Herbal dietary supplement: continuing to explore cardiovascular protection

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This editorial refers to ‘EGb761 ameliorates the formation of foam cells by regulating the expression of SR-A and ABCA1: role of haem oxygenase-1’ by J.-Y. Tsai et al., pp. 415–423, this issue.

The initial step of atherogenesis is the development of so-called ‘fatty streaks,’ which are small, subendothelial deposits of monocyte-derived macrophages. Both the dysregulation of modified lipoprotein uptake and cholesterol efflux in macrophages play an important role in the pathogenesis.1 Macrophage scavenger receptors, such as type A scavenger receptor (SR-A) and CD36, mediate foam cell formation by facilitating the uptake of modified lipids.2 On the other hand, reverse cholesterol transport is the primary mechanism by which high-density lipoprotein and its major protein, apolipoprotein A-I, protect against atherosclerosis. Specifically, ATP-binding cassette transporter A1 (ABCA1) mediates cholesterol efflux from macrophages to lipid-free apolipoprotein A-I.3 Any effective treatments for inhibiting the uptake of modified lipoproteins and/or enhancing cholesterol efflux are considered important anti-atherosclerotic drugs to prevent or delay the onset of cardiovascular events.4

Ginkgo biloba is a deciduous tree that has survived unchanged for around 150 million years. The fruits and seeds of the G. biloba tree have been used in traditional Chinese medicine for over 5000 years, whereas Ginkgo leaves began to be used much later for skin infection.5,6 The standardized extract preparation of the ginkgo leaf, EGb761, was developed by Beaufor-Ipsen Pharma (Paris, France) and Dr Willmar Schwabe Pharmaceuticals (Karlsruhe, Germany). The extract contains 24% flavonoid glycosides, 6% terpene lactones (ginkgolides and bilobalide), and <5 p.p.m. ginkgolic acid.5,7 In particular, flavonoids make a considerable contribution to its potent anti-oxidant, anti-inflammatory, and vasodilatory actions, whereas ginkgolides inhibit platelet aggregation. Cardiovascular protective effects of Ginkgo leaf extract are supposedly mediated through anti-oxidant and anti-platelet activity and increased blood flow by releasing nitric oxide and prostaglandins5 (Figure 1). Indeed, EGb761 was initially developed as a treatment for peripheral artery disease.6,8 In addition, based on the biological properties, the compound might also have potential benefits for ameliorating the development of atherosclerosis.

The study by Tsai et al.,9 examined the detailed mechanisms by which the G. biloba extract EGb761 inhibits the formation of macrophage foam cells in response to oxidized low-density lipoprotein. The key findings of the study are that EGb761 affected both modified lipoprotein accumulation and cholesterol efflux by selectively inhibiting the expression of SR-A and by increasing the expression of ABCA1 in THP-1-derived or primary macrophages. Interestingly, EGb761 modulated SR-A through transcription factors while regulating ABCA1 post-translationally. A more fascinating finding of this study was that haem oxygenase (HO)-1 activity, crucial for alleviating the progression of atherosclerosis,10 is involved in the mechanism of EGb761 action. Importantly, HO-1 affected EGb761-mediated molecules with regards to both lipid accumulation and efflux in macrophages (Figure 1). The authors further investigated whether EGb761 administration affects atheroma formation in hyperlipidemic mice. Consistent with in vitro experiments, they found that EGb761 prevented the development of atherosclerotic lesions at the aortic sinus, which was accompanied by the specific modulation of SR-A and ABCA1 protein expression in the aorta of mice. This study supports the important therapeutic targets of SR-A and HO-1 to reduce atherosclerosis.10,11 In the current study, it was not addressed which component of EGb761 showed beneficial action with regards to lipid accumulation and efflux and their associated molecules. Also, it will be necessary to determine the effect of EGb761 on a model of established atherosclerosis, i.e. whether the extract is able to regress plaque formation. Another important concern is that whether EGb761 can stabilize atheromatous plaque to prevent rupture, as it was found that EGb761 reduced the activity of matrix metalloproteinase-9 in macrophage cells. Taking the previous reports together with the inhibition of smooth muscle cell proliferation and expression of adhesion molecules, etc., as discussed in this report, the herbal dietary supplement EGb761 is promising for the treatment of cardiovascular diseases.

Although a number of beneficial actions of EGb761 have been shown in experimental studies, its pharmacological action was not proven in a double-blind randomized trial, which enrolled 3069...
artery disease is thus far inconclusive. Questions raised regarding the mechanisms behind these findings may help to elucidate the reasons for the discrepancies.

Figure 1  Ginkgo biloba extract EGb761 has multiple effects on alleviating the development of atherosclerosis. Tsai et al. reported the novel mechanism for EGb761 to inhibit atherosclerosis through modified lipoprotein accumulation and cholesterol efflux by modulating SR-A and ABCA1 in macrophages. This action mediates HO-1 activity. SR-A, type A scavenger receptor; ABCA1, ATP-binding cassette transporter A1.

participants over 75 years of age to receive 240 mg/day of EGb761 administration for a mean 6.1 years and showed no benefit for blood pressure or atherosclerosis-associated cardiovascular mortality and morbidity. Moreover, the effect of EGb761 on peripheral artery disease is thus far inconclusive. Questions raised regarding the discrepancy between experimental data and clinical trials remain to be answered. Although the substantial different experimental designs between human trials and animal experiments are assumed to have contributed the inconsistencies, there is a concern whether the advanced atherosclerotic plaque frequently observed with old age is treatable by EGb761 to alter the outcome, or whether it will take more years for the pharmacological effect of EGb761 to manifest in patients who have developed advanced atherosclerosis. Atherosclerosis develops progressively over 40 years, whereas fatty streaks are reported to be predominantly present in youngsters aged 10–14 years in the coronary artery and aorta in autopsy cases. Therefore, earlier intervention with patient selection may take advantage of the potential beneficial action of EGb761 for preventing or ameliorating cardiovascular diseases.

It is important to investigate the potential benefits of a traditional herbal medicine on a mechanistic level, allowing us to better understand why curative effects have been reported or assumed for a long time. But what if—as in this case—controlled clinical studies fail to confirm this effect in patients? Wouldn’t the experimental findings then encourage us to search even harder for the chemical factors with clear beneficial effects contained in these natural mixtures? This study nevertheless presents the important issue that G. biloba extract EGb761 has the potential to protect the cardiovascular system, and it suggests that we continue to pursue further studies from the bench to the clinic and from the clinic back to the bench.

Conflict of interest: none declared

References