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LETTER TO THE EDITOR

The potential use of flavonoids as venoactive drugs and the role of citrus fruits

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Sir,

This letter addresses the reported phlebotonic activity of some flavonoids (Fls) recommended in venous conditions such as chronic venous insufficiency (CVI) and varicose veins, both having considerable socioeconomic impact [1]. Supplementation of Fl as drugs or nutritional supplements versus enhanced consumption of citrus fruit is also discussed in this letter. It is known that substances with unproven efficiency are sometimes promoted as evidence-based medications. Besides, certain pharmaceuticals can be replaced by a diet modification [2,3].

Fls constitute the largest part of dietary polyphenols; they can be found in many fruits, vegetables, and cereals [4,5]. Some supposedly venoactive Fls (rutin, escin, quercetin) have been extracted from medicinal plants. Today, the micronized purified Fl fraction (MPFF) is broadly used, consisting of 90% diosmin and 10% hesperidin. Diosmin is synthesized from hesperidin, which is extracted from a type of small immature oranges [6]. Other preparations which have been associated with the treatment of venous disease are hydroxyethylrutosides, also known as troxerutin, and pycnogenol [7,8]. In the U.S., Fl preparations are classified as dietary supplements, and in some European countries as drugs, which does not necessarily mean extensive use. So, in Scandinavia drugs are hardly ever prescribed for chronic venous disease [9]. In Spain, for certain phlebotonics the indication for CVI has been withdrawn, and for several other countries—such as diosmine, hidrosmine, escin, and some rutosides—the use during exacerbations of CVI has been limited to two or three months [10].

The following effects of venoactive Fls have been discussed: phlebotonic, anti-edematous, anti-inflammatory, and anti-oxidative. The action mechanisms are not well established [6,10,11] and not clearly understandable theoretically. The smooth muscles (SM) of large and medium-sized veins studied *in vitro* had no tone and did not relax under the impact of vasodilators [12]. The lumen of collapsed veins is slit-like, the circular SM layer is thin, bunches of SM alternating with connective tissue. In post-thrombotic syndrome and varicose veins, where Fls are generally recommended, venous walls are partly distended, SM being atrophic and replaced by fibrous tissue [1,13]. All these are against any significant phlebotonic effect of Fls; in particular, its durability is doubtful. This pertains to potentiation of norepinephrine action under the influence of Fls discussed in the literature [6,13–15]. The vasoconstrictor effect of norepinephrine is short-term, its blood concentration fluctuates in stress, etc., whereas Fls have been proposed for the treatment of chronic conditions such as CVI and varicose veins. At the same time, there were reports on the inhibition by quercetin of vascular contraction induced by norepinephrine [16]. A significant phlebotonic effect seems to be improbable without any impact on arterial SM and the blood pressure [11]. Should Fls considerably enhance the action of norepinephrine or otherwise cause vasoconstriction, it would probably elevate blood pressure in arterial hypertension. Although some degree of venous tone does exist *in vivo* [17,18], there is no convincing evidence that it can be significantly influenced by Fls. If vasoconstriction is indeed favorable in venous

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diseases, known vasoconstrictor agents could be used instead of the substances with unproven efficiency.

There are objective assessment methods of drug effects in the vascular bed, e.g., using isolated veins [18]. For example, dihydroquercetin did not modify the basal tone of isolated rat veins [19]. On the basis of experiments with rat femoral veins, it was reported that diosmin increases the sensitivity of SM to calcium, which could explain the phlebotonic action [6,20]. On the contrary, hesperetin (aglycone form of hesperidin) induced vasodilatation in humans and hypertensive rats [21,22]. The vasorelaxing property was demonstrated also for eriodictyol, an Fl from lemon [21]. Further independent research could estimate the magnitude and duration of the phlebotonic effect, if any, for different Fls.

Overall, the quality of reporting on this topic is regarded to be poor and loaded with biases, and beneficial effects tending to be exaggerated [7,11]. For example, the most rigorously conducted trial did not show any additional benefit from Fls in the treatment of venous leg ulcers [7]. Among positive results, subjective improvements (quality of life, pains, cramps, sensation of swelling, heavy legs) are often reported [6,13,23,24], which may be caused by a placebo effect. Admittedly, an improvement under the influence of MPFF of venous hemodynamics assessed by strain gauge plethysmography and supramaleolar circumference in patients with CVI has been reported [25–27]. The data of foot volumetry have been unconvincing [9], also in the recent study [28].

Mechanisms of supposed anti-inflammatory and anti-edematous effects of Fls are hardly comprehensible. It can be asked in this connection why, instead of the substances with unproven efficiency, known anti-inflammatory, or diuretic drugs cannot be used. However, these medications are not generally applied in edema due to venous disease [24]. Furthermore, the anti-oxidative capacity of Fl has been discussed [4]. In general, antioxidants are regarded to be far from scientifically founded clinical application [29]. It largely remains unclear whether, when, and how much antioxidants should be taken [29–31], the more so as some antioxidants may act as pro-oxidants [32]. In any case, it is unclear why antioxidants should be used in conditions associated with tissue hypoxia, such as CVI.

Finally, Fls are not free from adverse effects reported to be mild to moderate across studies. The most common events were skin changes (including eczema), gastrointestinal disturbances, and hypertension [7,10]. Without going into details of Fl biology, their role as repellents should be noted, protecting plants from herbivores. Certain Fls were reported to be toxic for insects or other organisms [5,33,34]. Presumably, Fls may act as mild toxin stimulating endogenous defense mechanisms [35], so that their abundant intake is not *a priori* beneficial especially for individuals with compromised defense mechanisms, e.g., in chronic diseases or advanced age [2].

Despite the arguments presented above, there are many publications reporting favorable effects of Fl in vein diseases. Some of such studies were sponsored by manufacturers. Obviously, verification in large-scale independent experiments is needed. Should the useful properties of Fl be confirmed, the question will arise whether pharmaceuticals could be replaced by enhanced consumption of citrus fruits known to be among the most common phenolic-rich dietary sources [4]. Taking into account the maximum concentration of total Fl in grapefruit juice (up to 84.28 mg/100 ml) [36], the average for commercial grapefruit juice (65 mg/100 ml) [4] and the higher content of Fl in whole fruits than in juice [21,37], consumption of 1–2 grapefruits means the intake of about 500 mg of Fls (naringin, narirutin, hesperidin, etc.) Naringin and naringenin are bitter and occur predominantly in grapefruits [4,5]. Relatively high concentration of hesperidin (a component of MPFF) was found in orange and mandarin juices (25–40 mg/100 ml), being the highest in *C. clementina* (39.9 mg/100 ml on average) [4]. The concentration of diosmin (another component of MPFF) is relatively high in commercial sweet orange juice (3.46 mg/100 ml) [4]. Lemon is also an important source of hesperidin and diosmin [4,6]. Detailed information on different Fls in citrus juices is available from the review by Prof. Giuseppe Gattuso and co-workers [4]. Remarkably, some commercial citrus juices contain more Fls than hand-pressed ones [4], which may be caused by forceful pressing or use of the pulp. However, there are local differences: some commercial products labeled as citrus juices in the former Soviet Union have been apparently diluted, contained added sugar and artificial flavors. The concentration of Fls in drugs and nutritional supplements is higher than in a typical diet. Excessive amounts of polyphenols reaching the colon may inhibit the growth of beneficial microbiota potentially leading to dysbiosis [38]. Considering the above, and also vitamins and microelements in fruits, consumption of citrus fruits and juices might be preferable to the supplementation of Fls by drugs and dietary supplements.

In conclusion, the data in favor of the phlebotonic action of Fl are inconsistent, while clinically significant effects are hardly comprehensible theoretically. The effectiveness of venoactive drugs needs verification in large-scale studies protected from conflicts of interest, using objective methods such as measurements of supramaleolar circumference, plethysmography, water volumetry, and optoelectronic methods building three-dimensional models of legs [1,39]. Potential difficulties in performing water volumetry are described in [39]. Finally, considering limited bioavailability and rapid metabolism of some dietary polyphenols [5,40,41], further research and review of pharmacokinetics of different Fls is needed.

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