


**Gamma-Oryzanol**

**DESCRIPTION**

Gamma-oryzanol, a phytosterol derived from rice bran oil, is comprised of a mixture of plant sterols esterified to the phenol, ferulic acid. Rice bran oil is the richest source of gamma-oryzanol, but it is also found in corn, barley and other food oils, and in rye and wheat bran. Phytosterols play a number of roles in plants, including in growth and development, for membrane fluidity and as antioxidants. Rice bran oil also contains tocotrienols, members of the vitamin E family. The gamma-oryzanol concentration of rice bran oil is variable. High gamma-oryzanol rice bran oil contains about 1% or 10 mg per gram. Crude rice bran oil contains about 1.5%. (See Phytosterols and Phytostanols.)

Gamma-oryzanol was first isolated by the Japanese in the 1950s and has been used by the Japanese as a medicine for the treatment of anxiety, menopausal symptoms, peptic ulcers, gastritis and elevated lipids. It is a popular substance among bodybuilders for its supposed anabolic effects. It is also often used in cosmetics as a sunscreen, demulcent, lightener and brightener.

Studies have shown that gamma-oryzanol has antioxidant, anti-inflammatory and lipid-lowering activities. However, there are no credible studies demonstrating anabolic activity for this plant product.

Gamma-oryzanol is not just one substance, but a mixture of ferulic acid esters of ten triterpene alcohols; delta7-stigmastenyl ferulate, stigmasteryl ferulate, cycloartenyl ferulate, 24-methylene cycloartenyl ferulate, delta7-campestenyl ferulate, campesterol ferulate, delta7-sitostenyl ferulate, sitosterol ferulate, compsteryl ferulate and sitostanyl ferulate. Cycloartenyl ferulate, 24-methylene cycloartanyl ferulate, and campesterol ferulate are the three major components of gamma-oryzanol. The fundamental structure of gamma-oryzanol is the ferulic acid aromatic nucleus esterified to cyclopentanoperhydrophenanthrene (see accompanying figures). The fundamental structure can be chemically described as (3beta)-9,19-cycloanost-24-en-3-ol-3-(4-hydroxy-3-methoxyphenyl)-propenoate. It is also called cycloartenyl ferulate. Its CAS Registry number is 21238-33-5, its empirical formula is C_{40}H_{58}O_{4} and its molecular weight is 602.88. The chemical structures below are described within this monograph.

**Oryzanol—Fundamental Structure**

**Ferulic Acid**

**ACTIONS AND PHARMACOLOGY**

**ACTIONS**

Gamma-oryzanol may have anti-inflammatory, antioxidant and hypcholesterolemic activities.

**MECHANISM OF ACTION**

**Anti-inflammatory activity:** A number of studies have found that gamma-oryzanol has anti-inflammatory activity. In one study, gamma-oryzanol was shown to inhibit the activity of the proinflammatory transcription factor NF-kappaB in macrophages.

A recent study demonstrated anti-inflammatory effects of gamma-oryzanol in dextran sulfate sodium (DSS)-induced experimental colitis in mice. This is one of the animal models of inflammatory bowel disease (IBD), which in-
cludes ulcerative colitis and Crohn's disease, and is a widely used model for the study of the mechanisms of colonic inflammation and to evaluate candidate drugs for the treatment of IBD. This model exhibits a number of symptoms comparable to those of human ulcerative colitis, such as diarrhea, bloody stools, loss of weight, mucosal ulceration and shortening of the length of the colon. Gamma-oryzanol significantly suppressed DSS-induced colitis in the mice, improved their body weight and the consistency of their stools and decreased their intestinal bleeding. Prior to administration of gamma-oryzanol, elevations of the proinflammatory cytokines tumor necrosis factor-alpha (TNF-alpha), interleukin 1-beta (IL-1beta), interleukin-6 (IL-6) and others were noted in the DSS colitis tissue. Administration of gamma-oryzanol significantly inhibited the production of these cytokines. Gamma-oryzanol was also found to reduce COX-2 expression in DSS-induced colitis. One of the major transcription factors involved in proinflammatory gene regulation is NF-kappaB, and it was thought that this was the main target of the anti-inflammatory effect of gamma-oryzanol and that the anti-inflammatory effect on DSS colitis may be mediated, at least in part, by the inhibition of NF-kappaB via the scavenging of free radicals. Importantly, NF-kappaB activation is associated with free radical generation.

Clearly, gamma-oryzanol appears to have anti-inflammatory activity in the animal colitis model. However, the mechanism of action is not completely understood. Much clinical and experimental data suggest that chronic inflammation of the gut may be due to sustained oxidative stress. Ferulic acid, a metabolite of gamma-oryzanol, has potent antioxidant activity and has been demonstrated to reduce inducible nitric oxide synthase (iNOS), COX-2 and NF-kappaB p63 protein expression in the colonic mucosa of rats with colitis. Thus, ferulic acid seems a good candidate for the anti-inflammatory action of gamma-oryzanol in the above study. However, although ferulic acid did significantly inhibit inflammatory parameters of the DSS-induced colitis in the study, it seemed that the inhibition was not potent enough for it to be considered the only explanation of the anti-inflammatory effect of gamma-oryzanol. Much more study of the anti-inflammatory effect of gamma-oryzanol is needed and warranted.

Antioxidant activity: Gamma-oryzanol has been demonstrated to have a number of antioxidant activities, including scavenging of hydroxyl radicals, superoxide anion radicals and DPPH radicals (2,2'-diphenyl-1-picrylhydrazyl, a stable radical). It also inhibits lipid peroxidation initiated by the azo compound AMVN (2,2'-azobis [2,4-dimethylvaleronitrile]). It is thought that the antioxidant activity of gamma-oryzanol can be mainly attributed to its phenolic ferulic acid moiety/metabolite. Ferulic acid has potent antioxidant activity, including all those mentioned above. Its antioxidant activity centers on its phenolic hydroxyl group, which donates electrons to quench radicals. Ferulic acid is also known to induce a robust cell stress response through the upregulation of cytoprotective enzymes, such as heme oxygenase-1, heat shock protein 70, extracellular signal-regulated kinase 1/2 and Akt (protein kinase B). In addition, ferulic acid has been shown to inhibit the expression and/or activity of cytotoxic enzymes, including inducible nitric oxide synthase (iNOS), caspas and cyclooxygenase-2 (COX-2). Ferulic acid is considered to be a hormetin, a substance that via mild stress-induced mechanisms stimulates protective mechanisms in cells resulting in biologically beneficial effects.

More research on the biological role of ferulic acid in gamma-oryzanol is needed and warranted.

Antilipidemic activity: Several animal studies over many years have found that gamma-oryzanol lowers total cholesterol and LDL-cholesterol levels. A few human studies have shown that as well. Phytosterols and phytostanols are known to lower total and LDL-cholesterol levels, and so it is not surprising that gamma-oryzanol may do so as well. The mechanism of the cholesterol-lowering activity of phytosterols is not completely understood. Phytosterols appear to inhibit the absorption of dietary cholesterol and the reabsorption (via the enterohepatic circulation) of endogenous cholesterol from the gastrointestinal tract. Consequently, the excretion of cholesterol in the feces leads to decreased serum levels of this sterol. Phytosterols do not appear to affect the absorption of bile acids.

The combination of a cholesterol-lowering phytostanol with an antioxidant and possible anti-inflammatory agent such as ferulic acid in one molecule makes gamma-oryzanol, which contains 10 different versions of this theme, an attractive substance that may help prevent atherogenesis. What is called for, though, are large, prospective, placebo-controlled and randomized clinical trials to investigate the possible lipid-lowering and antiatherogenic activities of gamma-oryzanol and to determine the optimal dosage of the substance for these possible effects.

PHARMACOKINETICS
The pharmacokinetics (PK) of gamma-oryzanol in humans is not complete. The PK below is a composite of a number of animal studies and a few human studies.

Supplemental gamma-oryzanol, following ingestion, undergoes hydrolysis in the small intestine, catalyzed by such enzymes as cholesterol esterase to yield the various phytosterols comprising the substance, including beta-sitosterol, campesterol, and stigmasterol, and the polyphenol ferulic acid. The efficiency of absorption of the phytosterols is low and only about 5% or so of the various gamma-oryzanol...
phytosterols are absorbed from the intestinal lumen into the small intestine enterocytes. Prior to their absorption into the enterocytes, the phytosterols are incorporated into mixed micelles (mixtures of bile salts, lipids and sterols). A transporter called the Niemeyer Pick C1-like-1 (NPC1L1) sterol transporter channel is the transporter that is responsible for uptake of all sterols (phytosterols and cholesterol) into the enterocytes in the proximal small intestine. Parenthetically, the cholesterol-lowering drug ezetimibe works by inhibiting this transporter channel. Ezetimibe also inhibits the absorption of phytosterols. Most of the phytosterol portion in the enterocytes is expelled back into the enterocyte lumen via two sterolin pumps called ATP-binding cassette (ABC) half transporters ABCG5 and ABCG8A, which are expressed in the mucosal cells. The expelled portion of phytosterols is ultimately excreted in the feces. A portion of the absorbed phytosterols, which is incorporated into chylomicrons, makes its way to the liver. A portion of the phytosterols that makes its way to the liver becomes glucuronated. Both free and glucuronated phytosterols are secreted from the liver into the bile. Once again, this is accomplished by the above ATP-binding cassettes that are also found in the canalicular membrane. These secreted phytosterols ultimately have the same fate of being excreted in the feces. The low serum concentrations of phytosterols relative to cholesterol can be explained by decreased intestinal absorption and increased excretion of phytosterols into bile. For comparison, 50% to 60% of cholesterol is absorbed.

Sitosterolemia is a rare autosomal recessive disease, but a very serious one, marked by elevated levels of phytosterols—mainly sitosterol and campesterol, the most abundant phytosterols in the diet. However, any dietary phytosterol can be elevated in sitosterolemia. About 20% of the total sterols in the plasma is in the form of phytosterols; the remaining 80% comes from cholesterol. Those with sitosterolemia have arthralgias, tendon xanthomas and premature cardiovascular diseases. The defect in this disease is in either one or both of the genes that encode the ATP-binding cassettes, causing them to lose the ability to expel phytosterols.

The phenol ferulic acid has a high efficiency of absorption. About 60% of the ferulic acid derived from gamma-oryzanol enters the enterocytes of the small intestine by a yet unidentified mechanism. Some of the ferulic acid appears to get conjugated in the intestine and enters the portal circulation along with unconjugated ferulic acid. Some of the conjugated ferulic acid enters the hepatocytes and is secreted in the bile. The remaining ferulic acid enters the circulation and is distributed to various tissues of the body. Metabolites of ferulic acid, 3-hydroxyphenyl and 3-methoxy-4-hydroxy derivatives of phenyl propionic acid, hydroacrylic acid and glycine conjugates are excreted in the urine. Some ferulic acid glucuronide is also found in the urine.

**INDICATIONS AND USAGE**

Gamma-oryzanol, a phytosterol constituent of rice bran oil, has antioxidative and anti-inflammatory effects. These effects, reportedly, may position this substance as an antiatherogenic agent and as a gastrointestinal protectant in some circumstances. Claims that it has anabolic effects are unsubstantiated. The idea that it might have favorable neuroendocrinological effects is poorly supported.

**RESEARCH SUMMARY**

First isolated in Japan in the early 1950s, gamma-oryzanol is an active component of rice bran oil (RBO). It is a mixture of ferulic acid esters of triterpene alcohols and sterols. RBO itself has been studied for some time for its possible lipid lowering effects. These have been demonstrated in a variety of animal models and, to some extent, in humans. There have been fewer studies in this context using isolated gamma-oryzanol, which many have presumed is the most important component in terms of favorable lipid modulation. A review of the literature concluded that, despite flaws in many of the studies, both RBO and its constituent gamma-oryzanol significantly reduce lipid and some other cardiovascular risk factors in rats, rabbits and hamsters. They also cited a few small human trials in which gamma-oryzanol was given credit for lowering total cholesterol, LDL-cholesterol and increasing HDL-cholesterol. No significant adverse side effects were reported in any of these studies. While the data reviewed convinced the researchers that gamma-oryzanol shows promise in controlling hyperlipidemia, they stopped short of saying it has an established role in that context and called for more rigorous clinical investigation.

More recently, researchers reported that RBO and gamma-oryzanol reduced plasma lipid and lipoprotein cholesterol concentrations and aortic cholesterol ester accumulations more effectively in hamsters than did ferulic acid alone. In a study of hypercholesterolemic men, however, another group of researchers, while noting that RBO does, indeed, seem to exert significant favorable lipid-regulating effects, questioned the exact role the gamma-oryzanol component of RBO plays in this. They found that raising the level of the gamma-oryzanol content of the RBO did not increase the favorable effects. They pointed out, as well, that other constituents of the RBO can, independently, have favorable lipid-modulating actions. They hypothesized, however, that even if the increased quantities of gamma-oryzanol did not demonstrate increased lipid effects, its presence might nonetheless be useful for preventing oxidative degradation of other RBO components (such as unsaturated fatty acids, tocopherols and tocotrienols). This same group faulted most
prior research on this issue as flawed in various ways. Clearly more research is needed to help determine whether gamma-oryzanol might emerge as a clinically useful substance in the prevention and treatment of heart disease.

Antiulcerogenic effects have been suggested for gamma-oryzanol in some preliminary in vitro and animal research. It has shown some indication of being able to reduce serum gastrin levels and was said to be slightly effective in another study as an inhibitor of histamine-stimulated acid secretion. RBO has been hypothesized to stimulate synthesis of prostaglandins, known inhibitors of gastric secretion. Dyspepsia symptoms were reportedly alleviated in human subjects using gamma-oryzanol in one dated study. Recently an experimentally induced colitis in mice was alleviated by gamma-oryzanol. In this study, the substance reportedly inhibited some proinflammatory factors, and the researchers concluded that it might have potential in treating inflammatory bowel disease (for example, ulcerative colitis and Crohn’s disease). More research is needed and warranted.

Some bodybuilders and other athletes have used gamma-oryzanol for its claimed anabolic and performance-enhancing properties. These properties, however, have never been convincingly demonstrated. In fact, various animal studies indicate that, when injected, this substance induced anti-anabolic or catabolic activity. Others have reported that, contrary to some popular claims, it may lower, rather than elevate, testosterone levels. In a human study, using oral supplementation, weight-trained males were randomly divided into supplemented (500 mg/day) and control (placebo) groups. Both groups participated in a resistance exercise program over a period of some weeks. No differences were noted in performance levels between the two groups. Nor were any differences seen in a battery of hormone tests that included testosterone, cortisol, growth hormone and several others. Cardiovascular variables were also the same between the groups.

Some animal studies have noted various effects of gamma-oryzanol on anterior pituitary hormone secretion. In humans, a decrease in thyroid stimulating hormone was observed upon administration of the substance. It is hypothesized, on the basis of some further studies, that gamma-oryzanol may be able to increase levels of norepinephrine in the brain. The clinical relevance of these scattered data is unknown.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS
Gamma-oryzanol supplementation is contraindicated in those who are hypersensitive to any component of a gamma-oryzanol-containing dietary supplement. Gamma-oryzanol is also contraindicated in those with the rare genetic disorders sitosterolemia and cerebrotendinotic xanthomatosis.

PRECAUTIONS
Those who wish to use gamma-oryzanol supplements for any health condition should first discuss this with his or her physician.

Gamma-oryzanol supplements should be avoided by pregnant women and nursing mothers, because there are no long-term safety studies of this substance in these groups. There is no present information that high dietary intake of naturally occurring phytosterols, such as those consumed by vegetarians, adversely affects pregnancy or lactation.

ADVERSE REACTIONS
Adverse reactions are rare and mainly mild gastrointestinal ones.

INTERACTIONS
DRUGS
Ezetimibe may inhibit the uptake of the phytosterols into the enterocytes of the small intestine.

Administration of an HMG-CoA reductase inhibitor (a "statin") along with gamma-oryzanol may have an additive effect on the lowering of total and LDL-cholesterol

Gamma-oryzanol was found to have no more than a slight inhibitory effect on cytochrome P450 activities in human liver microsomes, indicating that gamma-oryzanol would not be expected to cause clinically significant interactions with cytochrome P450-metabolized drugs.

NUTRITIONAL SUPPLEMENTS
Administration of the omega-3 long chain polyunsaturated acids DHA (docosahexaenoic acid) and EPA (eicosapentaenoic acid) along with gamma-oryzanol may produce a synergistic effect in lipid lowering.

HERBS
None known.

FOOD
None known.

OVERDOSAGE
No reports.

DOSAGE AND ADMINISTRATION
Gamma-oryzanol supplements are available in the form of capsules, tablets and liquid. Dosage ranges from 30 mg to 300 mg daily.

The gamma-oryzanol concentration of rice bran oil is variable. High gamma-oryzanol rice bran oil contains about 1%, or 10 milligrams per gram. A teaspoon of this oil (five milliliters) contains about 50 milligrams.

LITERATURE
Akiyama Y, Hori K, Hata K, et al. Screening of chemiluminescence constituents of cereals and DPPH radical


**Gamma-Tocopherol**

**DESCRIPTION**

Gamma-tocopherol is one of the four natural tocopherol homologues or isomers, the others being alpha-, beta- and delta-tocopherol. Tocopherols and tocotrienols comprise the vitamin E family (See Vitamin E). Gamma-tocopherol is the principal tocopherol found in the lipid fraction of many seeds and nuts, including soybeans, corn and walnuts, and is the major tocopherol in the American diet. Because of the wide use of oils derived from these sources, gamma-tocopherol makes up approximately 65 to 70% of the total dietary intake of tocopherols, the other major dietary tocopherol being alpha-tocopherol.

Although gamma-tocopherol is the principal dietary tocopherol, plasma levels of this tocopherol average five times lower than alpha-tocopherol. Apparently, alpha-tocopherol is the only tocopherol maintained in human plasma. This situation is believed to be accounted for by the presence in the liver of alpha-tocopherol transfer protein (alpha-TPP). Alpha-TPP preferentially secretes alpha-tocopherol from the liver into the blood. This protein binds most strongly to alpha-tocopherol. Because alpha-tocopherol is the only tocopherol maintained in human plasma, the Food and Nutrition Board in their most recent report, and for the purpose of establishing RDAs for vitamin E, included only certain alpha-tocopherol forms in their definition of vitamin E activity.

Gamma-tocopherol is also known as d-gamma-tocopherol, RRR-gamma-tocopherol, 2R, 4'R, 8'R-gamma-tocopherol and 2, 7, 8-trimethyl-2 (4', 8', 12'-trimethyldecyl)-6-chromanol. It is abbreviated as gamma-TOH, gamma-T and gamma-TH. Gamma-tocopherol is a slightly viscous, pale yellow oil which is practically insoluble in water. Alpha-tocopherol differs from gamma-tocopherol by the presence of a methyl group in the 5 position of the chromanol ring. Gamma-tocopherol lacks this methyl group. Practically all supplemental RRR-alpha-tocopherol, commonly known as d-alpha-tocopherol, is produced from soybean oil-derived gamma-tocopherol by a chemical methylation. The structure is identical to natural d-alpha-tocopherol, but, since it is a semi-synthetic product, it is called natural-source alpha-tocopherol. In contrast to alpha-tocopherol, synthetic forms of gamma-tocopherol, such as *all rac*-gamma-tocopherol or d1-gamma-tocopherol, are not sold as nutritional supplements. Supplemental gamma-tocopherol is marketed as the free or unesterified form.

**ACTIONS AND PHARMACOLOGY**

**ACTIONS**

Gamma-tocopherol has antioxidant activity. It may also have anti-atherogenic, anti-apoptotic, anti-thrombotic, anticoagulant, anticarcinogenic and immunomodulatory actions.

**MECHANISM OF ACTION**

Gamma-tocopherol is a lipid soluble, chain-breaking, peroxyl radical scavenger. It can protect polyunsaturated fatty acids (PUFAs) within membrane phospholipids, as well as PUFAs within such plasma lipoproteins as low density lipoproteins (LDL), from oxidation. In this regard, gamma-