COSMECEUTICAL CRITIQUE

Luteolin

The flavone luteolin, 3',4',5,7-tetrahydroxyflavone, is a polyphenol commonly found in fruits, vegetables, and medicinal herbs (Curr. Cancer Drug Targets 2008;8:634-46). Luteolin is most often present in leaves, but is also found in rinds and other parts of plants.

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The flavone and its glycosides have been identified in *Bryophyta*, *Magnoliophyta*, *Pinophyta*, *Pteridophyta*, and *Salvia* (Mini Rev. Med. Chem. 2009;9:31-59).

Luteolin is believed to have the potential to play a significant role in health, as it is considered to exhibit broad-ranging anti-inflammatory benefits (Proc. Natl. Acad. Sci. U.S.A. 2008;105:7534-9), as well as anticarcinogenic, antimicrobial, antioxidant, and immunomodulatory effects. Cancer, hypertension, inflammation, and other conditions have been treated with luteolin-rich plants in traditional Chinese medicine (Curr. Cancer Drug Targets 2008;8:634-46).

Notably, this antioxidant is present in the typical human diet in relatively low amounts (less than 1 mg/day) (Molecules 2008;13:2628-51). Dietary sources of luteolin include carrots, chamomile tea, celery, olive oil, oregano, peppermint, peppers, perilla, rosemary, and thyme (Mini Rev. Med. Chem. 2009;9:31-59; FEBS Lett. 1998;438:220-4).

This column will focus on recent research conducted on this antioxidant, particularly studies that imply potential dermatologic applications.

Antitumor Actions

In 2002, Ueda et al. studied the effects of orally administered perilla leaf extract on mice, and found that it inhibited production of tumor necrosis factor–alpha. The in vitro phase of the study led to their identifying luteolin, caffeic acid, and rosmarinic acid as active constituents of perilla. The investigators noted that only luteolin exhibited in vivo activity, however. Luteolin was responsible not only for suppressing the production of serum tumor necrosis factor–alpha, but also for suppressing arachidonic acid–induced ear edema, 12-*O*-tetradecanoylphorbol-13-acetate (TPA)–induced ear edema, and oxazolone-induced allergic edema (Biol. Pharm. Bull. 2002;25:1197-202).

A year later, the same team reported on its examination of the effects of topically applied perilla leaf extract and luteolin on murine skin papillomas induced by TPA and 7,12-dimethylbenz[*a*]anthracene. Significant decreases in tumor incidence and multiplicity were observed in mice topically treated with perilla leaf extract before TPA treatment, especially in mice treated with luteolin prior to TPA (Biol. Pharm. Bull. 2003;26:560-3).

Anticancer Actions

Recent reviews on the diverse benefits of luteolin suggest that the flavone exhibits anti-inflammatory and anticarcinogenic properties, not all of which can be attributed to its antioxidant activity. By protecting against carcinogenic stimuli, luteolin is believed to have the capacity, in vitro and in vivo, to delay or inhibit cancer cell development, suppress tumor proliferation, induce cell cycle arrest, and spur apoptosis through intrinsic and extrinsic signaling pathways. Interestingly, some epidemiologic evidence points to an inverse relationship between luteolin consumption and the risk of developing some types of cancer (Molecules 2008;13:2628-51).

In a recent review of the distribution and biologic activities of luteolin, López-Lázaro summarized preclinical studies of the flavone, which have demonstrated that it has wide-ranging pharmacologic activities, particularly anticancer, anti-inflammatory, antimicrobial, and antioxidant properties.

Significant cancer chemopreventive and chemotherapeutic potential is suggested by the capacity of luteolin to block angiogenesis, induce apoptosis, prevent carcinogenesis in animal models, decrease tumor growth in vivo, and sensitize tumor cells to the cytotoxic impact of some anticancer drugs. López-Lázaro also noted a wide range of potential mechanisms of action for the various biologic activities of luteolin (Mini Rev. Med. Chem. 2009;9:31-59). In fact, luteolin has been found to sensitize cancer cells to induced cytotoxicity by inhibiting cell survival pathways (e.g., phosphatidylinositol 3'-kinase, nuclear factor kappa B, and X-linked inhibitor of apoptosis protein), and by promoting apoptosis pathways, leading to, for example, the induction of tumor suppressor p53 (Curr. Cancer Drug Targets 2008;8:634-46).

Seelinger et al. compared the anticarcinogenic effects of luteolin to those of other flavonoids, and found that luteolin was typically the most effective, inhibiting tumor cell proliferation with half-maximal inhibitory concentrations (IC50) between 3 and 50 mmol in vitro and in vivo by intragastric application or as a food additive. They concluded that because luteolin has also been demonstrated to penetrate human skin, this polyphenolic compound is potentially a suitable agent for preventing and treating skin cancer and photoaging (Molecules 2008;13:2628-51).

Antioxidant Actions

In a 2004 study of the components of *Zostera marina* leaves, Kim et al. found that the constituents apigenin, chrysoeriol, and luteolin scavenged radicals and reactive oxygen species, specifically the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical and the superoxide radical in the xanthine/xanthine oxidase system.

Luteolin also inhibited matrix metalloproteinase-1 (MMP-1) expression by up to 44%, and suppressed the synthesis of interleukin-6, a cytokine known to spur MMP-1 expression.

The investigators concluded that the antioxidant capacity of luteolin and the other *Zostera marina* constituents tested, as well as their ability to suppress MMP-1 expression, suggests the potential use of these compounds as agents to prevent cutaneous photoaging (Arch. Pharm. Res. 2004;27:177-83).

In 2008, Seelinger et al. conducted a literature review to clarify luteolin's antioxidant, anti-inflammatory, and antiallergic activities. They found that luteolin is a natural antioxidant that exhibits less pro-oxidant potential than the most studied flavonoid, quercetin, and that it has a better safety profile than quercetin.

Luteolin also has been shown to possess superlative radical scavenging and cytoprotective qualities, particularly in complex biological systems, where it can interact with other antioxidants. Luteolin acts as an anti-inflammatory agent by activating antioxidative enzymes, inhibiting the nuclear factor kappa B pathway, and suppressing proinflammatory compounds.

The authors concluded that more quantitative research is necessary to determine the potential therapeutic benefits of this potent antioxidant (Planta Med. 2008;74:1667-77).

Ultraviolet Protection

In 2005, Morquio et al. mixed extracts of plants known to contain potent antioxidants, specifically *Achyrocline satureioides* and *Epilobium parviflorum*, with a cosmetic base, and applied the compounds to the back skin of rabbits. Subsequently, they exposed the skin to ultraviolet irradiation for 1 hour, and intracutaneously injected the irradiated areas with sodium salicylate.

The researchers then evaluated hydroxyl radical production by measuring 2,3-dihydroxybenzoic acid (2,3-DHBA) synthesis resulting from the hydroxylation of sodium salicylate. The production of 2,3-DHBA was found to be significantly increased by the UV irradiation, but was markedly diminished in association with the application of the *Achyrocline satureioides* cosmetic formulation. The authors attributed this antioxidant effect to the presence of high concentrations of flavonoid aglycones, including luteolin (Phytother. Res. 2005;19:486-90).

In 2007, Sim et al. studied the structure-activity relationship of several flavonoid compounds and their antioxidant and inhibitory effects against MMP activity in vitro and in human dermal fibroblasts induced by ultraviolet A light. The compounds examined included luteolin, myricetin, quercetin, kaempferol, apigenin, and chrysin. Luteolin, with the highest number of OH groups in the B ring, was shown to have the most potent antioxidant efficacy as ascertained using the DPPH method and the xanthine/xanthine oxidase system. The authors also noted that in association with the relative antioxidant strength of the flavonoids, the compounds dose-dependently suppressed collagenase activity and MMP expression. They concluded that flavonoids with a higher number of hydroxyl groups may be the most effective at preventing UV-induced cutaneous aging (Arch. Pharm. Res. 2007;30:290-8).

Prostaglandin Inhibitor

In a 2008 study, Papaliodis et al. investigated the effect of flavonoids on niacin-induced flush in a rat model, and sought to determine whether prostaglandin D2 (PGD2) and 5-hydroxytryptamine (5-HT) were involved.

The researchers recorded three skin temperature measurements from each ear for each time point immediately before intraperitoneal injection with either niacin or a flavonoid (quercetin or luteolin). They then measured temperature every 10 minutes for 1 hour. Ear temperature was increased by niacin to a maximum of 1.9 plus or minus 0.2 °C at 45 minutes.

Quercetin and luteolin administered intraperitoneally 45 minutes before niacin blocked the niacin effect by 96% and 88%, respectively, while aspirin inhibited the niacin effect by 30%. Plasma PGD2 and 5-HT were increased twofold by niacin, while luteolin suppressed plasma PGD2 and 5-HT by 100% and 67%, respectively, and aspirin lowered only PGD2 (by 86%).

The investigators concluded that the increased skin temperature in rats caused by niacin is linked to increases in PGD2 and 5-HT, and that luteolin may be the most suitable inhibitor of niacin-induced flush because it suppresses both mediators (Br. J. Pharmacol. 2008;153:1382-7).

Currently, luteolin is included as a minor ingredient in some nutritional and herbal supplements.

Conclusion

Much more research is necessary to ascertain whether the bioactive properties of luteolin can be readily harnessed for application in dermatologic and other medical conditions. Currently, the preponderance of evidence suggests that this flavonoid is at least as promising as its fellow flavonoid quercetin. ■

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