

# **Preserving Vision in Patients with Macular Degeneration**

## **The Neuroprotective Effects of Dietary Flavonoids.**

Cell damage is the primary cause of visual loss in patients with macular degeneration. Thirty percent of patients over the age of 75 suffer from one of these conditions and the incidence is expected to increase as the population ages. Restoring the function of injured nerve cells has been particularly difficult both in the central nervous system and in the setting of ocular diseases.

We formed a research team with Dr. Pamela Maher at the Salk Institute to explore the ability of dietary flavonoids to prevent oxidative stress, the type of cellular injury that is thought to occur in macular degeneration. This collaboration was started and the approach was validated after a large, ten-year clinical trial sponsored by the National Eye Institute indicated that specific antioxidants could reduce the progression of macular degeneration.

Flavonoids have four properties that make them promising candidates for the treatment of macular degeneration. The compounds are potent antioxidants and free radical scavengers; they induce neuronal recovery after injury; they inhibit blood vessel growth and they are well tolerated orally. Specific flavonoids can enhance the production of glutathione, block the production of reactive oxygen species and prevent the late influx of calcium, activities which prevent specific events in the nerve cell death pathway. In addition, the flavonoids can activate the antioxidant response element, which induces the expression of genes which function to increase the cells resistance to oxidative stress. The ability of flavonoids to restore the health of injured neuronal cells and induce the outgrowth of neurites gives these compounds a unique set of advantages compared to other antioxidants.

The goal of our research was to determine the specific classes and the chemical structures of dietary flavonoids that were the most effective at preventing oxidative stress-induced cell death in retinal pigment epithelial cells (RPE), which are the cell type that dies in both wet and dry forms of macular degeneration. We screened multiple different flavonoids for their ability to protect these cell types from oxidative stress induced by the peroxides, H<sub>2</sub>O<sub>2</sub> and t-BOOH and investigated the mechanisms behind this protective activity. Specific flavonoids were identified that are both potent and highly efficacious at preventing RPE cell death.

This figure shows the protective effect of luteolin, a flavonoid present in spinach. In the presence of oxidative injury from either t-BOOH or H<sub>2</sub>O<sub>2</sub>, RPE cells die (left panels). Luteolin prevents the death of the retinal pigment epithelial cells and shows no sign of cellular toxicity over a wide range of concentrations. Other flavonoids, including quercetin, fisetin and eriodictyol are also effective.

On the basis of these early findings, we compiled a list of the fruits and vegetables which contain the highest concentrations of the flavonoids that are the most effective at preventing oxidative stress-induced cell death in cells derived from the eye.

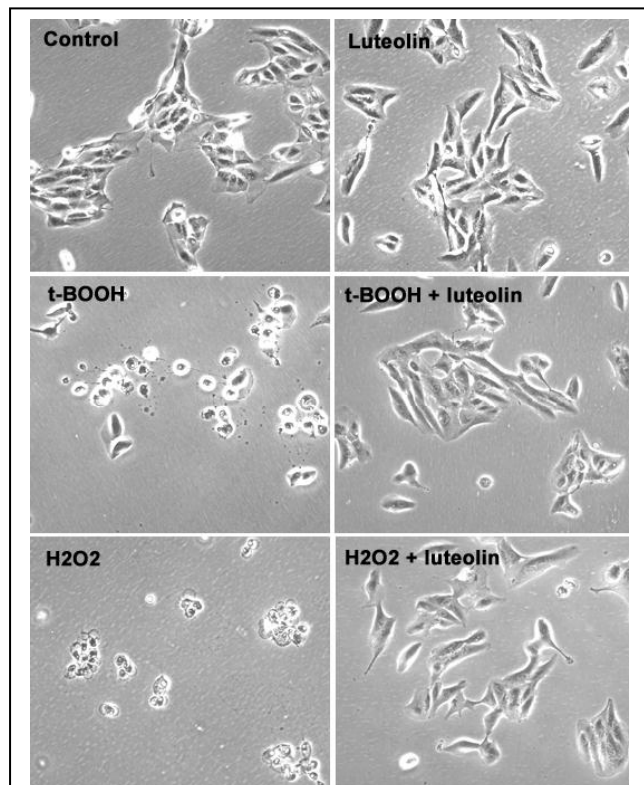


Figure 1. Luteolin protects RPE cells from oxidative-stress induced cell death.

Flavonoid	Dietary Sources
Luteolin	Spinach, wild greens, peppermint, hot peppers, celery, herbs-thyme, parsley, mint
Quercetin	Onion (esp. yellow), cranberries, cocoa, wild greens, capers, fennel, spinach, chives, celery, cherries, blueberries, apples, kale, red wine.
Eriodictyol	Peppermint, citrus juices (lemon, lime, sour orange).
Fisetin	Strawberries, tomatoes, onion, oranges, apples, peaches, grapes, kiwi, persimmons.

The mechanisms associated with the protective effects were examined in subsequent experiments and are outlined in the publications below.

**Hanneken, A**, Lin, F., Johnson, J., Maher, P. and. Flavonoids protect human retinal pigment epithelial cells from oxidative stress-induced death. Invest Ophthalmol Vis Sci. 47: 3164-3177, 2006

Jennifer Johnson, Pamela Maher, and **Hanneken, A.** The flavonoid, eriodictyol, induces long-term protection in ARPE-19 cells through its effects on Nrf2 activation and phase II gene expression. *Invest Ophthalmol Vis Sci* 50(5):2398-406, 2009.