

EDITORIAL

Luteolin supplements: All that glitters is not gold

It has been well known that polyphenolic compounds, such as flavonoids, have potent antioxidant, anti-allergic, anti-inflammatory, and cytoprotective properties.¹ However, unlike the original belief that their beneficial properties are due to the number of phenolic hydroxyl groups present, it is now known that these phenolic groups are more important for antioxidant than anti-inflammatory activity.^{2–5} Nevertheless, since oxidation stress contributes to inflammation, the antioxidant activity of flavonoids also provides indirect anti-inflammatory activity. Some of the most popular phenolic compounds found in dietary supplements are quercetin (5 phenolic hydroxyl groups), epigallocatechin gallate (EGCG, 8 phenolic hydroxyl groups), and pyrogallol (15 phenolic hydroxyl groups). The high number of phenolic groups could be a problem both because they reduce oral absorption, and for individuals who are phenol intolerant due to mutations in the genes encoding for the enzymes catecholamine-ortho-methyl transferase (COMT) and phenol sulfur transferase (PST) responsible for phenol catabolism. Curcumin is found as a constituent of dietary spices called turmeric and has two (2) phenolic and one (1) enolic hydroxyl group that exhibits keto-enol tautomerism, which can exist in different types of conformers depending on the environment and can thus also exert *pro-oxidative* effects.⁶ Consequently, it is important to select a flavonoid with the least number of phenolic hydroxyl groups, but still potent protective activities.

In the present collection of articles, different groups report on the anti-inflammatory and cytoprotective actions of luteolin (3',4',5,7-tetrahydroxyflavone, not lutein which is a carotenoid). Luteolin has been known to have anti-inflammatory properties^{2–5} and inhibits mast cells,^{2,7} which have been implicated in allergies,^{8,9} but also inflammation¹⁰ and COVID-19.^{11,12} In fact, a novel luteolin analogue, tetramethoxyluteolin (3',4',5,7-tetramethoxyflavone) is even more potent and can also inhibit secretion from human mast cells of the pro-inflammatory cytokines TNF and IL-1 β ,^{2–4} as well as the chemokines CCL2 and CCL5.⁵ Luteolin has also been shown to have broad antiviral properties.¹² Luteolin specifically binds to the surface spike protein of SARS-CoV-2 and inhibits entry of the virus into host cells, as well as serine proteases, including the SARS-CoV 3CL protease required for viral infectivity.¹² Both

luteolin and quercetin were recently identified via a molecular docking software to have the best potential to act as COVID-19 inhibitors.¹² Moreover, these flavonoids inhibit synthesis of platelet activating factor (PAF), which was recently implicated in inflammation and microthromboses associated with COVID-19.¹³

Luteolin and quercetin are generally considered safe^{14–17} and may be more appropriate to use as anti-inflammatory agents than the steroid dexamethasone.¹⁸ However, most of the dietary supplements available contain various luteolin formulations that are very confusing and sometimes outright misleading (Table 1). Such supplements are marketed as “bioflavonoids,” “citrus flavonoids,” and “luteolin complex,” with dubious amounts of luteolin, often mixed with high amounts of the less effective and much cheaper quercetin glycoside rutin. Moreover, neither the purity nor the source of the luteolin and/or other flavonoids is mentioned in most dietary supplements. For instance, the cheapest source of luteolin and quercetin is either peanut shells that may affect persons allergic to peanuts, or fava beans, consumption of which could cause hemolytic anemia to those persons mostly of Mediterranean origin, who lack the enzyme glucose-6-phosphate dehydrogenase (G₆PD). An additional problem with available supplements containing flavonoids in powder form is their poor absorption (<10%) from the intestine.¹⁴ This problem has been at least partially overcome in those dietary supplements containing luteolin (with or without quercetin) in a liposomal formulation using olive pomace oil (Table 1), which has its own anti-inflammatory molecules.¹⁹

The total amount of flavonoids combined should not exceed 1.5 g/day, especially in those who are slow metabolizers, because they may inhibit liver metabolic enzymes when they reach micromolar concentrations in the serum.²⁰ Moreover, giving higher amounts of flavonoids will accumulate in the intestine and inhibit the gut microbiome.²¹

In conclusion, luteolin (alone or together with quercetin) could have significant protective effects in conditions involving inflammation²² including COVID-19,¹² where mast cells could release IL-1 β and IL-6 directly^{4,23} or stimulate release IL-1 β release from other immune cells leading to cytokine storms.²⁴ Luteolin is more likely

TABLE 1 Comparison of content, amount, purity, and formulation of luteolin containing dietary supplements

Trade name	Flavonoid	Amount (mg/unit) ^b	Purity	Formulation	Source	Patents
Liposomal ^a						
BrainGain [®]	Luteolin +++ hydroxytyrosol	150	>87%	Softgel capsule with olive pomace oil	<i>Citrus paradisi</i>	Yes
FibroProtek [®]	Luteolin/quercetin	150/85	>87%	Softgel capsule with olive pomace oil	<i>Citrus paradisi/Sophora japonica</i>	Yes
NeuroProtek [®]	Luteolin/quercetin/rutin	100/70/30	>87%	Softgel capsule with olive pomace oil	<i>Citrus paradisi/Sophora japonica</i>	Yes
NeuroProtek [®] Low Phenol	Luteolin/quercetin/rutin	100/30/1	>87%	Softgel capsule with olive pomace oil	<i>Citrus paradisi/Sophora japonica</i>	Yes
PureLut [®]	Luteolin	100	>87%	Softgel capsule with olive pomace oil	<i>Citrus paradisi</i>	Yes
Powder						
Mirica [®]	Luteolin/palmitoyl ethanolamide	12	UN	Capsule	UN	No
Lutimax Luteolin Complex	Luteolin/rutin	100/100	UN	Chewable tablet	UN	No
Swanson Luteolin Complex	Luteolin/rutin	50/50	UN	Veggie capsule	UN	No
Piping Rock Luteolin Complex	Luteolin/rutin	50/50	UN	Veggie capsule	Orange peel	No
Supersmart Luteolin	Luteolin	50	80	Veggie capsule	Groundnut extract also contains Acacia gum	No
Horbaach Luteolin Complex 100	Luteolin/rutin	50/50	UN	Veggie capsule	UN	No
Senolyfe Luteolin 100	Luteolin	100	90	Veggie capsule	Perilla leaf	No
QuickSilver Hista-Aid	Vitamin C/luteolin/quercetin diindolylmethane	UN	UN	Mouth spray nanoemulsified suspension	UN	No
Life Extension Mix	Bioquercetin/luteolin ++++++++other ingredients	1.25/0.66	UN	Hard capsule	<i>Sophora japonica</i>	No
Advanced Nutritionals Memory Formula	Luteolin ++++++++ other ingredients	15	UN	Tablet	UN	No

Note: Any product of 60 capsules claiming 100 mg luteolin/capsule and priced <\$35 is unlikely to contain high purity luteolin, which is very expensive. +++ indicates the presence of additional active ingredients.

Abbreviation: UN, unknown.

^aPer unit (capsule or tablet) NOT per serving that may be two units or more (e.g., Life Extension Mix serving is 12 capsules/day).

^bBrainGain, FibroProtek, NeuroProtek (published clinical studies), Neuroprotek-Low Phenol, and PureLut have FDA's Certificate of Free Sale applicable to export outside the United States.

to enter the brain and it could, therefore, be useful in neuropsychiatric diseases that involve inflammation of the brain,^{17,25} including autism spectrum disorder.²⁶

Selecting a liposomal formulation containing high purity luteolin is critical in order to achieve any significant benefits.

DATA AVAILABILITY STATEMENT

N/A

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