

Brain Inflammation, Neuropsychiatric Disorders, and Immunoendocrine Effects of Luteolin

Theoharis C. Theoharides, BA, MS, MPhil, MD, PhD,*†‡§ Pio Conti, DSc,||
and Marina Economu, MD, DSc¶

The potential role of brain proinflammatory cytokines in the brain in the pathogenesis of psychiatric diseases was discussed almost 10 years ago.¹ Increasing evidence implicates brain inflammation in neuropsychiatric diseases,² including depression,³ bipolar disease,⁴ and autism spectrum disorders (ASD).^{5,6} Genome analysis of brains from deceased patients with bipolar disorder, depression, and schizophrenia showed increased expression of inflammatory genes and decreased expression of mitochondrial function.⁷ Other studies have also implicated mitochondrial dysfunction and neuroinflammation in Alzheimer disease,⁸ as well as in ASD,⁹ in which it was shown that extracellular mitochondrial components were increased in the serum of patients with ASD and could trigger autoinflammatory responses.¹⁰ In fact, nonsteroidal anti-inflammatory drugs have been considered in schizophrenia.¹¹ However, nonsteroidal anti-inflammatory drugs reduce the antidepressant action of specific serotonin receptor antagonists.¹² Moreover, corticosteroids that have strong anti-inflammatory effects can induce or exacerbate depression.¹³

In this void, certain natural flavonoids with anti-inflammatory actions¹⁴ have been used for neuropsychiatric diseases,¹⁵ and their intake was associated with decreased incidence of dementia in a 23-country study.¹⁶ Moreover, the use of polyphenolic compounds that contain flavonoids in psychiatric and cognitive disorders has been reviewed recently.¹⁷ Quercetin is a flavonol, and luteolin is a structurally related flavone, with 1 less hydroxyl group in the center ring.¹⁴ Both are rich in onions, tea, apples, and broccoli,¹⁸ with luteolin being more plentiful in olive FRUIT extract, CHAMOMILE,^{19,20} celery, spinach,²¹ and oregano.²² Luteolin reduces amyloid-beta peptide production in human transgenic-bearing neuronlike cells and primary neurons.²³ A number of comprehensive reviews have shown that the flavonol quercetin and its structurally related flavone luteolin are safe.^{24,25} In fact, these flavonoids seem safer than most of the psychotropic drugs prescribed to children.^{26,27} A recent study actually showed that a formulation of luteolin and quercetin was both well tolerated and resulted in significant improvement of children with ASD.²⁸ The case of luteolin is particularly interesting. Luteolin has been shown to have anti-inflammatory,^{29,30} antiallergic,^{31,32} and neuroprotective^{33,34} properties. It also inhibits mercury-induced activation of human mast cells,³⁵ T-cell activation,^{36,37} and activation of peripheral blood mononuclear cells derived from patients with multiple sclerosis.³⁸ In animal models, luteolin inhibited ASD-like symptoms, along with related biochemical changes.³⁹ Moreover, luteolin increases spatial memory in mice⁴⁰ and reduces cognitive decline in rats.⁴¹

It, therefore, came as a surprise that a recent publication reported that luteolin and quercetin have detrimental effects on the hormonal “system” and in “models” of breast and endometrial cancer.⁴² In particular, these authors reported that luteolin has estrogenic activity and antagonizes progesterone receptor activation. These results were obtained using transformed cell lines that can hardly qualify as a system or model of any disease. Moreover, other authors using different cell lines have reached opposite conclusions. For instance, 1 study reported that luteolin *inhibits estrogen production*,⁴³ whereas another showed that progesterone *does not bind to the progesterone receptor*.⁴⁴ In fact, there are hundreds of publications showing that these flavonoids,^{14,45} and especially luteolin,⁴⁶ have potent anticancer actions. Most importantly, recent articles reported that combining luteolin with quercetin,^{47–50} as well as with celcoxib,⁵¹ had more potent anticancer effect than each one individually.

Finally, the consumption of luteolin or quercetin at 200 to 400 mg/d found in some GMP-manufactured dietary supplements would never reach the concentrations used in the aforementioned article⁴² because oral absorption of these flavonoids is less than 10%.^{52,53} Even if one were to assume that the entire body is 1 compartment, the blood concentrations reached after consuming

From the *Molecular Immunopharmacology and Drug Discovery Laboratory, Department of Integrative Physiology and Pathobiology, †Department of Biochemistry, ‡Department of Internal Medicine, §Department of Psychiatry, Tufts University School of Medicine, Tufts Medical Center, Boston, MA; ||Immunology Division, Department of Clinical and Experimental Medicine, University of Chieti, Chieti, Italy; and ¶Department of Psychiatry, Athens Medical School, Aiginitio Hospital, Athens, Greece.

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Reprints: Theoharis C. Theoharides, MS, MPhil, MD, PhD, Department of Integrative Physiology and Pathobiology, Tufts University School of Medicine, 136 Harrison Ave, Boston, MA 02111 (e-mail: theoharis.theoharides@tufts.edu).

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these dietary supplements would be 10 to 100 times smaller than the recent article reporting endocrine-disrupting effects.⁴²

One should, therefore, be very cautious in making far-reaching conclusions, especially when the apparent benefits far outweigh any concerns. A similar “scare” was raised years ago based on cell cultures about tricyclic antidepressants promoting cancer, only to be proven a false alarm.⁵⁴ The best advice would be to avoid aggregate daily consumption of more than 2000 mg flavonoids, including curcumin, Pycnogenol, and concentrated berry extracts. This is most important in children taking psychotropic or antiseizure medications because all flavonoids, especially the most estrogenic, genistein, have variable effects on the liver-metabolizing enzymes⁵⁵ and could also interact with other natural molecules and drugs.⁵⁶

Naturally, the question of safety especially in children is an important one. However, any results based on “cell culture models” are fraught with danger of misleading conclusions. Only well-designed studies using *in vivo* models and clinical trials on appropriate patient populations⁵⁷ can provide convincing evidence of tolerability and effectiveness.⁵⁸

In conclusion, flavonoids such as luteolin and quercetin cannot be called *hormonal disruptors*. Luteolin, as other flavonoids, can affect liver metabolism and possibly sex hormone levels, but its anticancer effects are more significant than any effect on hormonal homeostasis.

AUTHOR DISCLOSURE INFORMATION

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