cytochrome P450 (specifically 2C9, 2D6, and 3A4) and P-glycoprotein {Fujita, 2008, 18451520; Choa, 2009, 19505375}. When used in patients with musculoskeletal disorders, or in patients taking muscle relaxants {Guilhou, 1997, 8995348; Galley, 1993, 8376915}. When used in patients with gastrointestinal disorders, or in patients taking antacids or anti-emetics {Cospite, 1989, 2698903; Beltramino, 2000, 10917578; Cospite, 1994, 8203789; Buckshee, 1997, 9184951; Guilhou, 1997, 8995348, Misra, 2000, 10931020; Galley, 1993, 8376915}. When used in patients prone to headaches {Cospite, 1994, 8203789; Guilhou, 1997, 8995348}.
- **Likely Unsafe**: When used in patients with a known allergy/hypersensitivity to hesperidin or hesperidin-containing foods and supplements, such as citrus.
- **Note**: Diosmin is a flavonoid that may be derived from hesperidin. According to secondary sources, Diosmin Complex (containing 90% diosmin and 10% hesperidin) 6g daily for up to one year has been found to be safe and tolerable. In toxicological and safety studies, diosmin has been found to have a large safety margin with no evidence of genotoxicity or mutagenic effects. There is a lack of information

regarding its use in children as well as during pregnancy or lactation; however, according to secondary sources, teratogenic effects have not been noted.

Glycomacropeptide (GMP):

- **Likely safe**: When used in recommended amounts for weight loss for up to one year {Keogh, 2008, 18541546}. When used in recommended amounts in infant formulas for up to 4.5 months {Andersson, 2009, 19734215; Sandström, 2008, 18400715; Brück, 2006, 17130747}.
- **Possibly safe**: When used in patients with phenylketonuria (PKU) when ultrapurified and supplemented with indispensable amino acids and taken as a replacement for synthetic amino acid dietary supplements {Lim, 2007, 17644019}.
- **Possibly unsafe**: When used in pregnant or lactating women, due to lack of sufficient data. When used in patients with blood disorders or those using anticoagulants or antiplatelets, as based on a review, GMP may inhibit platelet aggregation {Rutherfurd, 2000, 11242453} and theoretically increase the risk of bleeding. When used in patients with diabetes or those using hypoglycemic agents, as based on human study, GMP may reduce blood glucose levels {Keogh, 2008, 18541546; Royle, 2008, 18062832} and theoretically increase the risk of hypoglycemia. When used in patients using hypotensive agents, as based on human study, GMP may lower blood pressure {Keogh, 2008, 18541546} and theoretically increase the risk of hypotension. When used in patients with autoimmune disorders or those using immunosuppressants, as based on animal and human study, GMP may have immunomodulatory effects {Mikkelsen, 2006, 16507674; Requena, 2010, 20178776; Rusu, 2009, 19106313; Requena, 2009, 19558546; Li, 2004, 15113179; Mikkelsen, 2005,16190615}. When used in patients with a history of anorexia or other eating disorders or those who are using weight loss agents, as based on human and animal study, GMP may enhance satiety and cause weight loss {Keogh, 2008, 18541546; Veldhorst, 2009, 19185957; Veldhorst, 2009, 19101599; Burton-Freeman, 2008, 17964616; Keogh, 2010, 20205966}. When used in patients with a history of constipation or those using laxatives, as based on human study, GMP may inhibit these effects {Brück, 2003, 12960649}. When used in combination with probiotics, due to the risk of altering the population of microflora present in the digestive tract {Brück, 2006, 17130747; Stan, 1983, 6871439; Brück, 2003, 12807453; Brück, 2002, 19709257}. When nonpurified commercial GMP is used, because it may contain residual phenylalanine and may not provide the essential amino acids needed to use it as a replacement for synthetic amino acid dietary supplements {Lim, 2007, 17644019}.
- **Likely unsafe**: When formula containing GMP is given to premature babies, due to the risk of hyperthreoninemia {Gunther, 1998, NO PMID; Quero, 1997, NO PMID; Rigo, 2001, 11321379}. When used in patients with known allergy/hypersensitivity to casein, whey, milk, or cheese, due to the risk of allergic reaction {Andersson, 2009, 19734215; Sandström, 2008, 18400715}. When large quantities of GMP are ingested on an empty stomach, due to the risk of cyclic-repetitive vomiting, as shown in animal study {Stan, 1983, 6871439}.

Green tea (*Camellia sinensis*):

- **Likely safe**: When used orally in low to moderate amounts. Traditionally, green tea is consumed throughout the day in Asian countries (e.g., China and Japan) and is considered safe and nontoxic. Green tea extract has been suggested to be safely used for up to one year {Bettuzzi, 2006 1802 /id;Shimizu, 2008, 18990744}.
- **Possibly unsafe**: Green tea contains up to 50mg of caffeine per cup. When more than 500mg of caffeine (16 cups) is consumed daily, both short-term and long-term adverse effects are possible. Caffeine is a nervous system stimulant, and it is not recommended for excessive use. Chronic use may result in tolerance, habituation, and psychological dependence {Boozer, 2001 2882 /id}. When used in patients using hepatotoxic agents or with liver disorders or on an empty stomach as, according to various case reports and a review, hepatotoxicity {Javaid, 2006 3054 /id;Federico, 2007 3055 /id;Molinari, 2006 3056

/id;Favreau, 2002 2910 /id;Sarma, 2008, 18484782} and acute hepatitis {Martinez-Sierra, 2006 3041 /id;Jimenez-Saenz, 2006 3042 /id} have been associated with use of green tea products when taken on an empty stomach. When used in patients with pre-existing mitral valve prolapse, as intractable ventricular fibrillation has been reported in a case associated with high dosage caffeine consumption {Cannon, 2001 395 /id}. When used in patients with cardiac arrhythmias, due to theoretical exacerbation of disease {Dobmeyer, 1983 1380 /id}. When used in patients with psychiatric disorders, due to theoretical wide-ranging dysregulating effects of caffeine upon emotional states {Boulenger, 1982 2324 /id;Boulenger, 1984 2163 /id;Charney, 1985 2124 /id;Uhde, 1984 2234 /id} and possibility of symptoms during withdrawal. When used in patients with diabetes or in patients using antidiabetic drugs, due to possible increases and decreases in blood sugar as shown in animal and human study {Pizziol, 1998 2975 /id;Tuomilehto, 1990 2976 /id; Watson, 2000 3070 /id}. When used in patients with breast disease, due to possible association with fibrocystic breast disease and breast cancer {Boyle, 1984 3062 /id}. When used in patients at risk for prostate cancer, due to possible association between green tea consumption and prostate cancer risk {Mizuno, 1992 2915 /id}. When used in patients using iron or consuming iron-rich foods or in patients with iron deficiency, as caffeine reduces the absorption of iron and has been associated with the development of anemia {de Alarcon, 1979 204 /id; Merhav, 1985 144 /id}. Impaired iron metabolism and microcytic anemia {Hardy ML, 2000 1157 /id}, and transient acceleration of intravascular hemolysis {Iwamoto, 1994 138 /id} have been reported. According to a review, it is recommended that vegetarians drink tea between meals, as tea binds to dietary iron found in plant sources and decreases the availability (absorption) of iron {Dufresne CJ, 2001 1031 /id}. When used in postmenopausal women, due to theoretical potential for estrogen decrease {Wu, 2005 3040 /id}. When used in patients undergoing gastrointestinal magnetic resonance imaging (MRI), due to potential for enhancement of the gastrointestinal tract {Sato, 1994 2916 /id}. When used in patients using anticoagulants and antiplatelets or in those with bleeding disorders as, according to human, animal, and *in vitro* study, both catechins and caffeine in green tea have been reported to have antiplatelet activity {Ali, 1987 2919 /id;Son, 2004 1604 /id;Taylor, 1999 17 /id;Heck, 2000 113 /id}, and contain vitamin K {Booth, 1995 1032 /id}. When used in patients at risk for osteoporosis based on the theoretical idea that consuming caffeinated products may increase urinary excretion of calcium, although this is debated {Barger-Lux, 1990 2963 /id;Dufresne CJ, 2001 1031 /id}. When used in patients prone to development of headaches, as L-theanine, a constituent of green tea, has been suggested to increase headache ratings {Haskell, 2008 3043 /id}. When used in elderly women, because high caffeine intake (>400mg daily) has been shown to worsen the condition of detrussor instability (unstable bladder) {Arya, 2000 502 /id}. When used in conjunction with alcohol as, according to a review, alcohol consumption may increase caffeine serum concentrations and the risk of caffeine adverse effects {Sinclair, 2000 3067 /id}. When used in patients using analgesics such as acetaminophen, as clinical trials suggest that caffeine enhances the analgesic efficacy of acetaminophen {Laska, 1983 2284 /id;Laska, 1984 2200 /id}, codeine {Desjardins, 1986 2013 /id}, and when combined with aspirin {Silberstein, 1999 622 /id;Goldstein, 1999 581 /id}, although conflicting evidence exists {Zhang, 1996 873 /id}. When used in patients using monoamine oxidase inhibitors (MAOIs), as concomitant administration may theoretically increase the risk of hypertensive crisis. When used in patients using antifungals as, according to human study, fluconazole has been suggested to decrease caffeine clearance from the blood {Nix, 1992 3002 /id}. When used in patients with glaucoma or using antiglaucoma agents, as ingestion of caffeine was found to increase intraocular pressure in two glaucoma patients {Davis, 1989 2967 /id}. Clinical reports, however, present conflicting results {Adams, 1990 2885 /id;Higginbotham, 1989 2887 /id}. When used in patients using antihypertensives or in those with high blood pressure as, according to clinical trials, green tea {Hodgson, 1999 53 /id}, green tea extracts {Laurie, 2005 1767 /id}, and specifically caffeine {Lang, 1983 37 /id;Nussberger, 1990 2889 /id;Pincomb, 1985 2098 /id;Pincomb, 1996 930 /id;Stensvold, 1989 2902 /id;Sung, 1994 2958 /id;van Dusseldorp, 1989 2903 /id;Conrad, 1982 2357 /id;Smits, 1993 1204 /id} may increase systolic and diastolic blood pressure. Several clinical trials, however, have shown a lack of an

effect {Eggertsen, 1993 2998 /id;MacDonald, 1991 2999 /id;Rosmarin, 1990 2928 /id;Bak, 1991 3008 /id} or have demonstrated blood pressure-lowering effects {Nagao, 2007 3025 /id}. When used in patients using cimetidine (Tagamet®) as concurrent use may increase caffeine blood levels or the length of time caffeine acts on the body {Broughton, 1981 3044 /id}. When used in patients using benzodiazepines as, in a clinical trial, caffeine has been found to antagonize the effects of lorazepam and diazepam {File, 1982 2358 /id;Mattila, 1982 2355 /id;Mattila, 1983 3071 /id}. When used in patients using other agents containing caffeine, including prescription medications and products such as guarana, cola nut, and yerba mate, as green tea is a source of caffeine. When used in patients using central nervous system (CNS) stimulants, as concurrent use may theoretically increase the risk of stimulatory adverse effects. A case report cited ischemic stroke after the nasal ingestion of amphetamine and caffeine {Lambrecht, 1993 2972 /id}. When used in patients using contraceptives, as concurrent use may increase caffeine concentrations and adverse effects based on clinical study through inhibition of CYP1A2 {Pollock, 1999 593 /id; Abernethy, 1985 2990 /id;Rietveld, 1984 2221 /id;Patwardhan, 1980 2991 /id}. When used in patients using decongestants such as phenylpropanolamine (PPA) (no longer available in the United States) and pseudoephedrine, as additive blood pressure elevating effects may occur. According to a review and a survey, PPA increased plasma caffeine levels approximately four fold {Lake, 1990 2992 /id;Lake, 1990 2993 /id}. The combination of PPA and caffeine induced psychotic symptoms in one woman with no previous history of mental illness {Lake, 1990 2992 /id}. When used in patients using diuretics, as concurrent use with caffeine may cause additive diuretic effects and increase the risk of electrolyte imbalances {Bryant, 2002 3005 /id}. When used in patients using drugs that may lower seizure threshold, as concurrent use with caffeine may increase the risk and length of seizures {Hinkle, 1987 3061 /id; Shum, 1997 800 /id}. When used in patients using estrogen, as estrogen inhibits caffeine metabolism {Pollock, 1999 593 /id}. However, in one study consumption of green tea resulted in decreased estrogen levels in humans {Wu, 2005 3040 /id}. When used in patients using vasoconstrictors like sympathomimetic agents, as concurrent use with caffeine may cause additive vasoconstriction {Smits, 1990 2964 /id}. Concurrent use of caffeine with sympathomimetic stimulants like ephedrine may increase the risk of adverse stimulatory effects {Astrup, 1991 1017 /id;Astrup, 1992 2996 /id;Dulloo, 1986 1015 /id;Smits, 1990 2964 /id}.

- **Likely unsafe**: When used in pregnant women, as caffeine crosses the placenta; caffeine intake has been associated with spontaneous abortion {Parazzini, 1998 2914 /id}, premature deliveries, low birth weight {Cnattingius, 2000 1751 /id;Weathersbee, 1977 2988 /id;Eskenazi, 1999 2871 /id;Cook, 1996 2872 /id;Caan, 1989 2870 /id;Fenster, 1991 2874 /id;Fenster, 1991 2876 /id;Martin, 1987 2877 /id;Vlajinac, 1997 2878 /id;Santos, 1998 2879 /id}, and impaired iron metabolism and microcytic anemia {Merhav, 1985 144 /id}. However, studies in pregnant women drinking moderate amounts of caffeine have shown inconsistent results, with more recent studies reporting no adverse effects on the fetus {Clausson, 2002 1750 /id}. When used in breastfeeding women, as caffeine is rapidly transferred to breast milk and may produce effects such as irritability or anxiety in infants {Stavchansky, 1988 1789 /id}, as well as impaired iron metabolism and microcytic anemia {Merhav, 1985 144 /id}. When used in children, due to caffeine content. When used orally in large amounts due to high caffeine content. When used in patients with uncontrolled hypertension, as caffeine has been shown to increase blood pressure {Lang, 1983 37 /id;Nussberger, 1990 2889 /id;Pincomb, 1985 2098 /id;Pincomb, 1996 930 /id;Stensvold, 1989 2902 /id;Sung, 1994 2958 /id;van Dusseldorp, 1989 2903 /id;Conrad, 1982 2357 /id;Smits, 1993 1204 /id;Boozer, 2001 2882 /id} and may be associated with an increased risk of thromboembolic stroke {Hakim, 1998 682 /id}. When used in patients with severe liver impairment, as the clearance of caffeine is impaired (decreases with increasing dose of caffeine) {Cheng, 1990 2966 /id;Desmond, 1980 2483 /id}.
- **Note**: Some green tea extracts are decaffeinated, a process that does not alter polyphenol levels. Precautions, warnings and contraindications of green tea are predominantly theoretical and based mainly upon the adverse effect profile of caffeine.

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Guggul (*Commiphora mukul*):

- **Likely Safe**: When taken at normal doses for up to six months (20).
- **Possibly Unsafe**: When used by patients using lipid lowering agents (particularly 3-hydroxy-3-methyl-glutaryl-CoA [HMG-CoA] reductase inhibitors) as a case of rhabdomyolysis has been reported and was associated with the use of guggul {Bianchi, 2004, 15187214}; further human and animal study demonstrated antilipemic effects (4;5;10;50;68-75; 76; 138-145;147-149;151-153). When used by patients with coagulation disorders or those using anticoagulants or antiplatelets as, based on human and lab study, guggul inhibited platelet aggregation (10;57;77;78) and may theoretically increase the risk of bleeding. A case report has been published documenting antagonism of the anticoagulant effect of warfarin caused by the use of guggul {Al Faraj, 2005, 15814041}. When used by patients on beta-blockers or calcium channel blockers as co-administration of guggulipid has been reported to decrease the bioavailability of the beta-blocker propranolol (61) and the calcium channel blocker diltiazem (62) in humans. When used by patients using cytochrome P450 3A4 substrates as, based on *in vitro* study, guggul induced cytochrome P450 3A4 and altered levels of agents metabolized by this isoenzyme{Brobst, 2004, 15075359}. When used by patients with thyroid disorders or taking thyroid agents as, in animal model, guggulsterone Z stimulated thyroid function (40-42; 63); however, results from other research indicated no difference in thyroid-stimulating hormone (TSH) levels with the use of guggul (64). In patients using antidiabetics as, in animal study, guggulipid demonstrated peroxisome proliferator-activated receptor-alpha (PPARalpha), PPARgamma, and liver X receptor-alpha (LXR-alpha) agonist activity that may contribute to antidiabetic effects {Cornick, 2009, 18926687}. Commipheric acid was also found to activate PPARalpha and PPARgamma. When used by patients using red yeast rice as acute hepatitis was reported in a 63 year-old woman who was using a lipid lowering product containing guggulsterol and red yeast rice extract (Equisterol®) after six months {Grieco, 2009, 19398239}. When used by patients with gastrointestinal disorders as, according to clinical evidence and anecdote, guggul and guggulipid have been associated with stomach discomfort, diarrhea, loose stools, nausea, and vomiting {Ulbricht, 2005, 16338199; Nohr, 2009, 19114224} (34-39).
- **Likely Unsafe**: When used by patients with known allergy/hypersensitivity to guggul (*Commiphora mukul*), other members of the *Commiphora* family, or any constituents of guggul. When used by patients who are pregnant or attempting to become pregnant due to possible abortifacient effects (24;25). When guggulsterones are used in large amounts in patients using estrogens as guggulsterones may activate estrogen receptors and increase the risk of adverse effects {Brobst, 2004, 15075359}.

Lotus (*Nelumbo nucifera*):

- **Possibly Unsafe**: When used in patients with a bleeding disorder or those using antiplatelet or anticoagulant herbs or drugs, due to the possibility of increased bleeding risk (<citations><citation>1</citation></citations>). When used in patients who are taking antihypertensive medications, due to the potential for blood pressure lowering (<citations><citation>2</citation></citations>). When used in patients who are taking antiarrhythmics, due to possible additive effects (<citations><citation>3</citation>; <citation>4</citation>; <citation>5</citation></citations>). When used in patients who are taking CNS depressants, due to increased risk of sedation, according to animal study (<citations><citation>6</citation></citations>). When used in patients with constipation and stomach distension, according to secondary sources. When used in patients with diabetes, as lotus may reduce blood sugar levels and increase the risk of hypoglycemia (<citations><citation>8</citation></citations>).

When used in women who are trying to become pregnant, as lotus seed may have antifertility activity (<citations><citation>7</citation></citations>).

- **Likely Unsafe**: When used in patients with known allergy/hypersensitivity to *Nelumbo nucifera*, its constituents, or related species from the Nelumbonaceae family.

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DOSING

General:

- Doses may be based on those most commonly used in available trials, or on historical practice. However, with natural products it is often not clear what the optimal doses are to balance efficacy and safety. Preparation of products may vary from manufacturer to manufacturer, and from batch to batch within one manufacturer. Because it is often not clear what the active component(s) of a product is, standardization may not be possible, and the clinical effects of different brands may not be comparable.

Standardization:

- **Achiote leaf (*Bixa orellana* L.)**: There is no well-known standardization for *Bixa orellana*.
- ***Cassia nomame***: There is no well-known standardization for nomame.
- **Chuchuhuasi (*Maytenus krukovii, Maytenus macrocarpa, Maytenus laevis*)**: There is no well-known standardization for chuchuhuasi. Based on secondary sources, extraction methods provide about 500mg of chuchuhuasi bark (species not specified) per milliliter of extract.
- **Citrus bioflavonoids (hesperidin)**: There is no well-known standardization for hesperidin as a dietary supplement by itself. However, for combination products, there is dosage information available from clinical studies. Near-infrared spectroscopy (NIRS) combined with least squares support vector machines (LS-SVM) has been developed to measure the amount of hesperidin in guogongjiu medicinal wine {Zhu, 2009, 19950655}. The extraction and quantitation of hesperidin from *Citrus sinensis* (or sweet orange) from waste orange peel was performed. Two extraction methods were employed. One procedure (isolated hesperidin from orange peel by extracting the dry peel first with petroleum ether, removing the essential oil and then extracting with methanol) produced high extraction yield. Pure hesperidin 11.7% was obtained from one purification cycle using this method. The other procedures (alkaline extraction followed by acidification of the extract, purified by treatment with formamide-activated charcoal) yielded 7.39% {Aghel, 2008, 19137859}.
- **Glycomacropeptide (GMP)**: There is no well-known standardization for GMP. The concentration of sialic acid in sweet whey has been used to estimate the amount of GMP present {Nakano, 1999, 10552534}. Concentrations of total and GMP sialic acid determined in a sweet whey sample prepared from fresh milk were 2.0 and 1.5mcg/mg of dry weight, respectively. Analysis of commercial samples showed that the concentration of total sialic acid in sweet whey was one-ninth of that in whey protein concentrate, but 18 times higher than that in whey permeate. A similar trend was observed in the variation of sialic acid concentration between sweet whey and whey protein concentrate, where the concentration of sialic acid differed 10 times between two samples of whey protein isolate.
- **Green tea (*Camellia sinensis*)**: Green tea extracts (GTE) from some of the major supplement manufacturers have considerable variation in the amount of GTE milligrams per capsule. This range may be as much as 100mg-750mg per capsule {Cronin JR, 2000 1020 /id}. Extracts of green tea may be standardized to 60%-97% polyphenols {McKenna, 2000 1019 /id}.
- **Guggul (*Commiphora mukul*)**: Guggulipid preparations are often standardized to contain 2.5-5% of guggulsterones. In July 2003, a review by ConsumerLab.com evaluating five guggulsterone supplements reported that Vitamin World® Select Herbals Standardized Extract Guggul Plex 340mg, standardized to contain 2.5% guggulsterones (8.5mg per capsule, three per day), manufactured by Vitamin World, Inc. was "approved" based on its claimed constituents. The remaining four brands contained from as little as 4% to 74% of the expected ingredient. None of the products were found to be contaminated with lead or arsenic. A recent human trial using guggulipid provided by Sabinsa Corporation (Piscataway, NJ), standardized to contain at least 2.5% guggulsterones E and Z, found the tablets to contain 2.1% guggulsterones (85% of the claimed ingredients) (26). This was judged to be satisfactory for research and clinical use.
- **Lotus (*Nelumbo nucifera*)**: There is no well-known standardization for lotus.

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Dosing:

Adult (age ≥18):

Slimple®:

- **General**: Slimple® is available in capsule form.

Achiote leaf (*Bixa orellana* L.):
Oral:

- **Tablets/Capsules**: Traditionally, a typical oral dose is 1-2g of the powdered *Bixa orellana* leaf in tablets or capsules twice daily.
- **Tea**: Although not widely available in the United States, standard decoctions of *Bixa orellana* leaves have been taken by the half-cupful two or three times daily for prostate and urinary difficulties, as well as for high cholesterol and hypertension. Ground *Bixa orellana* seed powder has also been used in small dosages of 10-20mg daily.
- **Tincture**: Based on anecdote, *Bixa orellana* has been used historically as a 4:1 tincture in a dose of 2-4mL twice daily.
- **Urinary disorders (benign prostatic hyperplasia)**: 250mg of encapsulated dried *Bixa orellana* leaf three times daily for 12 months has been used without evidence of benefit {Zegarra, 2007, 17767753}.

Cassia nomame
Oral:

- **Weight loss**: Anecdotally, doses of 100-900mg of nomame have been taken 2-3 times daily before meals.

Chuchuhuasi (*Maytenus krukovii, Maytenus macrocarpa, Maytenus laevis*)
Oral:

- **General**: Oral dosing regimens are based on traditional health practice patterns, expert opinion, and anecdote; there are no available reliable human trials demonstrating the safety or efficacy of a particular dose. *Maytenus macrocarpa* is often macerated with honey, wine, rum or aguardiente {Sanz-Biset, 2009, 19146943}. It is also frequently mixed with *Calliandra angustifolia*, *Clusia*, *Tovomita foldatsii* and *T.* aff. *stylosa* {Sanz-Biset, 2009, 19146943}. According to traditional guidelines and some herbal experts, chuchuhuasi should be taken before breakfast for at least a month to be effective. Sixty drops (2mL) of chuchuhuasi bark extract 2-3 times daily has been suggested. As a decoction, one cup 2-3 times daily, and as a tincture, 3-5mL 2-3 times daily, have been suggested. The concentrated powder extract (4:1) (1-3g daily) may be used to make a tea or consumed in a smoothie. Other dosing suggestions include boiling 1tbsp. of ground chuchuhuasi in 1L of water for 20 minutes, straining, and chilling overnight. It has been suggested to drink a cup of the decoction a cup before breakfast and two more cups between the remaining meals. According to secondary sources, the bark releases its chemicals more slowly than the leaves, stems, or fruits.
- **Stimulant**: According to secondary sources, the Siona Indians of Colombia suggest boiling a small piece of the bark (5cm) in 2L of water until 1L remains and then drinking the decoction three times daily for one week.
- **Tonic**: According to secondary sources, the inner bark of *Maytenus krukovii* may be chewed or decocted and ingested before eating breakfast for one month. Typically this is given as a tonic to patients recovering from various illnesses, including tuberculosis, bronchitis, fever, and stomach upset.

Citrus bioflavonoids (hesperidin)
Oral:

- **General**: There is insufficient available data concerning dosing of hesperidin as a dietary supplement by itself, although available clinical trials have used combination products containing hesperidin.
- **Diabetes**: Daflon® 500mg either alone or with an oral hypoglycemic agent, twice daily for 45 days has been shown to reduce serum glucose in female patients with type 2 diabetes {Rizk, 2009, no PMID}.

Glycomacropeptide (GMP)
Oral:

- **Obesity/weight loss**: One 50g dose of bovine cheese whey product (containing GMP) was not more effective than a similar product that did not contain GMP {Keogh, 2010, 20205966}. Meal replacements containing 15g of protein from GMP-enriched whey protein isolate diluted with 200mL of water taken twice daily for 12 months was not more effective than skim milk powder {Keogh, 2008, 18541546}. One beverage containing whey protein isolate plus added GMP was not more effective than a similar beverage without GMP {Lam, 2009, 18948128; Burton-Freeman, 2008, 17964616}. Breakfast containing whey (with GMP) with 10/55/35 or 25/55/20 percentage protein/carbohydrate/fat was more effective than other protein sources in one study, but was not more effective in other study {Veldhorst, 2009, 19101599; Veldhorst, 2009, 19185957}.

Green tea (*Camellia sinensis*)
Oral:

- **General**: Three cups daily (total polyphenol content of 240-320mg daily) of green tea has been traditionally consumed on average. For medicinal purposes, dosages may be as high as 10 cups daily. More than 10 cups daily (≥300mg caffeine daily) increases the risk of adverse affects from caffeine content {Hardy ML, 2000 1157 /id}. However, evidence derived from epidemiological data suggests that long-term consumption of ≥10 cups of green tea daily is without adverse effects and may be associated with significant health benefits {Mitscher, 1997 126 /id}. A dose of 4.2g/m^2 once daily or 1.0g/m^2 three times daily (equivalent to 7-8 Japanese cups [120mL]) has been used for six months {Pisters, 2001 68 /id}.
- **Cardiovascular health**: In the Rotterdam study, the relative risk of an acute myocardial infarction was lower in tea drinkers with a daily intake >375mL than in non-tea drinkers {Geleijnse, 2002 1101 /id}. Subjects ingested green tea containing 75-576mg catechins once daily for 24 weeks in a clinical trial {Matsuyama, 2008, 18356827}. In epidemiologic study, drinking >10 cups of green tea daily was associated with an increased proportion of HDL cholesterol and a decreased proportion of LDL and VLDL cholesterol (p=0.02) {Imai, 1995 3 /id}.
- **Diabetes**: Green tea containing 582.8mg of catechins has been used daily for 12 weeks {Nagao, 2009, 19008868}. A packet of green tea extracts containing 544mg polyphenols (456mg catechins) has been used daily for two months {Fukino, 2005 2954 /id}.
- **Hypercholesterolemia**: A dose of 375mg theaflavin-enriched green tea extract has been used for 12 weeks {Maron, 2003 1716 /id}. 3g of green tea in 500mL of water has been used daily for 90 days {Bertipaglia de Santana, 2008, 18455656}.
- **Hypertriglyceridemia**: A dose of 224 or 674mg green tea catechins with a meal has been suggested to decrease postprandial triglyceride response {Unno, 2005 2868 /id}.
- **Obesity**: One capsule of green tea extract (400mg) has been used three times daily for 12 weeks without effect {Hsu, 2008, 18468736}. GTE high in catechins (583mg of catechins) has been studied for its effects on body weight with some evidence of benefit {Nagao, 2007 3025 /id}. Two capsules of a GTE AR25 (Exolise®) has been taken twice daily for 12 weeks, but no significant effects were found {Chantre, 2002 1129 /id}. Green tea with 582mg catechins has been used daily for 12 weeks {Nagao, 2009, 19008868}.

Green tea with 573mg catechins for 13 weeks {Kovacs, 2004} and a single dose of 500mg GTE {Eichenberger, 2007, 19839000; Belza, 2009, 17882140} have been used with no evidence of benefit.

Guggul (*Commiphora mukul*)

Oral:

- **Hyperlipidemia**: The following doses of guggulipid have been studied: 2-16g of guggul in divided doses for up to three months {Jain, 1980, no PMID; Sharma, 1976**,** no PMID; Upadhyaya, 1976, no PMID; Kuppurajan, 1973, no PMID; Nohr, 2009, 19114224**}**.
- 25-2000mg of guggulsterone two to three times daily for up to eight weeks {Beg, 1996, 8950139; Ghorai, 2000, 16338199; Szapary, 2003, 12915429}.
- 50-500mg of guggulipid two to three times daily for up to 12 weeks {Singh, 1994, 7848901; Agarwal, 1986, 3552974; Gaur, 1997, no PMID; Kotiyal, 1985, no PMID; Nityanand, 1989, PMID; Gopal, 1986, 3531151}.
- 1.5g daily in divided doses of a fraction of guggul for up to 75 weeks has been administered {Malhotra, 1971, no PMID; Malhotra, 1977, 924552; Kotiyal, 1979, no PMID}.
- Gum guggul has been used at a level of 2-4.5g in purified form one to three times daily for 16 weeks {Kuppurajan, 1978, 730716; Verma, 1988, 3169888} and 10-15g daily for three months {Tripathi, 1978, no PMID}.
- **Obesity**: A 500mg dose of a guggul fraction three times daily has been administered {Kotiyal, 1985, no PMID}. A 1.5g dose of guggulipid three times daily plus dietary control for 30 days has been used {Bhatt, 1995, 10740691}. A 4g dose of gum guggul three times daily for four weeks has been administered {Sidhu, 1976, no PMID}.

Lotus (*Nelumbo nucifera*)

- Insufficient available evidence.

Children (age <18):

Slimple®:

- Insufficient available evidence.

Achiote leaf (*Bixa orellana* L.)

- Insufficient available evidence.

Cassia nomame

- Insufficient available evidence.

Chuchuhuasi (*Maytenus krukovii, Maytenus macrocarpa, Maytenus laevis*)

- Insufficient available evidence**.**

Citrus bioflavonoids (hesperidin)

- Insufficient available evidence.

Glycomacropeptide (GMP)

- **Nutrition (infant)**: Infants were fed alpha-lactalbumin-enriched formulas, with GMP accounting for 15% or 10% of the protein for approximately 4.5 months without benefit compared to other formulas or breastfeeding {Andersson, 2009, 19734215; Sandström, 2008, 18400715; Brück, 2006, 17130747}.
- **Phenylketonuria (PKU)**: GMP food products taken for four days showed beneficial effects compared to similar foods made using synthetic amino acids {MacLeod, 2010, 20466571}.
- **Supplementation in preterm and very low birthweight infants**: A formula based on sweet whey with GMP for seven days was detrimental (caused hyperthreoninemia) compared to a formula based on acid whey (without GMP) {Rigo, 2001, 11321379}.

Green tea (*Camellia sinensis*)

- **General**: Green tea is generally not recommended for infants or children due to caffeine content.
- **Cardiovascular conditions**: Green tea containing 576mg catechins has been used once daily for 24 weeks {Matsuyama, 2008, 18356827}.
- **Obesity**: Green tea containing 576mg catechins has been used once daily for 24 weeks {Matsuyama, 2008, 18356827}.

Guggul (*Commiphora mukul*)

- Insufficient available evidence.

Lotus (*Nelumbo nucifera*)

- Insufficient available evidence.

Pregnancy & Lactation:

Slimple®

- Not recommended due to lack of sufficient data.

Achiote leaf (*Bixa orellana* L.)

- The use of *Bixa orellana* during pregnancy and lactation has not been thoroughly studied in human clinical trials. However, *Bixa orellana* is considered likely safe when used orally in amounts found in foods, due to its long history of use as a food additive. The use of medicinal amounts of annatto during pregnancy and lactation is not recommended, due to insufficient available data.
- Information concerning the toxicology and developmental toxicology, as well as potentially hazardous substances, of *Bixa orellana* is currently available in the National Institute of Health's Lactation and Toxicology Database (LactMed). In animals, doses of up to 500mg of annatto per kg of body weight given by gavage for seven days had no adverse effects on mothers or fetuses {Paumgartten, 2002 40 /id}. No increases in embryo lethality or reduction of fetal body weight were observed among annatto-exposed rats. Annatto did not cause an increase in the incidence of externally visible, visceral, or skeletal anomalies in the exposed offspring. These findings suggest that annatto is safe for both mother and embryo. Therefore, the no-observed-adverse-effect level (NOAEL) for annatto-induced maternal and developmental toxicity was equal to or greater than 500mg/kg of body weight daily (or ≥140mg of bixin/kg of body weight daily) orally.

Cassia nomame

- Not recommended due to lack of sufficient data.
- Information on nomame's effects on lactation is currently lacking in the National Institute of Health's Lactation and Toxicology Database (LACT-MED).

Chuchuhuasi (*Maytenus krukovii, Maytenus macrocarpa, Maytenus laevis*)

- Not recommended due to lack of sufficient data.
- *Maytenus macrocarpa* has been used traditionally as an abortifacient and contraceptive {Sanz-Biset, 2009, 19146943}.
- There is currently a lack of information on the effects of chuchuhuasi in the National Library of Medicine's Drugs and Lactation database (LactMed).

Citrus bioflavonoids (hesperidin)

- Not recommended due to lack of sufficient data.
- Based on safety review, Daflon® 500mg minimally crossed the placenta or into breast milk {Meyer, 1994, 8203791}. There is a lack of information regarding the use of Diosmin complex® during pregnancy or lactation; however, according to secondary sources, teratogenic effects have not been noted. There is a lack of information on hesperidin in the National Library of Medicine's Drugs and Lactation database (LactMed).

Glycomacropeptide (GMP)

- Not recommended due to lack of sufficient data.
- Information on GMP's effects on lactation is currently lacking in the National Institute of Health's Lactation and Toxicology Database (LactMed).

Green tea (*Camellia sinensis*)

- **General**: Precautions and contraindications of green tea related to pregnancy and lactation are predominantly theoretical and based upon the adverse effect profile of caffeine. The U.S. Food and Drug Administration (FDA) has advised that women who are or may become pregnant should avoid caffeine-containing products, as there is evidence from animal studies that caffeine may be teratogenic {Nagao, 1979 141 /id}. Caffeine crosses the placenta and has been associated with fetal loss, low birth weight, and premature deliveries in some human studies {Caan, 1989 2870 /id;Eskenazi, 1999 2871 /id;Cook, 1996 2872 /id;Fenster, 1991 2876 /id;Martin, 1987 2877 /id;Vlajinac, 1997 2878 /id;Santos, 1998 2879 /id}.
- High levels of caffeine consumption (≥301mg) may result in delayed conception among women who do not smoke cigarettes {Stanton, 1995 944 /id}. According to a recent population-based case control study of 1,515 women in Sweden, caffeine consumption (≥100mg daily) may increase the risk of an early spontaneous abortion among non-smoking women {Cnattingius, 2000 1751 /id}. This has been supported by others who report that high intake (≥600mg daily) negatively effects pregnancy outcome, with consumption related to spontaneous abortion, stillbirth, or premature birth {Weathersbee, 1977 2988 /id;Dlugosz, 1996 1752 /id}. In a case-control study of 1,891 women, the consumption of caffeine >300mg daily with associated nausea doubled the risk for spontaneous abortion. The heavy caffeine consumers who decreased their caffeine intake early in pregnancy had no greater risk of spontaneous abortion than nonconsumers {Fenster, 1991 2875 /id}. A meta-analysis reported a small but significant increase in the risk of spontaneous abortion and low birth weight babies in pregnant women consuming >150mg daily caffeine {Fernandes, 1998 1753 /id}. However, maternal age, smoking, and ethanol use confounded data, and may have been contributing risk factors. In a prior trial, light caffeine use (1-150mg daily), was associated with increased risk for spontaneous abortion only among women who aborted their last pregnancy {Srisuphan, 1986 2033 /id}.

- A population based study of 1,500 women found caffeine intake to be negatively associated with birth weight {Cook, 1996 2872 /id}. Heavy caffeine consumption was found to increase the risk of fetal growth retardation {Fenster, 1991 2876 /id} and intrauterine growth retardation {Fortier, 1993 1233 /id}. Heavy caffeine intake (400mg daily or more) throughout pregnancy was associated with a significant risk for sudden infant death syndrome in a case-control study in New Zealand {Ford, 1998 1754 /id}. Multiple socioeconomic variables need to be considered in this analysis {Furuhashi, 1985 2138 /id}.
- Studies in pregnant women drinking moderate amounts of caffeine have shown inconsistent results, with more recent studies reporting no adverse effects on the fetus. A large, seven year, prospective study on dietary caffeine use (tea, coffee, etc.) in pregnancy showed a lack of relation to outcome measures including height, weight, and head circumference in newborns and infants {Barr, 1991 2918 /id}. Also, a relationship was not found in IQ and attention tests of children seven years of age. A significant association between prenatal caffeine and the predominance of breech position was found. A published prospective population-based cohort of 873 women in Sweden found no association between moderate caffeine consumption and reduced birth weight, gestational age, or fetal growth {Clausson, 2002 1750 /id}.
- It is recommended that women avoid the use of caffeine while breastfeeding, as caffeine is transmitted into breast milk, and may interfere with iron metabolism {Merhav, 1985 144 /id;Stavchansky, 1988 1789 /id} and produce adverse effects in infants. A delay in caffeine elimination has been reported in breast-fed infants {Le Guennec, 1987 1948 /id}.
- Information of green tea's effects on lactation is currently lacking in the National Institute of Health's Lactation and Toxicology Database (LACT-MED). However, there are warnings about how rapidly caffeine appears in breast milk following maternal ingestion.

Guggul (*Commiphora mukul*)

- Not recommended due to lack of sufficient data.
- Guggul is likely unsafe when taken during pregnancy based on studies suggesting the possibility of abortive effects (24;25).
- Information on guggul's effects on lactation is currently lacking in the National Institute of Health's Lactation and Toxicology Database (LactMed).

Lotus (*Nelumbo nucifera*)

- Not recommended due to lack of sufficient data.
- In preliminary animal studies, *Nelumbo nucifera* was shown to have antifertility activity (<citations><citation>7</citation></citations>).
- Information on lotus's effects on lactation is currently lacking in the National Institute of Health's Lactation and Toxicology Database (LactMed).

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MECHANISM OF ACTION

Pharmacology

Slimple®

- **General**: The purported effects of Slimple® may be attributable to its active constituents achiote leaf, *Cassia nomame*, chuchuhuasi, citrus bioflavonoids (such as hesperidin), MaCoca™, glycomacropeptide (GMP), green tea, guggulsterones, and lotus leaf extract.

Achiote leaf (*Bixa orellana* L.)

- Insufficient evidence.

Cassia nomame

- **Weight loss effects**: In animals, an extract of nomame reduced weight and prevented obesity {Yamamoto, 2000, 10878683}. According to secondary sources, nomame is thought to act as a lipase inhibitor {McCarty, 2005, 15533633}, thereby reducing fat breakdown in the intestinal tract, resulting in less fat absorption and a reduction in total caloric intake and blood triglyceride levels. According to secondary sources, nomame may also have diuretic and thermogenic properties, believed to play a role in its purported weight loss effects. However, there is a lack of clinical or basic science research regarding the effects of nomame on body weight, body composition, or fat metabolism in humans.

Chuchuhuasi (*Maytenus krukovii, Maytenus macrocarpa, Maytenus laevis*)

- Insufficient evidence.

Citrus bioflavonoids (hesperidin)

- **Hypoglycemic effects**: In humans, Daflon®, a hesperidin-containing product, has been found to lower blood glucose {Rizk, 2009, no PMID}. In animals, hesperidin reduced blood glucose, in part, by increasing hepatic glycolysis and glycogen concentration or by lowering hepatic gluconeogenesis {Akiyama, 2009, 19966469; Jung, 2004, 15465737}. It was also found to increase hepatic glucokinase activity, reduce hepatic glucose transporter 2 protein expression, and elevate the expression of adipocyte glucose transporter 4 and hepatic and adipocyte peroxisome proliferator-activated receptor gamma in animal study {Jung, 2006, 16427799; Jung, 2004, 15465737; Akiyama, 2009, 19966469}.
- **Lipid-lowering effects**: In animal study, hesperidin reduced total cholesterol and triglyceride levels {Chiba, 2003, 12771335; Jung, 2006, 16427799} through decreased activity of hepatic enzymes (β-hydroxy-β-methylglutaryl-CoA reductase, acyl CoA: cholesterol acyltransferase, fatty acid synthase complex, glucose-6-phosphate dehydrogenase, phophatidate phosphohydrolase) and increases in fecal concentrations of cholesterol and triglyceride {Jung, 2006, 16427799}. In HepG2 human hepatoma cells, glucosyl hesperidin was found to down-regulate the assembly of apo B-containing lipoproteins by reducing cellular cholesteryl ester synthesis with oleate and thereby suppressing excess apo B secretion from the cells {Miwa, 2006, 16967768}.
- In mouse adipocytes, hesperidin inhibited TNF-alpha-stimulated free fatty acid secretion {Yoshida, 2010, 20230793}. In laboratory study, adipocytes were reportedly not the target site for the lipid-lowering effects of flavones like hesperidin {Morikawa, 2008, 18980325}.
- In laboratory study, hesperidin was found to act on sterol regulatory element-binding proteins in the LDL receptor gene with polymethoxylated flavones being initially activated {Morin, 2008, 18567747}.

Glycomacropeptide (GMP)

- **Hypoglycemic effects**: In human and animal study, GMP has been shown to reduce glucose and insulin {Keogh, 2008, 18541546; Royle, 2008, 18062832}; however, the exact mechanism of action is not well understood.
- **Lipid-lowering effects**: In a clinical trial of overweight and obese men and women who took a GMP-enriched whey powder meal replacement supplement, total cholesterol, LDL cholesterol, and triacylglycerols decreased, and HDL increased after 12 months {Keogh, 2008, 18541546}; the mechanism of action is not well understood.
- **Weight loss effects**: Dietary protein plays a role in body weight regulation, partly due to its effects on satiety. Whey protein has been found to be more satiating than other protein types. The effects of GMP added to the diet have not been consistent in clinical trials. Some studies reported that GMP increased satiety over a short-term period but did not affect the amount of food eaten at a subsequent meal {Keogh, 2010, 20205966; Lam, 2009, 18948128}. Other studies have reported that GMP did not have an effect on satiety {Veldhorst, 2009, 19185957; Veldhorst, 2009, 19101599; Veldhorst, 2007, NO PMID; Burton-Freeman, 2008, 17964616; Keogh, 2010, 20205966} or weight loss {Keogh, 2008, 18541546}. Although one human study found that GMP stimulated the release of cholecystokinin (thereby promoting satiety) {Burton-Freeman, 2008, 17964616}, another study reported conflicting results {Keogh, 2010, 20205966}. Based on clinical research, the satiety effects may be more pronounced in females than males {Burton-Freeman, 2008, 17964616}.
- In male rats, GMP did not significantly influence body weight gain compared to a whey protein isolate (WPI) diet, however, renal and carcass fat mass, as well as plasma insulin levels, were significantly reduced in rats on a GMP diet compared to a WPI diet {Royle, 2008, 18062832}. Plasma triacylglycerol levels were also lowered by the diet containing WPI and GMP, compared to the diet containing casein and beef.

Green tea (*Camellia sinensis*)

- **Anti-diabetic effects**: In human study, caffeine was shown to modulate blood sugar levels {Watson, 2000 3070 /id}; however, this was not shown in various clinical trials {Fukino, 2005 2954 /id; Nagao, 2009, 19008868; Eichenberger, 2007, 19839000}. Green tea extract decreased streptozotocin-induced increases in blood glucose in rats {Babu, 2007, 17336542}. (-)-Catechin, a green tea phenol, has been shown to promote adipocyte differentiation in human bone marrow mesenchymal stem cells (hBM-MSCs) *in vitro* {Shin, 2009, 18951882}. This effect was accompanied by an increase in mRNA levels of adipogenic markers, including adiponectin, peroxisome proliferator-activated receptor gamma (PPARgamma), FABP4, and LPL.
- **Lipid-lowering effects**: *In vitro* {Ikeda, 2008, 18296354}, animal {Richard, 2009, 19416635}, and human {Hooper, 2008, 18614722;Erba, 2005 2927 /id;Hsu, 2008, 18468736;Maron, 2003 1716 /id;Unno, 2005 2868 /id;Babu, 2008, 18691042} studies have demonstrated the antilipemic effects of green tea and green tea catechins. A lack of effect on lipid profiles, however, has also been reported in human trials using green tea {Sung, 2005 2924 /id;Young, 2002 2921 /id} or caffeine alone {Rosmarin, 1990 2983 /id;Schwarz, 1990 2984 /id;Lancaster, 1994 2985 /id;Bak, 1989 2986 /id}. A diet enriched with green tea in rats resulted in a decrease in total cholesterol, LDL cholesterol, triglyceride levels, and serum leptin levels {Al-Sowyan, 2009, 19579931}. EGCG decreased ileal apical sodium bile acid transporter (ASBT) activity *in vitro*; however, inhibition of protein kinase C (PKC), phosphatidylinositol 3-kinase, and MAPK-dependent pathways failed to block this effect {Annaba, 2010, 20056894}. The antilipemic effects of catechins from green tea have been reviewed {McGowan, 2009, 19852889}.
- **Metabolic effects**: Green tea may increase energy expenditure {Dulloo, 1986 1015 /id;Dulloo, 1999 91 /id;Dulloo, 2000 89 /id;Cronin JR, 2000 1020 /id;Komatsu, 2003 2943 /id}. In human study, green tea extract AR25® inhibits gastric and pancreatic lipases and stimulates thermogenesis {Chantre, 2002 1129

/id}. Based on a randomized controlled trial in healthy young men, acute ingestion of green tea extract (890 ± 13mg polyphenols and 366 ± 5mg EGCG) may increase fat oxidation during moderate-intensity exercise and may improve insulin sensitivity and glucose tolerance {Venables, 2008, 18326618}. Average fat oxidation rates were 17% higher after ingestion of GTE than after ingestion of placebo (0.41 ± 0.03 and 0.35 ± 0.03g per minute, respectively; $p<0.05$). The contribution of fat oxidation to total energy expenditure was also significantly higher, by a similar percentage, after green tea extract supplementation. There was a concomitant increase of 13% in insulin sensitivity. The effects of tea catechins on obesity have been reviewed {Grove, 2010, 20089791} but further details are lacking.

- **Weight loss effects**: A diet enriched with green tea in rats resulted in a decrease in body weight and adipose tissue weight {Al-Sowyan, 2009, 19579931}. In healthy normal weight humans, green tea extract did not produce a significant thermogenic effect compared to controls {Belza, 2009, 17882140}. However, dietary supplementation with EGCG increased compliance with diet in overweight but otherwise healthy subjects {Rondanelli, 2009, 18590587}. Under sedentary conditions, EGCG with caffeine raised energy expenditure and fat oxidation (not significantly), whereas a catechin/caffeine mixture had a maximum observed effect on energy expenditure of about 2 % {Gregersen, 2009, 19445822}. In leptin-deficient (ob/ob) mice, the administration of decaffeinated green tea significantly slowed their rate of weight gain compared to controls and was associated with lower cholesterolemia, triglyceridemia, and adiponectin concentrations {Richard, 2009, 19416635}.

Guggul (*Commiphora mukul*)

- **Hypoglycemic effects**: In animal study, guggulipid demonstrated peroxisome proliferator-activated receptor-alpha (PPARalpha), PPARgamma, and liver X receptor-alpha (LXR-alpha) agonist activity which may contribute to antidiabetic effects {Cornick, 2009, 18926687}. Commipheric acid was also found to activate PPARalpha and PPARgamma
- **Lipid-lowering effects**: Guggulipid extracted from guggul using ethyl acetate has been observed to have hypolipidemic effects in clinical practice {Saxena, 2007, 17477963}. Typical guggulipid preparations have been reported to contain 2.5-5% of the plant sterols guggulsterones E and Z, and they have also been reported to exert antilipemic effects {Nityanand, 1971 81 /id; Singh, 1990 37 /id; Brobst, 2004, 15075359; Urizar, 2003, 12626688}. Several hypotheses have been advanced to explain these effects. Guggulsterones, particularly guggulsterone (4,17(20)-pregnadiene-3,16-dione), have been reported to function as antagonists of the farnesoid X receptor (FXR) and the bile acid receptor (BAR), nuclear hormones that are involved with cholesterol metabolism and bile acid regulation {Brobst, 2004, 15075359; Urizar, 2003, 12626688; Urizar NL 237 /id;Cui, 2003 243 /id;Wu, 2002 6 /id; Cui, 2003, 12525500; Yu, 2009, 19102680}. However, it has also been reported that guggulsterone and cembranoids (natural monocyclic diterpene derived from cembranes) did not exert their lipid effects on mice lacking FXR {Yu, 2009, 19102680}. Using a kinetic model, the cembranoid, cembren-1-ol, was found to lower the cholate-activated rate of hydrolysis by human pancreatic IB phospholipase A2 (hPLA2) with significant structural specificity {Yu, 2009, 19102680}. In animal study, guggulipid demonstrated peroxisome proliferator-activated receptor-alpha (PPARalpha), PPARgamma, and liver X receptor-alpha (LXR-alpha) agonist activity which may contribute to hypolipemic effects {Cornick, 2009, 18926687}. Other publications have proposed that guggul may inhibit lipogenic enzymes and HMG-Co A reductase in the liver (100;101), increase uptake of cholesterol by the liver via stimulation of LDL receptor binding (102), directly activate the thyroid gland (103-106), and/or increase biliary and fecal excretion of cholesterol (107). Several extracts from guggul have also been shown to inhibit lipid peroxidation and cyclooxygenase (COX) enzyme inhibitory activities {Francis, 2004, 17191820}. Human study indicated that guggul lowered lipid levels (50; 139-145;147-149;151-153). Other human study, however, has demonstrated somewhat conflicting results {Szapary, 2003, 12915429} (36). The exact mechanisms of action, however, are unclear.

- **Metabolic effects**: Guggulipid demonstrated peroxisome proliferator-activated receptor-alpha (PPARalpha), PPARgamma, and liver X receptor-alpha (LXR-alpha) agonist activity which may contribute to antidiabetic effects {Cornick, 2009, 18926687}.
- **Weight loss effects**: Guggul has been commonly noted as one of the components of various traditional Ayurvedic formulations to treat obesity {Francis, 2004, 17191820; Shishodia, 2007, 17475222; Burris, 2005, 15602004}. In human study, guggul has demonstrated weight loss effects (5;163;164). Guggul combination products have also been used in clinical trial, resulting in antiobesity effects (165); the effects of guggul monotherapy for this study, however, are unclear. The exact mechanisms of action are also unclear.

Lotus (*Nelumbo nucifera*)

- **Hypoglycemic effects**: In animal study, neferine, a constituent of lotus green seed embryo, enhanced insulin sensitivity in insulin-resistant rats {Pan, 2009, 19527823}. The levels of fasting blood glucose, fasting blood insulin, triglycerides, tumor necrosis factor-alpha (TNF-α), and the oral glucose tolerance test two-hour plasma glucose level all decreased significantly. Oral administration of an ethanolic extract of rhizomes of *Nelumbo nucifera* markedly reduced the blood sugar level of normal, glucose-fed hyperglycemic and streptozotocin-induced diabetic rats, when compared with control animals (<citations><citation>8</citation></citations>). The extract improved glucose tolerance and potentiated the action of exogenously injected insulin in normal rats. When compared with tolbutamide, the extract exhibited activity of 73 and 67% of that of tolbutamide in normal and diabetic rats, respectively Also, in animal study, a methanolic extract of the stamens of *Nelumbo nucifera* Gaertn, as well as constituent flavonoids, inhibited rat lens aldose reductase (an enzyme involved with diabetic complications) {Lim, 2006, 16881021}.
- TZQ-F, a traditional Chinese medicine compound that contains lotus, had regulation effects on intestinal disaccharase and lipase; according to the author, this may play a role in treating abnormal glucose and lipid metabolism associated with diabetes {Tao, 2010, 20123010}.
- **Lipid –lowering effects**: In animal study, lotus leaf extract reduced triglyceride and total cholesterol levels {Kulkarni, 2008, 20046740; Lin, 2009, 19499892; Pan, 2009, 19527823; Ono, 2006, 16495025}. TZQ-F, a traditional Chinese medicine compound containing lotus, significantly decreased levels of serum total cholesterol, triglycerides, glucose, LDL cholesterol, and HDL cholesterol in rats on a high-fat diet.{Tao, 2010, 20123010}.
- **Metabolic effects**: In animal study, *Nelumbo nucifera* leaf extract caused a concentration-dependent inhibition of the activities of alpha-amylase and lipase, and upregulated lipid metabolism and expression of UCP3 mRNA in C2C12 myotubes (<citations><citation>33</citation></citations>). *Nelumbo nucifera* leaf extract prevented an increase in body weight, parametrial adipose tissue weight, and liver triacylglycerol levels in mice with obesity induced by a high-fat diet. UCP3 mRNA expression in skeletal muscle tended to be higher when mice were administered *Nelumbo nucifera* leaf extract and were exercised.
- **Weight loss effects**: In animal study, lotus leaf extract had antiobesity effects {Ono, 2006, 16495025}. Increases in body weight, parametrial adipose weight increase, and liver triglycerides were prevented. The extract also caused a concentration-dependent inhibition of the activities of α-amylase and lipase, and upregulated lipid metabolism and expression of UCP3 mRNA in C2C12 myotubes *in vitro*. In mice, lipolysis of white adipose tissue was stimulated {Ohkoshi, 2007, 17893829}. The beta-adrenergic receptor (beta-AR) pathway was involved in these effects. In mice fed a high-fat diet, body weight gain was prevented.

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HISTORY

Slimple®

- Slimple™ was developed by Rich Gelso, Founder and CEO of MB Innovations, a nutraceutical company located in Hollywood, Florida. Founded in 2002, MB Innovations aims to provide healthful products made with natural ingredients that have been used for centuries by indigenous cultures to benefit health.

Achiote leaf (*Bixa orellana* L.)

- The scientific species name *orellana* comes from the name of Francisco de Orellana, a Spanish explorer of the 16th Century.

Cassia nomame

- Nomame is widespread in Africa, tropical and temperate areas of Asia, the Pacific Islands, and Australia. It is naturalized in other geographic locations and has been recorded anecdotally in the Americas. In Japan, it has been tested as a companion crop in rice paddies.
- Medicinally, nomame is reported to have been used in folk remedies. Currently, it is typically marketed in weight-loss formulations, and has been studied for its potential antiobesity {Yamamoto, 2000, 10878683} and antilipemic {Yamamoto, 2000, 10878683} effects.

Chuchuhuasi (*Maytenus krukovii, Maytenus macrocarpa, Maytenus laevis*)

- Chuchuhuasi may refer to several different species of the *Maytenus* genus, including but not limited to *Maytenus macrocarpa*, *Maytenus krukovii* (*Maytenus chuchuhuasha*), *Maytenus laevis*, and occasionally *Maytenus colasii* (*Salacia colasii*) {Gonzalez, 2000, No pmid}. Other species that have been associated with chuchuhuasi include *Maytenus ebenifolia*, *Maytenus boaria*, and *Maytenus guyanensis* (secondary sources). Typically, however, *Maytenus macrocarpa*, *Maytenus krukovii* (*Maytenus chuchuhuasha*), and *Maytenus laevis* are the more widely accepted species for chuchuhuasi. *Maytenus* spp. native to South America may be found in the tropical rainforests of Bolivia, Brazil, Colombia, Ecuador, Peru, and Venezuela.
- *Chuchu huashu* means "trembling back," and chuchuhuasi has been used by several indigenous communities in South America for arthritis, back pain, and rheumatism. The Quijos Quichua people of Ecuador chew or decoct the inner bark of *Maytenus krukovii*. Typically this is given as a tonic to patients recovering from various illnesses, including tuberculosis, bronchitis, fever, and stomach upset. An indigenous ethnic group, the Siona people of Colombia, decocts the bark and uses this as a stimulant or treatment for rheumatism.

Citrus bioflavonoids (hesperidin)

- In the mid 20th Century the medical literature included early reports of hesperidin for arthritis, capillary fragility, diabetic retinopathy, edema, pedal problems, poliomyelitis, and prevention of abortion.
- As time passed from the 1980s, in the medical literature concerning humans, papers mostly were about the pharmacodynamic and therapeutic effects of preparations that included hesperidin; these included *Ruscus aculeatus* root extract plus hesperidin methyl chalcone and <ref id="vitaminc">ascorbic acid</ref>, and micronized purified flavonoid fraction that consisted of 90% (450mg) diosmin and 10% (50mg) flavonoids as hesperidin {Rudofsky, 1982, 7106687; Rudofsky, 1989, 2668140; Bouaziz, 1999, 10811519; Marshall, 1984, 6500447; Geroulakos, 1994, 8203786; Guillot, 1994, 8203785; Launois, 1994, 8203779; Meyer, 1994, 8203791; Struckmann, 1994, 8203767; La Torre, 1999, 10736998; Struckmann, 1999, 10474049; Ramelet, 2001, 11510597; Roumy, 2001, 11669105; Boisseau, 2002, 12515978; Garner, 2002, 11782895; Coleridge Smith, 2003, 12934756; Nicolaides, 2003, 12934755; Ramelet, 2001, 11510597; Takase, 2004, 15465369; Bouskela, 1997, 9158383; Friesenecker, 1994, 7960444; Damon, 1987, 3481266; Bergan, 2001,

11510596; Korthuis, 1999, 10474047; Smith, 1999, 10474048; Jean, 1994, 8203787; Cypriani, 1993, 8385947; Santus, 1991, 1822683; Manuel, 1999, 10782751; Amiel, 1998, 9772947; Juteau, 1995, 8919257; Ibegbuna, 1997, 8995343; Belcaro, 1995, 8748889; Allegra, 1995, 8748890}. That literature mostly concerned the use of those preparations for chronic venous insufficiency, venous leg ulcers, and hemorrhoids.

- The contemporary medical literature also covers hesperidin's aglycone, which is not a dietary supplement; hesperidin in the juice of oranges or grapefruit; hesperidin as a constituent; glucosyl hesperidin, which is not available as a dietary supplement; neohesperidin dihydrochalcone, which is a sweetener; and flavones or flavonoids in general {Clayton, 1967, 6019088; Essien, 1976, 1037149; Kaul, 1985, 2981979; Mucsi, 1985, 2989000; Canton, 1987, 3445227; Cummings, 1988, 3235538; Larocca, 1990, 2207000; Scambia, 1990, 2131036; Scambia, 1990, 2249899; Scambia, 1990, 2257224; Limasset, 1993, 8216378; Nguyen, 1993, 8381480; Piantelli, 1993, 8416715; Ishii, 1997, 9518163; Borradaile, 1999, 10405973; Di Mauro, 1999, 10552823; Kawaii, 1999, 10563860; Kim, 1999, 10664851; Doostdar, 2000, 10781868; Kroeze, 2000, 11015327; Kurowska, 2000, 11063434; Ross, 2000, 10727812; Erlund, 2001, 11160539; Gil-Izquierdo, 2001, 11262068; Ly, 2001, 11124214; Wilcox, 2001, 11352979; Erlund, 2002, 12209378; Yoo, 2002, 12510833; Ansorge, 2003, 12939048; Choi, 2003, 12672908; Manach, 2003, 12571654; Proteggente, 2003, 14556312; Yen, 2003, 12843645; Kanaze, 2004, 14751808; Kanaze, 2004, 15351063; Miwa, 2004, 15386934; Braune, 2005, 15740074; Jeong, 2005, 15975156; Miwa, 2005, 1916521708; Xie, 2005, 15923087; Al Majed, 2006, 16879905; Lu, 2006, 1516816988; McKay, 2006, 1616767798; Miwa, 2006, 1316967768; Nielsen, 2006, 16424119; Kobayashi, 2006, 16465400; Basile, 2000, 10930721; Lee, 2004, 15240993; Bae, 1999, 10454900; So, 1996, 8875554; Sgro, 1995, 7790717; Ross 2002, 12055336; Franke, 1998, 9781307; Vinson, 2002, 12083455; Cantón, 1987, 3445227}
- Hesperidin's therapeutic effectiveness apparently is a subject of the recent past but research continues on its pharmacodynamic effects {Garg, 2001, 11746857, Ou, 2002, 14974499; Corpet, 2003, 12750232; Liu, 2004, 15147818}.

Glycomacropeptide (GMP)

- GMP is part of the whey that is formed during cheese production. Recently, it has been tested as a protein additive in foods and beverages. It has also been marketed as a weight loss supplement, although the evidence supporting these claims is conflicting. Since GMP is the only known naturally occurring protein that does not contain phenylalanine, research is ongoing on how to incorporate it into the diet of patients with PKU, who cannot metabolize phenylalanine.

Green tea (*Camellia sinensis*)

- Green tea is made from the dried leaves of *Camellia sinensis*, a perennial evergreen shrub. Green tea has a long history of use, dating back to China approximately 5,000 years ago. Green tea, black tea, and oolong tea are all derived from the same plant. Tea varieties reflect the growing region (e.g. Ceylon or Assam), the district (e.g. Darjeeling), the form (pekoe is cut, gunpowder is rolled), and the processing method (green, black, or oolong). The tea plant is native to Southeast Asia and may grow up to a height of 40 feet, but is usually maintained at a height of two to three feet by regular pruning. The first spring leaf buds, called the *first flush*, are considered the highest-quality leaves. When the first flush leaf bud is picked, the next bud to grow is called the *second flush*, and this continues until an *autumn flush*. The older leaves picked farther down the stems are considered to be of poorer quality.
- Green tea is produced by lightly steaming the freshly cut leaf, thus not allowing oxidation of the enzymes within the leaf to take place. Green tea is produced and consumed primarily in China, Japan, and a few countries in North Africa and the Middle East. Allowing the leaves of *Camellia sinesis* to oxidize produces black tea, a fermentation process that allows the principal flavor to emerge, but also converts the enzymes

present in the tea to less potent compounds. Oolong tea is a partially oxidized tea and only accounts for 2% of all the tea produced {Bushman, 1998 1 /id;Graham, 1992 112 /id}.

- Tea is the most frequently consumed beverage in the world apart from water. India, Sri Lanka, and China are the major producers of tea. Historically, tea has been served as part of sacred ceremonies and has been consumed in order to stay alert during long meditations. An ancient legend from India, describes the origin of the tea plant. This story is of the Prince Siddhartha Gautama, the founder of Buddhism, ripping off his eyelids in frustration of his inability to stay awake during meditation during his journey through China. A tea plant sprouted from the spot where his eyelids fell, thus providing him with the ability to stay up, meditate, and reach enlightenment.
- Turkish traders reportedly introduced tea to Western cultures in the sixth century. Tea reached America with the first settlers in 1492.

Guggul (*Commiphora mukul*)

- Guggulipid derives from a small, thorny tree native to the dry zones of the Deccan Plateau, west to northwest India, as well as Karachi, Sind, and Balochistan in Pakistan. In recent times, the plant's natural population has declined due to unsustainable exploitation of the gum, especially in its more southerly distribution, although it remains relatively common in its northern distribution. Guggul was designated as a vulnerable species after an assessment by CAMP Workshops on Medicinal Plants, India. The export of the species has since been banned by the government of India.
- Resin from the guggul (*Commiphora mukul*) tree has been used in Ayurvedic medicine since at least 600 B.C. {Satyavati, 1988, 3049326; Dev, 1997, no PMID} and has been prescribed by ancient healing traditions for weight loss, heart conditions, and other ailments. Most famous for its purported hypolipidemic properties, guggul was first scientifically evaluated as an antilipemic beginning in the 1960s. In 1986, guggul oleoresin was approved in India for marketing as a lipid-lowering agent (123;124), and has more recently aroused interest in Western research (125).
- In Ayurveda, gum resin from guggul has been used to treat tumors, obesity, liver disorders, malignant sores and ulcers, urinary complaints, intestinal worms, leucoderma (vitiligo), sinuses, edema and sudden paralytic seizures {Shishodia, 2008, 19189646}. Based on secondary sources, it is cultivated commercially in India and Pakistan, but due to overuse, guggulipid is less prevalent in parts of India.

Lotus (*Nelumbo nucifera*)

- Lotus (*Nelumbo nucifera*) has been cultivated as an ornamental and food plant in Japan for more than 1,000 years (<citations><citation>35</citation></citations>). In ancient times, *Nelumbo nucifera* was common along the Nile River in Egypt. The Pharaonic Egyptians purportedly venerated the lotus and used it in worship. From Egypt, it was brought to Assyria and was planted throughout Persia, India, and China. Today, lotus is rare or extinct in Africa but widely naturalized in southern Asia and Australia, where it is grown in water gardens. It is the national flower of India and continues to be considered sacred and possesses great significance in Eastern religions.

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REVIEW OF THE EVIDENCE: DISCUSSION

Slimple®: EFFECT

- **Summary**: No available studies qualify for inclusion in the evidence discussion.

Achiote leaf (*Bixa orellana* L.)

- **Summary**: No available studies qualify for inclusion in the evidence discussion.

Cassia nomame: Weight loss

- **Summary**: In animals, an extract of nomame reduced weight and prevented obesity {Yamamoto, 2000, 10878683}. According to secondary sources, nomame may act as a lipase inhibitor similar to orlistat {McCarty, 2005, 15533633}. However, there is a lack of clinical or basic science research regarding the effects of nomame on body weight, body composition, or fat metabolism in humans. No available studies qualify for inclusion in the evidence discussion.

Chuchuhuasi: Weight loss

- **Summary**: No available studies qualify for inclusion in the evidence discussion.

Citrus bioflavonoids (hesperidin): Diabetes

- **Summary**: In preliminary research, Daflon® (either alone or in combination with oral hypoglycemic agents) reduced serum glucose in female patients with type 2 diabetes. Additional research is needed before a recommendation can be made.
- **Evidence**: Rizk et al. conducted a randomized, single-blind, parallel study to evaluate the efficacy and safety of Daflon® (alone or in combination with an oral hypoglycemic agent) {Rizk, 2009, no PMID}. Females with type 2 diabetes, with a disease history of less than eight years, who complied with regular visits to diabetes institutes, and had moderate hyperglycemia were included in the study. Subjects were excluded if they had type 1 diabetes, a disease history of more than eight years, were non-compliant, had severe hyperglycemia, were illiterate or suffered from acute or chronic renal disease, known liver disease, coronary artery disease, history of hyper- glycemic or hypo-glycemic coma, or severe diabetic complications. Subjects (N=36) were randomized to Daflon® 500mg, either alone or with an oral hypoglycemic, twice daily for 45 days. All patients were receiving a second generation sulfonylurea (glimepiride 20mg) or biguanide (metformin 500mg) and most patients were receiving vitamin B complex and aspirin. No adverse effects were noted throughout the treatment period. Liver and kidney function were within normal limits. Subjects treated with either Daflon® alone or oral hypoglycemic therapy showed significant decrease in serum glucose; fructosamine; total cholesterol; LDL-cholesterol; triglycerides ($p<0.05$); malondialdehydes (as index of lipid peroxidation) and C-reactive protein (CRP) levels; increases in the levels of nitric oxide and blood glutathione were also noted.

Glycomacropeptide (GMP): Obesity / Weight Loss

- **Summary**: Dietary protein plays a role in body weight regulation, partly due to its effects on satiety. Whey protein has been found to be more satiating than other protein types. The effects of GMP added to the diet have not been consistent in clinical trials. Some studies reported that GMP increased satiety over a short-term period but did not affect the amount of food eaten at a subsequent meal {Keogh, 2010, 20205966; Lam, 2009, 18948128}. Other studies have reported that GMP did not have an effect on satiety {Veldhorst, 2009, 19185957; Veldhorst, 2009, 19101599; Veldhorst, 2007, NO PMID; Burton-Freeman, 2008, 17964616; Keogh, 2010, 20205966} or weight loss {Keogh, 2008, 18541546}. Although one human study found that GMP stimulated the release of cholecystokinin (thereby promoting satiety) {Burton-Freeman,

2008, 17964616}, another study reported conflicting results {Keogh, 2010, 20205966}. Longer-term clinical studies are needed.

- **Evidence**: Keogh et al. conducted a randomized, double-blind, crossover study to assess the effects of different GMP fractions relative to glucose on cholecystokinin (CCK) levels, satiety, and food intake in 22 overweight or obese males {Keogh, 2010, 20205966}. Inclusion criteria were unrestrained-eating males, age 20–65 years, with a BMI >25kg/m2, a sedentary lifestyle, and no recent history of weight loss or changes to diet or physical activity routine. Exclusion criteria were type 1 or type 2 diabetes, active liver or kidney disease, current gastrointestinal disease, past history of gastrointestinal surgery, hypersensitivity to study foods, medications which affect gastrointestinal motility or hunger or appetite, or anticholinergic drugs. Two participants withdrew for personal reasons unrelated to the study. Twenty overweight or obese males (56.9 ± 7.2 years, 97.4 ± 8.1kg, 31.5 ± 3.0kg/m2) completed the study. Participants were randomized to consume four 50g preloads produced from bovine cheese whey (two GMP preparations, GMP-depleted whey and glucose) containing 895kJ, with a three-day interval between study treatments. The minimally glycosylated GMP contained 3.5% N-acetylneuraminic acid and 1.5% galactose, and the glycosylated GMP contained 12.0 N-acetylneuraminic acid and 4.2% galactose. A controlled meal was provided to each participant for consumption on the evening before trial commencement. The study participants were asked to abstain from alcohol consumption, to avoid excessive exercise, and to record any food eaten on the evening before each clinic visit. Blood samples and subjective measures of satiety were collected before and at 15, 30, 60, 90, 120, and 180 minutes after the consumption of the preload, and CCK levels were measured. A lunchtime meal was provided, which subjects ate ad libitum until satisfied. Energy and nutrient intakes from the food consumed were calculated. Subjects rated their appetite using a validated visual analog scale before the preload and after every blood sample collection. There was no significant difference in CCK levels, subjective measures of satiety, or food intake between treatments at the given preload level, indicating that the protein fractions at the dose employed did not influence satiety, CCK levels, or energy intake at a subsequent meal. This study is limited by the fact that there were not any replicates of any of the study conditions.
- Keogh et al. conducted a double-blind, randomized, parallel-design study using meal replacements to examine whether greater weight loss could be achieved and sustained with a GMP-enriched whey powder supplement than with a skim milk powder supplement in 127 overweight and obese men and women {Keogh, 2008, 18541546}. Inclusion criteria were: body mass index between 27 and 40kg/m2, age 20–70 years with a normal recent medical history. Exclusion criteria included type 1 or 2 diabetes; a history of heavy alcohol consumption; frequent dining out; pregnancy or breastfeeding; hypersensitivity to the test food; a current attempt to lose weight or recent weight loss; gastrointestinal, renal, or hepatic disease; an eating disorder in the past; or taking any medication that was likely to affect the study outcomes (lipid-lowering or antihypertensive medication were allowed provided the medication doses were not altered during the study). Of the 127 participants (95 women, 32 men, 95.5 ± 15.4kg, body mass index: 33.4 ± 3.4kg/m2, 50.0 ± 12.4 years), 82 completed the six-month study, and 72 completed the 12-month study. Reasons for study withdrawal were not given. Meal replacements contained 15g of protein from GMP-enriched whey protein isolate containing 90% GMP (GMP-WPI; NatraPepTM; MG Nutritionals, Victoria, Australia) or skim milk powder (SMP; NatraProTM, MG Nutritionals), both diluted to 200mL with water before consumption. Participants consumed two sachets daily to replace two meals; consumed one energy restricted meal containing 120g of raw weight meat, fish, or chicken; and ate two servings (300g) of fruit, two cups cooked, and one serving of raw vegetables, 250mL of reduced fat milk, and 30g of high-fiber cereal daily. Bran or psyllium supplements were recommended to relieve constipation. At six months, participants were advised to reduce the supplements to one daily and to have two meals daily, and they were provided with sample meals. Outcome measures were weight, body composition, blood pressure, fasting lipids, glucose, and insulin measured at baseline, six, and 12 months. At six months, weight loss was 9.5 ± 5.8kg with GMP-WPI compared with 11.0 ± 6.0kg with SMP, and at 12 months weight loss was

9.9 ± 8.8kg with GMP-WPI compared with 10.8 ± 7.4kg with SMP (p<0.001compared with baseline), with no differences between treatments. Total and LDL cholesterol, triacylglycerols, glucose, insulin, and systolic and diastolic blood pressure decreased at six and 12 months (all p<0.01 compared with baseline with no difference between treatments). HDL cholesterol increased at 12 months (p<0.001 compared with baseline). Overall there was no difference between treatments for weight, body composition, blood pressure, fasting lipids, glucose, or insulin. This study was well designed.

- Lam et al. conducted a randomized, single-blind, crossover study to determine the short-term effect of mixtures of whey protein and GMP versus a carbohydrate control on satiety in healthy adults {Lam, 2009, 18948128}. Fifty-five subjects were recruited; five dropped out due to compliance issues. The ages of the 19 men and 31 women were 25.4 ± 1.3 years and 24.1 ± 0.9 years, respectively. The BMI for the men and women were 23.9 ± 0.5kg/m2 and 22.8 ± 0.7kg/m2, respectively. Cognitive dietary restraint scores were 7.14 ± 0.56 overall; for the men and women they were 4.84 ± 0.59 and 8.55 ± 0.72, respectively. Inclusion criteria were being 18–40 years old, a nonsmoker, no known food allergies, no known current medical problems, not taking medications known to affect appetite, being regular breakfast consumers, not following a diet to lose or gain weight, and not being pregnant or breastfeeding. Each subject participated on four test days, each one week apart. In each of the four sessions, each subject consumed his or her usual breakfast meal at home before 9:00 a.m., followed only by water as desired until consumption of the test drink. On four separate days, subjects received a subject-specific breakfast (at 8:00 a.m.), a preload drink (at noon), and lunch (at 12:30 p.m.). The preload drink was presented as a milkshake containing maltodextrin carbohydrate (control), whey protein isolate (WPI) with no GMP, WPI with naturally present 21% GMP, or WPI with naturally present 21% GMP plus added GMP. Drinks were made up to be 300mL and were approximately isoenergetic. The amount of WPI in 300mL of 21% GMP WPI, 21% GMP WPI+GMP, and WPI with no GMP was calculated to be 31.6, 15.8, and 40g respectively. The 21% GMP WPI and 21% GMP WPI+GMP preloads contained 8.4g and 24.2g of GMP per 300mL, respectively. Satiety was assessed using visual analog scales (VAS) and by determining ad libitum food intake during a cafeteria style meal offered 30 minutes after the preload. The VAS indicated that the lower GMP treatment induced a greater feeling of fullness immediately after consumption of the preload compared with the other treatments. Energy and macronutrient intake at lunch did not differ significantly between treatments, although subjects chose to eat foods higher in carbohydrates and lower in protein after the protein preloads. Women consumed the least amount of protein after the protein preloads, whereas no difference was found in men. The authors concluded that there was some evidence that whey proteins and their components enhanced satiety over a short-term period compared to carbohydrates, but there was no consistent effect of either whey protein alone or GMP. This study is limited by the fact that there were not any replicates of any of the study conditions.
- Burton-Freeman et al. conducted a randomized, double-blinded, crossover study to investigate the role of GMP in whey protein-induced satiety, as measured by subjective satiety, cholecystokinin (CCK) release, and food intake at a test meal in men and women with a healthy weight {Burton-Freeman, 2008, 17964616}. Twenty subjects (10 men, 10 women) consumed one of four preload shakes (300mL, 1MJ), one week apart. Exclusion criteria included food allergies or intolerances, current modification of diet or exercise patterns to gain or lose weight, excessive exercisers or trained athletes, or any medications that would affect appetite. Inclusion criteria were men and women that had a BMI of 22–27kg/m2, were 21–50 years old, were moderate-to-light exercisers, consumed diets with dietary fat intake of 30–35% of total energy, and had normal plasma glucose. The BMI for the men and women were 24 ± 327kg/m2 and 23 ± 227kg/m2, respectively. The ages of the participants were 25 ± 4 and 24 ± 1 years, respectively. Cognitive dietary restraint scores for men and women were 3 ± 1 and 6 ± 3, respectively. All subjects maintained their body weight within 1.0kg throughout the study. All subjects completed the study, but one male was excluded from analysis due to noncompliance with study protocol. Four study-specific preloads were prepared as semisolid shakes using a base of varying proportions of frozen, whole strawberries, rice milk,

vanilla flavoring, noncaloric sweetener (Splenda®), and ice. One of three test proteins was added to the preload base: (1) whey protein isolate, (2) whey protein minus GMP, (3) GMP isolate, or (4) low protein (control). Protein energy of preloads was 44, 44, 2, and 3%, respectively. Subjective satiety and CCK were measured at 0, 15, 30, 45, 60, 75, and 105 minutes post-preload consumption. A lunch test meal was provided at 75 minutes. Food records were completed weekly. Premeal satiety was greater after whey protein preloads compared to control and GMP preloads in women, but no difference was evident in men ($p<0.03$). In women, after-lunch CCK concentrations were higher after the GMP preload compared to control or whey minus GMP preloads ($p<0.05$). In men, after-lunch CCK concentrations (105 minutes) were higher after the GMP preload, but they were not significantly different from other preload concentrations. Test meal intake was not different by preload; however, compensation relative to usual daily intake was achieved after whey-containing and GMP-containing preloads in women and after GMP and control preloads in men. The authors concluded that GMP alone was not critical to whey-induced satiety, but may have had a unique role in energy intake regulation through CCK. This study is limited by the fact that there were not any replicates of any of the study conditions.

- Veldhorst et al. conducted a randomized, single-blind, crossover study to compare the effects on satiety and energy intake (EI) of whey versus whey without GMP in a high and a normal amount of protein in a breakfast custard {Veldhorst, 2009, 19101599}. Twenty-five healthy subjects (11 males and 14 females, BMI: 23.9 ± 0.3kg/m2; age: 22 ± 1 years) received a breakfast containing whey or whey without GMP as protein type with 10/55/35 or 25/55/20 percentage protein/carbohydrate/fat. Inclusion criteria were being in good health, being non-smokers, being non-vegetarian, being unrestrained eaters, not using medication apart from oral contraceptives, and having moderate alcohol intake at most. Each week, participants consumed one of four experimental breakfasts, separated by at least one week. After an overnight fast, subjects received one of four types of the subject-specific standardized custard breakfasts and consumed an ad libitum lunch 180 minutes after breakfast. The custards were prepared with whey containing GMP (whey, Ultra Whey 90®, Volactive Functional Food Products, Orwell, United Kingdom) or whey without GMP (WPC 80, DMV International, Veghel, The Netherlands) as a single protein source, with protein/carbohydrate/fat percentage: 10/55/35 (normal protein) or protein/carbohydrate/fat percentage: 25/55/20 (high protein). The custards were produced by NIZO Food Research (Ede, The Netherlands) and had tapioca starch and sunflower oil, respectively, as carbohydrate and fat sources, and were citrus-vanilla flavored. Outcome measures included concentrations of amino acids (AA), glucose, insulin, glucagon-like peptide-1 (GLP-1), and ghrelin. Appetite ratings were completed just before breakfast and at 20, 40, 60, 80, 100, 120, 180, and 240 minutes after breakfast. After a breakfast with 25% protein, increases in insulin and GLP-1 and decreases in ghrelin concentrations were larger, and increases in satiety ratings were lower, than after 10% ($p<0.05$); there was a treatment × time interaction effect on glucose and insulin concentrations ($p<0.001$). After a breakfast with whey without GMP, insulin concentrations were increased more than after whey ($p<0.05$). EI at lunch was lower after whey than after whey without GMP (2877 ± 165kJ versus 3208 ± 178kJ, $p<0.05$), coinciding with more increased concentrations of serine, threonine, alanine, alpha-aminobutyric acid, and isoleucine ($p<0.05$). There was no interaction effect of protein concentration or protein type on the satiety response. There was no significant difference in the pleasantness of taste of the breakfasts. The authors concluded that GMP as a whey-fraction reduced energy intake coinciding with increased concentrations of certain amino acids (serine, threonine, alanine, alpha-aminobutyric acid, valine, and isoleucine), irrespective of the concentration of whey-protein. Although between different concentrations of whey-protein, variations in hormone responses were observed, these were unrelated to satiety ratings or energy intake. A limitation of this study is that it was not double-blinded.
- Veldhorst et al. conducted a randomized, single-blind, crossover trial to compare the effects of casein, soy, whey, whey without GMP, alpha-lactalbumin, gelatin, or gelatin with tryptophan (TRP)-protein breakfasts at two concentrations on subsequent satiety and energy intake (EI) {Veldhorst, 2009, 19185957}. Twenty-four healthy subjects (10 male, 14 female) received a breakfast composed of custard with casein, soy,

whey, whey-GMP, alpha-lactalbumin, gelatin, or gelatin+TRP as a protein source with one of 10/55/35 (normal) or 25/55/20 (high) percentage protein/carbohydrate/fat diets. The custards were produced by NIZO Food Research (Ede, The Netherlands), had tapioca starch and sunflower oil, respectively, as carbohydrate and fat sources, and were citrus-vanilla flavored. Inclusion criteria included being in good health, being non-smokers, being non-vegetarian, being unrestrained eaters, not using medication apart from oral contraceptives, and having moderate alcohol intake at most. Mean age was 25 ± 2 years, and mean body weight was 72.8 ± 2.2kg (BMI: 24.8 ± 0.5kg/m2). All subjects came to the testing center on 14 occasions, separated by at least three days. On each test day subjects received a subject-specific standardized breakfast. Three hours after breakfast an ad libitum lunch was offered, and participants were instructed to eat until they were satiated; appetite ratings were obtained until six hours after breakfast. Outcome measures included appetite profile (visual analog scales) and EI. Appetite ratings were completed at 30, 60, 90, 120, and 180 minutes after breakfast. Both at the level of 10 and 25% from protein, EI at lunch was approximately 20% lower after an alpha-lactalbumin or gelatin (+TRP) breakfast (2.5 ± 0MJ) compared with after a casein, soy, or whey-GMP breakfast (3.2 ± 0.3MJ, $p<0.05$). Appetite ratings at 180 minutes differed between 15-25mm (approximately 40%; $p<0.05$) when different types of protein were compared. Differences in EI were a function of differences in appetite ratings ($R2=0.4$, $p<0.001$). The authors concluded that different proteins (alpha-lactalbumin, gelatin, gelatin+TRP) that were approximately 40% more satiating than other proteins (casein, soy, whey, whey-GMP) induced a related, approximately 20%, reduction of subsequent energy intake. This study is limited by the fact that there were not any replicates of any of the study conditions.

Green tea: Cardiovascular conditions

- **Summary**: There have been several heterogeneous large sample studies conducted to examine a possible association between green tea and cardiovascular variables {Sasazuki, 2000 1266 /id;Tsubono Y, 1997 133 /id;Imai, 1995 3 /id;Sato, 1989 131 /id}. Studies have investigated lipid profiles, blood pressure, and arteriographically determined coronary atherosclerosis, and have not identified consistent significant benefit. One study reported that drinking green tea safely improved blood pressure and cholesterol levels in obese children. A sampling of epidemiological studies in this field is discussed below. Further research is indicated with clearly defined methodology before a firm conclusion can be drawn concerning green tea in the treatment or prevention of cardiovascular illness. Furthermore, clinical trials with appropriate endpoints are required.
- **Evidence**: Matsuyama et al. conducted a double-blind, randomized, controlled study to evaluate the effects of a catechin-rich beverage on body fat and cardiovascular disease risk factors in obese children and to verify the safety of its use {Matsuyama, 2008, 18356827}. Forty obese or near-obese Japanese children were recruited. Exclusion criteria included current treatment for obesity, severe systemic, liver, and renal disorders, hypersensitivity to caffeine or catechins, or use of medications containing iron preparations. Subjects ingested green tea containing 576mg catechins (catechin group, N=21) or 75mg catechins (control group, N=19) once daily for 24 weeks. The study design included a four week lead-in, a 24-week beverage ingestion period, and a 12-week follow-up. Randomization was stratified by gender, age, and body mass index (BMI). Subjects were instructed to maintain their usual lifestyles during the study period. Catechin safely improved higher levels of fatness, blood pressure, and cholesterol in children. There were no significant differences in major outcome variables, such as body fat mass, between the catechin and the control groups. When the analysis was stratified using the median of the baseline values, the decrease at week 24 in waist circumference, systolic blood pressure, and low-density lipoprotein cholesterol in the catechin group was significantly greater than that in the control group for the above-median category ($p<0.05$ for all). Ingestion of the catechin-rich beverage was not associated with any adverse effects. One girl and one boy in the catechin group dropped out due to extracurricular activities in school and diarrhea of unknown cause, respectively. Limitations of this study include a small sample size.

- **Select epidemiologic studies (not included in the Evidence Table)**: Kuriyama et al. conducted a population-based prospective cohort study (the Ohsaki Study) to examine the association between green tea consumption and mortality from cardiovascular disease (CVD), cancer, and all causes with 40,530 persons in northern Japan {Kuriyama, 2008, 18641205}. An inverse association of mortality from CVD with green tea consumption was more pronounced in women (p=0.08). In women, the multivariate hazard ratios (95% confidence intervals) of CVD mortality across increasing green tea consumption categories were 1.00, 0.84 (0.63-1.12), 0.69 (0.52-0.93), and 0.69 (0.53-0.90) (p=0.004). Within CVD mortality, the stronger inverse association was observed for stroke mortality.
- In a recently published cross-sectional study, Sasazuki et al. examined the relationship between green tea consumption and arteriographically determined coronary atherosclerosis {Sasazuki, 2000 1266 /id}. Participants included 512 patients (302 men and 210 women) who underwent coronary arteriography over the course of one year. The overall prevalence of coronary artery disease (CAD) was 38.7% in men and 23.8% in women. The consumption of green tea was inversely associated with coronary atherosclerosis in men but not in women. In male diabetic patients, the average amount of green tea consumed daily was 5.2 cups for those with significant coronary stenosis and three cups for those without (p=0.07). The corresponding figures in females were 5.5 and 4.8, respectively (p=0.56). In the subgroup of 262 men without diabetes, the odds ratio of significant stenosis for consumption of 2-3 cups and four or more cups daily was 0.5 and 0.4, respectively, as compared with one or fewer cups daily. The authors concluded that green tea might be protective against coronary atherosclerosis, at least in men.
- Tsubono et al. conducted a cross sectional study on the relationship between green tea intake and serum concentrations of total cholesterol, triglycerides, and HDL cholesterol {Tsubono Y, 1997 133 /id}. Six hundred and thirty men aged 40-49 and their wives (N=373) participated in the study, which lasted two years. Total cholesterol, triglycerides, and HDL-cholesterol were the outcomes measured. Green tea had no association with total cholesterol, a non-significant inverse relationship with triglycerides, and a positive non-significant correlation with HDL cholesterol in the men. In women, crude analysis of the data showed a positive relation between green tea, and both total cholesterol (p=0.018) and HDL cholesterol (p=0.222), and no association with triglycerides.
- In another cross sectional study, Imai et al. examined the effects of green tea on cardiovascular diseases in 1,371 Japanese men for four years {Imai, 1995 3 /id}. Measured outcomes were total cholesterol, triglycerides, and lipoprotein fractions. Patients (N=316) who drank >10 cups of green tea daily had lower concentrations of total cholesterol (p<0.001) and triglycerides (p<0.02). Drinking >10 cups of green tea daily was associated with an increased proportion of HDL cholesterol and a decreased proportion of LDL and VLDL cholesterol (p=0.02). The study failed to mention their inclusion and exclusion criteria.
- In a Japanese cohort study of 5,910 women, Sato et al. examined tea consumption and stroke incidence over four years {Sato, 1989 131 /id}. Outcomes measured were the presence of hypertension and stroke. The proportion of women with a history of hypertension was essentially uniform at 24-28%, independent of the amount of green tea consumed. The incidence of stroke and cerebral hemorrhage was two or more times higher in those who consumed less green tea (less than five cups a day), than in those who consumed more (greater than five cups daily).

Green tea: Diabetes

- **Summary**: Preliminary research suggests green tea has no effect on blood sugar or insulin levels in individuals with diabetes. Additional well-designed controlled research, using appropriate endpoints, is needed before a firm conclusion can be drawn concerning green tea in the treatment or prevention of diabetes.
- **Evidence**: In a randomized controlled trial of 66 participants, Fukino investigated the effect of green tea extract in individuals with diabetes {Fukino, 2005 2954 /id}. Subjects in the intervention group were asked to take a packet of green tea extract containing 544mg polyphenols (456mg catechins) daily, and were

asked to divide the green tea powder into three or four fractions dissolved in hot water, and to take a fraction after every meal or snack for two months, in addition to daily food intake. The subjects in the control group were simply followed. After two months, there were no significant changes in body weight, BMI, systolic and diastolic blood pressures, blood glucose levels, HbA1c levels, insulin levels, and homeostatic model assessment (HOMA) indexs. Side effects were not discussed. Limitations to this study include the lack of placebo and blinding.

- Nagao et al. conducted a double-blind controlled trial to examine the effects of a catechin-rich beverage on obesity and blood glucose control in 43 patients with type 2 diabetes (T2DM) {Nagao, 2009, 19008868}. Patients whose treatment for T2DM had not yet progressed to insulin therapy, and whose prescribed medication and diet therapy were unlikely to change were considered eligible to participate. Exclusion criteria included complications, such as nephropathy, hyperlipidemia, or being medicated with triglyceride-lowering drugs, and a judgment of ineligibility by the study investigator. The participants ingested green tea containing either 582.8mg of catechins (catechin group; N=23) or 96.3mg of catechins (control group; N=20) daily for 12 weeks. The primary endpoint was the change of waist circumference, and secondary endpoints were the changes of glucose, hemoglobin A1c, and insulin levels. Two patients in the catechin group were excluded because of poor compliance with dietary management and test beverage ingestion, and five subjects in the control group were excluded because of poor compliance with dietary guidelines prior to clinic visits, including prohibition of alcohol consumption and test beverage ingestion. At week 12, the decrease in waist circumference was significantly greater in the catechin group than in the control group ($p<0.05$). Adiponectin increased significantly only in the catechin group at week 12 ($p<0.05$). Although an increase in insulin was observed in the catechin group at week 12 ($p<0.05$), no difference was noted between the two groups in glucose and hemoglobin A1c. In patients being treated with insulinotropic agents, the increase in insulin at week 12 was significantly greater in the catechin group than in the control group ($p<0.05$). In the catechin group receiving other treatments, insulin levels remained unchanged. Also, in patients treated with insulinotropic agents, the decrease in hemoglobin A1c at week 12 was significantly greater in the catechin group than in the control group ($p<0.05$). This study is limited by a lack of randomization and also by a lack of a description of blinding methods.

Green tea: Hypercholesterolemia

- **Summary**: Preliminary research suggests green tea has beneficial effects on blood lipids in individuals with hypercholesterolemia. Additional well-designed controlled research is needed before a firm conclusion can be drawn concerning green tea in the treatment or prevention of hypercholesterolemia.
- **Evidence**: Bertipaglia de Santana conducted a randomized controlled trial to evaluate the hypolipemic and antioxidant effects of soy and green tea alone and/or in association in dyslipidemic subjects {Bertipaglia de Santana, 2008, 18455656}. One hundred dyslipidemic individuals were allocated into four groups. Inclusion criteria included patients older than 18 years old with total cholesterol plasma levels greater than or equal to 220mg/dL. Individuals who presented with diabetes mellitus, hypothyroidism, or other causes of secondary dyslipidemia were excluded. Women receiving hormone replacement therapy and patients who were using hypolipemic medication, isoflavones, soy, and/or green tea for greater than or equal to 40 days before entry into the protocol were also excluded. No modification occurred in the treatment of patients receiving antihypertensive medication. The soy group (N=25) ingested 50g of soy daily, and the green tea group (N=25) ingested 3g of green tea (dry leaves 3g/vol, prepared by brewing for 10 minutes in 500mL of water containing 145mg of EGCG) daily. A third group (N=25) ingested 50g of soy and 3g of green tea daily, and the control group (N=25) had a hypocholesterolemic diet (decreased red meat intake, eggs, bacon, and replacing milk and butter with skimmed milk and margarine). Evaluations were performed at baseline and after 45 and 90 days. Soy and green tea, alone or in combination, increased the total antioxidant potential in hypercholesterolemic patients, whereas only the combination decreased total cholesterol levels. No significant difference occurred in LDL or HDL cholesterol, or triglyceride (TG)

levels across groups. However, a statistically significant difference in total cholesterol occurred within the soy/green tea group at 45 and 90 days. No statistically significant difference occurred in plasma levels of lipid hydroperoxides or those linked to LDL cholesterol in any of the groups studied. All of the groups that used soy and/or green tea presented increased total plasma antioxidant potential. Dropouts/withdrawals and adverse effects were not discussed. Another limitation is the use of self-report.

- In a randomized controlled trial of 240 moderately hypercholesterolemic participants, Maron investigated the effect of a theaflavin-enriched green tea extract on plasma lipids {Maron, 2003 1716 /id}. All patients were also on a low-fat diet. Patients were randomly assigned to receive a daily capsule containing theaflavin-enriched green tea extract (375mg) or placebo for 12 weeks. Main outcome measures were mean percentage changes in total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels compared with baseline. After 12 weeks, the mean ± SEM changes from baseline in total cholesterol, LDL cholesterol, HDL cholesterol, and TG levels were -11.3% ± 0.9% (p=0.01), -16.4% ± 1.1% (p=0.01), 2.3% ± 2.1% (p=0.27), and 2.6% ± 3.5% (p=0.47), respectively, in the tea extract group. The mean levels of total cholesterol, LDL cholesterol, HDL cholesterol, and TG did not change significantly in the placebo group. No significant adverse events were observed. It was concluded that the theaflavin-enriched green tea extract was effective as an adjunct to a low-saturated-fat diet to reduce LDL-cholesterol in hypercholesterolemic adults.

Green tea: Hypertriglyceridemia

- **Summary**: Preliminary research suggests green tea decreases postprandial triglyceride levels in individuals with hypertriglyceridemia. Additional well-designed controlled research is needed before a firm conclusion can be drawn concerning green tea in the treatment or prevention of hypertriglyceridemia.
- **Evidence**: Unno et al. measured the effects of tea catechins on postprandial plasma lipid responses in individuals with mild hypertriglyceridemia {Unno, 2005 2868 /id}. In a randomized triple-crossover design, nine male subjects consumed 10mg (control), 224mg (moderate dose), and 674mg (high dose) of the assigned tea catechins three times daily along with a standardized light meal consisting of a piece of bread spread with 20g butter. Plasma lipids were measured in the fasting state and one, two, three, four, and six hours after consuming the light meal. Results showed that, compared with the control, moderate and high doses of tea catechins significantly reduced the incremental area under the plasma TG curves by 15.1 and 28.7%, respectively. Also, the rapid elevation of remnant-like particle cholesterol was significantly inhibited by a high dose of tea catechins two hours after consuming the light meal ($p<0.01$). No significant differences were observed in the postprandial responses for plasma total cholesterol or free fatty acids.

Green tea: Obesity

- **Summary**: There are mixed results concerning the effect of green tea on obesity. One randomized controlled trial did not find a statistical difference in body weight, BMI, or waist circumference between green tea extract and placebo groups after 12 weeks of treatment. Another study suggested that ingestion of green tea may ameliorate serious obesity and cardiovascular disease risk factors without raising any safety concerns in Japanese children. Further study is needed in this area before firm conclusions can be drawn.
- **Evidence**: Hsu et al. conducted a randomized controlled trial to examine the effect of green tea extract (GTE) on 100 obese women, and to explore the relationship between GTE and obesity-related hormone peptides {Hsu, 2008, 18468736}. Inclusion criteria included subjects aged 16-60 years with BMI greater than 27kg/m^2 who had not used other weight-control maneuvers within the last three months. Exclusion criteria included endocrine disease, heart disease, allergy and immunology disease; high aminotransferases serum creatinine levels; pregnant or lactating; childbirth within six months; stroke or otherwise unable to exercise; and management for weight control within three months. The subjects were randomly divided into two groups. Group A (N=41) received GTE, while Group B (N=37) took cellulose as a placebo, one capsule (400mg) three times daily for 12 weeks. The subjects were not allowed to receive other obesity

management and were asked to keep their former diet during the study period. No exercise paradigm was included in this study. Body weight (BW), body mass index (BMI), and waist circumference (WC) were measured at the beginning of the study and after 12 weeks of treatment with GTE. Seventy-eight of 100 obese women completed this study. There was only a 0.3% reduction in BW (0.15kg) after 12 weeks of treatment with GTE. There was no statistical difference in % reduction in BW, BMI, and WC between the GTE and placebo groups. Within group comparison revealed that the GTE group had significant reduction in LDL cholesterol and triglyceride, and marked increase in the level of HDL cholesterol, adiponectin, and ghrelin. The placebo group showed significant reduction in TGtriglyceride and a marked increase in the level of ghrelin. No subjects withdrew from the study because of discomfort or adverse effects associated with the treatment. Three subjects developed mild constipation and two patients had abdominal discomfort after GTE treatment, while two subjects had mild constipation and one patient had abdominal discomfort after cellulose treatment. All the symptoms were noted in the first week after treatment. No major adverse effects were noted. Nine subjects of Group A and 13 subjects of Group B withdrew due to personal reasons. It was noted that some subjects showed improvement of mild diarrhea (two in the GTE group and one in the placebo group), and insomnia (two in the GTE group). A limitation of this study was a 22% dropout rate but otherwise the study was well designed.

- Matsuyama et al. conducted a double-blind, randomized, controlled study to evaluate the effects of a catechin-rich beverage on body fat and cardiovascular disease risk factors in obese children and to verify the safety of its use {Matsuyama, 2008, 18356827}. Forty obese or near-obese (BMI $\geq$ 28kg/m^2) Japanese children were recruited for this study. Subjects ingested green tea containing 576mg catechins (catechin group, N=21) or 75mg catechins (control group, N=19) once daily for 24 weeks. Study design included a four-week lead-in, a 24-week beverage ingestion period, and a 12-week follow-up. Randomization was stratified by gender, age, and BMI. Subjects were instructed to maintain their usual lifestyles during the study period. Catechin safely improved higher levels of fatness, blood pressure, and cholesterol in children. There were no significant differences in major outcome variables, such as body fat mass, between the catechin and the control groups. However, when the analysis was stratified using the median of the baseline values, the decrease at week 24 in waist circumference, systolic blood pressure, and LDL cholesterol in the catechin group was significantly greater than that in the control group for the above-median category ($p<0.05$). Ingestion of the catechin-rich beverage was not associated with any adverse effects. Limitations of this study include a small sample size.
- Kovacs et al. conducted a randomized, parallel, placebo controlled study to assess the effects of green tea on weight maintenance (104mg caffeine daily and 573mg catechins daily; 323mg EGCG) in overweight and moderately obese subjects, who had recently lost weight {Kovacs, 2004 43 /id}. A total of 104 male and female subjects (BMI 25-35kg/m^2) participated. The study consisted of a very low energy dietary intervention (2.1MJ daily) for four weeks followed by a weight maintenance period of 13 weeks in which the subjects received green tea or placebo. Subjects lost 6.4kg (SD 1.9) or 7.5% (SD 2.2) of their original body weight during the low energy period. Body-weight regain was not significantly different between the green tea and the placebo group (30.5% and 19.7%, respectively).
- Belza et al. conducted a randomized double-blind placebo controlled crossover trial to examine the effect of caffeine, green tea, and tyrosine on thermogenesis and energy intake {Belza, 2009, 17882140}. Twelve healthy, normal weight men (age: 23.7 ± 2.6 years, mean ± s.d.) were included. In order to be included subjects had to be weight-stable, nonsmoking, non-athletic, and had no use of dietary supplements or frequent use of medication, and a low-to-moderate coffee intake. Subjects received 500mg GTE, 400mg tyrosine, 50mg caffeine, or placebo (microcrystalline cellulose), which were separated by at least three days. The acute thermogenic response was measured in a ventilated hood system for 4 hours following ingestion. Blood pressure, heart rate (HR), and subjective appetite sensations were assessed hourly. The thermogenic responses to GTE and tyrosine were not significantly different from placebo. Ad libitum energy intake was not significantly different between treatments but was reduced by 8% (-403 ± 183kJ),

8% (-400 ± 335kJ), and 3% (-151 ± 377kJ) compared to placebo after intake of tyrosine, GTE, and caffeine, respectively. No significant difference in hemodynamics was observed between treatments. It is unclear if any subjects withdrew from the study. A lack of description of randomization methods and small sample size limits the usefulness of this study.

- Nagao et al. conducted a randomized, controlled trial to examine the effect of a green tea extract high in catechins on body weight and cardiovascular disease risk factors in Japanese women and men with visceral fat-type obesity {Nagao, 2007 3025 /id}. Two hundred seventy subjects were included in study, and results from 240 were analyzed, as per protocol. After a two-week run-in period, subjects were randomized using gender and body mass stratification to a 12 week session of green tea containing 583mg of catechins or green tea containing 96mg of catechins daily. Usual dietary intake and physical activity was maintained. In the group consuming green tea with added catechins, decreases in body weight (-1.7kg vs. -0.1kg), body mass index (-6.0 vs. no change), body fat ratio (-2.5% vs. -0.7%), body fat mass (-2.3kg vs. -0.5kg), waist circumference (-2.5cm vs. no change), hip circumference (-2.3cm vs. -0.1cm), visceral fat area (-10.3cm^2 vs. -3.9cm^2), and subcutaneous fat area (-5.7cm^2 vs. 4.0 cm^2) were significantly greater than in the control group. Also, in individuals with systolic blood pressure >130mmHg, systolic blood pressure levels were decreased in the catechin group compared with the control group, and LDL cholesterol was also decreased in this group. There were no reported adverse effects. In this study, randomization and blinding were not adequately discussed. Also, the study was not specifically determining the effect of green tea, but rather the addition of a green tea extract high in catechins vs. a control green tea extract lower in catechins. This study showed that high levels of green tea catechins resulted in increased weight loss as opposed to ingestion of green tea.
- Eichenberger et al. conducted a randomized double-blind crossover trial to examine the effects of consumption of green tea extracts on whole body metabolism during cycling exercise in endurance-trained men {Eichenberger, 2007, 19839000}. Ten male endurance-trained cyclists were included. Subjects were included if they had a normal body mass index (18.5-25.0kg/m^2) and were engaged in regular endurance exercise (> six hours per week). Subjects were excluded if they were smokers and consumers of green tea or any food rich in polyphenolic compounds. Subjects received 500mg GTE, which was commercially prepared and distributed as OM24 (Omni-medica, Switzerland), and contained 68mg EGCG, 58mg EGC, 22mg ECG, 12mg epicatecin, 159 total catechins, and 28mg caffeine or placebo (400mg corn starch). There was no mention of any adverse effects as a result of GTE administration. The men exercised for two hours at 50 % W(max) before and after three weeks of placebo or GTE supplementation. Dropouts were not discussed. Primary outcome measurements included markers of energy metabolism (i.e., VO_2, VCO_2, RER, EE), plasma levels of glucose, fatty acids (FA), lactate, creatine kinase (CK), and 3β-hydroxybutyrate (BHB), markers of inflammation and oxidative stress (i.e., IL-6, C-reactive protein (CRP), thiobarbituric acid (TBARS), and lipid profile (total cholesterol, TG, HDL cholesterol, and LDL cholesterol). GTE supplementation did not produce any effect on any markers of energy metabolism or on plasma levels of lactate, FA, BHB, or glucose compared to placebo. No differences were observed between GTE and placebo for markers of inflammation and oxidative stress or lipid profile. GTE treatment did not affect heart rate, mean body mass, or mean body fat. GTE supplementation did significantly decrease CK ($p<0.039$) and increase HDL ($p<0.043$) compared to placebo. This study is limited by a lack of a description of randomization and blinding methods.
- Gregersen et al. conducted a randomized double-blind placebo controlled crossover trial to examine the effect of moderate intakes of tea catechins and caffeine on acute measures of energy metabolism under sedentary conditions {Gregersen, 2009, 19445822}. Fifteen healthy, normal weight (mean BMI of 22.4 (SD 1.6) kg/m^2) males received capsules containing placebo, caffeine alone (150mg), or caffeine plus a catechin mixture (600mg) enriched in EGCG, EGC, or a mix of catechins. Smokers, elite athletes, individuals with habitual caffeine and catechin intakes above 250 or 200mg daily, respectively, and users of any dietary supplements, including vitamins, during and from three months before the study were excluded.

On each test day energy expenditure (EE), respiratory quotient (RQ), and substrate oxidation were measured under sedentary conditions in a respiratory chamber for 13.5 hours. No significant treatment effect on EE or RQ was observed. EGCG with caffeine insignificantly raised EE and fat oxidation vs. caffeine-only and placebo. Catechin/caffeine combinations at these dosages and mode of application had non-significant acute effects on EE and fat oxidation. It is unclear if any subjects withdrew from the study. Furthermore, a description of randomization and blinding methods is lacking. The effect of green tea is unclear from this study.

- Nagao et al. conducted a double-blind controlled trial to examine the effects of a catechin-rich beverage on obesity and blood glucose control in 43 patients with type 2 diabetes (T2DM) {Nagao, 2009, 19008868}. Patients whose treatment for T2DM had not yet progressed to insulin therapy, and whose prescribed medication and diet therapy were unlikely to change were considered eligible to participate. Exclusion criteria included complications, such as nephropathy, hyperlipidemia, or being medicated with TG-lowering drugs, and a judgment of ineligibility by the study investigator. The participants ingested green tea containing either 582.8mg of catechins (catechin group; N=23) or 96.3mg of catechins (control group; N=20) daily for 12 weeks. The primary endpoint was the change of waist circumference, and secondary endpoints included changes of glucose, hemoglobin A1c, and insulin levels. Two patients in the catechin group were excluded because of poor compliance with dietary management and test beverage ingestion, and five subjects in the control group were excluded because of poor compliance with dietary guidelines prior to clinic visits, including prohibition of alcohol consumption and test beverage ingestion. At week 12, the decrease in waist circumference was significantly greater in the catechin group than in the control group ($p<0.05$). Adiponectin increased significantly only in the catechin group at week 12 ($p<0.05$). Although an increase in insulin was observed in the catechin group at week 12 ($p<0.05$), no difference was noted between the two groups in glucose and hemoglobin A1c. In patients being treated with insulinotropic agents, the increase in insulin at week 12 was significantly greater in the catechin group than in the control group ($p<0.05$). In the catechin group receiving other treatments, insulin levels remained unchanged. Also in patients treated with insulinotropic agents, the decrease in hemoglobin A1c at week 12 was significantly greater in the catechin group than in the control group ($p<0.05$). This study is limited by a lack of randomization and also by a lack of a description of blinding methods.
- In a double-blind, placebo controlled, parallel study, 46 female subjects (BMI 27.7 ± 1.8kg/m^2) were fed in energy balance from days one to three, followed by green tea supplementation (N=23) or placebo (N=23) from days four to 87 {Diepvens, 2006 2956 /id}. Body composition and fasting blood samples were determined on days four, 32, and 87. No significant differences were observed between the blood parameters of the green tea and placebo groups. The rate of weight loss was 0.09 ± 0.05kg daily by day 32 and 0.03 ± 0.03kg daily by day 87 ($p<0.001$). No information was given on dosing or placebo. No randomization was done.
- Chantre et al. conducted an open study to examine the effects of green tea extract AR25 (Exolise®) in 70 obese subjects (N=7 male, N=63 female) {Chantre, 2002 1129 /id}. The main exclusion criteria were any systemic disease, pregnancy or lactation, or the use of any weight-loss product within the previous month. AR25® was administered as two capsules twice daily for 12 weeks. The outcomes measured were weight, waist circumference, cholesterol, and blood pressure. After three months, the subjects mean body weight was decreased by 4.60% and waist circumference by 4.48%. No significant differences were observed in blood pressure and plasma cholesterol levels. Adverse side effects reported included abdominal pain, diarrhea, and increased transaminase. Limitations of the study included the uncontrolled nature of the study and its small sample size.
- **Select combination studies (not included in the Evidence Table)**: Hursel et al. conducted a randomized double-blind placebo controlled trial to examine the effects of green tea catechin plus caffeine supplementation with a high-protein diet on body weight maintenance after weight loss {Hursel, 2009, 19176733}. Eighty overweight and moderately obese subjects (aged 44 ± 2 years with a body mass index

of 29.6 ± 2.0kg/m^2 were included. Subjects were included if they were considered in good health, a nonsmoker, not using medication, ingesting <100mg caffeine daily (from coffee, tea, chocolate, cola, or energy drinks; the main source of caffeine intake was coffee), not drinking green tea habitually, and being at most a moderate alcohol user. Twelve subjects dropped out of the study; eight because of moving, changing jobs, or going on vacation, and four because of not being able to follow the very low energy diet (VLED). No adverse events were reported. A VLED intervention for four weeks was followed by three months of weight maintenance. During the weight maintenanceperiod, the subjects received a green tea-caffeine mixture (270mg epigallocatechin gallate + 150mg caffeine daily) or placebo, both in addition to an adequate protein (AP) diet (50-60g protein daily) or a high protein (HP) diet (100-120g protein daily). Subjects lost 7.0 ± 1.6kg, or 8.2 ± 2.0%, body weight ($p<0.001$). During the weight maintenance phase, weight, resting energy expenditure, and fat-free mass increased relatively in all groups ($p<0.05$), whereas respiratory quotient and body fat mass decreased, all compared with the AP + placebo group. Satiety increased only in both HP groups ($p<0.05$). The green tea-caffeine mixture was only effective with the AP diet. The methods of randomization and blinding were not adequately described. The effects of EGCG or green tea alone cannot be discerned from this study.

- Rondanelli et al. conducted a randomized double-blind placebo controlled parallel-arm trial to examine the effects of a complex of a metabolite of N-oleyl-phosphatidylethanolamine (NOPE) and epigallocatechin-3-gallate (EGCG) on diet compliance in healthy overweight subjects {Rondanelli, 2009, 18590587}. One hundred thirty-eight healthy, overweight women (N=106) and men (N=32) were included. In order to be included, subjects could not present significant alterations in lipid and carbohydrate metabolism, be pregnant or breastfeeding, have any signs of heart disease, or be affected by any acute or disabling conditions or by endocrinological, neoplastic, and autoimmune diseases. Patients were also excluded if they met DSM-IV criteria for major depressive disorder or had a history or current diagnosis of bulimia, panic disorder, obsessive compulsive disorder, post-traumatic stress disorder, bipolar I or II disorder, or schizophrenia. No psychoactive drugs, including anti-obesity agents, were permitted throughout the study. Subjects received a complex of NOPE and EGCG via the commercially available supplement PhosphoLEAN™, which is a soft-gel capsule containing 85mg NOPE extracted from soya lecithin and 121mg of a dry green tea extract standardized at 50mg EGCG; manufactured by GELFIPHARMA Lodi (Milan, Italy) on behalf of CHEMI Cinisello Balsamo (Milan, Italy) or placebo. Patients received two capsules daily for two months. Both groups observed a 3344kJ daily energy restriction. Primary endpoint was compliance to diet. Secondary endpoints were body composition, metabolic parameters, sensation of appetite, depressive symptoms, and severity of binge eating. Dropout was 6% in the NOPE-EGCG group and 27 % in the placebo group ($p< 0.001$). The reason for patient drop out was declared an inability to continue following the prescribed dietary regimen because of hunger. The treatment induced a significant weight reduction in both groups (-3.28kg and -2.67kg in NOPE-EGCG and placebo groups, respectively) (not significant). NOPE-EGCG treatment improved insulin resistance ($p<0.001$), satiety ($p<0.05$), depressive symptoms ($p<0.004$), and severity of binge eating ($p<0.0001$). This study was well described and conducted; however, the effects of EGCG alone cannot be discerned from this study.

Guggul: Hyperlipidemia

- **Summary**: Guggulipid supplements have been taken for high cholesterol, though their relative effectiveness remains controversial {No authors listed, 2004, 15199914; Shields, 2005, 15901582; Sahni, 2005, 16085931}. Scientific evidence has suggested that guggulipid may elicit reductions in low-density lipoproteins (LDL) (10; 142; 149), non-esterified fatty acids (4), serum lipids (145), cholesterol (4; 10; 36; 138-145; 147-153), and triglycerides (4; 138-139; 143-145; 147-150; 153), and increases in high-density lipoprotein (HDL) (4;5;10;126-133). However, many of the underlying studies reporting these effects have been small and methodologically flawed. In August 2003, a well-designed trial reported small increases in serum LDL levels associated with the use of guggul (1000-2000mg, three times daily) compared to placebo

(134). Studies attempting to measure changes in total cholesterol, high-density lipoprotein (HDL), or triglycerides, have yielded results inconsistent with prior published case reports indicating no changes in total cholesterol, HDL, or triglyceride levels (13;14). Currently, reliable research comparing guggul preparations with other accepted antilipemic therapies such as <ref id="7">HMG-CoA reductase inhibitors ("statins")</ref>, or evaluating the long-term effects of guggul on cardiac morbidity or mortality outcomes is lacking. The question of guggul's therapeutic benefit in the treatment of dyslipidemia remains unsettled. Further research is required.

- **Systematic reviews**: Singh et al. conducted a literature review to determine the effectiveness of guggul (among other Ayurvedic herbs) in managing hyperlipidemia {Singh, 2007, 17658119}. PubMed, the National Library of Medicine, National Center for Complementary and Alternative Medicine, Ovid, and EBSCO Information Services were searched in 2003, 2004, and 2007. Assessments of safety and a determination of the reported efficacy of the randomized controlled trials and quasi-experimental designs were made by the authors. Fifty-one studies were included, of which ten were on guggul (138, 139, 140, 142, 144, 152, 153) {Tripathi, 1984, No PMID; Szapary, 2003, 12915429; Kotiyal, 1980, No PMID}. According to the authors, in general, many of the included RCTs received high-quality scores, with more than 80% of the relevant studies of guggul reporting product effectiveness.
- Nies et al. conducted a literature review to examine the use of alternative therapies in the management of dyslipidemia {Nies, 2006, 17047144}. MEDLINE and PubMed (1965-March 2006) were searched using the key terms "omega-3-fatty acids," "policosanol," "plant stanols and sterols," "flaxseed," "red yeast rice," "guggulipid," "garlic," "fiber," "almonds," and "cholesterol and/or lipids." The review also included meta-analyses that were published in English and involved randomized controlled trials on alternative therapies for dyslipidemia. Of the alternative therapies included in the review, randomized controlled trials were found for <ref id="fishoil">omega-3-fatty acids</ref>, <ref id="policosanol">policosanol</ref>, plant stanols and sterols, <ref id="flaxseed">flaxseed</ref>, <ref id="redyeast">red yeast rice</ref>, guggulipid, <ref id="garlic">garlic</ref>, fiber, almonds, and <ref id="soy">soy</ref>. Three studies were included that evaluated the efficacy of guggul {Szapary, 2003, 12915429; Singh, 1994, 7848901; Nityanand, 1989, 2693440}. Results from these studies varied. Based on the available data, the authors concluded that further research is required to elucidate any potential therapeutic benefit with regard to guggul supplementation.
- Ulbricht et al. conducted a literature review to evaluate the scientific evidence on guggul supplementation for the amelioration of hyperlipidemia {Ulbricht, 2005, 16338199}. Electronic searches were conducted in nine databases, 20 additional journals (not indexed in common databases), and bibliographies from 50 selected secondary references with no restrictions on language or quality of publication. Data collected from literature included information on efficacy in humans, dosing, precautions, adverse effects, use in pregnancy or lactation, interactions, alteration of laboratory assays, and mechanism of action. Twenty trials were identified (138; 10; 139; 5; 140; 141; 142; 143; 144; 145; 4; 147; 148; 36; 149; 150; 151){Szapary, 2003, 12915429}. Based on the available data, much of which is conflicting, the authors concluded that the effects of guggul in patients with high cholesterol are not clear.
- **Evidence**: Szapary et al. reported the results of a randomized, double-blind, placebo controlled trial, in which the effects of guggul on hypercholesterolemia were evaluated {Szapary, 2003, 12915429}. Subjects consisted of 103 adults with hypercholesterolemia assigned to receive either 1000mg or 2000mg (in the form of tablets) of a standardized guggul extract (2.5% guggulsterones E and Z) or placebo three times daily for eight weeks. Tablets were tested for constituents using high-pressure liquid chromatography. The authors reported that after eight weeks, directly measured mean levels of LDL significantly decreased by 5% in the placebo group (p=0.01), but increased in the 1000mg guggul group by 4%, and increased in the 2000mg guggul group by 5% (p=0.006). No significant changes in total cholesterol, high-density lipoprotein (HDL), or triglycerides were noted. A borderline trend towards reduced HDL was, however, seen in the guggul groups. Notably, in patients with baseline LDL levels greater than 160mg/dL

(4.14mM/L), a reduction in triglyceride levels of 14% was seen, compared to a 10% increase in the placebo group. A favorable response in LDL levels to guggul was seen in 18% of patients, compared to greater than 80% in prior reports. This study was well-designed.

- Nityanand et al. described the findings of two multicenter research studies of patients diagnosed with hyperlipidemia (elevated total cholesterol and/or triglycerides) at seven sites in India (138). The first study, a 12-week case series of 205 individuals, found that guggulipid (500mg) administered three times daily yielded a significant reduction in total cholesterol (mean 22%) and triglycerides (mean 25%) (p-value pending full text analysis). The second study, a 12-week double-blind, crossover trial of 125 subjects, compared guggulipid to clofibrate. Decreases in total cholesterol (13-15%) and triglycerides (16-23%) occurred in both groups compared to baseline, mean HDL levels increased by 16% for guggulipid patients compared to 8% in clofibrate patients. Effects on cholesterol and triglyceride levels persisted for 6-8 weeks after drug withdrawal. Although these results are suggestive, neither randomization nor blinding procedures were adequately described, no placebo group was utilized, and no power calculation was conducted prior to conducting the latter study. It should also be noted that the sample size may not have been adequate to detect differences between the guggulipid and clofibrate groups.
- Gaur et al. conducted a randomized, controlled trial to assess the effects of guggulipid on cholesterol levels in 68 patients following acute ischemic stroke (10). Subjects were assigned to receive aspirin monotherapy 320mg daily or daily aspirin plus guggulipid 500mg three times daily. Following four weeks of treatment, a significant reduction in LDL and an increase in HDL occurred in the aspirin/guggulipid group vs. the aspirin group (p-value pending full text analysis). A non-significant decrease in total cholesterol and triglycerides occurred in the aspirin/guggulipid group vs. the aspirin group. Notably, lipid levels can be affected by acute illnesses such as stroke, a factor which may have confounded results. Blinding and randomization were not clearly described, and the effects of guggul monotherapy are unclear.
- A randomized, controlled, double-blind study was conducted on the effects of purified gum guggul on cholesterol in 40 patients with hyperlipidemia (139). Subjects were randomized to receive placebo or 4.5g of gum guggul in two divided daily doses. After 16 weeks, total cholesterol levels decreased by 21.75% and triglyceride levels decreased by 27% compared to baseline. Significant decreases were also noted in LDL and very-low-density lipoproteins (VLDL), while high-density lipoprotein levels rose by 35.8% (p-value pending full text analysis). Significant changes were not noted in the placebo group, although a trend towards improved cholesterol levels was observed. Although these results are suggestive, direct comparisons were not made between the guggul and placebo groups.
- Kotiyal et al. conducted a randomized, double-blind trial in 85 obese patients to evaluate the effect of guggul on various lipemic measures (5). Subjects were given 500mg of a guggul fraction three times daily, or placebo. After 12 weeks, a reduction was noted in the guggul group in levels of cholesterol vs. baseline (15% reduction) and triglycerides vs. baseline (37% reduction) (p-value pending full text analysis). No significant changes were registered in the control group. However, no between-group comparisons were reported. Information on the method of statistical analysis or dropouts was also not presented.
- Kuppurajan et al. reported the results of a randomized, placebo controlled, double-blind trial in 120 patients with hyperlipidemia (140). Subjects were randomized to receive one of four treatments: gum guggul (2g three times daily), guggul fraction (500mg twice daily), clofibrate (500mg three times daily), or placebo. Over a 21-day period, all three treatment groups experienced deceases in serum cholesterol levels compared to placebo (p-value pending full text analysis). However, results were not adequately quantified.
- Ghorai et al. conducted a three-arm, double-blind comparison study in 30 healthy individuals comparing guggulipid with other alternative treatments for efficacy in the reduction of cholesterol (141). Subjects were assigned to receive either guggulipid (guggulsterone 25mg twice daily), allicin (a thioaminoacid from <ref id="garlic">garlic</ref>), or germinated Bengal gram seeds. Following eight weeks of therapy, guggulipid patients experienced a mean reduction in cholesterol levels by 32%, vs. 13% with allicin and 17% with

Bengal seeds (p-value pending full text analysis). Although these are suggestive, it should be noted that the study design lacked a placebo arm, and statistical analysis and dropouts were not well described.

- Singh et al. conducted a randomized, single-blind, placebo controlled trial evaluating the effect of guggulipid in patients with hypercholesterolemia (average baseline total cholesterol: 245mg/dL, LDL: 150mg/dL) (142). All subjects (N=64) were initially placed on a 12-week stringent diet, which excluded meat, eggs, certain oils, and butter. At the end of this run-in period, total cholesterol was observed to decrease by 10–12% in both groups. Subjects were then randomized to receive either guggulipid 50mg twice daily or placebo for 24 weeks. The authors reported that an additional 12–13% drop occurred in total cholesterol and LDL in the guggulipid group, compared with a slight increase in these parameters in the placebo group. Although the changes in the guggulipid group were statistically significant compared to baseline values (p-value pending full text analysis), they were not statistically significant compared to placebo. However, the lack of statistical significance between groups may also reflect a sample size too small to detect differences. This trial was not adequately blinded, and no information was reported regarding compliance.
- Kotiyal et al. conducted a randomized, controlled, crossover trial examining the effect of guggul in 48 subjects with hypercholesterolemia (4). Patients received either placebo or guggul fraction (500mg three times daily) for four weeks, followed by crossover for an additional four weeks. The authors reporteded significant reductions in total cholesterol (12%), triglycerides (21%), and non-esterified fatty acids (23%) (p-value pending full text analysis). However, results were reported in comparison to baseline values, rather than between-groups. Blinding procedures were not described.
- Tripathi et al. conducted a controlled trial in 75 patients evaluating the antilipemic effects of gum guggul (143). Subjects were assigned to receive either gum guggul 10-15g daily (N=50) or placebo (N=25) for three months. The authors reported a 25% reduction in serum cholesterol and a 30% decrease in triglycerides in the guggul group vs. placebo (p-value pending full text analysis). However, study methods, baseline patient characteristics, and statistical analysis were not adequately reported.
- Malhotra et al. conducted a comparison trial contrasting the effects of guggul and clofibrate in 51 patients with hyperlipoproteinemia (144). Subjects received either guggul 1.5g daily (N=41) or clofibrate 2g daily (N=10). After 75 weeks of treatment, reductions of 37% and 50% were noted in cholesterol and triglycerides, respectively, compared to baseline values. In the clofibrate group, reductions in cholesterol and triglycerides were 43% and 50%, respectively, compared to baseline. However, it should be noted that the results for each group were not compared statistically. It should also be noted that the study design lacked a placebo arm.
- Malhotra and Ahuja reported a comparative study evaluating the relative efficacy of treatments in 44 patients with hyperlipoproteinemia (145). Subjects were randomized to receive one of three treatment regimens: guggul fraction (500mg twice daily), ethyl-p-chlorophenoxyisobutyrate (500mg three times daily), or the formulation "Ciba-13437 Su" (100mg three times daily) for 6-34 weeks. The guggul group experienced reductions in serum lipids, cholesterol, and triglycerides by 34%, 27%, and 29%, respectively, compared to baseline, although no significant differences in these values were observed compared to the other two treatment groups. It is not clear if this trial was too small to detect between-group differences, or if there was true equivalence between these therapies. Without a placebo arm, it is also not clear if the observed changes in cholesterol levels might have been due to confounding factors.
- **Studies of lesser design strength**: A number of additional studies of lesser methodological quality have been conducted investigating the antilipemic properties of guggul. Many of these have suffered from an unclear or suboptimal design, and an inadequate reporting of results and statistical analyses. Using a validated quality measurement scale developed by Jadad et al. (146), these studies have scored less than "3," indicating a lower methodological quality. The majority of these trials have reported positive results, although due to the afore-mentioned weaknesses, their conclusions are of limited clinical value.

- Sharma et al. described the results of a randomized, controlled, crossover trial in 60 obese subjects investigating the antilipemic effects of guggul (147). Patients received either placebo or guggul (4g daily) for four weeks, followed by crossover to the alternate treatment for four weeks. The authors reported decreases in cholesterol and triglyceride levels associated with guggul vs. placebo, although clear quantification and statistical significance were not reported. Descriptions of blinding and randomization were not presented, and a 40% dropout rate was reported in the placebo group.
- Kuppurajan et al. conducted a 21-day comparative study of two different guggul treatments in 120 patients with hypercholesterolemia (36). Subjects received crude guggul (2g daily), guggul fraction (500mg three times daily), or placebo. After 10 days, a significant decrease in serum cholesterol was observed compared to baseline values for crude guggul but not for the guggul fraction. After 21 days, no significant changes in lipid levels were observed in either guggul group (vs. baseline). However, it should be noted that all values were compared to baseline rather than the placebo group.
- Beg et al. conducted a study in 50 patients evaluating guggulsterone's effects in hyperlipidemia associated with nephrotic syndrome (149). Subjects were administered guggulsterone 25mg three times daily. After eight weeks of therapy, the authors reported mean reductions in total cholesterol by 24% and LDL by 20%, compared to baseline. Confidence intervals were large for these results, and the methods of statistical analysis were not clearly described.
- Agarwal et al. reported the results of a two-part (phase I/II) case series evaluating guggul's effects in patients with hyperlipidemia (153). In the first phase, guggulipid 400mg was administered three times daily to 21 patients for four weeks, during which time no significant adverse effects were noted. In phase II, 19 subjects ingested 500mg of guggulipid three times daily for 12 weeks followed by placebo for eight weeks. The authors stratified subjects according to whether they "responded" to therapy during the treatment period vs. the placebo period, where a positive response was defined by a 17.5% reduction in total cholesterol and 30% reduction in triglycerides. By these criteria, 78.9% of subjects were reported as "responders." It is not clear if baseline differences existed between subjects that were or were not "responders."
- In a case series, Gopal et al. investigated the effect of guggulipid in 22 patients with primary hyperlipidemia (152). Subjects were administered guggulipid 500mg three times daily for six weeks. Patients demonstrating a fall in cholesterol levels by ≥2 standard deviations, which represented 59% of the sample, were considered to be therapy "responders." Cholesterol-lowering effects reached a plateau at four weeks, with a mean reduction of 24.5% compared to baseline. Six weeks after discontinuation of guggul therapy, cholesterol levels returned to pretreatment values. No significant drop in triglycerides was noted. Although a placebo group was mentioned in the study's description, no details concerning the placebo subjects, including number and outcomes, were included in the results.
- In a case series, Jain reported the results of guggul administration in 93 patients with obesity and hyperlipidemia (151). Patients were given placebo for one month followed by guggul 2g three times daily. After three months of guggul therapy, a significant drop was observed in cholesterol levels, which persisted for three months after guggul cessation. However, it should be noted that 50% of subjects dropped out before study completion. This study was not well described, and results were not adequately quantified.
- Upadhyaya et al. administered guggul 12-16g daily to 25 subjects for three months (148). The authors reported a decrease in serum cholesterol and triglyceride levels by 28% and 33%, respectively, compared to baseline. However, the methods of statistical analysis were not adequately reported.
- **Select combination studies (not included in the Evidence Table)**: Nohr et al. conducted a randomized, double-blind, placebo controlled trial to evaluate the effects of guggul on blood lipids in healthy adults with moderately elevated cholesterol {Nohr, 2009, 19114224}. Individuals between the ages of 25 and 70 years were included if serum cholesterol was between 6 and 8 mM/L and LDL-cholesterol was above 4 mM/L. They were excluded if they were presently using prescription drugs for hyperlipidemia, coronary artery disease, diabetes mellitus, or had triglycerides above 4 mM/L. Participants were randomly allocated to

placebo or guggul capsules. The guggul-containing capsules were comprised of raw guggul (from the resin of the *C. mukul* tree) 540mg as well as 45mg of *Terminalia belerica*, 45 m*g of Terminalia chebula*, 45mg of *Emblica officinalis, 25mg* of ginger, *25mg of long pepper*, and 25m*g of black pepper.* Participants were instructed to take two capsules (active or placebo) with tempered water, half an hour before breakfast and evening meal, for 12 weeks. All participants also took Triphala Plus (194mg of *Terminalia belerica*, 350mg of *Terminalia chebula*, 350mg of *Emblica officinalis, and* 78mg of ros*e leaves) to detox*ify the sys*tem. Fasting total* cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides were tested at sixand 12 weeks. S-ALAT and S-creatinine were also evaluated for possible renal and/or hepatic effects. Forty-three patients were randomized (N=22 active; N=21 placebo); 18 subjects in the guggul group were eligible for analysis and 16 for the placebo group. At 12 weeks, significant reductions were noted in total cholesterol and HDL-cholesterol ($p<0.47$ and $p<0.010$, respectively). Non-signficant reductions were observed for LDL-cholesterol, triglycerides, and the total cholesterol/HDL-cholesterol ratio. Nonsignificant changes were noted in S-ALAT or S-creatinine. Adverse effects noted with guggul use included loose stools, obstipation, altered taste, nausea, skin rash, and tiredness. The influence of other herbal agents including those in Triphala Plus is not well understood.

- In a poorly described study, Singh et al. administered a combination therapy to investigate its effect on lipemic status in 200 patients with ischemic heart disease (150). Subjects received a mixture of powders from guggul and root Puhkarmool (6-8g daily) for six months. The authors noted a decrease in cholesterol (39%) and triglycerides (51%). However, limited information regarding study design and statistical analysis was reported.

Guggul: Obesity

- **Summary**: Guggul has been commonly noted as one of the components of various traditional Ayurvedic formulations to treat obesity {Francis, 2004, 17191820; Shishodia, 2007, 17475222; Burris, 2005, 15602004}. In spite of the historical precedence, scientific evidence supporting this application is lacking. Further research is required.
- **Evidence**: Bhatt et al. evaluated the weight-loss effects of guggulipid in 58 patients (163). Subjects were assigned to receive either dietary control alone or dietary control plus guggulipid 1.5g three times daily. After 30 days, the authors noted a modest non-significant trend towards weight loss in a guggulipid sub-group weighing >90kg. Additional details of study design and results were scant.
- Kotiyal et al. conducted a study in 85 patients and found negative results, although a small decrease in triceps skin folds was associated with guggul therapy (5).
- Sidhu et al. conducted a randomized, controlled, crossover trial examining the effect of guggul in 60 obese subjects (164). Patients were administered either gum guggul (4g daily) or placebo for four weeks, followed by crossover to the opposite therapy for an additional four weeks. Outcome measures included measurements of weight and subcutaneous tissue folds. The authors reported a non-significant trend towards weight loss in the guggul group, but no significant differences between groups.
- **Select combination studies (not included in the Evidence Table)**: Antonio et al. conducted a randomized, controlled, three-arm trial examining the effect of a combination therapy including guggulsterone in 20 overweight subjects (165). Patients were assigned to receive capsules containing guggulsterone 750mg, phosphate, and "other possible promoters of weight loss," or a "placebo" containing maltodextrin, or no treatment. All subjects were maintained on a standardized diet and physical exercise program. After six weeks, the authors noted a significant 3.2% decrease in body weight and a 20.6% decrease in fat mass in the guggulsterone group compared to baseline values. Fat mass decreased significantly by 8.6% in the control group. Notably, no significant differences were observed in any results between groups, suggesting either a lack of efficacy or too small a sample size. Due to the composite nature of the trial therapy, results of this study cannot be directly extrapolated to guggul monotherapy.

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Lotus

- **Summary**: No available studies qualify for inclusion in the evidence discussion.

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FORMULARY: BRANDS USED IN CLINICAL TRIALS/THIRD-PARTY TESTING

Brands used in statistically significant clinical trials:

- **Slimple®**: Not applicable.
- **Achiote leaf (*Bixa orellana* L.)**: Not applicable.
- ***Cassia nomame***: Not applicable.
- **Chuchuhuasi (*Maytenus krukovii, Maytenus macrocarpa, Maytenus laevis*)**: Not applicable.
- **Citrus bioflavonoids (hesperidin)**: Daflon® 500mg (Les Laboratoires Servier, France; not domestically available in U.S.A.) {Amato, 1994; Cesarone, 2006; Cesarone, 2005; Cospite, 1989; Cospite, 1994, Godeberge, 1994; Guilhou, 1997; Guilhou, 1997; Ho, 2000; Ho, 1995; Pecking, 1997; Rizk, 2009, no PMID; Cesarone, 2006, 16708123}, Detralex® (Les Laboratoires Servier, France) {Mlakar, 2005; Pokrovsky, 2007, 18004259; Aliev, 2008, 18522184}, Cyclo 3 Fort (not domestically available in U.S.A.) {Beltramino, 2000; Cluzan, 1996; Guex, 2008, 19018827}, Daflon® 500mg (Les Laboratoires Servier, France; not domestically available in U.S.A.) {Amato, 1994; Cesarone, 2006; Cesarone, 2005; Cospite, 1989; Cospite, 1994, Godeberge, 1994; Guilhou, 1997; Guilhou, 1997; Ho, 2000; Ho, 1995; Pecking, 1997; Rizk, 2009, no PMID; Cesarone, 2006, 16708123}, Detralex® (Les Laboratoires Servier, France) {Mlakar, 2005; Pokrovsky, 2007, 18004259; Aliev, 2008, 18522184}, Cyclo 3 Fort (not domestically available in U.S.A.) {Beltramino, 2000; Cluzan, 1996; Guex, 2008, 19018827}, Diosmin complex (Nutratech, Inc. Fairfield, NJ, USA).
- **Glycomacropeptide (GMP)**: Not applicable.
- **Green tea (*Camellia sinensis*)**: Exolise® (Arkopharma) {11924761; 19159172}, Polyphenon E® (MediGene AG, Munich, Germany) {18363746; 7958849; 14512803}, FertilityBlend (Daily Wellness Company) (a proprietary nutritional supplement containing chasteberry, green tea, L-arginine, vitamins (including folate) and minerals) {17211965}, ImmuneGuard® {Rowe, 2007 3029 /id}.
- **Guggul (*Commiphora mukul*)**: Guglip (Cipla, Bombay, India) (171), Guggulipid tablets (Sabinsa Corporation, Piscataway, NJ), standardized to contain 2.5% guggulsterones E and Z, were found to contain at least 2.1% guggulsterones (85% of claimed ingredients) {Szapary, 2003, 12915429}.
- **Lotus (*Nelumbo nucifera*)**:

Brands shown to contain claimed ingredients through third-party testing:

Slimple®:

- **Consumer Lab**: Not applicable.
- **Consumer Reports**: Not applicable.
- **Natural Products Association**: Not applicable.
- **NSF International**: Not applicable.
- **U.S. Pharmacopeia**: Not applicable.

Achiote leaf (*Bixa orellana* L.):

- **Consumer Lab**: Not applicable.
- **Consumer Reports**: Not applicable.
- **Natural Products Association**: Not applicable.
- **NSF International**: Not applicable.
- **U.S. Pharmacopeia**: Not applicable.

***Cassia nomame*:**

- **Consumer Lab**: Not applicable.

- **Consumer Reports**: Not applicable.
- **Natural Products Association**: Not applicable.
- **NSF International**: Not applicable.
- **U.S. Pharmacopeia**: Not applicable.

Chuchuhuasi (*Maytenus krukovii, Maytenus macrocarpa, Maytenus laevis*):

- **Consumer Lab**: Not applicable.
- **Consumer Reports**: Not applicable.
- **Natural Products Association**: Not applicable.
- **NSF International**: Not applicable.
- **U.S. Pharmacopeia**: Not applicable.

Citrus bioflavonoids (hesperidin):

- **Consumer Lab**: Not applicable.
- **Consumer Reports**: Not applicable.
- **Natural Products Association**: Not applicable.
- **NSF International**: Not applicable.
- **U.S. Pharmacopeia**: Not applicable.

Glycomacropeptide (GMP):

- **Consumer Lab**: Not applicable.
- **Consumer Reports**: Not applicable.
- **Natural Products Association**: Not applicable.
- **NSF International**: Not applicable.
- **U.S. Pharmacopeia**: Not applicable.

Green tea (*Camellia sinensis*):

- **Consumer Lab**: Nature's Bounty® Green Tea Extract (Nature's Bounty, Inc.), Puritan's Pride® Green Tea Extract (Puritan's Pride) (Posted: 11/2005). Nature's Bounty® Green Tea Extract (Nature's Bounty, Inc.) (Approved); Pharmanex® Tegreen® 97 (Nu Skin Enterprises) (Approved) (Posted: 4/2006 Puritan's Pride® Green Tea Extract (Puritan's Pride, Inc.) (Approved); In their green tea review, a green tea supplement was found contaminated with lead and with fewer catechins (such as EGCG) than claimed. Another green tea extract supplement had 74% more caffeine than promised.
- **Consumer Reports**: Not applicable.
- **Natural Products Association**: NA.
- **NSF International**: Report on "Determination of Total Catechins and Gallic Acid in Green Tea." Report on "Chromatogram for Green Tea Method."
- **US Pharmacopeia**: Update on the USP Green Tea Extract Monograph.

Guggul (*Commiphora mukul*):

- **Consumer Lab**: Consumer Lab conducted a review of 16 “cholesterol-lowering” supplements containing sterols, policosanol, or guggulsterones. The following is a list of the brands tested: AccuTech (CholesBlock), Albi, Carlson, Essential Phytosterolins (ModuChol), FutureBiotics, GNC, Health From the Sun /Arkopharma (Basikol), Kaire, Life Extension, Lifewise Naturals, Nature Made, Nature's Formulary, Olympian Labs, Puritan's Pride, Rx Vitamins, Vitamin World, Window Rock (Relestrol). Three of the 17 supplements failed the test. One product would not release its ingredients and two others were missing more than half of the expected ingredients (Posted: 7/17/2006).

- The following guggul supplement was approved: Vitamin World® GuggulPLEX 340mg standardized to contain 2.5% guggulsterones (three capsules daily) (Posted: 2006).
- **Consumer Reports**: Consumer Reports Health presents a list of products containing guggul.
- **Natural Products Association**: Not applicable.
- **NSF International**: Gugulipid 2.5% 1200mg (Sabinsa Corporation).
- **U.S. Pharmacopeia**: *Reference standards*: Purified Guggul Extract 500mg Lot F0H359.

Lotus (*Nelumbo nucifera*):

- **Consumer Lab**: Not applicable.
- **Consumer Reports**: Not applicable.
- **Natural Products Association**: Not applicable.
- **NSF International**: Not applicable.
- **U.S. Pharmacopeia**: Not applicable.

U.S. equivalents of most commonly recommended European brands:

- **Slimple®**: Not applicable.
- **Achiote leaf (*Bixa orellana* L.)**: Not applicable.
- ***Cassia nomame***: Not applicable.
- **Chuchuhuasi (*Maytenus krukovii, Maytenus macrocarpa, Maytenus laevis*)**:
- **Citrus bioflavonoids (hesperidin)**: Not applicable.
- **Glycomacropeptide (GMP)**: Not applicable.
- **Green tea (*Camellia sinensis*)**:
- **Guggul (*Commiphora mukul*)**:
- **Lotus (*Nelumbo nucifera*)**:

Select patents outside of the United States:

Slimple®

- Not applicable.

Achiote (*Bixa orellana* L.)

- FR2693372 Tanning cream promoting moisturising surface skin layers - contains pure lambs' tallow, lard, annatto oil, powdered pine resin and extract of onion skin
- FR2589728 Process for obtaining a concentrate of annatto (*Bixa orellana* seeds) which can be used as an agent for screening actinic radiation, and sun protection composition based on this concentrate
- FR2555447 Anti-sun cosmetic composition containing natural annatto: mixture of four natural vegetable oils. Annatto oil, product claimed as well as the methods of extraction

Cassia nomame

- CN101152346 - Traditional Chinese medicine for treating dermatitis caused by radiation ray
- CN101406663 - Method for treating cancer and method for producing the same
- CN101433579 - Antivirus transdermal emulsifiable paste containing penciclovir, liquorice, astragalus, *Cassia nomame*, and basil
- CN101433646 - Emergency powder for treating children’s infantile convulsion
- CN101444157 - Seed treating method used in culture of *Idesia polycarpa* Maxim. var. *vestita* Diels
- CN101449696 - Preparation method of livestock and poultry intestine tripe cleaning agent

- CN101451093 - *Myristica fragrans* tree leaf and gleditsiae washing agent and production method
- CN101455767 - Traditional Chinese medicine paste for treating infantile bronchial asthma
- CN101559158 - Preparation technology of traditional Chinese medicine tablet for treating thyroma
- CN1010433646 - Emergency powder for treating children's infantile convulsion
- EP0923936 - Flavor-improved extract from *Cassia mimosoides* L. var. *nomame* Makino and method of preparing the same
- EP0930019 - Composition for treating obesity and foods and drinks containing the same
- JP1020076 - Blended tea of *Cassia mimosoides* L. var. *nomame* Makino-*Gynostemma pentaphyllum* Makino
- JP2003048844 - Urease activity inhibitor
- JP2006149354 - Health tea for diabetes
- JP2005343808 - Agent for suppressing obesity and lifestyle-related disease
- JP2007089450 - Food for controlling eyestrain
- JP2007186457 - Tryptase activity inhibitor and its utilization
- JP7101830 - Hair restoring agent
- JP8259557 - New tannins and inhibitor to lipase containing the same as active ingredient
- JP8283172 - Active oxygen scavenger and skin preparation for external use containing the scavenger
- KR20060080131 - Composition comprising an extract of *Cassia mimosoides* var. *nomame* Makino for the prevention and treatment of ischemic diseases

Chuchuhuasi (*Maytenus krukovii, Maytenus macrocarpa, Maytenus laevis*)

- JP 8012565 Skin External Preparation

Citrus bioflavonoids (hesperidin)

- Not applicable.

Glycomacropeptide (GMP)

- EP0393850 - Process for producing kappa-casein glycomacropeptides
- NZ508746 - Improvements in and relating to the isolation of components from whey protein product
- WO02074790 – Large scale production of low fat and SDS gel pure kappa-casein glycomacropeptides (GMP) from bovine deproteinized whey
- WO0245522 – Isolation method

Green tea (*Camellia sinensis*)

- US2009232749 - Compositions for the acute and/or long term treatment of periodontal diseases
- LV13840 – Slimming anti-cellulite composition of gel and method for its production
- WO2009063068 – Cosmetic product for protecting the skin from environmental influences

Guggul (*Commiphora mukul*)

- WO2005072761 - COMPOSITIONS AND METHODS FOR REDUCING CHOLESTEROL COMPRISING GUGGUL AND BETA-GLUCAN AND/OR PLANT STEROLS
- WO0105356 - WEIGHT CONTROL PRODUCT COMPRISING A SYNERGISTIC MIXTURE OF GUGGUL EXTRACT, PHOSPHATE SALT AND METABOLIC STIMULANT
- EP1715877 - COMPOSITIONS AND METHODS FOR REDUCING CHOLESTEROL COMPRISING GUGGUL AND BETA-GLUCAN AND/OR PLANT STEROLS

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Lotus (*Nelumbo nucifera*)

- Not applicable.

United States Patents:

Slimple®

- Not applicable.

Achiote leaf (*Bixa orellana* L.)

- 3066074 Extract of bixa orellana plant for use as a pharmaceutical
- 2009041870 Annatto Extract Compositions Including Tocotrienols and Tocopherols and Methods of Use
- 2008031985 Annatto Extract Compositions, Including Geranyl Geraniols And Methods Of Use
- 2003104090 Supplements containing annatto extracts and carotenoids and methods for using the same

Cassia nomame

- 20050276869 - Appetite-suppressing, lipase-inhibiting herbal composition
- 20050287233 - Compositions for preventing or ameliorating multiple risk factor syndromes
- 20060142382 - Skin lightening composition
- 20060204599 - Dietary supplement and method of using same
- 20060239928 - Transmucosal administration of drug compositions for treating and preventing disorders in animals
- 20060134095 - Antioxidant composition and composition for external use
- 20070238784 - Anthracenedione compounds
- 20080182787 - Agent and compositions comprising the same for inhibiting lipases and phospholipases in body fluids, cells, and tissues
- 20080207747 - Lipase Inhibitors
- 20080275258 - Epigallocatechin dimers or trimers having lipase inhibitory activity and/or antioxidant activity
- 20080299234 - Medication comprising plant extracts as a lipase inhibitor
- 20080306284 - Lipase inhibitors
- 20080317821 - Lipase inhibitors
- 20090104295 - Agent for hair growth
- 20090202677 - Method for manufacturing health food containing enzyme, and health food
- 20070286930 - Carotenoid-containing emulsion compositions, process for its production, and food and cosmetic product containing the same
- 20100021568 - Anti-obesity product and its method of preparation
- 20100112099 - Phytochemical compositions and methods for activating amp-kinase
- 4802907 - N-substituted chloroacetanilides processes for production thereof, and herbicidal composition comprising the same
- 4895587 - Haloacetamide compounds, process for production thereof, and use thereof as herbicide
- 5629338 - Tannins and lipase inhibitors containing the same as active ingredients
- 5674498 - Blood-lipid depressant and victuals containing the same
- 6054129 - Flavor-improved extract from *Cassia mimosoides* L. var. *nomame* Makino and method of preparing the same
- 6251421 - Pharmaceutical compositions containing psyllium fiber and a lipase inhibitor

- 7202222 - Methods for treatment of obesity and effective fat loss promotion
- 7368529 - Agent and compositions comprising the same for inhibiting lipases and phosphlipases in body fluids, cells, and tissues
- 7371727 - Methods and compositions for the treatment of gastrointestinal disorders

Chuchuhuasi (*Maytenus krukovii, Maytenus macrocarpa, Maytenus laevis*)

- 20070191495 Lipase inhibitor
- 20090017140 Maytenus abenfolia extract and methods of extracting and using such extract

Citrus bioflavonoids (hesperidin)

- 5,627,157, Alpha-glucosyl hesperidin and its uses.
- 5,652,124, Alpha-glucosyl hesperidin and its preparation and uses.
- 4,150,038, Conversion of hesperidin into hesperidin.
- 6,048,712, Process for producing alpha-monoglucosyl hesperidin-rich substance.
- 2,350,804, Derivatives of hesperidin and process for preparing the same.
- 5,885,969, Enzyme-treated hesperidin, process for producing the same and method of using enzyme-treated hesperidin.
- 3,751,570, Polynicotinic esters of hesperidin.
- 3,441,557, Dialkylaminoalkyl- hesperidin containing compounds.
- 5,763,414, Hesperidin and hesperidin as 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase inhibitor.
- 10/519,386, Use of hesperidin or one of its derivatives for making a medicine for bone formation stimulation.

Glycomacropeptide (GMP)

- 20010021694 - Nutritional intervention composition for enhancing and extending satiety
- 20020183489 - Large scale production of low fat and SDS gel pure kappa-casein glycomacropeptides (GMP) from bovine deproteinized whey
- 20030008810 - Nutritional intervention composition for enhancing and extending satiety
- 20050106218 - Compositions and methods for treatment of body weight conditions
- 20050133420 - Control scheme for enhanced filtered water systems
- 20060182868 - Dairy product
- 20060204549 - Method of improving nutrient utilization and a composition for use therein
- 20060246146 - Method of increasing the salivary sialic acid content in a mammal
- 20060247153 - Method of improving learning and memory in mammals
- 20060280840 - Universal protein formulation meeting multiple dietary needs for optimal health and enhancing the human immune system
- 20070191264 - Methods for inhibiting the growth of bacteria
- 20080003329 - Enriched infant formulas
- 20080003330 - Infant formulas for early brain development
- 20080108548 - Food composition for rapidly attenuating inflammatory responses
- 20080161227 - Blood pressure lowering peptides from glycomacropeptide
- 20080233245 - Liquid nutrient composition for improving performance
- 20090131316 – Glucagon-like peptide-1 secretagogue, glucagon-like peptide-1 secretagogue food or drink, inhibitor of postprandial rise in blood glucose, and inhibitory food or drink of postprandial rise in blood glucose
- 20090176000 – Dietary compositions for promoting weight loss

- 20090203592 – Infant nutrition with hydrolised proteins
- 20090214680 - Weight loss composition
- 5061622 - Process for the production of kappa-casein glycomacropeptide
- 5075424 - Process for producing kappa-casein glycomacropetides
- 5147853 - Infection protectant
- 5216129 - Production of kappa-caseino-glycomacropeptide
- 5260280 - Bacterial toxin neutralizer
- 5278288 - Process for producing kappa-casein glycomacropeptides
- 5280107 - Process for producing K-casein glycomacropeptides
- 5344820 - Infection protectant
- 5741773 - Storage stable dentifrice composition containing an antibacterial casein glycomacropeptide adjuvant
- 5853704 - Fluoride dentifrices of enhance efficiency
- 5952193 - Peptide mixture and products thereof
- 5968586 - Production of kappa-casein macropeptide for nutraceutical uses
- 6168823 - Production of substantially pure kappa casein macropeptide
- 6207138 - Fluoride free dental remineralization
- 6207638 - Nutritional intervention composition for enhancing and extending satiety
- 6232094 - DNA encoding human kappa casein and process for obtaining the protein
- 6372198 - Dentifrice for the mineralization and remineralization of teeth
- 6429190 - Method for extending the satiety of food by adding a nutritional composition designed to stimulate cholecystokinin (CCK)
- 6436899 - Nutritional intervention composition for enhancing and extending satiety
- 6462181 - Process for preparing a kappa-caseino glycomacropeptide or a derivative thereof
- 6468962 - Nutritional intervention composition for enhancing and extending satiety
- 6482396 - Methods for treating or preventing diseases of the oral cavity
- 6528622 - Method of separating and recovering proteins from a protein solution
- 6555659 - Process for isolating glycomacropeptide from dairy products with a phenylalanine impurity of 0.5% w/w
- 6558690 - Nutritional composition for improving the efficacy of a lipase inhibitor
- 6592863 - Nutritional composition
- 6716815 - Nutritional intervention composition for enhancing and extending satiety
- 6787158 - Process for treatment of a lactic raw material
- 6797290 - Compositions for appetite control and related methods
- 6827960 - Method and apparatus for separation of milk, colostrums, and whey
- 6942849 - Incorporation of exogenous lactic bacteria into the oral microflora
- 7169757 - Stabilizing cGMP in aqueous formulation
- 7618648 - Satiety inducing composition

Green tea (*Camellia sinensis*)

- 5071653 - Camellia sinensis extracts that promote the growth of bifidobacterium
- 5306486 - Cosmetic sunscreen composition containing green tea and a sunscreen
- 6168795 - Method for anticancer therapy using an herbal extract composition

Guggul (*Commiphora mukul*)

- 5273747 - Commiphora mukul extracts and therapeutical applications thereof

- 6113949 - Weight control product and method of treating hyperlipidemia and increasing vigor with said product
- 6436991 - Composition and method containing products extracted from Commiphora sp. for prevention and treatment of abnormal cell growth and proliferation in inflammation, neoplasia and cardiovascular disease

Lotus (*Nelumbo nucifera*)

- 6602526 - Oral compositions containing lotus
- 10565039 - Composition containing ground lotus and/or lotus extract and lactic acid

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ATTRIBUTION/MONOGRAPH CURRENCY

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