**ArterosilHP®** Supports a Healthy Glycocalyx and Endothelial Function

“Perhaps the arterial glycocalyx will become the most important [drug target] for future early prevention of people at risk of cardiovascular disease.”

A.J. Drake-Holland1, and M.I.M. Noble: Update on the Important New Drug Target in Cardiovascular Medicine – the Vascular Glycocalyx

**ArterosilHP®** is the only dietary supplement that helps maintain optimal endothelial function through regeneration of the vascular endothelial glycocalyx. Loss of glycocalyx-mediated endothelial function has been implicated in the development of a wide variety of diseases such as atherosclerosis, diabetes, sepsis, and trauma1.

**The Endothelial Glycocalyx**

The endothelial glycocalyx is a thin gel-like layer that coats the entire luminal side of vascular endothelium. It is a meshwork mainly of glycoproteins, proteoglycans and glycosaminoglycans at a thickness of approximately 1 µm magnitude2-4. Syndecans and glypicans are the core proteins of heparan sulfate (a glycosaminoglycan) proteoglycans bound to endothelial cells identified in the glycocalyx. Glycoproteins such as selectins and integrins are also anchored on endothelial cells while some other soluble proteins and proteoglycans simply dock in glycocalyx5.

**Functions of the Endothelial Glycocalyx**

Extensive research has revealed the importance of glycocalyx-mediated endothelial function in vascular and micro-vascular health. For example, the endothelial glycocalyx:

- Regulates vascular permeability and fluid balance due to the large size and negative charge of glycosaminoglycans6,7.
- Provides a physical barrier against inadvertent adhesion of platelets and leukocytes to the vascular wall8.
- Regulates coagulation as many of mediators of coagulation pathway are buried inside the glycocalyx under normal physiological condition5.

Most intriguingly, the glycocalyx is found to be a mechano-sensor and -transducer of the shear-force inside blood vessels3. The signal is believe to be transduced to endothelial nitric oxide synthase (eNOS) via heparan sulfate in the glycocalyx to either up- or down-regulate the synthesis of nitric oxide (NO) in response to the blood flow9,10. Figure 1 below illustrates the chemical structure of the endothelial glycocylax and its signal transduction to eNOS and subsequently sGC (soluble guanylnyl cyclase) to induce smooth muscle relaxation via shear stress.
Structure of the Endothelial Glycocylax and Its Activation of Vascular Muscle Relaxation Via NO In Response to Increased Shear Force

Damage to the Endothelial Glycocalyx
The endothelial glycocalyx is a delicate structure and can be damaged under many pathological conditions. It has been demonstrated that oxidized LDL reduces the endothelial glycocalyx and results in cholesterol penetration and leukocyte recruitment to endothelium in lab animals\textsuperscript{11,12}.

Hypoglycemia and the Endothelial Glycocalyx
Hyperglycemia is another condition that has been firmly identified to cause disruption of the endothelial glycocalyx\textsuperscript{13,14}. In fact individuals with hyperglycemia and diabetes are known to have less endothelial glycocalyx\textsuperscript{15}. Such a change may explain the endothelial dysfunction and increased microvascular permeability that lead to major complications in the diabetic population\textsuperscript{16,17}.

Other Pathologies Associated with Impaired Endothelial Glycocalyx
Impaired endothelial glycocalyx is also demonstrated in the patients with:

- Coronary heart disease\textsuperscript{18}
• Renal diseases
• Lacunar stroke (a small vessel disease)
• Severe trauma

**Pharmaceutical Intervention**

Given the vital role the endothelial glycocalyx plays in the pathology of many vascular and micro-vascular related diseases, it naturally became a target for pharmaceutical intervention. The glycocalyx drug development is still in its infancy and no substantial progress has been made up to date.

**ArterosilHP®: A New Glycocalyx Dietary Supplement**

Now enters ArterosilHP®, a glycocalyx dietary supplement many years in the making. It started when a medical doctor in the United States searched for a natural alternative of heparin for his heart patients some 20 years ago. That journey led him to a rare green seaweed, *Monostroma nitidum*, in east Asia.

**The Active Ingredient: Rhamnan Sulfate**

*Monostroma nitidum* is rich in rhamnan sulfate, a negatively charged polysaccharide, that has been shown posses a wide range of biological activities with potential health benefits. Rhamnan sulfate has a similar chemical structure to heparan sulfate found abundantly in the human endothelial glycocalyx and may exert its bioactions by regenerating the glycocalyx.

We first tested this hypothesis in lab animals and showed rhamnan sulfate reversed the leukocytes adherence to endothelium induced by enzymatic removal of the endothelial glycocalyx (unpublished data). Others also reported that rhamnan sulfate enhances the endothelial glycocalyx and decreases the LDL permeability of human coronary artery endothelial cells.

A Japanese study demonstrated that daily supplementation of a crude rhamnan sulfate extract for 6 weeks significantly lowered total and LDL cholesterol in borderline or mild hypercholesterolemia human subjects. Another study also from Japan later showed that oral administration of crude extract of rhamnan sulfate to carbohydrate-loaded rats significantly reduced their blood glucose level compared to the control animals.

**Clinical Study of ArterosilHP®**

To evaluate ArterosilHP® for supporting healthy endothelial function, we conducted a randomized double blinded clinical study at Medicus Research in California. Twenty healthy human subjects were placed on ArterosilHP® for 4 weeks. At the beginning and the end of the study, the subjects were challenged with a high fat high sugar meal in the morning and then followed up for 8 hours at the clinics. The endothelial glycocalyx thickness was estimated by the measurement of sublingual capillary blood flow as described by Nieuwdorp et al. Endothelial function is evaluated by reactive hyperemia index (RHI). At the beginning of the study, the
subjects experienced a compromised glycocalyx at 1.5 hours after consumption of the high fat high sugar meal. With 4 weeks of ArterosilHP® supplementation, the same subjects showed a significantly improved glycocalyx at 1.5 hours after the high fat high sugar meal. In both visits, the glycocalyx recovered back close to normal 8 hours after the meal. Similar trend was also observed with RHI in the subjects (see Figure 2 below). Before ArterosilHP® supplementation (blue baseline), subjects experienced a dramatic drop of RHI 1.5 hours following the high fat high sugar meal. After 4 weeks on ArterosilHP® supplementation (red ArterosilHP®), the drop of RHI for the same subjects 1.5 hours after the high fat high sugar meal was significantly reduced. Again RHI showed significant recovery after 8 hours in both visits. These results clearly demonstrate that ArterosilHP® supplementation ameliorates the damage of endothelial glycocalyx and the loss of endothelial function caused by a high fat high sugar meal in the healthy human subjects.

Safety Assessment
To assess the safety of ArterosilHP®, fasting blood samples were taken during both visits and tested for complete metabolic panel (CMP), thyroid stimulating hormone (TSH), complete blood count (CBC), and partial thromboplastin time (PTT). No significant changes were observed for any of these tests and all results fell in normal ranges. For example, the normal range for PTT is 17-33 seconds. The mean PTT at the baseline is 25.83 seconds and the mean PTT after ArterosilHP® supplementation is 25.16 seconds with a standard deviation of 3.15 seconds for both. Safety and tolerability were also assessed by reviewing vital signs during the visits and the
adverse event reports. There was no serious adverse event reported for the study and ArterosilHP® was well tolerated by all subjects.

Summary
ArterosilHP® is a dietary supplement containing rhamnan sulfate derived from green seaweed Monostroma nitidum. It supplies phytonutrients that can be used by the human body as building blocks for its vascular and/or microvascular glycocalyx. ArterosilHP® has been thoroughly studied and researched. It is the first and only product that has been proven to be safe and effective to help maintain a healthy endothelial glycocalyx and its mediated endothelial function.
References


