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Sesame Seed Lignans

DESCRIPTION

Sesame (*Sesamum indicum* L.) has a fascinating history. It is one of the oldest cultivated plants in the world and has been around for about 6,000 years. Sesame seed and its oil have been utilized as an important foodstuff and also for medicinal purposes, including providing energy and mental tranquility and preventing aging. It has also been used as an insecticide, for the preparation of mummies by the ancient Egyptians and as the fundamental body massage oil in Ayurvedic medicine. These days, bodybuilders use lignans from sesame seeds for supposed performance enhancement and weight loss. Recently, there has been a great deal of interest in studying sesame seed lignans for their biological effects and possible health benefits.

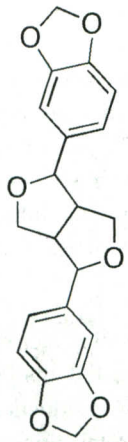
Sesame seed is one of the two major dietary sources of plant lignans, the other major source being flaxseed. The major sesame seed lignan is sesamin. Sesame seed contains about 0.4% sesamin in sesame oil or about 4 mg per gram. Sesame seed also contains about half as much of the lignan sesamolin and smaller amounts of sesamol, sesaminol, and the water-soluble lignans, sesaminol diglucoside and sesaminol triglucoside. (The aglycosides are lipid-soluble.) In addition, it contains small amounts of matairesinol, lariciresinol, pinoresinol and syringaresinol.

Sesamin, like all plant lignans, is a phenylpropanoid dimer. However, in contrast with the flaxseed lignan secoisolariciresinol diglucoside (see Flaxseed Lignans) and the spruce lignan 7-hydroxymatairesinol (see Spruce Lignans), which are of the dibenzylbutyrolactone structural type, sesamin is of the tetrahydrofuran, or furofuran structural type. The two major structural types of lignans in the plant kingdom are the dibenzylbutyrolactone and the tetrahydrofuran, or furofuran types. Sesamin and all of the sesame seed lignans are also classified as phytoestrogens.

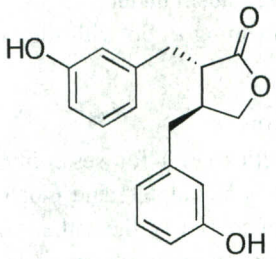
The chemical names for sesamin are: 5,5′-(Tetrahydro-1*H*,3*H*-furo[3,4-*c*]furan-1,4-diyl)bis-1,3-benzodioxole; tetrahydro-1,4-bis[3,4-(methylenedioxy)phenyl]-1*H*,3*H*-furo[3,4-*c*]furan, and 2,6-bis(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane.

The molecular formula is $C_{20}H_{18}O_6$ and the molecular weight is 354.35. The CAS Registry Number for sesamin is 606-80-7. The sesamin preparation obtained as a by-product of the refining of edible sesame oil consists of a 1:1 ratio of sesamin and its epimer episesamin. Pure sesamin is available.

The chemical structures that follow are described within this monograph.



Sesamin



Enterolactone

ACTIONS AND PHARMACOLOGY

ACTIONS

Sesamin has possible anticancer, antihypertensive, antioxidant/pro-antioxidant/hepatoprotective, estrogenic/antiestrogenic, neuroprotective, lipid metabolism and hypocholesterolemic activities.

MECHANISM OF ACTION

Anticancer: Sesamin was shown to downregulate cyclin D1 protein expression in the human tumor cell line, MCF-7. Cyclin D1 belongs to a family of cyclin proteins that function as subunits of cyclin/cyclin-dependent kinase holoenzymes that regulate entry into and progression through the cell cycle. Overexpression of cyclin D1 may be involved in several cancers, including prostate, breast and colon cancer.

Sesamin was found to suppress the carcinogenic effect of 7, 12-dimethylbenz[a]anthracene (DMBA)-induced mammary carcinogenesis in female Sprague-Dawley rats. The mechanism of action of this effect is unclear. Possibilities include immunopotentiation and increased antioxidant activity.

Antihypertensive: The antihypertensive effect of sesamin has been demonstrated in three animal models of hypertension—the two kidney, one clip (2k,1c) renal hypertension rat model, the stroke-prone spontaneous hypertensive rat (SHR) model and the deoxycorticosterone acetate (DOCA) salt hypertensive rat model. The greatest antihypertensive activity was noted in the DOCA salt hypertensive rats. It is thought that the blood pressure-lowering effect of sesamin can be partly explained by its inhibitory effect on vascular superoxide production.

Blood pressure is regulated by arteriolar vascular tone. The endothelial bioavailability of endothelial nitric oxide (NO), produced by eNOS (endothelial nitric oxide synthase), is the major factor in the regulation of vascular tone. Superoxide anions react with NO-producing peroxynitrite, resulting in decreased endothelial bioavailability of vascular NO, arteriolar constriction and elevation of blood pressure. NADPH oxidase, a member of the NOX family of enzymes, produces superoxide anions, which is a major factor in the dysregulation of arteriolar tone. Inhibition of NADPH oxidase could play a major role in the maintenance of normal blood pressure. A recent paper (Nakano, et al., 2008) demonstrated suppression of aortic NADPH oxidase by administration of sesamin to DOCA hypertensive rats. More research and human studies are certainly warranted to determine if sesamin could have a role in the treatment of hypertension in humans.

Antioxidant/Pro-antioxidant: Sesamin itself does not appear to have antioxidant activity *in vitro*. Sesamin does not demonstrate radical scavenging effects on superoxide anions (O_2^-) or DPPH (2,2-diphenyl-2-picrylhydrazyl hydrate) radicals. Neither does it show inhibitory effects against lipid peroxidation. On the other hand, the minor sesame seed lignans that carry a phenolic hydroxyl group (sesamin does not)—sesaminol, episesaminol and sesamolinol—do exhibit antioxidant activity *in vitro*. It turns out that when sesamin was orally administered to rats, at least three compounds were formed via metabolism in the rats' livers, compounds that possessed phenolic hydroxyl groups and which did have strong superoxide anion (O_2^-) and hydroxyl radical (OH) scavenging activities. The methylenedioxyphenyl moiety in the structure of sesamin was shown to be converted into a methylenedihydrophenyl or catechol moiety. Sesamin has been shown to possess hepatoprotective activity against liver damage caused by ethanol or carbon tetrachloride. The mechanism of action of this hepatoprotective effect is most likely due to the antioxidant metabolites formed in the liver from sesamin.

In addition, sesamin is converted in the large intestine to the mammalian lignan, enterolactone (ENL), which is known to have antioxidant properties.

Prodrugs are drugs that are inactive but become active when they get metabolized. In this sense, sesamin can be considered a pro-antioxidant in that it does not have antioxidant activity until it is metabolized to active antioxidants.

Estrogen/Antiestrogen: In a study of postmenopausal women, it was found that ingestion of sesame seed caused an increase in sex hormone binding protein (SHBP) and also an increase in urinary 2-hydroxyestrone. This has also been seen in studies with flaxseed lignans and is possibly due to an estrogen/antiestrogen effect of an important metabolite of both sesame seed lignans and flaxseed lignans, the mammalian lignan, enterolactone. The amount of sesamin in the sesame seeds was approximately 250 mg and the total amount of lignans about 380 mg. An increase in the ratio of 2-hydroxyestrone over 16-hydroxyestrone is thought to favor a less mitogenic (carcinogenic) estrogen environment for women. Likewise, an increase in SHBP would result in a lower amount of free estrogen in the serum, also thought to create a less mitogenic estrogen environment for women. Much more work needs to be done in this area to in order to determine the role that sesamin might play in women's health.

Hypocholesterolemic: A few but not all animal studies have demonstrated cholesterol-lowering by sesamin, and a few human studies have done so as well. The mechanism of this possible cholesterol-lowering action is unclear and requires further research for elucidation. Possibilities offered have been inhibition of absorption of cholesterol and inhibition of the biosynthesis of cholesterol.

Lipid metabolism: Sesamin has been demonstrated to increase the activity and gene expression of enzymes involved in fatty acid oxidation in rat liver. This is thought to be through the activation of peroxisome proliferator activated receptor (PPAR)-alpha. Sesamin has also been demonstrated to lower the activity and gene expression of hepatic enzymes involved in fatty acid biosynthesis, through the downregulation of sterol regulatory element binding protein (SREBP)-1. Subsequent studies compared sesamin with the related sesamin lignan, sesamolin, and found that although sesamin was more effective in reducing serum and liver lipid levels in rats, sesamolin more strongly increased fatty acid oxidation. Because of these effects of sesamin on lipid metabolism, it has been speculated that sesamin might have an effect on adiposity. Studies of sesamin and related sesame lignans on hepatic fatty acid metabolism in humans are necessary and indicated, as are studies in humans on the possible effect of sesamin on weight control.

Neuroprotective: Neuroinflammation is a major factor in the pathogenesis of neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease and multiple sclerosis. Microglia are macrophage-like cells that act as the first and main form of active immune defense in the central nervous system. Reactive oxygen and reactive nitrogen species (eg, nitric oxide, or NO) that are released from activated microglia may participate in neuroinflammatory and neurodegenerative processes. Bacterial lipopolysaccharide (LPS), cytokines and amyloid all rapidly cause the transcription and expression of inducible nitric oxide synthase (iNOS) in microglia. Activated microglia facilitate tumor necrosis factor (TNF)-alpha or NO-mediated neuronal cell death. Sesamin has been shown to suppress LPS-induced NO production in microglia via inhibition of signal transduction pathways or via inhibition of nuclear transcription factors.

Further investigation of this activity in a murine BV-2 microglial cell line indicated that sesamin inhibited LPS-induced IL (interleukin)-6 production by suppression of the p38 mitogen-activated protein kinase (MAPK) signal pathway and suppression of nuclear factor-kappaB (NF-kappaB) activation. The mechanism underlying this action is not clear and may have something to do with the antioxidant activity of sesamin.

PHARMACOKINETICS

The pharmacokinetics (PK) for sesamin and other sesame lignans in humans is incomplete and much work is yet to be performed in order to clarify the rather complex aspects of the absorption, distribution, metabolism and excretion of the sesame seed lignans. What follows is what we presently know about the PK of sesamin.

After ingestion, some sesamin is absorbed from the small intestine and some is converted by the intestinal microflora in the proximal or upper part of the large intestine to the mammalian lignan, enterolactone (ENT), and to a lesser degree to the mammalian lignan, enterodiol (END). Reports vary as to the extent of the conversion of sesamin to the mammalian lignans. Some sesamin is also absorbed in the small intestine and winds up in the liver where the methylenedioxyphenyl moiety of sesamin undergoes oxidative biotransformation and demethylation to form a number of hydroxylated catechol metabolites. In contrast to sesamin, which does not demonstrate antioxidant properties *in vitro,* the catechol metabolites are diphenols and do demonstrate antioxidant activity *in vitro*. There is evidence that some of the metabolism of sesamin takes place in the enterocytes of the small intestine before it gets to the liver. It appears that the major catechol metabolite of sesamin is a compound that goes by the cumbersome name of (1*R*,2*S*,5*R*,6*S*)-6-13, 4-dihydroxyphenyl)-2-(3,4-methylenedioxyphenyl)-3,7-dioxabiclo 3,7-[3,3,0]octane. This compound may be responsible for some of the biologic actions of sesamin, especially for the hepatoprotective activity of sesamin.

The catechol metabolites may get excreted in the bile and then get metabolized by the intestinal flora of the large intestine to ENT and ENL. It is unclear as to the amounts of END and ENL that are produced directly from the microflora

metabolism of sesamin and from the catechol metabolites. The catechol metabolites form glucuronides and sulfates. The urinary excretion of the sesamin catechol metabolite described above ranges from about 22% to 39%, mostly in the glucuronide and sulfate forms.

INDICATIONS AND USAGE

Claims made for dietary lignans derived from sesame seeds include antioxidant, antihypertensive, anticarcinogenic, antithrombotic, cardioprotective and hepatoprotective effects. It has also been suggested that these lignans may help protect against type II diabetes and Alzheimer's disease, that they may have favorable immunomodulating effects and that they might be of benefit to postmenopausal women. The idea that the lignans might be beneficial in weight control has scant support.

RESEARCH SUMMARY

Sesame seed oil resists rancidification and heat degradation much better than many other oils, apparently owing primarily to the antioxidant properties of some of its lignans. The ancient Egyptians used sesame seed oil in the preservation of mummies, and, more recently, one group of Japanese researchers reported that sesame oil is considered best for deep-frying tempura because it excels at resisting heat-induced deterioration. In both *in vitro* and *in vivo* animal experiments, sesaminol significantly suppressed lipid peroxidation products. In one such experiment, it was found to be more effective in this regard than alpha-tocopherol and the lipid-lowering antioxidant agent probucol. *In vitro,* sesamin, on the other hand, shows little or no antioxidative effect. *In vivo*, however, there is evidence that sesamin, through various of its metabolites, also exerts significant antioxidative activity that may be beneficial. Sesamolin, another sesame lignan, resembles sesamin in that it, too, exhibits little antioxidant activity *in vitro* but seems to act as a prodrug *in vivo*, giving rise to derivatives that exert antioxidative activity that could have beneficial physiological effects.

Additionally, other research has suggested that the sesame lignans may synergize with and enhance the antioxidant properties of vitamins E and C. In one human study, elevated levels of vitamin E were attributed to daily feedings of muffins containing sesame seeds. In a rat study, sesaminol demonstrated a greater ability to elevate vitamin E than did sesamin. Other *in vitro* and animal studies also suggest that these lignans can potentiate vitamin E and synergize with it to reduce lipid peroxidation in the liver. Hairless mice exposed to ultraviolet irradiation suffered significantly less damage when treated with dietary compounds having vitamin E activity in combination with sesame lignans, when compared with controls. Another rat study indicates that dietary sesame seed and its lignans stimulate ascorbic acid synthesis and, synergistically, thus boost the antioxidative activity of both sesame seed lignans and vitamin C.

Various researchers have now found that sesame seeds and sesame oil lower serum cholesterol concentrations and inhibit the absorption of cholesterol in lymph. Sesamin, similarly, has demonstrated the ability to lower serum cholesterol in normal rats and to do so, as well, in hypercholesterolemic, stroke-prone spontaneous hypertensive rats. *In vitro* studies have shown that sesaminol is useful in protecting against the damaging effects of LDL oxidation. Sesamin and vitamin E together exhibited favorable lipid effects in hypercholesterolemic human subjects in one of only a few relevant clinical trials. Antihypertensive effects have been observed in animal hypertension models treated with dietary sesamin. Antithrombotic effects have been observed, as well, in some preliminary *in vitro* investigations. Because of the experimental data, it is hoped that the sesame lignans may ultimately prove to have clinical significance as cardioprotective and anti-stroke agents through favorable effects on lipid metabolism, platelet aggregation and other pathways. In addition, owing to findings in rats that sesamin can significantly decrease serum triglycerides, upregulate fatty acid oxidation and downregulate the biosynthesis of fatty acids, it has been suggested that dietary sesame lignan supplementation might have some ability to suppress adiposity. Far more research would be required, however, to establish that the sesame lignans might have any benefit as weight control agents.

In terms of cancer protection, sesame lignans have shown some ability to suppress chemically-induced breast cancer in an animal model. In another study, the growth of human lymphoid leukemia cells was increasingly inhibited with increased concentrations of sesame lignan *in vitro*. A type of DNA fragmentation characteristic of apoptosis was observed. Sesaminol, in this experiment, was more effective than sesamin, sesamolin and episesamin. The lignans did not damage normal cells. More research on the anticarcinogenic potential of these lignans is warranted.

Liver function was said to be enhanced in a study of rats given large amounts of alcohol and fed sesamin. Enhanced ethanol metabolism, induced by sesamin, had previously been reported in mice. And human volunteers given whisky demonstrated ethanol resistance in another study in which the subjects were given 100 mg of sesamin daily for a week prior to the alcohol challenge. Alcohol decomposed more quickly in the sesamin supplemented volunteers than it did in control subjects who did not receive the lignan. Researchers have concluded that sesamin does not inhibit the absorption of alcohol but that it increases its decomposition in the liver and diminishes the toxicity of acetaldehyde, an oxidative product of alcohol.

There is very preliminary experimental evidence that the sesame lignans might be helpful in some immune disorders, possibly food allergy, through immunoregulatory activity, that they might be helpful in impeding Alzheimer's disease and oxidative stress-induced neuronal disorders and that they may exert hypoglycemic activity, which could be helpful in type II diabetes. Much more research is needed, and indicated, to further elucidate these possibilities.

Finally, sesamin has been reported to have estrogenic effects, possibly through its conversion by intestinal microflora to enterolactone. In a randomized, placebo-controlled study of 26 healthy postmenopausal women, the researchers concluded that the lignan, compared with placebo, conferred benefits upon the postmenopausal subjects by improving blood lipids and antioxidant status and by "possibly" improving sex hormone status. This study is inconclusive in terms of establishing any positive estrogenic effects in postmenopausal women.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Sesame seed lignans are contraindicated in those who are hypersensitive to any component of a sesame seed lignan-containing product.

PRECAUTIONS

Pregnant women and nursing mothers should avoid the use of sesame lignan supplements pending long-term safety studies.

Men with prostate cancer or benign prostatic hyperplasia (BPH) should discuss the advisability of the use of sesame seed lignan supplements with their physicians before deciding to use them.

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

ADVERSE REACTIONS

None known.

INTERACTIONS

DRUGS

Antibiotics: Concomitant use with sesame seed lignans may decrease the production of the mammalian lignans enterolactone (ENT) and enterodiol (END) from sesame seed lignans.

Diclofenac: The sesame lignan sesamol has been shown to attenuate the acute gastric injury in rats caused by the diclofenac NSAID via its cyclooxygenase–independent antioxidant effect.

NUTRITIONAL SUPPLEMENTS

A single dose of the sesame seed lignans sesamin and sesamolin (136 mg) was found to reduce the urinary excretion of co-administered gamma-tocopherol in a human study. The sesame seed lignans sesamin and sesaminol were found to elevate the gamma-tocopherol concentrations in the tissues and serum of rats and to inhibit the formation of the gamma-tocopherol metabolite 2,7,8-trimethyl-2(2′-carboxyethyl)-6-hydroxychroman (gamma-CEHC) and its excretion in the urine via inhibition of the cytochrome P450-CYP3A-dependent metabolism of gamma-tocopherol.

Dietary sesamin, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) synergistically increased the gene expression of enzymes involved in hepatic peroxisomal fatty acid oxidation in rats, but not the gene expression of enzymes involved in mitochondrial fatty acid oxidation.

Vitamin E (alpha-tocopherol) and sesamin synergistically lowered blood pressure and decreased oxidative stress and cerebral thrombogenesis in stroke-prone spontaneous hypertensive rats (SHR).

Dietary tocotrienol was found to reduce UVB-induced skin damage in hairless mice, and sesamin was found to enhance the tocotrienol effect. In the study, tocotrienol was shown to protect the skin more strongly than D-alpha tocopherol. It was observed that sesamin produced higher alpha- and gamma-tocotrienols in the skin of rats fed diets containing alpha- and gamma-tocotrienols along with sesamin.

It has been demonstrated that the feeding of the sesame lignans sesamin and sesaminol to rats on a low D-alpha tocopherol diet or on a low gamma-tocopherol diet elevates alpha-tocopherol or gamma-tocopherol, respectively, in plasma, liver, kidney and brain. No change in either alpha-tocopherol or gamma-tocopherol levels was found when the sesame seed lignans were replaced by either the flaxseed lignan, secoisolariciresinol diglucoside (SDG), or the spruce lignan, 7-hydroxymatairesinol (HMR). Interestingly, both SDG and HMR are dibenzylbutyrolactone-type lignans, while the sesame lignans are tetrahydrofurofuran-type lignans.

FOODS

No known interactions.

HERBS

An extract of *Schisandra chinensis* berry, when combined with sesamin, was found to decrease blood viscosity and improve blood fluidity in a human clinical study.

OVERDOSAGE

There are no reports of flaxseed lignan overdosage.

DOSAGE AND ADMINISTRATION

Sesamin and other sesame seed lignans have been studied at doses of 300 mg to 400 mg daily for prolonged periods of time without any significant adverse events noted. However, the optimal dose for human consumption is not known.

The amount of sesamin in sesame seeds averages about 4 mg per gram.

Sesamin in capsules of 500 mg are available and used by bodybuilders for supposed weight reduction.

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Shark Cartilage

DESCRIPTION

Shark cartilage became popular as a nutritional supplement a number of years ago, based on the claim that sharks do not get cancer and that this substance must therefore be useful for the prevention and treatment of cancer. The fact is that sharks do get cancer. The claim that sharks do not, or rarely, get cancer originates from a 1992 book written by I. William Lane entitled *Sharks Don't Get Cancer.* In a 2004 review article published in *Cancer Research* and written by Gary Ostrander and his colleagues, both malignant and benign neoplasms of sharks and their relatives were described, including previously unreported cases from the Registry of Tumors in Lower Animals and two sharks with two cancers each. Although some components of cartilage, including shark cartilage, might have anticancer potential, the best scientific evidence to date supports neither the efficacy of crude shark cartilage extracts nor the ability of possible effective components to reach and irradicate cancer cells.

Cartilage is a tissue that lacks blood vessels and rarely develops malignancies. Angiogenesis, the formation of new capillaries, is now known to be important in a number of pathological conditions, including solid tumors, proliferative retinopathy, neovascular glaucoma and rheumatoid arthritis. The process is also important in other physiological events as well, such as neovascularization following coronary artery occlusion.

In 1976, Judah Folkman and his colleagues reported on the isolation of a fraction from the scapular cartilage of calves that inhibited the growth of new blood vessels supporting implanted tumors in rabbits. It also stopped the growth of the tumors. Subsequent reports demonstrated a fraction in shark cartilage that also inhibited tumor neovascularization and growth.

The study of angiogenesis inhibitors has become a new field in cancer research. Since the earliest anti-angiogenesis substances discovered were derived from cartilage, research continues looking at cartilage to try to identify and characterize novel anti-angiogenic agents. Because sharks are an abundant source of cartilage, shark cartilage is being used by several research groups.

Sharks have an endoskeleton comprised entirely of cartilage, and while cartilage comprises less than 0.6% of the body weight of calves, it comprises about 6% of the body weight of sharks. Shark cartilage, like other forms of cartilage, is mainly composed of collagen, which participates in giving cartilage its tensile strength, and proteoglycans, themselves composed of a core protein to which is attached polysaccharides known as glycosaminoglycans or mucopolysaccharides. Proteoglycans impart resilience to cartilage. The main glycosaminoglycans in shark cartilage are the chondroitin sulfates. In addition to collagen and chondroitin sulfate, shark cartilage contains about 5 to 10% water, a large percentage of calcium and phosphate, low-molecular-weight proteins and polypeptides. A few low-molecular-weight proteins and polypeptides that appear to possess antiangiogenic activity have also been identified in shark cartilage. These substances are being researched as possible therapeutic candidates.

ACTIONS AND PHARMACOLOGY

ACTIONS

Shark cartilage has putative antitumor, antioxidant, anti-inflammatory and anti-atherogenic actions, although these putative actions are so far poorly supported by credible clinical research.