Gelatin Hydrolysates

DESCRIPTION

Gelatin is a heterogeneous mixture of proteins derived from animal collagen by hydrolysis. It is not found naturally. It typically is obtained by boiling bovine, pig and ox skin and bones. Gelatin has many uses in the food and pharmaceutical industries. Nutritionally, it is an incomplete protein because it lacks L-tryptophan. It is used in foods as a stabilizer, thickener and texturizer. Pharmaceutically, it is used as an encapsulating agent. Gelatin capsules are widely used both in the pharmaceutical and nutritional supplement industries.

Recently, gelatin subjected to greater hydrolysis in order to produce water-soluble peptides of various molecular weights has entered the nutritional supplement marketplace for use in bone and joint health. The gelatin peptides are rich in the amino acids found in collagen, including L-proline, L-hydroxyproline and glycine. Gelatin and hydrolyzed collagen are similar (see Hydrolyzed Collagen).

ACTIONS AND PHARMACOLOGY

ACTIONS

Gelatin hydrolysates have putative activity against degenerative joint disease (DJD).

MECHANISM OF ACTION

The mechanism of the putative anti-arthritic activity of gelatin hydrolysates is a matter of speculation. Although the amino acids in gelatin hydrolysates are identical to those in collagen, it is unlikely that these amino acids would make a significant contribution to the synthesis of collagen in, for example, joint cartilage. L-hydroxyproline is not a genetic amino acid. Thus, it is not a precursor to protein synthesis but, rather, is formed post-translationally. Both glycine and L-proline are synthesized by the body, and it is unlikely that these amino acids in gelatin hydrolysates would play any role in the *de novo* synthesis of collagen. There is speculation that gelatin hydrolysates may contain certain oligopeptides, which may stimulate collagen synthesis. This is far from proven.

PHARMACOKINETICS

The digestion, absorption and metabolism of gelatin hydrolysates are similar to those that occur with dietary proteins and peptides.

INDICATIONS AND USAGE

Claims that gelatin can fight arthritis and help maintain healthy joint cartilage and bone are to date poorly supported.

RESEARCH SUMMARY

A mixture of gelatin, vitamin C and calcium has been promoted as an effective interventive in joint disease. Some preliminary studies supporting this claim need more rigorous follow-up.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Known hypersensitivity to a gelatin hydrolysate-containing product.

PRECAUTIONS

Pregnant women and nursing mothers should avoid supplemental gelatin hydrolysates.

Those with renal failure or liver failure should exercise caution in the use of supplemental gelatin hydrolysates.

Those who use gelatin hydrolysates produced from bovine sources should only use products derived from raw materials (bovine skin and bone) classified as carrying no detectable infectivity. Bovine nervous system parts may carry the bovine spongiform encephalopathy (BSE) agent, the etiological agent of mad cow disease.

ADVERSE REACTIONS

No reports.

INTERACTIONS

There is one report of a collagen hydrolysate enhancing the effect of calcitonin in the treatment of osteoporosis.

DOSAGE AND ADMINISTRATION

Gelatin hydrolysates are available in powder form, usually in combination with other nutritional supplements, such as vitamin C and calcium. A typical dose is 10 grams daily. Gelatin hydrolysates are also available in capsules, usually in combination with other supplements, such as glucosamine, curcumin, chondroitin sulfate and willow bark.

LITERATURE

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Genistein

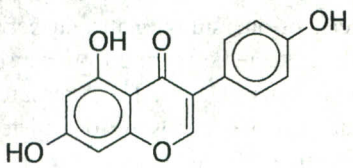
DESCRIPTION

Genistein belongs to the isoflavone class of flavonoids. It is also classified as a phytoestrogen. Phytoestrogens are plant-derived nonsteroidal compounds that possess estrogen-like biological activity. Genistein has been found to have both weak estrogenic and weak anti-estrogenic effects.

Genistein is the aglycone (aglucon) of genistin. The isoflavone is found naturally as the glycoside genistin and as the glycosides 6″-O-malonylgenistin and 6″-O-acetylgenistin. Genistein and its glycosides are mainly found in legumes, such as soybeans and chickpeas. Soybeans and soy foods are the major dietary sources of these substances. Nonfermented

soy foods, such as tofu, contain higher levels of the genistein glycosides, while fermented soy foods, such as tempeh and miso, contain higher levels of the aglycone.

Genistein is a solid substance that is practically insoluble in water. Its molecular formula is $C_{15}H_{10}O_5$, and its molecular weight is 270.24 daltons. Genistein is also known as 5, 7-dihydroxy-3- (4-hydroxyphenyl)-4*H*-1-benzopyran-4-one, and 4′, 5, 7-trihydroxyisoflavone. Genistin, which is the 7-beta glucoside of genistein, has greater water solubility than genistein. Genistein has the following structural formula:



Genistein

Genistein, when marketed as a nutritional supplement, is mainly present in the form of its glycoside genistin.

See also Soy Isoflavones.

ACTIONS AND PHARMACOLOGY

ACTIONS

Genistein may have estrogenic, antiestrogenic and nonestrogenic activities. It may also have antioxidant, anticarcinogenic, antiatherogenic, antiosteoporotic, antiperimenopausal hot flash and radioprotective activities.

MECHANISM OF ACTION

Genistein has weak estrogenic activity as measured in *in vivo* and *in vitro* assays. *In vivo*, its estrogenic activity is one-third that of glycitein and four times greater than that of daidzein.

Genistein has been found to have a number of antioxidant activities. It is a scavenger of reactive oxygen species and inhibits lipid peroxidation. It also inhibits superoxide anion generation by the enzyme xanthine oxidase. In addition, genistein, in animal experiments, has been found to increase the activities of the antioxidant enzymes superoxide dismutase, glutathione peroxidase, catalase and glutathione reductase.

Several mechanisms have been proposed for genistein's putative anticarcinogenic activity. These include upregulation of apoptosis, inhibition of angiogenesis, inhibition of DNA topoisomerase II and inhibition of protein tyrosine kinases. Genistein's weak estrogenic activity has been suggested as another mechanism for genistein's putative anti-prostate cancer activity. In addition to the above mechanisms, other mechanisms of genistein's putative anti-prostate cancer activity include inhibition of nuclear factor (NF)-Kappa B in prostate cancer cells, downregulation of TGF (transforming growth factor)-beta, inhibition of EGF (epidermal growth factor)-stimulated growth, and induction of the *p21WAF1/CIP1* and *p16INK4a* tumor suppressor genes in prostate cancer cells by epigenetic mechanisms involving active chromatin modification. Regarding the latter action, genistein was found to increase acetylated histones 3,4, and H3/K4 at the *p21* and *p16* transcription start sites.

Dietary genistein has been demonstrated to inhibit metastasis of human prostate cancer cells in mice. Prostate cancer cell detachment and invasion represent early steps in the metastatic process. Genistein has been shown to inhibit both of these processes *in vitro*. These processes appear to be regulated by activation of focal adhesion kinase (FAK) and the p38 mitogen-activated protein kinase-heat shock protein 27 (HSP27) pathway; genistein has been shown to inhibit this pathway. The same group that reported on the *in vitro* studies recently reported on an animal model that they developed in order to study the antimetastatic potential of genistein *in vivo*. The animal model was comprised of four-week-old inbred male athymic BALB/c mice, in which were orthotopically implanted PC3-M human prostate cancer cells that formed lung micrometastasis in most of the mice. Dietary genistein was found to decrease human prostate cancer metastasis dose-dependently, corroborating the *in vitro* studies. Further research on the antimetastatic potential of genistein, including early clinical trials in men with prostate cancer, is in progress and certainly warranted.

Genistein's anti-estrogenic action may be another possible mechanism to explain its putative anti-breast cancer activity. In the final analysis, our understanding of the mechanism of genistein's putative anticarcinogenic activity is still in its early stages.

The possible anti-atherogenic activity of genistein may be attributed, in part, to its antioxidant activity. Genistein may have some lipid-lowering activity in some, but the mechanism of this is unclear. The weak estrogenic activity of genistein may also contribute to its possible anti-atherogenic action.

Genistein's weak estrogenic effect may help protect against osteoporosis by preventing bone resorption and promoting increased bone density. Genistein has been found to maintain trabecular bone tissue in rats. A recent randomized, double-blind, placebo-controlled trial involving 389 osteopenic, postmenopausal women reported that after three years of treatment, genistein exhibited a promising safety profile—genistein did not significantly change mammographic breast density or endometrial thickness—and positive effects on bone formation were found. The mechanism of genistein's possible anti-osteoporotic effect is unclear.

Soy isoflavones' weak estrogenic actions may also aid in reducing hot flash symptoms (see Indications and Usage).

Genistein treatment has been demonstrated to protect mice from ionizing radiation injury. It also has been shown to stimulate hematopoietic recovery and increase survival in irradiated mice. The mechanism of action of the radioprotective effect is not completely understood. Possibilities include genistein's antioxidant properties, immunostimulatory activity and its role in signal transduction pathways, where it is an inhibitor of topoisomerase, protein kinases and caspases involved in apoptotic pathways.

PHARMACOKINETICS

The pharmacokinetics of genistein in humans is complex and not well understood. The major dietary and supplemental form of genistein is the glycoside genistin. Some genistin may be hydrolyzed by hydrochloric acid in the stomach to genistein and some may be hydrolyzed by beta-glucosidases in food to genistein. Most of ingested genistin, however, is delivered to the large intestine intact. In the large intestine, bacterial beta-glucosidases hydrolyze genistin to genistein. Genistein is either absorbed or further metabolized in the large intestine to dihydrogenistein and 6′-hydroxy-O-desmethylangolensin. Genistein, which is absorbed from the large intestine and small intestine, is eventually transported to the liver. There, it undergoes conjugation with glucuronate and sulfate via hepatic phase II enzymes (UDP-glucuronosyltransferases and sulfotransferases). The glucuronide and sulfate conjugates of genistein are excreted in the urine and in the bile. The genistein conjugates may be deconjugated to release genistein, which may be reabsorbed via the enterohepatic circulation.

There is considerable individual variation in the absorption and metabolism of ingested genistin and genistein. There are some data suggesting that genistein may be more bioavailable than genistin. However, other data suggest that the extent of absorption of genistein is similar for the aglycone and the glucoside forms. There are little data available on the tissue distribution of genistein.

INDICATIONS AND USAGE

There is a growing body of *in vitro* and animal studies suggesting that genistein may be helpful in preventing and treating some cancers, principally breast and prostate cancers. The clinical studies that might support or refute claims that genistein has anti-atherogenic properties, and that it can be safely and effectively used as "natural" estrogen-replacement therapy, are in their early stages. There are, however, preliminary data suggesting that soy isoflavones, including genistein, may be helpful in some problems associated with menopause, including osteoporosis and "hot flashes." See Soy Isoflavones.

Epidemiological data have long suggested that dietary isoflavones may confer protection against various cancers, especially breast and prostate cancer. High dietary intake of soy products in parts of Asia significantly correlated with reduced incidence of both breast and prostate cancers. Epidemiological data have not been entirely consistent in this regard, but most studies suggest protective effects. Some studies have shown, moreover, that this protection is lost in the second generation of those Asians immigrating to the United States.

These data led to experimental animal studies demonstrating protective effects. In one study, genistein perinatally fed to rats significantly protected offspring from subsequent chemically induced mammary cancers. These researchers concluded that adequate perinatal exposure to genistein can confer permanent protective effects against breast cancer. They have further speculated that protective effects in humans, with respect to breast cancer specifically, may depend upon exposure to genistein early in life. More research is needed to clarify this issue.

A number of studies have shown that genistein can inhibit prostate cancer-cell growth *in vitro.* Some *in vitro* studies suggest that genistein may be both chemopreventive and therapeutic in prostate cancers regardless of androgen responsiveness. Clinical trials are needed.

A symptom that most perimenopausal women experience is the annoying feeling of intermittent intense heat, commonly known as a "hot flash." Hot flashes result from a vasomotor response to declining estrogen levels and can be very disruptive to one's life. While hormone replacement therapy (HRT) is an effective treatment for hot flashes, many women are concerned over potential adverse events of HRT. This concern became even greater following publication in 2002 of the results of The Women's Health Initiative (WHI) Estrogen plus Progestin Study, which was stopped on July 7, 2002 because of increased risk of breast cancer and cardiovascular disease in women taking active study pills, compared with those on placebo. Many women began using soy isoflavones, which some, but not all, studies suggested might help with hot flashes. A recent review of isoflavone-hot flash studies reported that studies that consistently reported a significant decrease in hot flash symptoms (intensity and frequency) all supplied more than 15 milligrams of the isoflavone genistein (calculated as aglycone equivalents) per treatment. Also see Soy Isoflavones.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Genistein is contraindicated in those who are hypersensitive to any component of a genistin, or genistein-containing product.

PRECAUTIONS

Pregnant women and nursing mothers should avoid the use of genistein/genistin supplements pending long-term safety studies.

Men with prostate cancer should discuss the advisability of the use of genistein/genistin supplements with their physicians before deciding to use them.

Women with estrogen receptor-positive tumors should exercise caution in the use of genistein/genistin supplements and should only use them if they are recommended and monitored by a physician.

Women with estrogen receptor-positive breast cancer taking letrozole or tamoxifen should exercise caution in the use of genistein/genistin supplements and should only use them if they are recommended and monitored by a physician.

Those consuming soy isoflavones should ensure that they have an adequate intake of iodide. See Soy Isoflavones: Adverse Reactions.

INTERACTIONS

DRUGS

Letrozole. Letrozole is an aromatase inhibitor that is an approved drug for the adjuvant treatment of hormonally responsive breast cancer. Genistein may negate the inhibitory effect of letrozole. This is based on an animal study.

Tamoxifen. Tamoxifen is a selective estrogen response modulator (SERM) that is used in the treatment and prevention of estrogen receptor-positive breast cancer. Genistein may negate the inhibitory effect of tamoxifen. This is based on an animal study. However, another study found that genistein sensitized the inhibitory effect of tamoxifen on the growth of estrogen receptor-positive and HER-overexpressing human breast cancer cells.

DOSAGE AND ADMINISTRATION

Genistein is available in a few different isoflavone formulas. A standard soy isoflavone formula contains genistein mainly in the form of genistin, as well as daidzin and glycitin. The percentages of the various isoflavones present in this soy formula reflect the percentages of these substances as found in soybeans and are: genistin, about 50%; daidzin, about 38%; and glycitin, about 12%. A 50 mg dose of soy isoflavones—a typical daily dose—provides 25 mg of genistin, 19 mg of daidzin and about 6 mg of glycitin. Usually, 40% of the formula is comprised of soy isoflavones. Therefore, to get a dose of 50 mg of soy isoflavones, one needs 125 mg of the soy preparation.

Smaller amounts of genistein as the aglycone are available in some red clover preparations (see Biochanin A).

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Germanium

DESCRIPTION

Germanium is a metalloid element with atomic number 32 and atomic symbol Ge. Germanium is found in the earth's crust, in certain minerals and in living matter such as plants and the human body. Germanium is not an essential nutrient for humans.

A germanium-deficient diet fed to rats has been found to alter the mineral composition of bone and liver and decrease DNA in the tibia. Little more is known about the biologic role of this element.

Typical daily dietary intakes of germanium range from about 0.4 to 1.5 milligrams. Plant foods, such as wheat, vegetables, bran and leguminous seeds, are rich sources of germanium. Animal foods are low in germanium.

Some organic complexes of germanium are reported to inhibit tumor growth in animals. Some humans who consumed high amounts of these organic germanium supplements, which were contaminated with germanium dioxide (which is nephrotoxic), died from renal failure.

The main nutritional supplement form of germanium is known as Ge-132, Germanium-132, germanium sesquioxide or bis-carboxyethyl germanium sesquioxide. This is a synthetic organic product. It has not been found naturally. Noteworthy is that many of the clinical trials studying the effect of germanium on subjects with various cancers used another synthetic germanium compound, spirogermanium or 8,8-diethyl-N,N-dimethyl-2-aza-8-germaspiro (4,5) decane-2-propranamine dihydrochloride. Spirogermanium has great toxicity, especially neurotoxicity. Spirogermanium is not sold as a nutritional supplement.

Topical products containing inorganic germanium are marketed in Japan for relief of pain and swelling.

ACTIONS AND PHARMACOLOGY

ACTIONS

Bis-carboxyethyl germanium sesquioxide, Ge-132, may have antiproliterative activity. Ge-132 may also have antioxidant activity.

MECHANISM OF ACTION

The mechanism of the possible antiproliferative activity is unknown. Ge-132 is not effective in cell culture. It is speculated that Ge-132's possible antiproliferative activity is due to immune enhancement. There are reports that Ge-132 stimulates natural killer (NK) cell and cytotoxic T lymphocyte activity, as well as increased production of interferon.

Ge-132 was reported to prevent paraquat-induced hepatic oxidant injury in mice. The mechanism of this possible antioxidant effect is unknown.

PHARMACOKINETICS

Reported studies indicate that about 30% of an ingested dose of Ge-132 is absorbed from the small intestine. Little metabolism of Ge-132 appears to occur, and the substance is mainly excreted by the kidneys.

INDICATIONS AND USAGE

There are no indications for the use of supplemental germanium. Some inorganic forms of germanium, such as germanium dioxide, have been shown to be severely toxic to the liver and kidneys, resulting in some fatalities. Some organic forms of germanium, notably germanium lactate citrate, have also been shown to be severely toxic. The risk of contamination in putatively non-toxic forms of supplemental germanium outweighs any possible benefits, none of which, in any case, is yet well established.

RESEARCH SUMMARY

The Food and Drug Administration reported in 1997 that at least 31 human cases linked intake of germanium products