Kroger H, Hauschild A, Ohde M, et al. Nicotinamide and methionine reduce the liver toxic effect of methotrexate. *Gen Pharmacol.* 1999;33:203-206.

Lewis CM, Canafax DM, Sprafka JM, Barbosa JJ. Double-blind randomized trial of nicotinamide on early-onset diabetes. *Diabetes Care.* 1992;15:121-123.

Ma A, Medenica M. Response of generalized granuloma annulare to high-dose niacinamide. *Arch Dermatol.* 1983;119:836-839.

McCarty MF, Russell AL. Niacinamide therapy for osteoarthritis—does it inhibit nitric oxide synthase induction by interleukin 1 in chondrocytes? *Med Hypotheses.* 1999;53:350-360.

Melo SS, Arantes MR, Meirelles MS, et al. Lipid peroxidation in nicotinamide-deficient and nicotinamide-supplemented rats with streptozotocin-induced diabetes. *Acta Diabetol.* 2000;37:33-39.

Miesel R, Kurpisz M, Kroger H. Modulation of inflammatory arthritis by inhibition of poly(ADPribose)polymerase. *Inflammation.* 1995;19:379-387.

Olsson AR, Sheng Y, Pero RW, et al. DNA damage and repair in tumour and non-tumour tissues. *Br J Cancer.* 1996;74:368-373.

Papaccio G, Ammendola E, Pisanti FA. Nicotinamide decreases MHC class II but not MHC class I expression and increases intercellular adhesion molecule-1 structures in non-obese diabetic mouse pancreas. *J Endocrinol.* 1999;160:389-400.

Pero RW, Axelsson B, Siemann D, et al. Newly discovered anti-inflammatory properties of the benzamides and nicotinamides. *Mol Cellular Biochem.* 1999;193:119-125.

Petley A, Macklin B, Renwick AG, Wilkin TJ. The pharmacokinetics of nicotinamide in humans and rodents. *Diabetes.* 1995;44:152-155.

Polo V, Saibene A, Portiroli AE. Nicotinamide improves insulin secretion and metabolic control in lean type 2 diabetic patients with secondary failure to sulphonylureas. *Acta Diabetol.* 1998;35:61-64.

Pozzilli P, Browne PD, Kolb H. Meta-analysis of nicotinamide treatment in patients with recent-onset IDDM. The Nicotinamide Trialists. *Diabetes Care.* 1996;19:1357-1363.

Stevens MJ, Li F, Drel VR, et al. Nicotinamide reverses neurological and neurovascular deficits in streptozotocin diabetic rats. *J Pharmacol Exp Ther.* 2007;320(1):458-464.

Takahashi Y, Tanaka A, Nakamura T, et al. Nicotinamide suppresses hyperphosphatemia in hemodialysis patients. *Kidney Int.* 2004;65(3):1099-1104.

Ungerstedt JS, Blömback M, Söderström T. Nicotinamide is a potent inhibitor of proinflammatory cytokines. *Clin Exp Immunol.* 2003;131(1):48-52.

Vidal J, Fernandez-Balsells M, Sesmilo G, et al. Effects of nicotinamide and intravenous insulin therapy in newly diagnosed type 1 diabetes. *Diabetes Care.* 2000;23:360-364.

Wan FJ, Lin HC, Kang BH, et al. D-amphetamine-induced depletion of energy and dopamine in the rat striatum is attenuated by nicotinamide pretreatment. *Brain Res Bull.* 1999;50:167-191.

Zimhony O, Cox JS, Welch JT, et al. Pyrazinamide inhibits the eukaryotic-like fatty acid synthetase I (FASI) of *Mycobacterium tuberculosis*. *Nature Med.* 2000;6:1043-1047.

Nobiletin

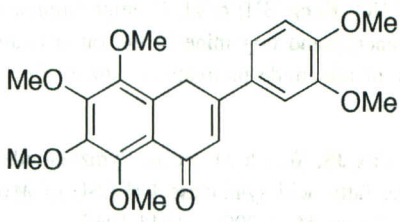
DESCRIPTION

Nobiletin is a member of the polymethoxyflavone family of flavones. Flavones themselves comprise a subclass of the large class of plant substances, the flavonoids. Polymethoxylated flavones (PMFs) exist almost exclusively in the *Citrus* genus, particularly in the peels and tissues of sweet oranges (*Citrus sinensis*), the peels and tissues of bitter oranges (*Citrus aurantium* L.) and, especially, the peels and tissues of tangerines *(Citrus reticulata* Blanco), including Dancy and Cleopatra tangerines and clementines. The two most common PMFs found in citrus peels are nobiletin and tangeretin (see Tangeretin). Sinensetin is the third most common PMF found in the peels and tissues of citrus fruits.

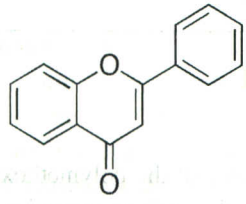
Nobiletin, like other flavonoids, is a plant secondary metabolite. Plant secondary metabolites comprise the defense system of plants against fungi, predators and pests, among other things. Mal seco is a fungal disease of citrus varieties, mainly lemons, caused by the pathogenic fungus *Deuterophoma tracheiphila* (or *Phoma tracheiphila)* and is widespread throughout the Mediterranean region. There is almost no nobiletin in lemons. Nobiletin, when inoculated in lemon seedlings infected with the mal seco fungus, was demonstrated to have strong fungistatic activity. Tangeretin was found to be weakly active. Nobiletin-containing citrus fruits are quite resistant to mal seco. Lemons (*Citrus limon*) and grapefruits (*Citrus paradisi*) are virtually devoid of nobiletin and other PMFs.

Recently, there has been great interest in studying nobiletin for its possible anti-inflammatory, anticarcinogenic, antiatherogenic and neuroprotective activities. It turns out that nobiletin and other PMFs appear to have greater oral bioavailability than their polyphenolic cousins.

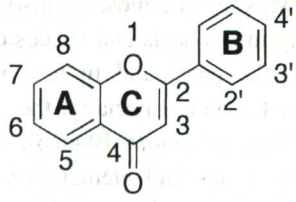
Nobiletin is chemically described as 5,6,7,8-tetramethoxy-2-(3,4-dimethoxyphenyl)-4H-1-benzopyran-4-one. Nobiletin is also known as 3′,4′,5,6,7,8-hexamethoxyflavone, and 5,6,7,8,3′,4′-hexamethoxyflavone. Its empirical formula is $C_{21}H_{22}O_8$ and its molecular weight is 402,39. The chemical structures below are described within this monograph.



Nobiletin



Flavone Skeleton



Flavonoid Skeleton

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. The polymethoxylated flavones have a benzo-gamma-pyrone skeleton with a carbonyl group at the C-3 position and methoxy groups in different positions on the benzo-gamma-pyrone skeleton. Polymethoxylated flavones (PMFs) typically do not possess free phenolic hydroxyl groups in their native structures (plants). And, in contrast to polyphenolic flavonoids that exist in their native states (in plants) as glycones, PMFs are typically aglycones in their native states.

ACTIONS AND PHARMACOLOGY

ACTIONS

Nobiletin has antifungal activity, particularly against the citrus pathogenic fungus *Deuterophoma tracheiphilia,* or *Phoma tracheiphila.* Nobiletin may have antiarthritic, antiatherogenic, anticarcinogenic, anti-inflammatory/immunomodulatory, neuroprotective, and cognitive-enhancing activities.

MECHANISM OF ACTION

Antiarthritic activity: In addition to the inflammatory processes that take place in the various arthritic disorders, there are other degenerative changes that lead to articular cartilage destruction.

The extracellular matrix in cartilage is mainly composed of type II cartilage, hyaluronic acid and aggrecan, a large aggregating proteoglycan. The loss of aggrecan in the matrix occurs early in the destruction of articular cartilage. This results in the disruption of the structural and functional integrity of cartilage. The enzymes aggrecanase-1 and aggrecanase-2 appear to play major roles in cartilage destruction in arthritic disorders. Nobiletin was shown to interfere with the IL(interleukin)-1beta-mediated aggrecanase-1 and aggrecanase-2 expression in cultured human synovial fibroblasts. And, in collagen-induced arthritic mice, nobiletin was found to suppress aggrecanase-1 and aggrecanase-2 mRNA expression in joint tissue, and to effectively inhibit aggrecanase-mediated degradation of aggrecan in cartilage, preventing cartilage destruction.

Antiatherogenic: Citrus polymethoxylated flavones, especially tangeretin, were found to significantly lower total cholesterol and LDL-cholesterol in hamsters. The mechanism of this putative lipid-lowering effect is unclear.

Unregulated uptake of oxidized low-density lipoproteins (ox-LDL), as well as modified LDL by macrophage scavenger receptors, are thought to be key events in the pathogenesis of atherosclerosis. The uptake of ox-LDL into the macrophage leads to their conversion to foam cells, a precursor to atheromas. Also, LDL modified by acetylation (acetyl-LDL) can be taken up by macrophage scavenger receptors into macrophages, where it undergoes oxidation, inducing foam cell formation. Nobiletin was found to inhibit the metabolism of acetylated LDL, suggesting a possible antiatherogenic role for this citrus flavone.

Anticarcinogenic activity: Nobiletin has been reported to induce differentiation of mouse myeloid leukemia cells, to show antiproliferative activity toward a human squamous cell line and to exert antimutagenic activity.

TPA (12,0-tetradecanoylphorbol-13-acetate) is a carcinogen that is known to cause malignant tumors in mouse skin. Nitric oxide (NO) appears to be closely associated with the pathogenesis of epithelial carcinogenesis. NO and superoxide (O_2^-) anions are generated when TPA is applied to human-differentiated promyelocyte HL-60 cells. When topical TPA is applied to ICR mouse skin, inflammatory and premalignant changes occur almost immediately, accompanied by the production of reactive oxygen and reactive nitrogen species. When nobiletin was applied to the mouse skin prior to the application of TPA, it was found to inhibit skin inflammation, oxidative stress and tumor promotion in the skin. The specific mechanism of this anticarcinogenic effect is not completely understood.

Nobiletin might have chemopreventive effects against colon carcinogenesis, partly via regulation of leptin levels.

Adipocytokines, including leptin, adiponectin and tumor necrosis factor–alpha (TNF-alpha), represent a group of adipocyte-secreted proteins that affect the metabolism of lipids and carbohydrates. It is thought that adipocytokines may be involved in the metabolic syndrome, the growing obesity epidemic, and other disorders. Recent studies suggest that some adipocytokines may even significantly influence the proliferation of malignant cells *in vitro*, and, possibly, *in vivo,* as well. When mice were injected with the carcinogen azomethane, the serum leptin levels in these mice were six times higher than in untreated mice. There were no significant differences in the levels of adiponectin, IL-6 or triglycerides. Colon tumors were also found in the mice. However, in mice that received azomethane and then given nobiletin orally, nobiletin was found to abolish colonic malignancy and significantly decreased leptin levels. In an HT-29 colon cancer cell line, nobiletin suppressed the leptin-dependent, but not the leptin-independent proliferation of cancer cells. Further, nobiletin decreased leptin secretion, but not that of adiponectin in differentiated 3T3-L1 mouse adipocytes, thought to be via inactivation of mitogen activated protein/extracellular signaling-regulated kinase (MEK). Thus, it appears that high levels of serum leptin may help promote colon carcinogenesis in mice, while nobiletin may have chemopreventive action against colon carcinogenesis, partly through regulation of leptin levels.

The activation of MEK is well known to be associated with tumor invasion and metastasis. Nobiletin has been shown to inhibit the phosphorylation of MEK, thereby suppressing MMP (matrix metalloproteinase) expression in a tumor-metastasis stimulator, TPA (12,0-tetradecanoylphorbol-13-acetate)-stimulated human fibrosarcoma HT-1080 cells. TPA was found to augment MEK activity in HT-1080 cells. However, the augmented MEK activity was diminished by nobiletin. This decrease was also found to inhibit the phosphorylation of extracellular regulated kinase, or ERK. Nobiletin appears to inhibit MEK activity and decrease the sequential phosphorylation of ERK, thus exhibiting antitumor metastatic activity by suppressing matrix metalloproteinase activity in HT-1080 cells.

Antifungal activity: The antifungal mechanism of action of nobiletin (see Description above) is not entirely clear.

Anti-inflammatory/immunodulatory: Articular cartilage destruction is a common feature in osteoarthritis, rheumatoid arthritis and other arthritic conditions. Matrix metalloproteinases (MMPs) appear to play important roles in the destruction of matrix components in the connective tissue of those with rheumatoid arthritis and osteoarthritis. Proinflammatory cytokines such as interleukin 1 (IL-1), TNF-alpha and interleukin-6 (IL-6) enhance the synthesis of precursors of MMPs, or proMMPs, and prostaglandin E2 (PGE2) from mesenchymal cells at inflammatory sites.

Nobiletin has been shown to effectively interfere with the production of proMMP-9/progelatinase B in rabbit synovial fibroblasts, to suppress the (IL-1)-induced production of PGE2 in human synovial fibroblasts, to selectively downregulate COX (cyclooxygenase)-2 but not COX-1 mRNA expression, to interfere with the lipopolysaccharide-induced production of PGE2 and the gene expression of proinflammatory cytokines, including IL-1alpha, IL-2beta, TNF-alpha and IL-6 in a mouse macrophage cell line, to downregulate the IL-2-induced gene expression and production of proMMP-1/procollagenase-1 and pro-MMP-3, or prostromelysin-1, in human synovial fibroblasts, and to upregulate the production of TIMP (tissue inhibitor of metalloproteinases)-1, the endogenous MMP inhibitor. These anti-inflammatory and immunomodulatory actions of nobiletin are similar in several particulars to that of the anti-inflammatory and immunomodulatory corticosteroids. The mechanism of action by which nobiletin suppresses the production of proMMPs while upregulating TIMP-1 production is unclear and further studies are needed and warranted to clarify the mechanism of the anti-inflammatory and immunomodulatory actions of this polymethoxylated flavone.

Asthma is a chronic airway inflammatory disease. The pathophysiology of airway inflammation may involve eosinophilic infiltration (especially if there is an allergic component to the asthma), mucous hypersecretion, epithelial denudation and airway remodeling. This may all be accounted for by the sustained activation of inflammatory cells (eosinophils, lymphocytes, macrophages, basophils and mast cells) and synthesis of proinflammatory mediators and cytokines. Nobiletin was demonstrated to inhibit eosinophilic airway inflammation in asthmatic rats. The mechanism of action of this effect is not clear but may have something to do with the lowering of levels of the chemokine eotaxin, relieving airway inflammation of eosinophils and promoting apoptosis of eosinophils via enhancing expression of fas-RNA. Clearly, more research is needed to understand the anti-inflammatory/antiasthma effect of nobiletin.

The synthesis of proinflammatory mediators is mainly regulated at the level of DNA to RNA transcription via the activity of transcription factors. Arguably, the most important of these is the transcription factor NF-kappaB (nuclear factor-kappaB). NF-kappaB is activated by a number of signals, including oxidative stress, cytokines and bacterial lipopolysaccharides (LPS). Inhibition of the expression of NF-kappaB is a major target in the development of anti-inflammatory substances. Nobiletin has been shown to

inhibit LPS-induced NF-kappaB transcriptional activation in mouse macrophages, as well as to inhibit NO and PGE2 production, iNOS (inducible nitric oxide synthase) and CPX-2 protein expression. Significantly, nobiletin was found to inhibit the DNA-binding activity of NF-kappaB and also to inhibit intracellular reactive oxygen species (ROS) production in the cells. ROS are known to regulate the activation of NF-kappaB. The mechanism of this anti-inflammatory action is not entirely clear.

The worst complication of pathogenic bacterial or fungal infection, short of death, is septic shock. In gram-negative bacterial sepsis, lipopolysaccharide (LPS) endotoxin is released from the bacteria and activates monocytes, endothelial cells, and epithelial cells, triggering a massive inflammatory response that is orchestrated by monocytes. In addition, the gram-negative, sepsis procoagulant molecule tissue factor (TF) is inducibly expressed via LPS stimulation by vascular endothelial cells, circulating monocytes, and renal and pulmonary epithelial cells. TF is a membrane glycoprotein that triggers the coagulation cascade/waterfall into motion, leading to a dangerous thrombotic situation.

The human-derived monocytic cell line THP-1, when stimulated with LPS, shows increased expression of both TF protein and mRNA levels. Also, binding of nuclear proteins from LPS-stimulated THP-1 cells to NF-kappaB and the AP (activator protein)-1 transcription factor is increased. Pretreatment with nobiletin leads to inhibition of LPS-induced expression of both TF protein and mRNA levels, as well as reduced binding of NF-kappaB and AP-1 to nuclear proteins. Sp1 (sequence-specific activator protein) is an essential transcription factor for LPS-induced TF expression in THP-1 cells. Nobiletin was demonstrated to prevent LPS-induced TF expression via the inhibition of Sp1, as well as by NF-kappaB and AP-1 activation.

Recently, it was found that some metabolites of nobiletin—3′,4′-didemethylnobiletin and 4′-demethylnobiletin—may have even greater anti-inflammatory activity than nobiletin itself. These metabolites may exert their anti-inflammatory activity by suppressing iNOS and COX-2 gene expression. (See PHARMACOKINETICS below).

Neuroprotective and Cognitive-Enhancing Activities: Alzheimer's disease (AD) is the most dramatic and most serious example of cognitive impairment. It is characterized by progressive decline in cognitive function and is associated with elevated levels of beta-amyloid (Abeta), cleaved from amyloid precursor protein (APP) and amyloid plaques in the brain. In addition, neuroinflammatory activity produced mainly by activation of microglia in the brain also appears to play a major role in the pathogenesis of AD.

Long-term potentiation (LTP) is the long-lasting enhancement in communication between two neurons that results from stimulating them simultaneously. An enormous effort has been made to understand the mechanism by which strengthening of synaptic connections can be achieved, and in this effort, the importance of LTP cannot be overestimated. 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. LTP is dependent on a cascade of cellular signaling events that are stimulated by an increase in cAMP (cyclic adenosine monophosphate) concentrations. These events include activation of PKA (protein kinase A), which leads to the activation of ERK (extracellular signal-regulated kinase) and, ultimately, to the activation of transcription factors such as CREB (cAMP response element-binding protein) and translation into proteins. cAMP and PKA activation is enhanced after induction of LTP.

Nobiletin has been found to enhance PKA/ERK/CREB signaling in cell cultures, including cultured rat hippocampal neurons. It has also been shown to induce LTP via the activation of PKA-dependent phosphorylation of the AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor subunit GluR1 (human glutamate receptor type1), in the hippocampus. Nobiletin has also been demonstrated to rescue Abeta-induced memory deterioration in AD model rats and to exert a preventive action on the Abeta-induced inhibition of phosphorylation of PKA and CREB in hippocampal neurons in cultures. Nobiletin also has been demonstrated to reverse learning impairment associated with NMDA (N-methyl-D-aspartate) receptor antagonism by activation of ERK signaling in the mouse hippocampus and to improve impaired memory in olfactory-bulbectomized mice.

Recently, it has been demonstrated that nobiletin improves cognitive deficits in amyloid precursor protein (APP) transgenic mice that overexpress human AP695 and markedly reduces the quantity of guanidine-soluble Abeta1-40 and Abeta1-42 in the brain. These studies should be continued.

PHARMACOKINETICS

The pharmacokinetics (PK) of nobiletin is interesting, but incomplete. Most of the PK of nobiletin has been studied in animals. Nobiletin is absorbed across the small intestine to some degree. Nobiletin has very low solubility in water, but its permeability is quite high, which ultimately contributes to a fair bioavailability for this citrus flavone. Nobiletin, following absorption, most likely enters first into the lymphatics and is transported to the systemic circulation, which transports it to various tissues and organs of the body, including the liver. In contrast to polyphenolic flavonoids, nobiletin is not glucuronidated by UDP-glucuronosyltrans-

ferase to a glucuronide. Nor does it get sulfated by sulfotransferases to a sulfate. This is because the hydroxyl groups are methylated.

Metabolites found in mouse urine following administration of nobiletin were 3′-demethylnobiletin, 4′-demethylnobiletin and 3′,4′-didemethylnobiletin. Some nobiletin was also found in the urine. Both 3′4′-didemethylnobiletin and 4′-demethylnobiletin were found to have anti-inflammatory activity, thought to be accounted for by the suppression of inducible NOS and COX-2 gene expression. Much more study is needed in order to understand the PK of nobiletin.

INDICATIONS AND USAGE

Though clinical data are lacking, experimental data suggest a number of possible uses for nobiletin, pending confirmatory studies: anticancer, anti-inflammatory (including antiarthritic), anti-hyperlipidemic, anti-neurodegenerative (including help in memory disorders and possibly Alzheimer's disease), skin depigmenter and possible acne treatment.

RESEARCH SUMMARY

Nobiletin, a dietary phytochemical derived from citrus peel and other sources, has demonstrated some anticancer effects *in vitro*. It inhibits various human cancer cell lines quite effectively *in vitro*, but, like a related substance, tangeretin (see Tangeretin), it seems to lack efficacy in some *in vivo* trials. It was inactive in a chemically induced hamster cheek pouch cancer model and failed to have significant effect on early rat hepatocarcinogenesis *in vivo*. Nonetheless, the researchers concluded that more study was warranted as there were indications that nobiletin might be more effective in late stages of hepatocarcinoma. Far more research will be needed, extending into the clinical arena, before it can be concluded that this substance shows any promise as a human anticancer agent.

Various *in vitro* and preliminary animal experiments indicate that nobiletin may have some significant anti-inflammatory effects. Nobiletin has exhibited anti-inflammatory actions similar to those achieved with such anti-inflammatory steroids as dexamethasone. Among other actions, nobiletin has demonstrated an ability to suppress interleukin-1-induced production of prostaglandin in human synovial cells in a dose-dependent manner and to favorably modulate a wide array of other proinflammatory processes. In one study, nobiletin effectively inhibited cartilage destruction in collagen-induced arthritic mice. Acne vulgaris, an inflammatory disease in sebaceous glands, might also be helped by nobiletin according to other researchers who showed that the flavonoid can inhibit sebum production and sebocyte proliferation, while also enhancing sebum excretion, in hamsters. Clearly more research in this area is warranted.

An *in vitro* study of mouse macrophages demonstrated an antiatherogenic effect separate from previously reported nobiletin-associated cholesterol-lowering effects. In this study, a favorable modulation of macrophage metabolism attributed to the flavonoid was observed. Three other flavonoids failed to show the same beneficial effects. Another study suggested that nobiletin might help inhibit oxidation of low-density lipoprotein, an important contributor to atherosclerosis. Yet another study suggests that nobiletin might be able to regulate fat cells in ways that could help prevent arteriosclerosis and diabetes. Again, far more study will be needed before any conclusions can be drawn with respect to the efficacy of this substance in human disease, but such study is again clearly warranted.

Researchers have reported that nobiletin can improve memory impairment and protect against neurodegeneration in mice. These findings are thought to have implications for Alzheimer's disease. In another study, this one using a rat model of Alzheimer's disease, memory deterioration was said to be inhibited by the use of nobiletin. It is hoped that this research may eventually lead to the development of a new drug for the treatment of memory impairment and Alzheimer's disease.

Finally, it has been reported that nobiletin is a tyrosinase inhibitor and, as such, may be an effective skin lightener for use in pigmentation problems. The search for inhibitors of tyrosinase, which catalyzes the oxidation of tyrosine and other substances in a process that gives rise to melanin, has been intense for some years, owing to the cosmetic potential of such products. Noting that citrus peel has been used in traditional Japanese medicine for some time as a skin lightener, one group of researchers tested nobiletin for its potential effectiveness, using a known skin lightener called Kojic acid as a positive control. In this *in vitro* test, nobiletin was shown to have significant tyrosinase inhibiting potency, double that of Kojic acid. More study is needed to determine whether nobiletin can be used as an effective topical treatment for human pigmentation problems.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

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

PRECAUTIONS

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

ADVERSE REACTIONS

None known.

INTERACTIONS

DRUGS, DIETARY SUPPLEMENTS, FOODS, HERBS

None reported.

OVERDOSAGE

There are no reports of overdosage.

DOSAGE AND ADMINISTRATION

The optimal dose of nobiletin is not known.

At present, only one dietary supplement containing a mixture of polymethoxylated flavones (PMF), tocotrienols and ascorbyl palmitate is being marketed in the U.S. The PMF-tocotrienol mixture contains a total of 150 mg per capsule; those using this supplement take about two per day.

The amount of nobiletin in citrus peel and juice is variable. One of the highest concentrations of nobiletin is found in the tangerine and a lime cross, *Citrus depressa* or shiikuwasha, which contains approximately 26.7 mg per gram of dry weight.

It is expected that other nobiletin dietary supplements will enter the dietary supplement marketplace.

LITERATURE

Ben-Aziz A. Nobiletin Is Main Fungistat in Tangerines Resistant to Mal Secco. *Science.* 1967;155(3765):1026-1027.

Choi SY, Hwang JH, Ko HC, et al. Nobiletin from citrus fruit peel inhibits the DNA-binding activity of NF-kappaB and ROS production in LPS-activated RAW 264.7 cells. *J Ethnopharmacol.* 2007;113(1):149-155.

Eguchi A, Murakami A, Ohigashi H. Nobiletin, a citrus flavonoid, suppresses phorbol ester-induced expression of multiple scavenger receptor genes in THP-1 human monocytic cells. *FEBS Lett.* 2006;580(13):3321-3328.

Hirata Y, Masuda Y, Kakutani H, et al. Sp1 is an essential transcription factor for LPS-induced tissue factor expression in THP-1 monocytic cells, and nobiletin represses the expression through inhibition of NF-kappaB, AP-1, and Sp1 activation. *Biochem Pharmacol.* 2008;75(7):1504-1514.

Ishiwa J, Sato T, Mimaki Y, et al. A citrus flavonoid, nobiletin, suppresses production and gene expression of matrix metalloproteinase 9/gelatinase B in rabbit synovial fibroblasts. *J Rheumatol.* 2000;27(1):20-25.

Ito A, Ishiwa J, Sato T, et al. The citrus flavonoid nobiletin suppresses the production and gene expression of matrix metalloproteinases-9/gelatinase B in rabbit synovial cells. *Ann N Y Acad Sci.* 1999;878:632-634.

Li S, Sang S, Pan MH, et al. Anti-inflammatory property of the urinary metabolites of nobiletin in mouse. *Bioorg Med Chem Lett.* 2007;17(18):5177-5181.

Li S, Wang Z, Sang S, et al. Identification of nobiletin metabolites in mouse urine. *Mol Nutr Food Res.* 2006;50(3):291-299.

Li S, Yu H, Ho CT. Nobiletin: efficient and large quantity isolation from orange peel extract. *Biomed Chromatogr.* 2006;20(1):133-138.

Lin N, Sato T, Takayama Y, et al. Novel anti-inflammatory actions of nobiletin, a citrus polymethoxy flavonoid, on human synovial fibroblasts and mouse macrophages. *Biochem Pharmacol.* 2003;65(12):2065-2071.

Luo G, Guan X, Zhou L. Apoptotic effect of citrus fruit extract Nobiletin on Lung Cancer cell line A549 in vitro and in vivo. *Cancer Biol Ther.* 2008;7(6):966-973.

Matsuzaki K, Miyazaki K, Sakai S, et al. Nobiletin, a citrus flavonoid with neurotrophic action, augments protein kinase A-mediated phosphorylation of the AMPA receptor subunit, GluR1, and the postsynaptic receptor response to glutamate in murine hippocampus. *Eur J Pharmacol.* 2008;578(2-3):194-200.

Matsuzaki K, Yamakuni T, Hashimoto M, et al. Nobiletin restoring beta-amyloid-impaired CREB phosphorylation rescues memory deterioration in Alzheimer's disease model rats. Neurosci Lett. 2006;400(3):230-234.

Minagawa A, Otani Y, Kubota T, et al. The citrus flavonoid, nobiletin, inhibits peritoneal dissemination of human gastric carcinoma in SCID mice. *Jpn J Cancer Res.* 2001;92(12):1322-1328.

Miyamoto S, Yasui Y, Tanaka T, et al. Suppressive effects of nobiletin on hyperleptinemia and colitis-related colon carcinogenesis in male ICR mice. *Carcinogenesis.* 2008;29(5):1057-1063.

Miyata Y, Sato T, Imada K, et al. A citrus polymethoxyflavonoid, nobiletin, is a novel MEK inhibitor that exhibits antitumor metastasis in human fibrosarcoma HT-1080 cells. *Biochem Biophys Res Commun.* 2008;366(1):168-173.

Miyata Y, Sato T, Yano M, et al. Activation of protein kinase C betaII/epsilon-c-Jun NH2-terminal kinase pathway and inhibition of mitogen-activated protein/extracellular signal-regulated kinase 1/2 phosphorylation in antitumor invasive activity induced by the polymethoxy flavonoid, nobiletin. *Mol Cancer Ther.* 2004;3(7):839-847.

Murakami A, Koshimizu K, Ohigashi H, et al. Characteristic rat tissue accumulation of nobiletin, a chemopreventive polymethoxyflavonoid, in comparison with luteolin. *Biofactors.* 2002;16(3-4):73-82.

Murakami A, Kuwahara S, Takahashi Y, et al. In vitro absorption and metabolism of nobiletin, a chemopreventive polymethoxyflavonoid in citrus fruits. *Biosci Biotechnol Biochem.* 2001;65(1):194-197.

Murakami A, Nakamura Y, Torikai K, et al. Inhibitory effect of citrus nobiletin on phorbol ester-induced skin inflammation, oxidative stress, and tumor promotion in mice. *Cancer Res.* 2000;60(18):5059-5066.

Murakami A, Song M, Katsumata S, et al. Citrus nobiletin suppresses bone loss in ovariectomized ddY mice and collagen-induced arthritis in DBA/1J mice: Possible involvement of

receptor activator of NF-kappaB ligand (RANKL)-induced osteoclastogenesis regulation. *Biofactors*. 2007;30(3):179-192.

Nagase H, Omae N, Omori A, et al. Nobiletin and its related flavonoids with CRE-dependent transcription-stimulating and neuritegenic activities. *Biochem Biophys Res Commun*. 2005;337(4):1330-1336.

Nagase H, Yamakuni T, Matsuzaki K, et al. Mechanism of neurotrophic action of nobiletin in PC12D cells. *Biochemistry*. 2005;44(42):13683-13691.

Nakajima A, Yamakuni T, Haraguchi M, et al. Nobiletin, a citrus flavonoid that improves memory impairment, rescues bulbectomy-induced cholinergic neurodegeneration in mice. *J Pharmacol Sci*. 2007;105(1):122-126.

Nakajima A, Yamakuni T, Matsuzaki K, et al. Nobiletin, a citrus flavonoid, reverses learning impairment associated with N-methyl-D-aspartate receptor antagonism by activation of extracellular signal-regulated kinase signaling. *J Pharmacol Exp Ther*. 2007;321(2):784-790.

Nogata Y, Sakamoto K, Shiratsuchi H, et al. Flavonoid composition of fruit tissues of citrus species. *Biosci Biotechnol Biochem*. 2006;70(1):178-192.

Okuno Y, Miyazawa M. Biotransformation of nobiletin by Aspergillus niger and the antimutagenic activity of a metabolite, 4′-hydroxy-5,6,7,8,3′-pentamethoxyflavone. *J Nat Prod*. 2004;67(11):1876-1878.

Onozuka H, Nakajima A, Matsuzaki K, et al. Nobiletin, a citrus flavonoid, improves memory impairment and Aβ pathology in a transgenic mouse model of Alzheimer's disease. *J Pharmacol Exp Ther*. 2008;326(3):739-744.

Saito T, Abe D, Sekiya K. Nobiletin enhances differentiation and lipolysis of 3T3-L1 adipocytes. *Biochem Biophys Res Commun*. 2007;357(2):371-376.

Sasaki K, Yoshizaki F. Nobiletin as a tyrosinase inhibitor from the peel of Citrus fruit. *Biol Pharm Bull*. 2002;25(6):806-808.

Sato T, Koike L, Miyata Y, et al. Inhibition of activator protein-1 binding activity and phosphatidylinositol 3-kinase pathway by nobiletin, a polymethoxy flavonoid, results in augmentation of tissue inhibitor of metalloproteinases-1 production and suppression of production of matrix metalloproteinases-1 and -9 in human fibrosarcoma HT-1080 cells. *Cancer Res*. 2002;62(4):1025-1029.

Sato T, Takahashi A, Kojima M, et al. A citrus polymethoxy flavonoid, nobiletin inhibits sebum production and sebocyte proliferation, and augments sebum excretion in hamsters. *J Invest Dermatol*. 2007;127(12):2740-2748.

Suzuki R, Kohno H, Murakami A, et al. Citrus nobiletin inhibits azoxymethane-induced large bowel carcinogenesis in rats. *Biofactors*. 2004;22(1-4):111-114.

Tanaka S, Sato T, Akimoto N, et al. Prevention of UVB-induced photoinflammation and photoaging by a polymethoxy flavonoid, nobiletin, in human keratinocytes in vivo and in vitro. *Biochem Pharmacol*. 2004;68(3):433-439.

Wu YQ, Zhou CH, Tao J, et al. Antagonistic effects of nobiletin, a polymethoxyflavonoid, on eosinophilic airway inflammation of asthmatic rats and relevant mechanisms. *Life Sci*. 2006;78(23):2689-2696.

Yasuda T, Yoshimura Y, Yabuki H, et al. Urinary metabolites of nobiletin orally administered to rats. *Chem Pharm Bull* (Tokyo). 2003;51(12):1426-1428.

Yoshimizu N, Otani Y, Saikawa Y, et al. Anti-tumour effects of nobiletin, a citrus flavonoid, on gastric cancer include: antiproliferative effects, induction of apoptosis and cell cycle deregulation. *Aliment Pharmacol Ther*. 2004;20(Suppl 1):95-101.

Zhang HQ, Ge H, Cheng MY. [Antitumor effects of nobiletin on Heps and its mechanism] [Article in Chinese.] *Yao Xue Xue Bao*. 2006;41(8):797-800.

Nucleic Acids/Nucleotides

DESCRIPTION

DNA (deoxyribonucleic acid), the molecule that comprises the genome, and RNA (ribonucleic acid) are marketed as nutritional supplements. DNA, which makes up the genetic material, is comprised of units called nucleotides. A nucleotide consists of a base, a sugar and a phosphate group. The major bases in DNA are the purines adenine and guanine and the pyrimidines cytosine and thymine. The sugar moiety of the nucleotide is 2′-deoxyribose. RNA, which is more abundant in tissues than DNA by about an order of magnitude, is also comprised of nucleotide units. In the case of RNA, the major bases are again the purines adenine and guanine, and the pyrimidines are cytosine and uracil. One of the major differences between DNA and RNA is the presence of uracil in RNA and of thymine in DNA. The other major difference is in the sugar moiety. In RNA, the sugar moiety of the nucleotide is ribose, whereas in DNA it is deoxyribose.

For years, nucleic acids and nucleotides were not considered essential nutrients. It was thought that the body can synthesize sufficient nucleotides to meet its physiological demands via *de novo* nucleotide synthetic pathways. Some research during the last several years indicates that this may not be completely correct. There are certain conditions in which the body requires dietary nucleic acids/nucleotides to meet its physiological requirements. These conditions include rapid growth, limited food supply and metabolic stress. Under these conditions, metabolic demand exceeds the capacity of *de novo* synthesis. Under these conditions, dietary nucleosides, nucleotides and nucleic acids become conditionally essential nutrients. Dietary nucleotides may spare the energetic cost of *de novo* synthesis of nucleotides.