Flavonoids and glaucoma: revisiting therapies from the past

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Flavonoids are a large family of phytonutrient compounds found in various plants (berries, tea, citrus fruits) as well as in chocolate and red wine. More than 5000 flavonoid compounds are currently known, grouped into five main categories (flavonols, flavan-3-ols, flavones, flavanones, and anthocyanidins). Flavonoids constitute 25 % of the *Ginkgo biloba* extract (GBE), processed from the leaves of one of the oldest living tree species, a “living fossil”, having survived since the Permian more than 250 million years ago. The *Ginkgo biloba* tree, which is found in the wild only in China, has been used for its therapeutic effects for more than 5000 years, both in China and worldwide. Today, the tree is cultivated across the world, and continues to be offered as alternative treatments for ailments associated with aging, such as neurodegenerative disorders, cognitive decline, vascular insufficiency and glaucoma, often with controversial results. *Ginkgo biloba* is the most common (50 %) herbal supplement used by elderly patients, often as an over-the-counter compound [1].

Due to their perceived antioxidant, anti-inflammatory and neuroprotective benefits, various flavonoids (and in particular GBE) have been proposed for the treatment of non-pressure-dependent risk factors associated with glaucoma [2]. This interest has been propelled by the fact that classic glaucoma treatments, based on reduction of the intraocular pressure

(IOP), may not always prevent glaucoma progression. This may be particularly true in patients with progressive primary open-angle glaucoma (POAG) despite IOP normalization, or in POAG patients with the normal-tension glaucoma (NTG) subtype. The use of flavonoids in glaucoma has been supported by many in vitro and in vivo studies, suggesting their active role in neuroprotection, reduction of mitochondrial oxidative stress and improvement of ocular blood flow [3]. Since impaired ocular blood flow can be more pronounced in NTG than in POAG, or in progressive versus stable forms of POAG, it has been suggested that GBE—and more generally, flavonoids—could represent a promising adjuvant therapy in these two settings [4]. The high safety profile of flavonoids also contributes to its current popularity and its large over-the-counter consumption [5].

Despite numerous attempts to evaluate the efficacy of flavonoids and GBE in the treatment of glaucoma, only a few randomized comparative studies have been published so far, with conflicting results [6, 7]. Many of these studies have individually suggested a beneficial role in glaucoma, especially in NTG, but the small number of included patients and the heterogeneity of the study design make it difficult to draw a firm conclusion.

In the current issue of *Graefes' Archive for Clinical and Experimental Ophthalmology*, Patel et al. evaluate the efficacy of flavonoids in glaucoma and ocular hypertension, performing a review and a meta-analysis of the currently published data, including only randomized controlled trials [8]. The number of included studies was surprisingly small: among the initially 16,840 screened articles, only six trials encompassing a total of 214 participants could be included, based on the inclusion criteria. Despite a rigorous effort to avoid risks of bias at each step of the study, the authors chose to include patient populations with a large variety of conditions (ocular hypertension, POAG, NTG, chronic angle-

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closure glaucoma). The flavonoid intervention was also variable across the studies, with three different compounds analyzed (GBE in two studies, epigallocatechin gallate in one study, anthocyanins in one study and *Erigeron breviscapus* (vant.) Hand-Mazz in two studies). The minimum duration of intervention was rather short (1 month), and the authors could not perform a separate meta-analysis of long-term trial results.

Interestingly, this meta-analysis found a statistical significant effect of flavonoids in maintaining or improving the visual field in glaucoma patients, even after short interventions of 4 weeks. This effect was more pronounced in a subgroup of glaucoma patients with more severe visual field loss (as measured by mean deviation), compared to patients with relatively mild visual field loss. A subgroup analysis was unable to detect a significant difference among types of flavonoids or intervention durations. Thus, the authors suggest that even short-term intervention with flavonoids may be sufficient to slow glaucoma progression. Consistent with the results of previous studies, flavonoids did not influence mean IOP in patients compared to controls. It was proposed that maintenance or improvement of the visual field after treatment with flavonoids could have been the result of improved retinal ganglion cell function, improved cognition, or both. A neuroprotective and microvascular effect of flavonoids may have played a role in this process, both at the ocular and cerebral level. In order to evaluate the effect of flavonoids on ocular blood flow, the same study [8] included a review of three reports (using different measurement methods, and therefore not submitted to meta-analysis). The review suggested a significant improvement of ocular blood flow (measured by laser Doppler flowmetry or by laser speckle flowgraphy) after flavonoid treatment. However, flavonoids did not affect the systemic systolic or diastolic blood pressure compared to placebo.

The conclusion of this meta-analysis was that flavonoids may be helpful in maintaining or restoring the visual field in patients with glaucoma and ocular hypertension, although they have no significant influence on IOP reduction. This effect was found after pooling various types of glaucoma

and various flavonoid compounds at various dosages in patients who sometimes had other concomitant glaucoma treatments. The authors recognize that data published by Quaranta et al. [6] may have heavily influenced the results of the meta-analysis, which nevertheless found a global beneficial effect of flavonoids on the visual field in glaucoma.

Although these therapies from the past seem promising, further studies (including larger populations and longer follow-up) are needed to provide evidence that treatments derived from flavonoid compounds may be of benefit in preventing visual loss from glaucoma.

Conflict of interest The authors have no conflict of interest related to this subject.

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