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File: ■ Luteolin
■ Quercetin
■ Autism Spectrum Disorders

HC 021453-499

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RE: Luteolin and Quercetin Formulation Improves Adaptive Functioning and Behavior in Children with Autism Spectrum Disorders

Taliou A, Zintzaras E, Lykouras L, Francis K. An open-label pilot study of a formulation containing the anti-inflammatory flavonoid luteolin and its effects on behavior in children with autism spectrum disorders. *Clin Ther*. 2013;35(5):592-602.

Autism spectrum disorder (ASD) is a term used to describe a range of neurodevelopmental disorders which are characterized by abnormal social interaction, communication difficulties, stereotyped or repetitive behaviors, activities, and interests, and in some cases, cognitive delays. The exact pathogenesis is unknown; however, there is some evidence that brain inflammation plays a role in ASD and several studies have found that children with ASD often have allergies. Immune system mast cells are implicated in both allergic and inflammatory reactions, are activated in autism, and the incidence of ASD is 10 times higher among children with mastocytosis (too many mast cells). The flavonoids luteolin and quercetin have potent anti-inflammatory and antioxidant activities, inhibit the release of inflammatory mediators from mast cells, and reduce autism-like behavioral deficits in mice. The purpose of this open-label study was to evaluate the safety and efficacy of a dietary supplement containing luteolin and quercetin in children with ASD.

Fifty children (42 boys and 8 girls, aged 4-10 years) with ASD based on clinical assessments and scores on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) symptom list and the Autism Diagnostic Observation Schedule diagnostic algorithm were enrolled in the study conducted at Athens University "Attikon" 2nd Psychiatric Clinic; Athens, Greece. Included children were medication and luteolin naive. The exclusion criteria were as follows: having a medical condition likely to cause ASD symptoms, having neurologic pathology above the brain stem (other than uncomplicated nonfocal epilepsy), diagnosed with probable neonatal brain damage, having mastocytosis, or a history of systemic inflammatory diseases.

The treatment was produced in a Good Manufacturing Practices certified facility (Tishcon Laboratories; Long Island, New York) under contract from Algonot, LLC (Sarasota, Florida; www.algonot.com) specifically for the study. The 200 mg capsules

contained >95% pure luteolin and quercetin; 100 mg/capsule luteolin from chamomile (*Matricaria recutita*) and 70 mg/capsule quercetin and 30 mg/capsule of the quercetin glycoside rutin, both derived from Japanese sophora (*Sophora japonica*) leaf. These flavonoids have poor oral absorption, so they were formulated in microspheres by mixing them in olive (*Olea europaea*) kernel oil of low (<0.01%) oleic acid and water content. The dose was 1 capsule per 10 kg (22 lb) body weight/day taken with food for 26 weeks.

The primary outcome measures were the age-equivalent scores in the 3 domains of the Vineland Adaptive Behavior Scales (VABS). The VABS is a validated parent interview tool that assesses the child's actual functioning in real life, rather than specific symptoms. Secondary outcome measures were the Aberrant Behavior Checklist (ABC), the Autism Treatment Evaluation Checklist (ATEC), and the Clinical Global Impression-Improvement score (CGI-I). Patients were evaluated at baseline, 18 weeks, and 26 weeks. For the analysis, patients were divided into 2 age groups (4-6 years old, n = 25; and 7-10 years old, n = 25).

Forty patients (35 boys, 5 girls) completed the study. The withdrawals were due to increased irritability (n=6, even though 2 were classified as good responders), poor compliance (n=1), parent unable to administer the treatment (n=2), and parent declined further participation after baseline (n=1). The patients received a mean of 7.75 hours/week of behavioral interventions, which did not change throughout the study. It was noted "that 55% of children had reported allergies or possible allergic symptoms."

At 26 weeks, there were positive changes in the VABS age-equivalent scores, which were significant for all domains ($P < 0.01$). The effect size was considered medium. All of the gains in the communication, daily living skills, and social domains were 4.0-6.10% greater than what would be expected by maturation alone. Further analysis of the age-equivalent scores indicated that only the initial adaptive function level influenced the final results. "More-able children responded better to the study formulation, whereas age, sex, and the presence of allergies were not good predictors for the final outcome."

On the secondary outcome measures evaluated with ABC, there was a large effect on decreasing hyperactivity and a medium effect on improving noncompliance, irritability and agitation, lethargy and social withdrawal, and stereotypic behavior ($P < 0.01$ for all), compared with baseline. However, there was no significant improvement on the ATEC except on the health/physical/behavioral domain. The CGI-I parent scores indicated a minor improvement, although the primary physicians rated 37.5% (15/40) children as much improved to very much improved.

On the scales assessing behavioral difficulties, children with the worst baseline scores on the ATEC speech/language/communication, ABC stereotypic, and ABC hyperactivity domains had the greatest improvements with treatment. Parents reported improvements in speech in 50%, better sociability in 48%, better cooperation in 43%, better and prolonged concentration in 30%, improvement in receptive language abilities in 30%, and better general communication intention and abilities in 20% of the patients.

The most frequent adverse event (AE) was increased irritability, which affected 54% of patients for various durations. Irritability was usually transient, lasting 1 to 8 weeks in 66% of cases. In 74% of the cases, irritability started 2 to 7 days after treatment began. There were other, infrequently occurring AEs such as sleeping difficulties and abdominal

pain, but without a placebo control group, the possible causal relationship between the AEs and the treatment could not be evaluated.

In summary, the treatment increased adaptive functioning and improved behavior. The data suggest that the luteolin and quercetin combination would be more beneficial for children who are higher functioning and have more behavioral problems (stereotypies, hyperactivity, language, and communication problems). The authors hypothesize that the irritability produced by the treatment may be related to the phenol content, and report that a new product with lower phenol content (NeuroProtek LP®; Algonot, LLC) has been developed.

The findings are encouraging considering that the gains were beyond what could be expected from a child's normal growth rate. However, it is unclear whether a 4-6% gain is clinically meaningful since there was no placebo control group and the participants were not blinded. The study did not include follow-up tests to evaluate whether the gains were long-lasting or acute. Another concern is that >40% of the children were not able to swallow the capsules. The parents had to open the capsules to sprinkle it on food, which could have altered the dose actually consumed. This study needs to be repeated as a randomized, placebo-controlled, double-blind study of the re-formulated low-phenol product to evaluate if efficacy is maintained while reducing the AE of irritability.

—Heather S. Oliff, PhD

The American Botanical Council has chosen not to include the original article.