hypertension and elevated serum lipids. EPO has been used with some preliminary success in some cancers, principally cerebral gliomas. It has not proved useful for tardive dyskinesia, premenstrual syndrome or menopausal flushing. It may be indicated in some cases for atopic dermatitis, particularly to help with itching, as well as for uremic skin conditions in hemodialysis patients. It should probably not be used in efforts to enhance immunity as it may be immunosuppressive.

RESEARCH SUMMARY

See GLA.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Known hypersensitivity to an EPO-containing product.

PRECAUTIONS

Pregnant women and nursing mothers should avoid EPO supplements. Those with a history of partial complex seizure disorders, such as temporal lobe epilepsy, should avoid using EPO. Likewise, those with other types of seizure disorders and schizophrenics who are being treated with certain neuroleptic drugs, such as aliphatic phenothiazines (e.g., chlorpromazine), which may lower seizure threshold, should avoid using EPO. Because of possible antithrombotic activity of EPO, those with hemophilia or other hemorrhagic diatheses and those taking warfarin should exercise caution in the use of this supplement.

EPO supplementation should be halted before any surgical procedure. Because of its possible inhibition of lymphocyte function, those with immune deficiency disorders, such as AIDS, should exercise caution in the use of EPO.

ADVERSE REACTIONS

EPO may cause gastrointestinal symptoms like nausea, vomiting, flatulence, diarrhea and bloating. Headaches have also been reported in those taking EPO. It may precipitate symptoms of undiagnosed complex partial seizures and should be used, if at all, with extreme caution in those with a history of seizure disorder or those taking drugs that lower the seizure threshold, such as aliphatic phenothiazines.

INTERACTIONS

DRUGS

Use of EPO in schizophrenics who are being treated with certain neuroleptic agents which lower seizure threshold e.g., aliphatic phenothiazines, such as chlorpromazine, may cause partial complex seizures (e.g., temporal lobe epilepsy), as well as other types of seizures. Interactions may occur between EPO and warfarin, aspirin and NSAIDs. Such interactions, if they were to occur, might be manifested by nosebleeds, increased susceptibility to bruising and hematuria. If these symptoms occur, EPO intake should be stopped.

NUTRITIONAL SUPPLEMENTS

Interactions may occur if EPO is used with supplements that have antithrombotic activity, such as fish oils. This may be manifested by nosebleeds and increased susceptibility to bruising.

HERBS

Interactions may occur if EPO is used with such herbs as garlic (*Allium sativa*) and ginkgo (*Ginkgo biloba*). Such interactions may be manifested by nosebleeds and easy bruising.

OVERDOSAGE

There are no reports of overdosage with EPO.

DOSAGE AND ADMINISTRATION

EPO is available in capsules and also in topical preparations for cosmetic use. A capsule of EPO typically contains about 9% GLA. Doses used for the management of rheumatoid arthritis range from about 360 milligrams to 2.8 grams daily in divided doses (expressed as GLA). For management of atopic dermatitis, doses of 320 to 480 milligrams daily are used in divided doses (expressed as GLA). Doses of up to 2 grams daily (expressed as GLA) have been used by those with hypertriglyceridemia. EPO supplements should contain an antioxidant, such as vitamin E, to protect the unsaturated fatty acids against oxidation.

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See GLA monograph for additional literature.

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Fisetin

DESCRIPTION

Fisetin is a member of the flavonol subclass of flavonoids. Related members of the subclass include kaempferol, myricetin and quercetin. Fisetin is found in fruits, including strawberries, persimmons, kiwi fruit, peaches, grapes, apples

and tomatoes, and in vegetables, including onions and cucumbers. Fisetin was a little known flavonoid until October 2006, when scientists from the Salk Institute reported that fisetin was found to boost memory in mice by stimulating the signaling pathways that enhance long-term memory and also play an important role in memory formation. Since cognitive deficits are common in those 60 years and older, this finding was looked upon as being a very significant one. Interestingly, older rats fed a diet enriched in strawberry extract for two months did much better in a test that measured cognitive performance than rats fed a control diet. Strawberries appear to be the highest natural source of fisetin.

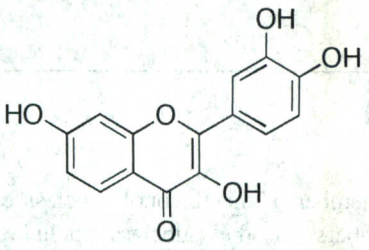
Research is ongoing on the neuroprotective and cognitive-enhancing activities of fisetin. In addition, fisetin has also been found to have possible anticancer activity, including against prostate cancer.

Fisetin is chemically described as 2-(3,4-dihydroxyphenyl)-3,7-dihydroxy-4*H*-1-benzopyran-one and 3,3′,4,7-tetrahydroxy-2-phenylchromen-4-one. It is also called 3,3′,4′,7-tetrahydroxyflavone, 6-desoxyquercetin and fisidenolon. Its CAS registry number is 528-48-3, its empirical formula is $C_{15}H_{10}O_6$ and its molecular weight is 286.24

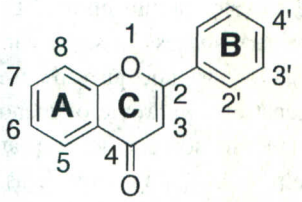
Fisetin usually is found in plants as the glycoside fisetin-8-glucoside.

All flavonoids possess a basic 15-carbon skeleton that can be represented as C_6-C_3-C_6 (see figure). The common structure is that of a diphenylpropane molecule, consisting of two aromatic rings linked through the three carbons. Flavonoids differ in the saturation of the heteroatomic ring C, in the placement of the aromatic ring B at positions C-2 or C-3 of ring C and in the overall hydroxylation or methoxylation patterns.

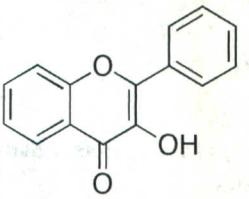
Flavonols possess a hydroxyl group on position 3 of the C ring (see figure), and fisetin possesses an additional three hydroxyl groups, one on position 7 of the A ring and the other two on the B ring (see figure). The chemical structures below are described within this monograph.



Fisetin



Flavonoid Skeleton



Flavonol Skeleton

ACTIONS AND PHARMACOLOGY

ACTIONS

Fisetin has antioxidant activity and possible antiallergy, anticancer, anti-inflammatory, cognition-enhancing and neurotropic activities.

MECHANISM OF ACTION

Antiallergy effects: Fisetin was found to inhibit T helper (Th) 2-type cytokine production by activated human basophils. The flavonoid was also demonstrated to have anti-inflammatory activity in activated human mast cells.

Activation of basophils via allergen stimulation releases cytokines, including interleukin (IL)-4, interleukin (IL)-13 and interleukin (IL)-5. These T helper 2-type cytokines are major participants in the allergic response and are key substances related to Ig (immunoglobulin) E production.

Mast cells also play a major role in the pathogenesis of allergic disorders. Activation of mast cells releases a number of inflammatory mediators, including histamine, cysteinyl leukotrienes, cytokines and chemokines. Fisetin was shown to modulate the inflammatory reaction in activated human mast cells.

The mechanism of fisetin's possible antiallergy action is unclear.

Anticancer activity: Fisetin has been shown to decrease the viability of three human prostate cancer cell lines: LNCaP, PC-3 and CWR22Rv1, and to have minimal effect on normal prostate epithelial cells. Fisetin demonstrated both cell-cycle arrest and apoptosis in human prostate cancer LNCaP cells.

The cell cycle is regulated by the cyclins in partnership with the cyclin-dependent kinases (CDKs). Fisetin was shown to induce arrest in the G1 phase of the cell cycle, accompanied by decreased levels of cyclins and CDKs and concomitant induction of the CDK inhibitors p21 and p27. Fisetin also

was found to induce apoptosis in the LNCaP cells, associated with the release of mitochondrial cytochrome c into the cytosol of the cells. The caspases, also known as "executioner" proteins, play essential roles in programmed cell death, or apoptosis. Eleven human caspases have so far been described. Fisetin treatment of LNCaP cells activated caspases-3,-8 and -9. Pretreatment of the cells with a caspase inhibitor blocked the fisetin activation of these caspases.

Fisetin has also been demonstrated to inhibit the proliferation of the human cancer cell line HT-29. The inhibition of proliferation of these cells was accompanied by decreases in the activities of the cyclin-dependent kinases (CDKs) CDK2 and CDK4, as well as decreases in the levels of cyclin E and D1, and an increase in the CDK inhibitor p21.

Antioxidant activity: Fisetin is a polyphenol and, like other polyphenols, it can scavenge reactive oxygen and nitrogen species such as hydroxyl radicals, superoxide anions and peroxynitrite radicals. It can also inhibit the peroxidation of lipids. However, it has more specific antioxidant activities that it does not share with other polyphenolics, such as the ability to maintain reduced glutathione (GSH) levels in nerve cells and the ability to activate the transcription factor Nrf2, which in turn activates the antioxidant response element (ARE). GSH is the major intracellular antioxidant.

Peroxynitrite is one of the most potent of the reactive oxygen and reactive nitrogen species that cells encounter. Treatment of rat neurons with the peroxynitrite donor, SIN-1 (3-morpholino-sychonimine), was demonstrated to decrease intracellular GSH levels and cell viability. Extracellular signal-related kinases 1/2 (ERK 1/2) are kinases downstream from Ras, Raf and MEK that are ultimately responsible for the phosphorylation of key activator proteins within the cell. The peroxynitrite treatment of the neurons led to hyperphosphorylation of ERK 1/2 and decreases in the phosphorylation of c-Myc, decreased expression of glutamate cysteine ligase (GCL) levels, the rate-limiting enzyme for GSH biosynthesis, decreases in the levels of intracellular GSH and a reduction in the nuclear expression of the transcription factor Nrf-2, which activates the antioxidant response element (ARE). Fisetin was found to abolish all of these peroxynitrite-mediated changes. More study is required to completely understand this unique antioxidant mechanism of fisetin.

Anti-inflammatory activity: Fisetin has been reported to suppress the inflammatory effects of lipopolysaccharide (LPS)-induced microglial activation and neurotoxicity in microglial cells in *vitro*.

Microglial cells are innate immune cells in the central nervous system (CNS) and are the CNS's first and main form of active immune defense. However, activation of glial cells can also have negative effects, such as causing CNS neuroinflammation, which plays an important role in neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease. Activation of microglial cells can produce various proinflammatory cytokines and nitric oxide (NO). Fisetin was found to suppress the production of tumor necrosis factor (TNF)-alpha, NO and prostaglandin (PGE_2), and to inhibit the gene expression of TNF-alpha, interleukin (IL)-1beta, cyclooxygenase (COX)-2 and inducible nitric oxide synthase (iNOS) at both mRNA (transcription) and protein (translation) levels in LPS-stimulated microglial cells.

Cognition-enhancing activity: Fisetin has been demonstrated to have significant effects on memory in a mouse object-recognition task assay study.

As discussed above, fisetin has been found to have neurotrophic activity, promoting the differentiation of nerve cells. The induction of nerve differentiation by fisetin depends to a large degree on the activation of the Ras-ERK (extracellular signal-regulated kinase) cascade. ERK activation ultimately leads to the phosphorylation and activation of the transcription factor CREB (cyclic AMP response element-binding) protein, and CREB activation appears to be a critical step in the signaling cascade that leads to the structural changes underlying the development of long-term potentiation.

Long-term potentiation (LTP) is the long-lasting enhancement in communication between two neurons that results from stimulating them simultaneously. LTP results in the strengthening of synaptic connections. LTP is considered to be an important model as to how memory is formed at the cellular level. Thus, the activation of the Ras-ERK cascade in neuronal cells by fisetin could result in changes in the brain that form the cellular basis of memory. Since neurons communicate by chemical synapses, LTP and its opposite process, long-term depression, are arguably the major cellular mechanisms that underlie learning and memory. Clearly, many more studies in this important area are necessary and warranted.

Neurotrophic activity: Neurotrophic factors comprise a family of proteins that play critical roles in the development, growth, maintenance and survival of nerve cells. Changes in the levels of these factors and/or their receptors are involved in the pathophysiology of neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis and Huntington's disease. However, the use of these factors in the treatment of neurodegenerative disease has been less than successful. Proteins are not easy to deliver to the brain and their bioavailability in the brain is poor. In a study looking at various small molecules that had possible neurotrophic properties, fisetin emerged as a strong candidate. Using an

assay for neurotrophic factor withdrawal with primary cortical neurons derived from rat embryos, it was demonstrated that these cells, which typically die within 24 hours in the absence of neurotrophic factors, survived when treated with fisetin and produced long neurites (immature or developing neurons).

PC12 is a rat pheochromocytoma cell line used as a model system for neuronal differentiation. In a study with PC12 cells, it was shown that fisetin promoted neuronal differentiation and was found to promote neuronal survival when exposed to oxidative stress.

In both of the above studies, the neurotrophic activity of fisetin (3,7,3′,4′ tetrahydroxyflavone [THF]) was compared with seven derivatives of fisetin: 3,3′ dihydroxyflavone, 3,4′ dihydroxyflavone, 3′4′ dihydroxyflavone, 3,3′,4′ trihydroxyflavone, 3,7,3′ trihydroxyflavone, 3,7,4′ trihydroxyflavone and 7,3′4′ trihydroxyflavone. In both protection from oxidative stress-induced death and in induction of PC12 cell differentiation, it turned out that although fisetin had good neuronal differentiation activity and good neuronal survival activity when faced with an oxidative stress challenge, both of these activities were somewhat better in the hands of 3,3′,4′ trihydroxyflavone. However, in the neurotrophic factor withdrawal assay, fisetin was found to be more effective than 3,3′,4 trihydroxyflavone. Analysis of the chemical structural requirements for the neurotrophic activity lead to the following conclusions: The best activity is obtained when there is a phenolic hydroxyl group in the C3 position, when there is 3′,4′ dihydroxy or catechol structure in the B ring and when there is unsaturation in the C ring. Also, the more hydrophilic the structure, the better the penetration into the nerve cells. Further, the 3-hydroxyl structure appears to antagonize the survival-promoting effects of fisetin, while the 7-hydroxyl structure enhances the survival-promoting effects, and a minimum of three hydroxyl groups seems optimal for both the differentiation effect and the promotion of survival effect in the neurotrophic factor withdrawal assay.

Although the mechanism of the neurotrophic effect of fisetin is not completely understood, there are a few things that can be said. The effect may be a result of antioxidant activity; there may be activation of signaling pathways, for example, the Ras-ERK cascade; glutathione levels may increase; and there may be increased proteasome activity in the neurons.

One can look at biological antioxidation in a number of ways. Fisetin and the fisetin derivatives are polyphenols, and polyphenols are known to be scavengers of superoxide anions and hydroxyl radicals and to protect against lipid peroxidation. Fisetin and the fisetin derivatives do all of that, but does that have anything to do with its neurotrophic activity? There are a number of assays for antioxidant activity, including TEAC, or the Trolox equivalent activity concentration. There was no correlation with antioxidant activity of fisetin and the various derivatives, as determined by the TEAC value, and protection from oxidative stress-induced death. The tripeptide, reduced glutathione (GSH), is the major cellular antioxidant. Fisetin can increase intracellular levels of GSH, while stress secondary to neurotrophic withdrawal can decrease levels. However, enhancement of GSH levels did not appear to play a significant role in the survival-promoting activity of fisetin or any of the fisetin derivatives.

Cells possess a number of different endogenous antioxidant mechanisms. Induction of phase II detoxification enzymes, including heme oxygenase (HO-1), can provide significant antioxidant protection of cells. The activation of the transcription of the genes for the phase II detoxification enzymes is via the *cis* acting enhancer, the antioxidant response element (ARE). Activation of the ARE is via the leucine zipper transcription factor Nfr2. A good way to determine if induction of heme oxygenase-1 by fisetin and its derivatives plays a role in their neurotrophic activity is to assay the activity of heme oxygenase-1. Activation of ARE and subsequently of heme oxygenase-1 does not appear to play a significant role in the neurotrophic activity of these flavonoids.

Fisetin and its derivatives activate several signaling pathways, some of which may be involved in protection of cortical neurons from trophic factor withdrawal. Fisetin, as well as some of its derivatives, can activate the Ras-ERK signaling pathway, and it appears that this mechanism may play a role in the neurotrophic activity of fisetin.

The proteasome is a large protein complex whose main role is to degrade unneeded or damaged proteins by proteolysis. Proteins are tagged for degradation by a small protein called ubiquitin, catalyzed by the enzyme ubiquitin ligase. This is a major biological housekeeping function. Recently, it has been learned that proteasomes have other functions, as well. Proteasome activity appears to be required for axon initiation, elongation and maintenance in primary, postmitotic neurons. Also, recently, it has been observed that proteasome activity is decreased in a number of degenerative neurological disorders, including Alzheimer's disease and Parkinson's disease. Therefore, increasing proteasome activity might play a critical role in the elimination of abnormal and oxidized proteins. Fisetin and several of its derivatives appear to enhance proteasome activity in a nerve cell line and this may account, in part, for the neurotrophic activity of fisetin. It is clear that much work needs to be done, and is certainly warranted, in order to better understand the mechanism of action of the neurotrophic activity of fisetin.

PHARMACOKINETICS

Very little is known about the pharmacokinetics of fisetin. The major food form of fisetin appears to be the glycan, fisetin-8-glucoside. After oral intake of fisetin-8-glucoside, it is likely that some is absorbed at the level of the small intestine and some may travel to the large intestine and undergo metabolism by bacterial enzymes and then get absorbed. The fisetin produced from the metabolism of fisetin-8-glucone and the fisetin-8-glucoside absorbed from the small intestine are likely to be very rapidly metabolized to form glucuronides and sulfates. The various metabolites are likely to be transported to various tissues of the body. Based on murine studies on the cognition-enhancing effects of fisetin, it is very likely that fisetin can cross the blood-brain barrier and be transported into nerve cells. Much work is needed and warranted on the pharmacokinetics of fisetin.

INDICATIONS AND USAGE

There are preliminary indications in the research that the flavonoid fisetin may have neuroprotective, anti-inflammatory and anticancer effects.

RESEARCH SUMMARY

In a number of *in vitro* investigations, fisetin demonstrated potent neuroprotective effects. In one of these studies, fisetin suppressed activation of microglia, immune cells found in the central nervous system. Activation of these cells has been associated with production of proinflammatory cytokines and nitric oxide which can exert neurotoxic effects leading to various neurodegenerative diseases, including, it is claimed, Alzheimer's disease. Based upon the exhibited strong anti-inflammatory activity of fisetin in these microglia, the researchers concluded that fisetin might ultimately prove a useful therapeutic agent in the treatment of many neuro-inflammatory diseases. In another study, fisetin helped protect retinal ganglion cells from oxidative-induced death. The researchers suggested that fisetin might thus become a candidate for preventing/treating such ocular diseases as glaucoma, diabetic retinopathy and age-related macular degeneration. And in a test of fisetin in the small clot embolism model of cerebral ischemia in rabbits, the flavonoid significantly reduced behavioral deficits following stroke, further reinforcing the idea that this substance may have broad-spectrum neuroprotective effects. There is also experimental animal data indicating that fisetin might have the ability to enhance long-term memory through its neuroprotective actions. Clinical data in support of these findings are entirely lacking at this time. Studies in the clinical domain are needed and warranted.

There is also very preliminary *in vitro* evidence that fisetin might be helpful in disorders characterized by allergic inflammation. In one study related to this, fisetin was reported to strongly downregulate human mast cell activation. Mast cell activation is associated with release of such inflammatory mediators as histamine, cytokines, chemokines and leukotrienes. Here, too, more research is needed.

Though again very preliminary, there is some evidence emerging that fisetin might have useful anticancer effects. In an *in vitro* study of human colon-cancer cells, fisetin, in a dose-dependent manner, inhibited cancer cell growth. In another *in vitro* trial, fisetin induced apoptosis and cell-cycle arrest in human prostate cancer cells. Follow-up in animal and clinical trials is clearly warranted.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Fisetin is contraindicated in those who are hypersensitive to any component of a fisetin-containing product.

PRECAUTIONS

Those who wish to try fisetin supplements for the support of any health condition should first discuss its use with his or her physician.

The use of fisetin-containing supplements by pregnant and nursing women should be avoided.

ADVERSE REACTIONS

None known.

INTERACTIONS

DRUGS

None known.

DIETARY SUPPLEMENTS

None known.

OVERDOSAGE

There are no reports of overdosage.

DOSAGE AND ADMINISTRATION

The optimal dose of fisetin for health benefits is not known.

Several dietary supplements contain low and probably insignificant amounts of fisetin as part of a blend.

Dietary supplements containing only fisetin are expected to enter the nutritional supplement marketplace in the near future.

Strawberries are probably the richest natural source of fisetin. However, it would probably require consuming pounds of strawberries daily to achieve the various health benefits claimed for fisetin. Obviously, this is not recommended.

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Fish Oils

DESCRIPTION

Fish oils, also known as marine oils, are lipids found in fish, particularly cold water fish, and other marine life such as phytoplankton. These oils are rich sources of long-chain polyunsaturated fatty acids (LCPUFA) of the n-3 (omega-3) type. The two most studied fish oils are the 20 carbon eicosapentaenoic acid (EPA; C20:5n-3) and the 22-carbon docosahexaenoic acid (DHA; C22:6n-3). EPA contains five double bonds and DHA, six double bonds. These double bonds are all in the cis configuration. DHA is a vital component of the phospholipids of human cellular membranes, especially those in the brain and retina.

Both EPA and DHA are found naturally in the form of triacylglycerols or TAGs. The docosahexaenate in the triacylglycerols of fish oil appears to be primarily in the sn-2 position (the middle carbon) of glycerol whereas there is more random distribution of eicosapantaenoate over all three positions of glycerol.

In September 2004, the Food and Drug Administration (FDA) announced the following qualified health claim for EPA and DHA omega-3 fatty acids: "Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease. One serving of (name of food, typically an oily fish, such as salmon, tuna and herring) provides (x) grams of EPA and DHA fatty acids." In 2000, the FDA announced a similar qualified health claim for dietary supplements containing EPA and DHA omega-3 fatty acids and the reduced risk of coronary heart disease (CHD). The FDA recommended that consumers not exceed more than a total of 3 grams per day of EPA and DHA omega-3 fatty acids, with no more than 2 grams from a nutritional supplement.

ACTIONS AND PHARMACOLOGY

ACTIONS

Supplemental fish oils have triglyceride-lowering activity. They may also have anti-inflammatory, anti-thrombotic and immunomodulatory actions.

MECHANISM OF ACTION

EPA and DHA have several actions in a number of body systems. EPA and DHA lower elevated triglyceride levels. In the cardiovascular system, EPA and DHA have anti-arrhythmic properties. EPA and DHA have anti-inflammatory