Orallo F. Comparative studies of the antioxidant effects of cis- and trans-resveratrol. *Curr Med Chem.* 2006;13(1):87-98.

Pace-Asciak CR, Hahn S, Diamandis EP, et al. The red wine phenolics trans-resveratrol and quercetin block human platelet aggregation and eicosanoid synthesis: implications for protection against coronary heart disease. *Clin Chim Acta.* 1995;235:207-219.

Palamara AT, Nencioni L, Aquilano K, et al. Inhibition of influenza A virus replication by resveratrol. *J Infect Dis.* 2005;191(10):1719-1729.

Paul B, Masih I, Deopujari J, Charpentier C. Occurrence of resveratrol and pterostilbene in age-old darakchasava, an ayurvedic medicine from India. *J Ethnopharmacol.* 1999;68:71-76.

Pearson KJ, Baur JA, Lewis KN, et al. Resveratrol delays age-related deterioration and mimics transcriptional aspects of dietary restriction without extending life span. *Cell Metab.* 2008;8(2):157-168.

Pinto MC, García-Barrado JA, Macías P. Resveratrol is a potent inhibitor of the dioxygenase activity of lipoxygenase. *J Agric Food Chem.* 1999;47:4842-4846.

Prokop J, Abrman P, Seligson AL, et al. Resveratrol and its glycon piceid are stable polyphenols. *J Med Food.* 2006;9(1):11-14.

Raval AP, Lin HW, Dave KR, Defazio RA, Della Morte D, Kim EJ, Perez-Pinzon MA. Resveratrol and ischemic preconditioning in the brain. *Curr Med Chem.* 2008;15(15):1545-1551.

Ray PS, Maulik G, Cordis GA, et al. The red wine antioxidant resveratrol protects isolated rat hearts from ischemia reperfusion injury. *Free Rad Biol Med.* 1999;27:160-169.

Sanders TH, McMichael RW Jr, Hendrix KW. Occurrence of resveratrol in edible peanuts. *J Agric Food Chem.* 2000;48:1243-1246.

Schneider Y, Vincent F, Duranton B, et al. Anti-proliferative effect of resveratrol, a natural component of grapes and wine, on human colonic cancer cells. *Cancer Lett.* 2000;158:85-91.

Seeni A, Takahashi S, Takeshita K, et al. Suppression of Prostate Cancer Growth by Resveratrol in The Transgenic Rat for Adenocarcinoma of Prostate (TRAP) Model. *Asian Pac J Cancer Prev.* 2008;9(1):7-14.

Soleas GJ, Diamandis EP, Goldberg DM. Resveratrol: A molecule whose time has come? And gone? *Clin Biochem.* 1997;30:91-113.

Sovak M. Grape Extract, Resveratrol, and Its Analogs: A Review. *J Med Food.* 2001;4(2):93-105.

Stewart JR, Christman KL, O'Brian CA. Effects of resveratrol on the autophosphorylation of phorbol ester-responsive protein kinases. *Biochem Pharmacol.* 2000;60:1355-1359.

Subbaramaiah K, Chung WJ, Michaluart P, et al. Resveratrol inhibits cyclooxygenase-2 transcription and activity in phorbol ester-treated human mammary epithelial cells. *J Biol Chem.* 1998;273:21875-21882.

Subbaramaiah K, Michaluart P, Chung WJ, et al. Resveratrol inhibits cyclooxygenase-2 transcription in human mammary epithelial cells. *Ann NY Acad Sci.* 2000;889:214-223.

Tang FY, Chiang EP, Sun YC. Resveratrol inhibits heregulin-beta1-mediated matrix metalloproteinase-9 expression and cell invasion in human breast cancer cells. *J Nutr Biochem.* 2008;19(5):287-294.

Tang FY, Su YC, Chen NC, et al. Resveratrol inhibits migration and invasion of human breast-cancer cells. *Mol Nutr Food Res.* 2008;52(6):683-691.

Tang W, Eisenbrand G. *Chinese Drugs of Plant Origin.* Berlin: Springer-Verlag: 1992;787-791.

Tessitore L, Davit A, Sarotto I, Caderni G. Resveratrol depresses the growth of colorectal aberrant crypt foci by affecting *bax* and $p21_{CIP}$ expression. *Carcinogenesis.* 2000;21:1619-1622.

Tomera JF. Current knowledge of the health benefits and disadvantages of wine consumption. *Trends Food Sci Technol.* 1999;10:129-138.

Tsai SH, Lin-Shiau SY, Lin JK. Suppression of nitric oxide synthase and the down-regulation of the activation of NFkappaB in macrophages by resveratrol. *Br J Pharmacol.* 1999;126:673-680.

Zou J, Huang Y, Chen Q, et al. Suppression of mitogenesis and regulation of cell cycle traverse by resveratrol in cultured smooth muscle cells. *Int J Oncol.* 1999;15:647-651.

Riboflavin (Vitamin B_2)

DESCRIPTION

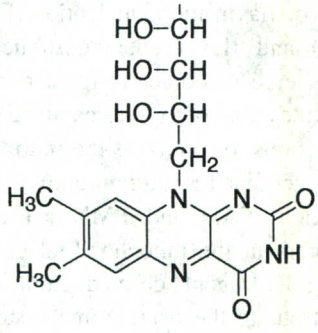
Riboflavin or vitamin B_2 is an essential nutrient in human nutrition and plays a key role in the production of energy. It is the precursor of flavin mononucleotide (FMN, riboflavin monophosphate) and flavin adenine dinucleotide (FAD). FMN and FAD serve as cofactors for a family of proteins called flavoenzymes. Flavoenzymes catalyze a wide range of biochemical reactions, typically of the redox type. They are key elements in cellular respiration, among other things. In cellular respiration, FAD and FMN act as intermediate hydrogen acceptors in the mitochondrial electron transport chain, accepting hydrogens derived from foodstuffs, and passing on electrons to the cytochrome system. During this process, cellular energy is produced. Recent research suggests that riboflavin may be effective in the prophylaxis of migraine headaches in some with altered cerebral bioenergetics.

Riboflavin deficiency or ariboflavinosis was originally known as *pellagra sin pellagra.* The most common cause of

riboflavin deficiency is dietary inadequacy, which occurs in those who do not consume rich dietary sources of the vitamin, such as organ meats, eggs, milk, cheese, yogurt, leafy green vegetables and whole grains. Deficiency of the vitamin can occur in the elderly subsisting on tea or coffee, toast and cookies. Riboflavin deficiency also occurs in those with chronic liver disease, chronic alcoholics and those who receive total parenteral nutrition (TPN) with inadequate riboflavin. Marginal riboflavin deficiency, in the context of nucleoside analog antiretroviral therapy, has been known to cause severe lactic acidosis.

The signs and symptoms of riboflavin deficiency include, cheilosis (fissuring of the vermilion surfaces of the lips), angular stomatitis, glossitis (magenta tongue), seborrheic dermatitis (particularly affecting the scrotum or labia majora and the nasolabial folds), sore throat, hyperemia and edema of the pharyngeal and oral mucous membranes and a normochromic, normocytic anemia associated with pure erythrocyte cytoplasia of the bone marrow. Isolated riboflavin deficiency is rare. Typically, riboflavin deficiency is accompanied by deficiency of other vitamins and other nutrients. Futher, the skin and mucosal signs of riboflavin deficiency may be difficult to interpret in the elderly. Esophageal lesions in the Turkoman people of Iran have been related to chronic riboflavin deficiency, and the greater incidence of esophageal cancer in this group has created interest in the relationship between esophageal cancer and riboflavin deficiency.

Riboflavin, in addition to being known as vitamin B_2, is also known as riboflavine, 7, 8-dimethyl-10- (1^1-D-ribityl)isoalloxazine, 7, 8-dimethyl-10- (D-ribo-2, 3, 4, 5-tetrahydroxypentyl)isoalloxazine and 7, 8-dimethyl-10-ribitylisoalloxazine. Its molecular formula is $C_{17}H_{20}N_4O_6$ and its molecular weight is 376.4 daltons. It has the following structure:



Riboflavin

Riboflavin is an orange powder, and water solutions have intense greenish yellow fluorescence. The 5^1-hydroxymethyl group of the ribityl side chain of riboflavin is metabolized in the body to form the coenzyme flavin mononucleotide or FMN. FMN is also known as riboflavin monophosphate, riboflavin-5^1-phosphate and riboflavin-5^1-(dihydrogen phosphate). FMN is metabolized in the body to form flavin adenine dinucleotide (FAD).

ACTIONS AND PHARMACOLOGY

ACTIONS

Riboflavin has antioxidant activity. It may have activity in the prophylaxis of migraine headaches and may have activity against esophageal cancer. It has putative anti-atherosclerotic activity and putative antimalarial activity.

MECHANISM OF ACTION

The antioxidant activity of riboflavin is principally derived from its role as a precursor of FAD and the role of this cofactor in the production of the antioxidant reduced glutathione. Reduced glutathione is the cofactor of the selenium-containing glutathione peroxidases (see Selenium), among other things. The glutathione peroxidases are major antioxidant enzymes. Reduced glutathione is generated by the FAD-containing enzyme glutathione reductase. Riboflavin deficiency is reported to be associated with compromised oxidant defense resulting in increased lipid peroxidation. Increased lipid peroxidation under conditions of riboflavin deficiency may be accounted for, in large part, by decreased regeneration of reduced glutathione which is necessary for the function of the antioxidant glutathione peroxidases. Riboflavin deficiency may also affect the mitochondrial pool of reduced glutathione which in turn may affect the activities of the flavoenzymes NADPH-cytochrome P450 reductase and NADPH-cytochrome b reductase. Elevated riboflavin levels have been reported to provide protection against oxidative forms of hemeproteins. Oxidative forms of hemeproteins have been implicated in reperfusion injury. Riboflavin has also been shown to protect against reperfusion injury in isolated rabbit hearts. The protection by riboflavin against oxidative damage caused by oxidized forms of hemeproteins may be mediated by an NADPH-dependent methemoglobin reductase which is also known as flavin reductase. In this case, riboflavin itself appears to act as an antioxidant via its conversion to dihydroriboflavin. Riboflavin has been found to protect the lungs, brain and heart from cellular oxidative injury, The protection has been proposed to be mediated through flavin reductase. It has been demonstrated that higher oxidation states of hemeproteins are rapidly reduced by dihydroriboflavin.

High-dose riboflavin has recently been demonstrated to be effective in the prophylaxis of migraine headaches in some. The rationale for studying riboflavin for migraine prophylaxis came from the findings, in migraine sufferers, of a decreased mitochondrial phosphorylation potential between migraine attacks. This indicates that those with a history of migraines have decreased brain mitochondrial energy reserve

between attacks. The studies were conducted using ^{31}P-NMR spectroscopy. Riboflavin is the precursor of flavin adenine mononucleotide (FMN) and flavin adenine dinucleotide (FAD), which are required for the activity of flavoenzymes involved in the electron transport chain and in the production of cellular energy. Riboflavin's effect on cerebral bioenergetics is a possible mechanism of riboflavin's antimigraine activity. There are most likely other mechanisms at work, as well.

Riboflavin deficiency has been associated with an increased incidence of esophageal cancer in certain parts of the world. Riboflavin supplementation has been found to reduce the prevalence of micronuclei in esophageal cells in a study performed in Huixan, People's Republic of China. Micronuclei are considered precancerous lesions. People living in this region have a high risk of esophageal cancer and poor riboflavin status. It remains unclear, however, whether riboflavin supplementation can decrease the incidence of esophageal cancer. The mechanism of the possible anticarcinogenic activity of riboflavin is also unclear. Riboflavin deficiency has been found to enhance the carcinogenicity of certain xenobiotics, such as azo dyes. The azo dyes are inactivated by a microsomal hydroxylase enzyme system that uses FAD. Riboflavin, as FAD, plays a key role in glutathione metabolism (see above). Glutathione is involved in the detoxification of xenobiotic substances. Riboflavin is also important for the maintenance of epithelial integrity.

The putative anti-atherosclerotic activity of riboflavin may be accounted for, in part, by its role in the metabolism of homocysteine. Elevated serum homocysteine is considered to be an independent risk factor for coronary heart disease. Vitamin B_6, folate and vitamin B_{12} are involved in the metabolism of homocysteine. The riboflavin metabolites FMN and FAD serve as cofactors for enzymes involved in the metabolism of vitamin B_6, folate and vitamin B_{12}. FMN serves as a cofactor for pyridoxine-5^1-phosphate oxidase, which is important for the formation of the active form of vitamin B_6, pyridoxal-5^1 - phosphate. FAD is a cofactor for methylenetetrahydrofolate reductase, which is important for the formation of 5-methyltetrahydrofolate. FMN and FAD are involved in vitamin B_{12} metabolism and serve as cofactors for methionine synthase reductase. Studies on riboflavin deficient subjects are needed to evaluate the usefulness of riboflavin supplementation in hyperhomocysteinemia. Riboflavin may also have anti-atherosclerotic activity secondary to its antioxidant action. Riboflavin, in the form of FAD, is necessary for the formation of reduced glutathione via the FAD-containing enzyme glutathione reductase. Glutathione is the cofactor of the glutathione peroxidases, antioxidant enzymes which protect against lipid peroxidation and oxidation of low-density lipoprotein (LDL). Oxidized-LDL is thought to be a key etiological factor in the pathophysiology of atherosclerosis.

Recently, riboflavin has been demonstrated to have antimalarial activity. The malarial parasite ingests a significant proportion of host cell hemoglobin in an acidic organelle called the food vacuole. The acidic pH of the food vacuole is favorable to the oxidation of hemoglobin to methemoglobin. The malarial parasite also digests hemoglobin and polymerizes the released free heme into hemozoin, also in the food vacuole. It has recently been shown that treatment of erythrocytes infected with *Plasmodium falciparum* with riboflavin decreased the production of methemoglobin and hemozoin, decreased the size of the food vacuole and inhibited asexual parasite growth in cultures. It is thought that the mechanism of the possible antimalarial action of riboflavin is via its acting as a substrate for the enzyme NADPH-methemoglobin reductase. During this reaction, methemoglobin is reduced while riboflavin is oxided to dihydroriboflavin. Thus, riboflavin acts as a reducing agent. Reduction of methemoglobin is correlated with inhibition of hemazoin formation and food vacuole development and arrest of asexual development to schizogony. It is thought that the reduction of methemoglobin plays a role in limiting the amount of hemoglobin which is available to the malarial parasite for further processing. The effects of riboflavin in this recent research differ from earlier studies showing that riboflavin deficiency has an antimalarial effect. The mechanism of antimalarial activity of riboflavin deficiency may be accounted for by a decrease in the activity of reductive enzymes, such as riboflavin reductase, which require riboflavin as a cofactor. This decreased activity lowers glutathione levels. This results in increased oxidative stress and lipid peroxidation, conditions detrimental to the malarial parasite. The use of high-dose riboflavin as an antimalarial strategy appears more attractive than that of causing riboflavin deficiency to treat malaria. Riboflavin deficiency may not only be detrimental to the malarial parasite, but can be detrimental to the host, as well. Continued research in this most important area is warranted and needed to determine, among other things, which approach—riboflavin treatment or riboflavin deficiency—should be the one to pursue regarding a possible new treatment of malaria.

PHARMACOKINETICS

In food, riboflavin is found mainly in the form of flavin mononucleotide (FMN, riboflavin-5^1-phosphate) and flavin adenine dinucleotide (FAD). Riboflavin is used for food fortification. Riboflavin and riboflavin-5^1 -phosphate are the principal nutritional supplement forms of riboflavin, with riboflavin being the major form. Coenzyme forms of riboflavin (FAD, FMN) that are not covalently bound to proteins are released from proteins in the acid environment

of the stomach. Covalently bound forms or riboflavin (e.g., in mitochondrial succinate dehydrogenase) are released from the proteins they are bound to following proteolysis. FAD and FMN are converted to riboflavin in the small intestine via the action of pyrophosphatase and phosphatase, respectively. Riboflavin is mainly absorbed in the proximal small intestine by a saturable transport system. The rate of absorption increases when riboflavin is ingested with food. The presence of bile salts appears to facilitate absorption of riboflavin. The maximal amount of riboflavin that is absorbed from a single oral dose appears to be about 27 milligrams. The amount of absorption of riboflavin-5[1]-phosphate and FAD appears to be very low. During the process of absorption, riboflavin, in part, appears to be converted to FMN which is either used by the enterocytes for their metabolic requirements, or converted back to riboflavin for further processing. Riboflavin is transported via the portal circulation to the liver and by the systemic circulation to the various tissues of the body.

A large percentage of serum riboflavin is carried by immunoglobulins. Some serum riboflavin is carried by albumin. Riboflavin is transported into cells via facilitated diffusion at physiological concentrations, and by passive diffusion at higher concentrations. Within cells, riboflavin is converted to FMN via flavokinase. FMN is converted to FAD via FAD synthetase. FAD is the predominant form of riboflavin in tissues.

Very little riboflavin is stored in tissues. Riboflavin in excess of body requirements is excreted mainly by the kidneys. A number of riboflavin metabolites are also found in the urine, including 7-hydromethylriboflavin, 8-hydroxymethylriboflavin, 8 alpha-sulfonylriboflavin, 5[1]-riboflavinyl peptide, 10-hydroxyethylflavin, lumiflavin, 10-formylmethylflavin and carboxymethylflavins. A significant percentage of large intakes of riboflavin—greater than 30 milligrams in a single dose—is excreted in the feces.

INDICATIONS AND USAGE

Riboflavin has been found to be an effective migraine prophylaxis in some. Riboflavin supplementation has resulted in full recovery of several patients who developed a sometimes fatal syndrome characterized by lactic acidosis and hepatic steatosis caused by treatment with nucleoside reverse-transcriptase inhibitors. Riboflavin has significant antioxidant-promoting activity which, experimentally, has protected against cardiac injury produced by reperfusion following ischemia. It has also exhibited notable ability to inhibit lipid oxidation and has protected against a number of oxidative injuries in the laboratory. It has demonstrated some activity against esophageal cancer. Intriguingly, riboflavin deficiency has been shown to be protective against malaria in both animals and humans. On the other hand, high doses of riboflavin may have antimalarial activity.

RESEARCH SUMMARY

Riboflavin has been called "a significant breakthrough" in migraine prophylaxis with "an outstanding efficacy-side effect profile" by one recent reviewer of migraine research developments.

In an open study, high-dose riboflavin showed significant effectiveness as a migraine prophylaxis. In a subsequent randomized trial, 400 milligrams of riboflavin and placebo were tested for three months in 55 migraine patients. In the riboflavin group, 59% improved by at least 50%, compared with 15% of the placebo group showing at least 50% improvement.

In a more recent clinical trial (open label), the efficacy of high-dose riboflavin—400 mg daily—for the prevention of migraine headaches was studied in 23 patients in a specialized headache outpatient clinic. Headache frequency, duration, intensity and the use of abortive drugs were recorded at baseline and 3 and 6 months after start of treatment. Headache frequency was significantly reduced from 4 days per month at baseline to 2 days per month after 3 and 6 months. The use of abortive drugs also significantly decreased after 3 and 6 months of treatment. The number of headache hours and headache intensity did not significantly change. The researchers concluded that "riboflavin is a safe and well-tolerated alternative in migraine prophylaxis." Further research on the effect of riboflavin on migraine headaches is needed and warranted.

Both riboflavin and beta-blockers were tested for their effects on the intensity dependence of auditory evoked cortical potentials. Intensity dependence is usually increased during migraines. In this study, the beta-blockers significantly decreased the intensity dependence, and this decrease correlated with significant clinical improvement. Riboflavin treatment did not affect intensity dependence but was, nonetheless, also associated with significant improvement. Thus, given that the two agents apparently act via two distinct pathophysiological mechanisms, the researchers concluded that a combination of the two treatments might enhance their efficacy without increasing central nervous system side effects. This hypothesis warrants investigation.

A 46-year-old woman who had been treated for AIDS with triple anti-retroviral therapy for four months developed lactic acidosis and marked hepatic steatosis. Suspecting that a riboflavin deficiency induced by amitriptyline, which she was also taking (see Interactions), might be contributing to these potentially life-threatening metabolic abnormalities, the physicians treated her with 50 milligrams of riboflavin daily. This was followed by rapid recovery.

Subsequently, these researchers similarly identified two other HIV-infected patients with less severe lactic acidosis. These patients had also been on triple drug therapy. Riboflavin again rapidly resolved the acidosis. This condition, they believed, results, in part, from impaired mitochondrial DNA replication caused by the HIV drug therapies.

Another researcher has also reported that 50 milligrams of riboflavin daily resolved the severe lactic acidosis of a 35-year-old pregnant HIV-infected patient. Blood lactate levels returned to normal within four days of beginning treatment. This syndrome is a rare complication of treatment with nucleoside reverse-transcriptase inhibitors, but, since it can be fatal, it is a significant one, as is riboflavin's apparent role in resolving it.

Riboflavin's antioxidant-promoting activity has been shown to provide protection against oxidative damage caused by oxidized forms of hemeproteins. In an animal model of ischemic reperfusion injury, riboflavin was significantly cardioprotective. In an *in vivo* animal experiment, it protected rat lungs from the oxidative injury initiated by injection of cobra venom factor. It also significantly protected rat brains from swelling after four hours of ischemia. Riboflavin is the precursor of co-enzymes that are required in potent antioxidant processes. Some researchers have concluded that riboflavin nutriture plays a crucial role in inactivation of lipid peroxides. Riboflavin supplementation has been shown to prevent hepatic lipid peroxidation both in *in vitro* and in animal studies.

Some studies have shown a synergy between Vitamin E and riboflavin as antioxidants. Riboflavin, for example, diminished lipid peroxidation and prevented the oxidation of Vitamin E in the livers of experimental animals. It has been suggested that riboflavin has a sparing effect on vitamin E or may help regenerate Vitamin E via production of reduced glutathione.

There is an epidemiological association between riboflavin and esophageal cancer. The incidence of this cancer is particularly high in parts of the world (some areas of China, Iran and Africa) where riboflavin deficiency is high. One study suggested that riboflavin supplementation might reduce the number of precancerous cells in the esophagus. This needs followup.

There is a finding, in both animals and humans, that a deficiency in riboflavin has significant antimalarial effects. Dietary riboflavin deficiency dramatically decreases malarial parasitemia with concomitant diminution of symptoms. Further, specific riboflavin antagonists have demonstrated antimalarial activity. Whether these findings can become the basis for a new pharmacological approach to the treatment of this challenging disease remains to be seen. On the other hand, a recent study reported that high doses of riboflavin may have antimalarial activity. Further research is necessary and warranted in order to resolve these seemingly contradictory findings.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Riboflavin is contraindicated in those hypersensitive to any component of a riboflavin-containing product.

PRECAUTIONS

The use of riboflavin for the treatment of riboflavin deficiency or for any medical indication must be medically supervised.

Most pre- and postnatal vitamin/mineral supplements deliver 3.4 milligrams daily of riboflavin. Pregnant women and nursing mothers should avoid intakes of riboflavin greater than this amount unless higher amounts are prescribed by their physicians.

High dose intake of riboflavin may interfere with the Abbott TDX drugs-of-abuse assay.

Riboflavin absorption is increased in hypothyroidism and decreased in hyperthyroidism.

Those who use nucleoside reverse-transcriptase inhibitors (see Interactions) should be aware that even mild riboflavin deficiency may increase the risk of lactic acidosis.

ADVERSE REACTIONS

Riboflavin is well tolerated. Doses of 400 milligrams daily for four months were found to cause diarrhea and polyuria in two out of 28 subjects who participated in a migraine prophylaxis study. Riboflavin supplements impart a yellow-orange discoloration to urine. This color has no pathological implication.

INTERACTIONS

DRUGS

Cholestyramine: Concomitant intake of cholestyramine and riboflavin may decrease the absorption of riboflavin.

Chlorpromazine: Chlorpromazine may inhibit the conversion of riboflavin to FMN and FAD.

Colestipol: Concomitant intake of colestipol and riboflavin may decrease the absorption of riboflavin.

Doxorubicin: Doxorubicin may inhibit the conversion of riboflavin to FMN and FAD.

Metoclopramide: Metoclopramide may decrease the absorption of riboflavin.

Nucleoside reverse-transcriptase inhibitors (didanosine, lamivudine, stavudine, zidovudine): Riboflavin has been found to reverse nucleoside analogue-induced lactic acidosis in

patients with mild riboflavin deficiencies. These mild riboflavin deficiencies may result from the use of drugs, such as amitriptyline, which may adversely affect riboflavin status.

Oral Contraceptive Agents: Use of oral contraceptive agents may result in decreased serum levels of riboflavin.

Probenecid: Probenecid may inhibit the absorption of riboflavin. It may also inhibit renal tubular secretion of riboflavin.

Propantheline bromide: Propantheline bromide may enhance the absorption of riboflavin by allowing the vitamin to remain at intestinal absorption sites for longer periods of time.

Quinacrine: Quinacrine may inhibit the conversion of riboflavin to FMN and FAD.

Tricyclic Antidepressants (amitriptyline, imipramine): Tricyclic antidepressant drugs may inhibit the conversion of riboflavin to FMN and FAD.

NUTRITIONAL SUPPLEMENTS

Boron: Boric acid may induce riboflavin deficiency, since it displaces riboflavin from plasma-binding sites and results in increased urinary excretion of the vitamin. Most forms of boron (see Boron) used for nutritional supplementation are readily converted to boric acid. High intakes of these boron supplements may result in riboflavin deficiency.

Psyllium: Concomitant intake of psyllium and riboflavin may decrease the absorption of riboflavin.

Vitamin E: Riboflavin may potentiate the antioxidant effect of Vitamin E.

FOODS

Concomitant intake of riboflavin with food enhances the absorption of riboflavin.

OVERDOSAGE

There are no reports of riboflavin overdosage in the literature.

DOSAGE AND ADMINISTRATION

Riboflavin and riboflavin 5[1]-monophosphate are the principal forms of riboflavin supplements, with riboflavin being the major available form. Riboflavin is typically present in multivitamin, multivitamin/multimineral and B-complex preparations. Riboflavin is also available as a single ingredient supplement. Typical doses range from 1.7 to 10 milligrams daily. Pre- and postnatal supplements usually deliver riboflavin at a dose of 3.4 daily. In the migraine prophylaxis studies, 400 milligrams daily of riboflavin were used. Use of riboflavin for any medical indication must be medically supervised. Doses of riboflavin greater than 30 milligrams should be taken in divided doses.

The Food and Nutrition Board of the Institute of Medicine of the National Academy of Sciences recommends the following dietary reference intakes (DRI) for riboflavin:

Infants	Adequate Intakes (AI)	
0-6 months	0.3 mg/day	0.04 mg/kg
7-12 months	0.4 mg/day	0.04 mg/kg

Children	Recommended Dietary Allowances (RDA)
1-3 years	0.5 mg/day
4-8 years	0.6 mg/day
Boys	
9-13 years	0.9 mg/day
14-18 years	1.3 mg/day
Girls	
9-13 years	0.9 mg/day
14-18 years	1.0 mg/day
Men	
19 years and older	1.3 mg/day
Women	
19 years and older	1.1 mg/day
Pregnancy	
14-50 years	1.4 mg/day
Lactation	
14-50 years	1.6 mg/day

The DV (Daily Value) for riboflavin (vitamin B_2), which is used for determining percentage of nutrient daily values on nutritional supplement and food labels, is 1.7 milligrams. This is based on the U.S. RDA for riboflavin.

LITERATURE

Akomporg T, Ghori N, Halder K. In vitro activity of riboflavin against the human malaria parasite Plasmodium faciparum. *Antimicrob Agents Chemother.* 2000; 44:88-96.

Boehnke C, Reuter U, Flach U, et al. High-dose riboflavin treatment is efficacious in migraine prophylaxis: an open study in a tertiary care centre. *Eur J Neurol.* 2004;11(7):475-477.

Christensen HN. Riboflavin can protect tissues from oxidative injury. *Nutr Rev.* 1998; 51:149-150.

Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline. Washington, DC: National Academy Press; 1998.

Dutta P, Pinto JT, Rivlin RS. Antimalarial effects of riboflavin deficiency. *Lancet.* 1985; 2:1040-1043.

Fraaije MW, van den Heuvel RH, van Berkel WJ, Mattevi A. Covalent flavinylation is essential for efficient redox catalysis in vanillyl-alcohol oxidase. *J Biol Chem.* 1999; 274:35514-35520.

Fraaije MW, Mattevi A. Flavoenzymes: diverse catalysts with recurrent features. *Trends Biochem Sci.* 2000; 25:126-132.

Fouty B, Frerman F, Reves R. Riboflavin to treat nucleoside analogue-induced lactic acidosis. *Lancet.* 1998; 352:291-292.

Huang S-N, Swaan PW. Involvement of a receptor-mediated component in cellular translocation of riboflavin. *J Pharmacol Exp Therap.* 2000; 294:117-125.

Hustad S, Ueland PM, Vollset SE, et al. Riboflavin as a determinant of plasma total homocysteine: effect modification by the methylenetetrahydrofolate reductase C677T polymorphism. *Clin Chem.* 2000; 468:1065-1071.

Kunsman GW, Levine B, Smith ML. Vitamin B_2 interference with TDx drugs-of abuse assays. *J Forensic Sci.* 1998; 43:1225-1227.

Lakshmi AV, Ramalakshmi BA. Effect of pyridoxine or riboflavin supplementation on plasma homocysteine levels in women with oral lesions. *Natl Med J India.* 1998; 11:171-172.

Luzzati R, Del Bravo P, Di Perri G, et al. Riboflavine and severe lactic acidosis. *Lancet.* 1999; 353:901-902.

McCormick DB. Riboflavin. In: Shils ME, Olson JA, Shike M, Ross AC, eds. *Modern Nutrition in Health and Disease.* 9th ed. Baltimore, MD: Williams and Wilkins; 1999:391-399.

Munoz N, Hayashi M, Bang LJ, et al. Effect of riboflavin, retinol, and zinc on micronuclei of buccal mucosa and of esophagus: a randomized double-blind intervention study in China. *J Natl Cancer Inst.* 1987; 79:687-691.

Rivlin RS. Riboflavin. *Adv Exp Med Biol.* 1986; 206:349-355.

Rivlin RS, Dutta P. Vitamin B_2 (riboflavin). Relevance to malaria and antioxidant activity. *Nutrition Today.* 1995; 30:62-67.

Sándor PS, Áfra J, Ambrosini A, Schoenen J. Prophylactic treatment of migraine with beta-blockers and riboflavin: differential effects on the intensity dependence of auditory evoked cortical potentials. *Headache.* 2000; 40:30-35.

Schoenen J. [Anti-migraine treatment: present and future]. [Article in French]. *Rev Med Liege.* 1999; 54:79-86.

Schoenen J, Jacquy J, Lenaerts M. Effectiveness of high-dose riboflavin in migraine prophylaxis. A randomized controlled trial. *Neurology.* 1998; 50:466-470.

Thurnham DI, Zheng SF, Munoz N, et al. Comparison of riboflavin, Vitamin A, and zinc status of Chinese populations at high and low risk for esophageal cancer. *Nutr Canc.* 1985; 7:131-143.

Wahrendorf J, Munoz N, Lu JB, et al. Blood, retinol and zinc riboflavin status in relation to precancerous lesions of the esophagus: findings from a vitamin intervention trial in the People's Republic of China. *Cancer Res.* 1988; 48:2280-2283.

Royal Jelly

DESCRIPTION

Royal jelly, also known as gelee royale and RJ, is the milky-white gelatinous substance secreted from the cephalic glands of nurse worker bees *(Apis mellifera)* for apparently the sole purpose of stimulating the growth and development of the queen bee. Without royal jelly, the queen bee would be no different from the worker bees and would live about as long (seven to eight weeks). With royal jelly, the queen bee can live five to seven years. This fact explains the popular belief that royal jelly has rejuvenating qualities.

Royal jelly, however, has not lived up to expectations that it is an important anti-aging substance. But it is not without medical interest. Royal jelly consists of an emulsion of proteins, sugars, lipids and some other substances in a water base. Proteins make up about 13% of royal jelly. Most of the proteins comprise a family called major royal jelly proteins. One protein in royal jelly called royalsin possesses antibiotic properties against gram-positive, but not gram-negative, bacteria. About 11% of royal jelly is made up of sugars, such as fructose and glucose, similar to those found in honey. Lipids comprise about 5% of the substance and consist mainly of medium-chain hydroxy fatty acids, such as trans-10-hydroxy-2-decenoic acid, which is also thought to possess antimicrobial properties.

Royal jelly also contains vitamins, such as pantothenic acid, minerals and phytosterols. Neopterin, or 2-amino-6- (1,2,3-trihydroxypropyl)-4 (3H)-pteridinone, was initially isolated from royal jelly. Neopterin is also found in humans, and, although its precise role is not known, it appears to play an important role in the human immune system.

Melbrosia, a mixture of royal jelly and bee pollen, is sometimes used by menopausal women to manage climacteric symptoms.

ACTIONS AND PHARMACOLOGY

ACTIONS

Royal jelly may have hypolipidemic, antibacterial, anti-inflammatory and antiproliferative activities.

MECHANISM OF ACTION

The mechanism of actions of royal jelly is not known. The possible antibacterial activity of some royal jelly proteins, while of interest for topical use, is unlikely to be expressed when ingested.

PHARMACOKINETICS

There are no reported pharmacokinetic studies of royal jelly. Proteins, carbohydrates and lipids in royal jelly should be digested, absorbed and metabolized in the same way that