SYNORx

Presents

LutiMax

a natural bioflavonoid product containing

Luteolin

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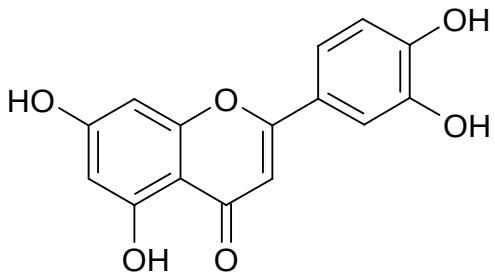
LUTEOLIN



$C_{15}H_{10}O_6$
Molar mass: 286.24 g/mol; CAS [491-70-3]

❖ General

- *Luteolin* (3´,4´,5,7-tetrahydroxyflavone) is a flavonoid widely distributed in the plant kingdom. It was isolated e.g. from *Reseda luteola L.*[1], *Achillea millefolium L.*[2], *Chamomillae requtita*[2,3], *Cynara scolymus*[4], *Thymus vulgaris, Limonium sinuatum*[5], *Vitex rotundifolia*[6], *Erigeron canadensis L.*[7,8], *Sophora angustifolia*[9], *Satureja obovata*[10], *Lonicera japonica*[11,12]. It was also found in *Propolis*, the bee glue.
- Chemically, *Luteolin* is a yellow microcrystalline powder. It is sparingly soluble in water, but soluble in alkali.

PHYSIOLOGICAL BENEFITS

Among possible therapeutic applications of oral *luteolin* are allergies, chronic inflammatory conditions (respiratory, gastrointestinal, musculoskeletal, etc) atherosclerosis and other vascular disorders, neoplastic disorders, diabetes and obesity. Externally *luteolin* can be used for skin allergic/inflammatory disorders and for skin cancer prevention. *Luteolin* is a promising agent for use in ophthalmology: for prevention and treatment of cataract and of vascular eye disorders.

Luteolin-containing herbal extracts have been used for a long time as traditional herbal remedies:

- Extracts from *Chamomillae requtita* (chamomile) and *Achillea millefolium L.* (yarrow), are rich in *Luteolin* and its 7-O-glycosides. They are well established in traditional medicine for a wide range of beneficial effects such as antiphlogistic, spasmolytic, analgesic and also moderate antihistamine properties.
- Extracts from *Cynara scolymus,* leaves of artichokes, are known for such properties as carminative (facilitating the eructation of gas from the stomach), spasmolytic and anti-emetic (reducing nausea). The dyspeptic syndrome, chronic gastrointestinal and metabolic diseases are traditional indications. Extracts from

artichoke also show hepatoprotective properties, strong antioxidative effects and reduce the cholesterol biosynthesis. This can be beneficial in artherosclerosis

- *Thymus vulgaris*, (thyme) extracts are used for spasmolytic and cough-relieving effects on bronchial diseases.
- *Vitex rotundifolia*, an evergreen shrub common to Eastern Asia, is used in Chinese medicine for the treatment of inflammation, headache and neuralgia
- *Propolis*, the bee glue, is also rich in *Luteolin* and its 7-O-glycosides. It is traditionally used in ointments and creams for the treatment of a variety of ulcers and eczemas.

❖ Antioxidant Activity

- *Luteolin*, constituent of artichoke leaf extract, showed a concentration-dependent inhibitory activity in several models of oxidative stress.[13]
- The antioxidant potential of *Luteolin*, measured in Trolox test, is twice stronger than that of vitamin E[14,15]. *Luteolin* is a significantly more potent antioxidant than the synthetic antioxidant butylated hydroxytoluene (BHT), which is generally used in oxygen sensitive processes[16].
- *Luteolin* has strong scavenging properties for superoxide radicals[20,17].
- *Luteolin* is a potent physical quencher of singlet oxygen[18]. *Luteolin* inhibits single strand break in DNA induced by singlet oxygen in a dose-dependent manner. Chromosomal aberrations are probably one of the causative incidents in the formation of cancer.

Via enzymatic process:

- Xanthine oxidase is considered to be the most prominent biological source of harmful superoxide radicals[19]. *Luteolin* is a strong competitive inhibitor of xanthine oxidase[20,19,17], which results in a reduced formation of H_2O_2. Some recent results showed an IC50 of 7,83 μM.[21]

Lipid Peroxidation

Lipid peroxidation leads to the oxidation of polyunsaturated fatty acids and subsequently to the formation of harmful compounds which are involved in the etiology of many diseases.

- *Luteolin* inhibits enzymatic and nonenzymatic-induced lipid peroxidation in rat liver homogenate[22,23].
- *Luteolin* shows strong antioxidant activities in vitro. *Luteolin* inhibited lipid peroxidation induced by $FeCl_2$ in rat liver (IC50 = 2,64 μg/ml). The effect was dose-dependent.
- The inhibiting effect of several flavonoids on CCl_4-induced lipid peroxidation of rat liver microsomes was studied. *Luteolin* was among the most effective[24].´

❖ Cardiovascular Activity

Luteolin affects the pathogenesis of atherosclerosis by several mechanisms: inhibiting cholesterol biosynthesis at different levels, increasing elimination of cholesterol from liver and inhibiting LDL oxidation.

- *Luteolin* causes an inhibition of cholesterol biosynthesis up to 60 % at EC_{50} values of 30µM[4,25].
- *Luteolin* showed the ability to increase coronary flow and relaxation velocity in perfused isolated guinea pig hearts[26].
- *Luteolin* and also *Luteolin-4´-O-glycoside* decreased the incidence and the importance of hyperkinetic ventricular and reperfusion arrhythmias.[27]
- Pretreatment of guinea pigs with *Luteolin* reduced significantly the ischaemic area by 43 % in experimental cardiac infarction
- *Luteolin* has moderate effects on blood coagulation *in vitro*[28]
- Experiments in cats and dogs showed that *luteolin* had significant effects on reducing blood pressure[29]

Due to vasodilatory properties

- *Luteolin* exhibits important vasorelaxant behavior. This was demonstrated on smooth muscle cells of rat aorta and rabbit thoracic aorta.[10,30] Vasorelaxation or inhibition of contraction is mediated by the influx or release of Ca^{2+}; the mechanism of vasodilatory action of *luteolin* apparently involves inhibition of protein kinase C and possibly the inhibition of cyclic nucleotide phosphodiesterase.[31,32]

Due to antiinflammatory properties

- *Luteolin* inhibits platelet aggregation, platelet thromboxane synthesis. It protects against endothelial injury induced by hydrogen peroxide and linoleic acid hydroperoxide (LOOH). Synergistic action with alpha-tocopherol against LOOH-induced cell damage is reported.[33,34]

❖ Cancer prevention and treatment (anticarcinogenic, antimutagenic, antiangiogenic properties

Luteolin in the low micromolar range inhibits the proliferation of normal and tumor cells, as well as in vitro angiogenesis. Inhibition of extensive neovascularization can contribute to prevention of certain chronic diseases, including solid malignancies. *Luteolin* shows strong antiproliferative activity against different human cancer cell lines (in some hormone-dependent cancer lines such as breast, prostate, and thyroid cancer for instance)[35,36,37,38,39].

- *Luteolin* inhibits tyrosine kinase, an enzyme involved in tumor cell proliferation. By modulating the activity of enzymes, toxicity and carcinogenicity of various xenobiotics may be affected[40].
- *Luteolin* is an important dietary cancer preventive agent[20,41,42]. Several studies demonstrated that the addition of *Luteolin* to the diet of rats inhibits the clastogenicity of salted, sun-dried, broiled and deep-fried food[43].
- *Luteolin* has strong chemopreventive activity by reducing the formation of carcinogens in food such as heterocyclic amines, polycyclic aromatic hydrocarbons and N-nitroso compounds from precursors. *Luteolin* is able to block the activation of carcinogens, increase the detoxification of carcinogens and stimulate the error-free DNA repair.

- 20-Methylcholanthrene is a strong mutagen that induces fibrosarcoma in 100% of mice fed with it. Dietary supplementation with *Luteolin* along with 20-methylcholanthrene showed a significant reduction on tumor expression to 60 %. The tumor growth and tumor volume decreased to 85 % compared with the control at the end of the experimental period[44].
- *Luteolin* has potential anticarcinogenic effects against estrogen-induced mammary carcinogenesis[45,46].

The ability of *luteolin* to inhibit N-acetlytransferase (see section antibacterial) is relevant also for its antineoplastic properties. *Luteolin* inhibited the arylamine N-acetyltransferase activity and DNA-2-aminofluorene adduct formation in human and mouse leukemia cells for 24h.[47]

Luteolin displays potent antimutagenic action against some dietary carcinogens (e.g. polychlorinated biphenyl).[48]

❖ Anti-inflammatory Activity

Luteolin is a component of herbs with anti-inflammatory action and has itself demonstrated effectiveness against inflammatory processes.
Inflammation responses are involved in the pathogenesis of atherosclerosis, rheumatoid arthritis, diabetic neuropathy and many other diseases.

- *Luteolin* decreases the formation of PAF due to the inhibition of lysoPAF acetyltransferase[12] (IC50= 45mM). (Platelet Activating Factor; PAF is a strong mediator involved in inflammation, anaphylactic reaction, etc). *Luteolin* is a strong non-specific inhibitor of platelet aggregation in rabbit aorta induced by arachidonic acid[30,49]
- It has been reported that anti-inflammatory properties of *luteolin* are related to its lipooxygenase inhibition activity. Reportedly, inhibition of both 12-lipoxygenase (12-LO) and 5-lipoxygenase (5-LO) are involved The inhibitory effects of flavonoids on arachidonate 12-lipoxygenase and 5-lipoxygenase were investigated. *Luteolin* was one of the most active compounds with IC_{50} = 20nM and 102nM, respectively in rat platelets and polymorphonuclear leukocytes.[50]
- Chen et al. demonstrated anti-inflammatory activity of *luteolin* in various animal models, such as inflammations induced by xylene, carrageenin, AcOH, croton oil, and some immunological agonists.[51] *Luteolin* also inhibited acute hypersensitivity in the ileum. Recently anti-inflammatory activity of *luteolin* was shown in oxazolone- and TPA-induced ear edema in mice.[52] *Luteolin* apparently inhibited the sensitization step, selectively inhibiting IgE.
- Tordera et al. studied the effects of *luteolin* on degranulation and arachidonic acid release in rat neutrophils.[53] The authors assessed the effects of 24 flavonoid derivatives, reported as anti-inflammatory, on lysosomal enzyme secretion and arachidonic acid release. *Luteolin* (along with apigenin, fisetin, kaempferol, and quercetin) was among the most potent inhibitors of beta-glucuronidase and lysozyme release. A correlation between degranulation and arachidonic acid release was found.
- Due to its skin-penetrating ability *Luteolin* was suggested for topical use as antiphlogistic agent[54].
- The efficacy of *Luteolin* was demonstrated against acetic acid-induced acute pleurisy (inflammation of the pleura membrane that lines the chest and contains the

lung), in rats with results showing a significant reduction in pleural exudate volume with no obvious changes in total exudate leukocyte number.[55]

- *Luteolin* suppressed nitric oxide production possibly through reduction of inducible nitric oxide synthase (iNOS) enzyme expression[56]. (Nitric oxide is produced by iNOS and is a mediator of inflammation.)

❖ Antidiabetic Activity and applications related to its complications

❖ Hypoglycemic action

- *Luteolin* inhibits alpha-glucosidase and alpha-amylase.[57] *Luteolin* inhibited alpha-glucosidase by 36% at the concentration of 0.5 mg/ml, suggesting that it can suppress postprandial hyperglycemia in patients with non-insulin dependent diabetes mellitus. The glucosidase inhibitory potency of *luteolin* was stronger than that of acarbose (=glucobay), the widely prescribed antidiabetic drug. (Alpha-glucosidase inhibitors are antihyperglycemic agents that inhibit the digestion and absorption of complex carbohydrates, reducing the rise in postprandial blood glucose). *Luteolin* also inhibited alpha-amylase effectively, although it was less potent than acarbose.

❖ Prevention of diabetes complication

The impaired glycemic control in diabetes leads to oxidative stress, and numerous micro- and neurovascular abnormalities, including disturbances in microcirculation, capillary hypoxia, and ischemic syndrome. They are of relevance for major diabetic complications, such as: nephropathy (renal disease, and eventually, kidney failure), eye disease (cataract or diabetic retinopathy), neuropathy (different types of nerve damage), and vasculopathy (atherosclerotic coronary and peripheral vascular disease). Due to their antioxidative, anti-inflammatory, vasoprotective etc. actions *luteolin* and its glycosides can be considered for the prevention and treatment of diabetes-related tissue injuries.

- Inflammatory responses are involved in the pathogenesis of diabetic neuropathy and other diabetic complications. *Luteolin* is an efficient anti-inflammatory and anti-allergic compound.[58] It protects against endothelial injury induced by hydrogen peroxide and linoleic acid hydroperoxide. *Luteolin* and its glycosides inhibit platelet aggregation and platelet thromboxane synthesis. *Luteolin* and its glycosides strengthen capillary wall and reduce capillary permeability.[59] Strong antioxidative properties of *luteolin* are well established in many different settings.

- Anticataract action:

It has been proven that *Luteolin* and *also Luteolin-7-O-ß-glucopyranoside* are among the active principles of Chinese crude drugs used in the treatment of diabetic cataract, keratopathy and nephropathy[60, 61]. *Luteolin* isolated from flowers of

Buddleja officinalis inhibited *in vitro* lens aldose reductase, an enzyme involved in the complications of diabetes (IC50=0.21 mcM).

- Anti-obesity

The ability of *luteolin* to inhibit enzymes involved in the digestion and absorption of carbohydrates can be employed in nutritionnal supplements for weight control. (see paragraph on hypoglycemic action)

❖ Antiallergy Activity

(Stabilization of mast cells (mast cells are important target in allergy processes); inhibition of histamine release, of cytokine production, PAF production, etc.)

- Flavone *Luteolin* is considered as one of the most active anti-inflammatory and anti-allergic compounds among bioflavonoids. Particularly it has been shown to inhibit immunoglobulin (IG)E-mediated histamine release from human cultured mast cells, human basophils, murine mast cells. [62] Evidence indicates that *luteolin* is a potent inhibitor of human mast cell activation through the inhibition of Ca^{2+} influx and protein kinase C activation. [63]
- *Luteolin* inhibits the production of platelet-activating factor (PAF) in rat peripheral white blood cells at IC50=45μM.(PAF is a strong mediator involved in inflammation, anaphylactic reaction etc. *Luteolin* inhibits acetyl-CoA:1-alkyl-2-lyso-snglycero-3-phosphocholine (lyso PAF) acetyltransferase activity;this inhibition is considered specific, since *luteolin* does not suppress the activity of cholineacetyltransferase.
- Anti-allergic properties of *luteolin* were demonstrated in various models. Cheong et al. studied hexosaminidase release from RBL-2H3 (rat basophilic leukemia mucosal-type mastocytoma line) cells. The authors compared properties of 22 flavonoids and found that luteolin was one of the most effective (with IC50 value for degranulation less than 10 mM). Earlier Kawasaki et al. used the same model to screen 40 flavonoids for inhibitory activity on antigen-induced histamine release from IgE-sensitized RBL-2H3 cells. *Luteolin* inhibited histamine and LTB4 release from rat peritoneal mast cells;[64] histamine release from bovine mast cells, from rat peritoneal mast cells.[65] Shen demonstrated that *luteolin* inhibited release of histamine and of SRS-A (slow-reacting substance of anaphylaxis) from ovalbumin-sensitized lungs of guinea pigs.[66]

- Park et al. identified *luteolin* as the dose-dependent IL-5 inhibitor. Interleukin (IL)-5 is a chemotactic factor that promotes the growth and survival of eosinophils, and plays an important role in the eosinophilia-associated allergic inflammation. *Luteolin* and several related flavonoid compounds were isolated from *Kummerowia striata* Thurn. (*Leguminosae*). The inhibitory potency on IL-5 bioactivity was in the following order: *luteolin* 4'-O-glucopyranoside (IC50=3.7m M)> apigenin (16.4 m M) » *luteolin* (IC50=18.7 m M) > (30.0 mM).[67]

❖ Antiviral Activity

Viral diseases are a major public health concern given the lack of effective methods of treatment. *Luteolin* has demonstrated anti-viral activity.

- *Luteolin* demonstrated the ability to inhibit herpes simplex virus (HSV-1)[68].
- *Luteolin* exhibits anti-poliovirus activity[69].
- *Luteolin* shows moderate inhibitory effects on avian myeloblastosis virus reverse transcriptase[70].

❖ Antibacterial Activity

- *Luteolin* has bacteriostatic properties against *Staphylococcus aureus*[71].
- *Luteolin* inhibits the growth of *Helicobacter pylori*, likely by the inhibition of arylamine N-acetyltransferase. The same mechanism apparently is involved in the inhibition of *Neisseiria gonorrhoeae*. *Luteolin* dose-dependently inhibited growth of the *N. gonorrhoeae* cultures for at least 4 hours.[72]

❖ Gastrointestinal disturbances

- *Luteolin* has antiinflammatory and anti spasmodic actions.[73]
- It has been demonstrated that *luteolin* can dose-dependently inhibit the growth of *Helicobacter pylori*, which is associated with gastritis, gastric and duodenal ulcers, and possibly gastric cancers. It is suggested that *luteolin* acts as an uncompetitive inhibitor of arylamine N-acetyltransferase in *H.pylori*.[74,75]
- Chamomile tea, rich in *Luteolin*, is traditionally used for the treatment of stomach and intestinal complaints[76]. It has been demonstrated that *Luteolin* and other flavonoids exert a spasmolytic activity on isolated guinea pig ileum.

❖ Radioprotective Activity

Luteolin may protect from damage induced by ionizing radiation.

- *Luteolin* shows a radioprotective effect against micronuclei induction in γ-ray irradiated mice. It reduces the frequency of micronucleated reticulocytes in mice after exposure to in γ-ray[77].

❖ Topical Application

- *Luteolin* is suitable for topical application; it is not only adsorbed on the skin surface, but penetrates into deeper skin levels. *Luteolin* is a promising external antiinflammatory agent.
- *Luteolin* inhibits the activation of protein kinase C, enzyme involved in the tumor-promoting effect. This makes *Luteolin* a candidate for preventing skin cancer.[78]

❖ Other Beneficial Effects

- *Luteolin* is an active inhibitor of different hyaluronidases, which modify hyaluronic acid[79]. Hyaluronic acid, a heteropolysaccharide, is one the polymers that accounts for the toughness and flexibility of cartilage and tendon.
- *Luteolin* exhibits spasmolytic effects: *Luteolin* significantly antagonized acetylcholine- and histamine-induced contraction of smooth muscle in the guinea pig model of modified air overflow[80,81] and showed strong anti-histamine properties[82,83].
- *Luteolin* displays anti-leishmanial activity.[84]
- *Luteolin* displays strong antinociceptive (against pain originating from peripheral nerves) action in mice[85]. This is in accordance with the fact that *Luteolin* is an active principle of Brazilian plant *Wedelia paludosa*, traditionally used against the variety of disorders, including painful conditions.

- *Luteolin* exhibits estrogenic properties in rats[86,67]. While orally administered from day 1 to day 4 of pregnancy it showed dose-dependent anti-implantation activity. A single oral dose prevented 100% implantation. The mean effective dose was found to be 25 mg/kg body weight.

Respiratory tract disturbances

Due to its anti-allergic, anti-inflammatory and smooth muscle-relaxing properties, *luteolin* has potential in the prevention and treatment of many respiratory disorders, including asthmatic conditions, chronic bronchitis, etc.[94,96]

Ophtalmology

- Prevention of the neovascular disease of the eye: *Luteolin* strongly inhibits corneal angiogenesis in vivo.[87]

❖ Beneficial effects of *luteolin* glycosides

- *Luteolin* -7-glucoside (isolated along with *luteolin* from *Genista rumelica*) displayed pronounced capillary strengthening.

- *Luteolin*-7- O-glucoside and luteolin-4'-O-glucoside (from *Ligustrum vulgare* and *Phillyrea latifolia*, *Oleaceae*) presented "remarkable" complement inhibiting effect on the classical pathway. [88]

- *Luteolin*-7-glucoside reportedly protects from ischemic tissue injury (possibly due to its antioxidative and phosphodiesterase-inhibiting properties).[89]

- *Luteolin* 4'-O-glucopyranoside from *Kummerowia striata* Thunb. (*Leguminosae*) was identified as the IL-5 inhibitor.[90] Interleukin (IL)-5 is a chemotactic factor of eosinophils; it promotes the growth and survival of eosinophils, which play an important role in the eosinophilia-associated allergic inflammation.

- *Luteolin* 7-O-rutinoside (scolymoside) (isolated from *Artemisia montana*) has strong radical scavenging properties. Its antioxidant activity is comparable to that of L-ascorbic acid.

- Some *luteolin* glycosides are reported to have antidiabetic activities. Particularly, *luteolin*-5-O-β-rutinoside, isolated from medicinal plant *Salvia lavandulifolia* and given orally to diabetic rats (2 mg/kg for 20 days) reduced glycemia and increased pancreatic insulin and pancreatic DNA contents. The authors relate the effect to the antioxidative action of the flavonoid, e.g., prevention of oxidative stress that causes the destruction of β-cells.[91]

- Protective effect of *luteolin* and its glycosides against tissue injury can be realized through various mechanisms: decrease of capillary fragility, scavenging active oxygen species, inhibition of lipid peroxidation, inhibition of release of leukotrienes and TNF-alpha, suppression of adhesion of leukocytes to endothelium, and so on.[92]

BIOAVAILABILITY AND PHARMACOKINETICS

Preliminary studies in rabbits and rats using [^{3}H]-*luteolin* and fluorescence spectrophotometry examined the absorption, metabolism and excretion of *luteolin*[93,94]

❖ Metabolism and Absorption

- In rats orally administered [^{3}H]-*luteolin* was rapidly absorbed and distributed in various tissues, with highest concentrations in liver and kidney. A comparison of the concentration-time curve of protocatechuic acid (PCA) with that of *luteolin* indicates that PCA is a product of *luteolin*.[77,79]
- In order to know whether *Luteolin* was absorbed by the small intestine, perfusion of the jejunum with *Luteolin* was performed. The HPLC analysis of the serosal fluid followed by a treatment with β-glucoronidase enabled to know if *Luteolin* was absorbed and in which form (free or as glucoronide conjugates). The comparative absorption of flavonoids and their glycosides across the jejunum and ileum in a rat intestinal model showed that measured levels of *luteolin* as aglycone were small relative to the amount of total *luteolin* glucoronides recovered. Treatment with β-glucuronidase indicated the presence of at least six different glucuronides[95].

❖ Excretion

- *Luteolin* was rapidly removed from the blood via the kidney and the liver. 12h-urinary excretion in rabbits was 37.7% of the total i. v. dose. In rats the 6h-biliary excretion was about 11.2% of the total i. v. dose[77,79].

GENERAL SAFETY

❖ Toxicity of *Luteolin*

General

Luteolin is considered nontoxic

- The determination of LD50 in various animals did not show acute toxicity

LD_{50} of *Luteolin*			
Animal	Route	Dose	Reference
Mouse	Intraperitoneal	>180 mg / kg	[96,97]
Rat	Intraperitoneal	411 mg / kg	[98]
Rat	Intramuscular	592 mg / kg	[81]
Rat	Oral	>5000 mg/kg	SYNORx
Mouse	Oral	2500 mg / kg	[99,100]

Table 12: LD50 data of Luteolin

❖ Mutagenicity of *Luteolin*

General

Luteolin is considered non-mutagenic

- *Luteolin* shows no mutagenicity in the Ames test with or without activation[101].

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