Summary of Key Scientific Studies: Leg Veins

Chronic Venous Insufficiency (CVI) is a fairly widespread disease in the Western Hemisphere. CVI is caused by abnormalities in the structure and functioning of superficial or deep veins of the lower extremities. Weakening of the vein walls and valves, decreased venous tone, phlebitis, history of varicose veins, oral contraceptives and various environmental factors (sitting or standing for long periods, age, smoking, etc.) all increase the risk of developing CVI (Eberhardt and Raffetto, 2005; Nicolaides, 2000). There is strong evidence that MASQUELIER's OPCs strengthen blood vessels and maintain a healthy venous system, thereby reducing risk of venous insufficiency in the legs, as elucidated through a series of scientific studies which are summarized below (and reviewed in a monograph published in *Alternative Medicine Review* in 2003).

The beneficial effect of MASQUELIER's OPCs on venous tone has been demonstrated in human intervention studies. In a double-blind, placebo-controlled study conducted by Paitel (1981) in 50 subjects for 1 month, 150 mg/day MASQUELIER's OPCs induced a significant improvement in venous tone based on the results from vascular rheography and thermography. Royer and Schmidt (1981) compared the effect of MASQUELIER's OPCs on venous tone to the effect of two veinotropic agents, namely Hamamelis/Hydrastis mixture and calcium dobesilate. The authors observed that while both MASQUELIER's OPCs and Hamamelis/Hydrastis mixture (but not calcium dobesilate) significantly ameliorated the decreased venous tone in subjects, MASQUELIER's OPCs were more beneficial in that they could be safely and effectively administered on a daily basis over a prolonged period.

Vein valve dysfunction, varicoses and capillary fragility are suggested risk factors for developing CVI. MASQUELIER's OPCs were also shown to cause a statistically significant decrease in vein valve dysfunction and varicoses in a double-blind, placebo-controlled study performed by Elbaz (1981), and induce a decrease in capillary fragility in a study performed by Beylot and Bioulac (1980).

In a double-blind, placebo-controlled study conducted by Thebaut et al (1985) in 92 subjects manifesting early indicators of venous insufficiency including edema, restlessness and cramps in legs, the authors observed that MASQUELIER's OPCs significantly reduced these indicators in 75% of subjects compared to only 41% of subjects taking placebo (p=0.05). In a similar double-blind study conducted by Delacroix (1981) in 50 subjects, MASQUELIER's OPCs was found to be more efficacious (significant improvement in indicators of CVI in 65% of subjects) compared to reference substance Diosmine (improvement in only 45% of subjects). In an Open-label study conducted by Henriet (1993) in 4729 subjects with indicators of veno-lymphatic insufficiency (including cramps, edema, tingling sensation) associated with hormonal therapy, supplementation with MASQUELIER's OPCs caused a statistically significant decrease in these indicators. The overall condition of the subjects after 90 days of MASQUELIER's OPCs intake was judged by the clinician to be excellent or good in 77.7% of the subjects and average or poor in 19% of the subjects.

The possible mechanisms by which MASQUELIER's OPCs have a beneficial effect on the venous system were revealed through animal and *in vitro* studies. Vein walls of human subjects with venous disease differ from normal venous walls by a loss of their collagen content and an increase of their glycosaminoglycan content, reflecting a dysregulation in the functioning of the vein wall. Drubaix et al (1997) demonstrated that MASQUELIER's OPCs significantly decrease glycosaminoglycan and hyaluron levels in cultured explants of vein wall from human subjects with biological indicators of venous disease (edema), suggesting a mechanism by which this phytonutirent reduces risk of CVI as observed in human studies. Further evidence for the ability of MASQUELIER's OPCs to protect and strengthen the blood vessel wall was indicated in a study conducted in guinea pigs by Pfister (1982). The study demonstrated that MASQUELIER's OPCs bind collagen and elastin, promote collagen synthesis and polymerization and inhibit degradation of collagen and elastin.

MASQUELIER's OPCs also showed high percentage of binding to collagen fibres in *in vitro* studies, and significantly protected collagen fibres from denaturation (Masquelier et al, 1981). The significant protective effect of the MASQUELIER's OPCs on vascular proteins such as collagen and elastin was also observed in experiments by Gavignet-Jennin et al (1988). Similarly, studies

demonstrated that when bound to elastin, MASQUELIER's OPCs induced a 10-fold inhibition of elastin degradation by elastase compared to control (untreated elastin). These results suggested that MASQUELIER's OPCs could significantly protect elastic fibres from enzymatic degradation *in vivo,* and could have a protective effect on elastin-rich tissues such as vascular wall and reduce risk of pathological conditions associated with decrease in levels of elastin such as venous insufficiency.

In summary, MASQUELIER's OPCs have been shown to have a positive effect on factors such as venous tone, weakened vein wall and vein valves, venous compliance and leg edema associated with restlessness, tingling and cramps, and thereby reduce risk of developing severe chronic venous insufficiency. The results from the animal and *in vitro* studies indicate that MASQUELIER's OPCs promote collagen and elastin synthesis, and protects them from degradation, all of which can greatly reinforce the vascular wall. These results therefore provide a likely mechanism for the observed significant beneficial effects of MASQUELIER's OPCs in reducing risk of CVI in human studies.

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