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REVIEW

# Nutritional recommendations for individuals with Flammer syndrome

**Zakieh Vahedian**[1] · **Ghasem Fakhraie**[1] · **Jerome Bovet**[2] · **Maneli Mozaffarieh**[2,3]

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**Abstract** The Flammer syndrome (FS) describes the phenotype of people with a predisposition for an altered reaction of the blood vessels to stimuli like coldness or emotional stress. The question whether such people should be treated is often discussed. On the one hand, most of these subjects are healthy; on the other hand, FS seems to predispose to certain eye diseases such as normal tension glaucoma or retinitis pigmentosa or systemic diseases such as multiple sclerosis or tinnitus. A compromise between doing nothing and a drug treatment is the adaption of nutrition. But what do we mean by healthy food consumption for subjects with FS? The adaption of nutrition depends on the health condition. Whereas patients with e.g. a metabolic syndrome should reduce their calorie intake, this can be counterproductive for subjects with FS, as most subjects with FS have already a low body mass index (BMI) and the lower the BMI the stronger the FS symptoms. Accordingly, while fasting is healthy e.g. for subjects with metabolic syndrome, fasting can even dangerously aggravate the vascular dysregulation, as it has been nicely demonstrated by the loss of retinal vascular regulation during fasting. To give another example, while reducing salt intake is recommended for subjects with systemic hypertensions, such a salt restriction can aggravate systemic hypotension and thereby indirectly also the vascular regulation in subjects with FS. This clearly demonstrates that such a preventive adaption of nutrition needs to be personalized.

**Keywords** Preventive · Personalized · Flammer syndrome · Oxidative stress · Antioxidative nutrition

✉ Maneli Mozaffarieh
maneli.mozaffarieh@gmail.com

Zakieh Vahedian
vahedian.z@gmail.com

Ghasem Fakhraie
gfakhraie@gmail.com

Jerome Bovet
jbovet@vision.tv

[1] Glaucoma Service, Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran

[2] Augen Glattzentrum, Zurich, Switzerland

[3] Department of Ophthalmology, University of Basel, Mittlere Strasse 91, 4031 Basel, Switzerland

## Background

The eyes, like all other organs of the body, depend upon nutrients, vitamins and minerals, to maintain their health and proper function. Thus, the way an individual eats affects the health of their eyes. Many individuals, including those with the Flammer syndrome (FS) [1, 2] are aware that their nutritional habits and lifestyle affect the health of their eyes, [3, 4] but may not know what they should be eating to support their eye health. The term 'Flammer Syndrome' refers to a clinical entity comprising a complex of clinical features caused mainly by dysregulation of the blood supply which has previously been called vascular dysregulation [2, 5, 6]. With an increase in allergies [7], heightened concerns over health [8], increased scrutiny of chemical additives and growing environmental concerns [9, 10], there is more attention being paid to nutrition and lifestyle today than perhaps ever before. Ophthalmologists are therefore often confronted with questions from people with the FS regarding nutrition. This may be partly due to the fact that people with the FS are often dissatisfied with conventional forms of treatment because they do not tolerate drugs in normal dosages as well as other people due to a different expression of ATP-binding cassette (ABC) transport proteins [11], or because the drug has produced adverse

effects, or simply because they want to actively do something themselves for their eye health by changing their nutrition and lifestyle. In Europe, we are slowly going to where the Eastern culture has been for hundreds of years back to the idea that food is medicine and that we cannot disassociate our health with what we eat. As ophthalmologists, we are doing no harm to the patient by providing them with additional information on nutrition and lifestyle for the following reasons: it is cheap, well accepted by the patient as it has a natural source and supports the FS patient with their subjective symptoms with some first studies showing objective improvements in measures such as increased retinal venous pressure [5, 6], decreased systemic oxidative stress or improvements in peripheral blood flow [12–14]. It is important to note, however, that nutritional recommendations for people with FS are quite different than those with a metabolic syndrome. Accordingly, while fasting is healthy e.g. for subjects with metabolic syndrome, fasting can even dangerously aggravate the vascular dysregulation. Similarly, while reducing salt intake is recommended for subjects with systemic hypertensions, such a salt restriction can aggravate systemic hypotension [2] and thereby indirectly also the vascular regulation in subjects with FS [15]. This demonstrates that such preventive adaptation of nutrition needs to be personalized [16].

This article provides an overview of beverages and foods with potential antioxidative effect, as well as lifestyle measures an individual can take to support the FS.

## Main text

### General background chemistry

Nutrients with antioxidative potential [17] either contain molecules that can donate a proton to a free radical to neutralize them such as polyphenols or contain molecules with the capacity to withdraw a lone electron from free radicals such as anthocyanosides [18]. Chemically, polyphenols are defined as molecules having more than one hydroxyl group in their structure which can readily donate a proton to a free radical (Fig. 1), whereas anthocyanosides have a positively charged oxygen atom in their central ring with the capacity to withdraw lone electrons [19] (Fig. 2). Foods and beverages containing polyphenols or anthocyanins are generally coloured (fruits and vegetables) as the presence of conjugated double bonds creates a delocalized electron system that absorbs light between 400 and 700 nm of the visible wavelength.

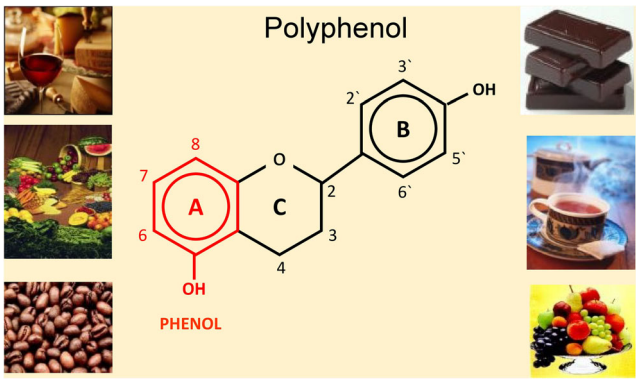


**Fig. 1** The general chemical structure of a polyphenol with a phenol ring depicted in *red*. Alongside are foods rich in polyphenols. From: Mozaffarieh M and Flammer J. Ocular blood flow and glaucomatous optic neuropathy. 2007 Springer. Page 45

## Beverages

### Tea

The source of black and green tea is the leaves of the plant *Camellia sinensis* [20] Fig. 3. Green tea has a much higher content of polyphenols (35% of its dry weight) [21] including catechin (C), epicatechin (EC), epigallocatechin (EGC) and their gallate esters. The difference between the polyphenolic contents of black and green tea is the result of the different processing methods once the tea leaves are picked [22]. Once picked, black tea leaves are exposed to warm dry air where they undergo an oxidation process. This process causes the leaves to darken and brings out a full-bodied tea flavour as the catechins in black tea are converted to complex fermentation products, namely theaflavins (TFs) and thearubigins (TGs) [23]. Green tea leaves are steamed immediately after they are picked so that no oxidation occurs which is why the polyphenolic content of green tea is higher and it has a characteristic greenish-gold colour.

Tea flavonoids are scavengers of the superoxide anion and nitric oxide [24] which plays an important role in the pathogenesis of glaucomatous damage as well as of hydrogen peroxide which plays a role in UV-induced oxidative damage. Tea flavonoids inhibit the formation of lipid peroxyl radical

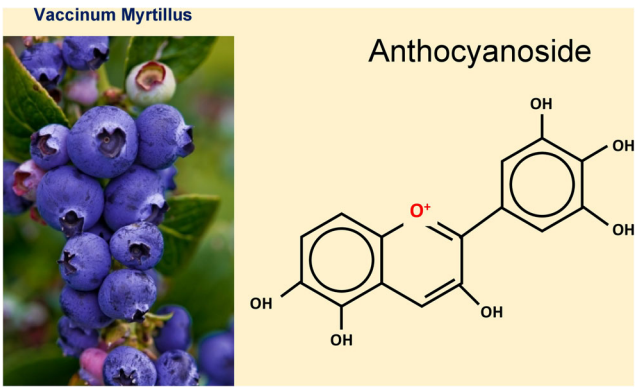


**Fig. 2** *Right*: The general chemical structure of an anthocyanoside with a positively charged oxygen atom in the central ring which has the capacity to scavenge a free radical. *Left*: Blueberries rich in anthocyanosides. From: Mozaffarieh M and Flammer J. Ocular blood flow and glaucomatous optic neuropathy. 2007 Springer Page 46

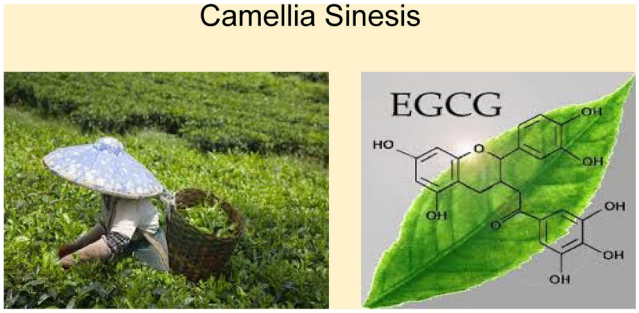


**Fig. 3** *Left*: Green tea plantation with leaves ripe for picking. *Right*: Green tea leaves are rich in polyphenols such as epigallocatechin gallate. From: Mozaffarieh M and Flammer J. Ocular blood flow and glaucomatous optic neuropathy. 2007 Springer. Page 77

species and thus inhibit LDL peroxidation [25]. Tea polyphenols may have protective effects against cancer [26], although studies are controversial.

### Coffee

Coffee beans have an antioxidative effect due to their polyphenols with radical scavenging and metal chelating activities [27–29] (Fig. 4). Coffee contains the molecule 3-methyl-1,2-cyclopentanedione (MCP) which is a selective scavenger of peroxynitrite (ONOO–) [30]. The chemistry of MCP enables it to easily donate a proton to peroxynitrite in order to neutralize it; this is brought about by the chemical conversion of one of its carbonyl groups which becomes reduced to a hydroxyl group. Polyphenols in coffee inhibit lipid peroxidation and exert a protective effect against mutagenicity [31].

### Wine

The polyphenolic content in red wine is higher than white wine [32], explaining why red wine exerts a stronger antioxidant capacity than white wines [33]. Polyphenols in wine lower the susceptibility of LDL lipids to oxidation [34] and improve endothelial dysfunction [35, 36] impairment which leads to damage to vascular cells and the surrounding tissue. Wine polyphenols affect endothelial function by stimulating


**Fig. 4** On the *right*, a hot cup of coffee brewed from red cherry-like coffee beans from the coffee plant depicted on the *left*. From: Mozaffarieh M and Flammer J. Ocular blood flow and glaucomatous optic neuropathy. 2007 Springer. Page 78

the production of endothelial nitric oxide synthase (eNOS) and thus increasing the production of nitric oxide (NO) which induces vasodilation [37]. In addition, wine polyphenols inhibit the synthesis of the potent vasoconstrictor endothelin-1 [35]. In experimental models, flavonoids in wine prevented the initiation of atherosclerotic plaque development [38, 39]. Extracellular levels of vascular endothelial growth factor (VEGF) were reduced by resveratrol [40], a polyphenol found in grapes and wine.

### *Ginkgo biloba*

The *Ginkgo biloba* tree is one of the oldest trees found in fossils dating back 270 million years ago [41]. This tree is indigenous to China, Japan and Korea where it currently exists in areas of higher altitude [42], which are well drained, and adapts relatively well to different ecological conditions. The leaves and the fruits rich in flavone glycosides and terpenoids of ginkgo [43, 44] have been used for medical purposes for thousands of years by the Chinese.

The flavonoid glycosides confer antioxidant properties to ginkgo particularly at the mitochondrial level while the terpenoids act as antagonists of platelet-activating factor [45–48]. In comparison to other antioxidants such as vitamin C or vitamin E, the extracts of ginkgo can stabilize and protect mitochondrial function [49–51] thereby preventing oxidative damage to mitochondria [49]. This property of ginkgo allows protection against retinal ischemia-reperfusion injury [52–54]. Gingko extracts inhibit LDL oxidation [55, 56], have a relaxing effect on vascular walls [57], increase ocular blood flow velocity in patients [58, 59], reduce systemic oxidative stress in glaucoma patients [12] (Fig. 5), and slow visual field progression in normal-tension glaucoma patients [60, 61]. A daily dosage of 120 mg is efficient and safe [62].

### Borage

Borage (*Borago officinalis*), also known as star flower, belongs to the flowering plant family Boraginaceae. This plant is native to the Mediterranean region but has a high resistance to cold climates and grows well in wet soils with good drainage and exposure to sunlight [63]. The beautiful violet-to-purple-coloured leaves of this plant are edible, and culinary borage oil can be extracted from the seeds of this plant. Traditionally, borage was cultivated for culinary as well as medicinal uses [64–67]. The leaves of borage contain polyphenols with antioxidative effect [68] whereas the seeds are a rich source of gamma-linolenic acid (GLA) [69], with anti-inflammatory effects. Borage leaves are used as an anticonvulsant [67], bronchodilator and vasodilator [70]. In a recent study, borage tea was shown to decrease increased retinal venous pressure in people with FS. This effect is most likely due to the calcium-antagonizing side effects of this plant [70].

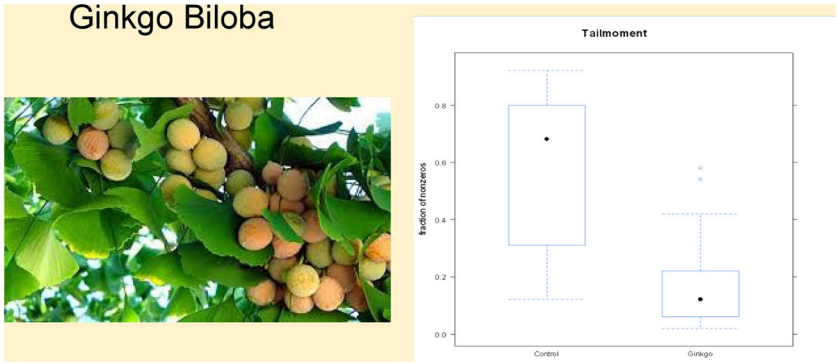


**Fig. 5** *Left*: Ginkgo tree with fruits rich in polyphenols. *Right*: *Ginkgo biloba* significantly reduces systemic oxidative stress in glaucoma patients. From Fang L, Neutzner A, Turtschi S, Flammer J, Mozaffarieh M. The effect of *Gingko biloba* and nifedipine on DNA breaks in circulating leukocytes of glaucoma patients. Expert Rev. Ophthalmol. 10(3), 313–318 (2015)

## Foods

### Fruits and vegetables

Diets rich in fruits and vegetables may reduce oxidative stress and inflammation [71, 72]. These beneficial effects are due to their high polyphenol content which may vary from season to season [73], and on their natural stage of fruit ripening [74]. Fruits and berries blue in colour are a rich source of anthocyanosides with free radical scavenging properties [75]. These fruits exert their beneficial properties even if taken in the dried form [76, 77].

### Omega 3 fatty acids

Omega-3 fatty acids also known as polyunsaturated fatty acids are considered essential fatty acids. Omega-3 fatty acids are found in fish, such as salmon, tuna and halibut, other seafoods including algae and krill and flaxseed oil [78]. Omega-3 fatty acid prevents development of intracranial atherosclerosis [79], reduce inflammation [80, 81], lower blood pressure [82], improve endothelial vascular function [83] and modulate intracellular calcium ion release and thereby the stabilization of circulation [84].

Other effects include increase in the production of uncoupling proteins and improvement of ATP-independent heat production which is most probably impaired in people with FS [78, 85].

### Cacao

The cacao tree or '*Theobroma cacao*' is native to the deep tropical regions of Central and South America [86]. The cacao beans are a rich source of polyphenolic flavonoids whose antioxidant capacity has been shown to be higher than that of wine or green tea [87]. The amount of cacao is double as high in dark chocolate in comparison to milk chocolate [88]. Besides, the milk in milk-chocolate interferes with the absorption of cacao polyphenols [89]. Consumption of cocoa-rich food, such as dark chocolate, is associated with a reduced risk for vascular disease [90–94]. This is due to the action of flavan-3-ols which augment endothelial NOS and thereby enhance the production of nitric oxide (NO), thereby improving endothelium-dependant vasorelaxation [95]. Cacao decreases blood pressure [96, 97], increases insulin sensitivity [96], increases HDL cholesterol concentrations [98] and reduces blood platelet stickiness and clotting [91, 92].

### Magnesium

Magnesium can be found in a variety of foods such as seeds (chia, flax and pumpkin), avocados, tofu, nuts, legumes including beans and peas, whole grains and leafy greens. Magnesium is a physiological calcium channel blocker that partially inhibits the effect of endothelin-1 [14] and improves blood flow [13]. A dosage of 10–20 mmol daily is recommended for adults to improve the regulation of blood flow [13, 99]. For the patient, it is important to note that the different forms of magnesium contain different amounts of

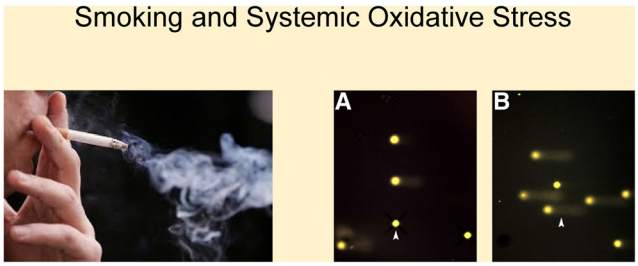


**Fig. 6** An addicted smoker (*left*) more than doubles systemic oxidative stress as shown in the bar chart on the *left* where the leukocytes from the blood sample taken from the smoker show a significantly higher amount of cells with DNA breaks depicted as *comet tails* (**b**) in comparison to the blood sample from an age- and sex-matched healthy control with intact cells (**a**). From: Mozaffarieh M, Konieczka K, Hauenstein D, Schoetzau A, Flamme J. Half a pack of cigarettes a day more than doubles DNA breaks in circulating leukocytes. Tob Induc Dis. 17;8:14 (2010)

magnesium, and in case they are uncertain of the correct daily dosage of the particular magnesium supplement, they should refer to their pharmacist. Forms of magnesium that dissolve well in liquid are more completely absorbed in the gut than less soluble forms [100].

Since this amount cannot be consumed solely by nutrition, we recommend the intake of magnesium in supplements. Unfortunately, it is difficult to compare the bioavailability of various forms of magnesium because different experimental methods and forms or qualities of magnesium supplements are used in various studies. One experimental study comparing the bioavailability of four inorganic and six organic mineral salts of magnesium suggested that although all ten organic and inorganic Mg salts were equally efficient in restoring blood Mg levels in plasma and red blood cells in rats, magnesium gluconate exhibited the highest magnesium retention and absorption values in the ten studied groups [101].

Finally, it is of note that although side effects are minimal, one potential side effect of magnesium supplementation is diarrhoea due to the osmotic activity of unabsorbed salts in the intestine and colon and the stimulation of gastric motility [102]. In case of diarrhoea, we recommend to take the supplement in small amounts throughout the day, perhaps together with some banana or bread.

### Spices

There is increasing interest in the antioxidant compounds of herbs and spices not only because they retard the oxidative degradation of lipids [103, 104] but also because they improve the flavour of food. Spices including curcumin, safran, ginger, cinnamon and pepper contain polyphenolic flavonoids with antioxidative activity. During cooking, heat brings forward mutagenic epoxides, hydroperoxides and unsaturated aldehydes, which are carcinogenic [105]. Heating changes the nature of the membranes because of decomposition of the cell walls allowing antioxidant molecules more access to the free radical, thus enhancing antioxidant activity of certain spices during the heating process [106].

## Lifestyle

There are certain lifestyle risk factors that can be changed to improve the FS. People with FS should try and avoid stress, as stress enhances levels of endothelin-1 in blood plasma leading to a vasoconstriction of the vessels [107] and induces transient myocardial ischaemia in approximately one third of patients with coronary artery disease [108]. Other bad habits to give up include smoking. Smoking reduces retinal blood flow, and the capacity of the retinal vessels to autoregulate to hyperoxia [109] more than doubles the levels of systemic oxidative stress in the body [3] (Fig. 6) and increases heart rate without affecting retinal venous pressure [4]. People with FS should take care to drink enough during the day as they tend to have a lack of thirst due to high levels of plasma endothelin-1 which upregulates the hormone prostaglandin E-2, thereby suppressing the centre of thirst in the brain [110]. Since low blood pressure is common amongst people with FS [2], an increased amount of salt intake is recommended [15, 111, 112].

## Conclusion

There is great interest today on natural compounds with antioxidative potential [15, 78].

Unfortunately, we still do not conclusively know whether nutritional sources of antioxidants can benefit people with FS. Growing evidence suggests, however, that oxidative stress resulting from FS may increase the risk of diseases such as glaucoma [99, 113, 114]. It is therefore worthwhile to summarize the present knowledge as nutritional and lifestyle changes with potential to reduce oxidative stress may benefit people with FS.

*ABC*, ATP-binding cassette; *C*, catechin; *EC*, epicatechin; *EGC*, epigallocatechin; *eNOS*, endothelial nitric oxide synthase; *FS*, Flammer syndrome; *GLA*, gamma-linolenic acid; *HDL*, high-density lipoprotein; *IOP*, intraocular pressure; *LDL*, low-density lipoprotein; *MCP*, 3-methyl-1,2-cyclopentanedione; *NO*, nitric oxide; *TFs*, theaflavins; *TGs*, thearubigins; *UV*, ultraviolet.

**Compliance with ethical standards**

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**Conflict of interest** The authors declare that they have no conflict of interest.

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