

# Hibiscus sabdariffa: a Potential Strategy to Decrease Aging-induced Cardiovascular Risk?

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## 1. Introduction

### Aging

- Progressive and inevitable deterioration of normal functions, which predisposes to diseases
- Main contributor to cardiovascular health in elderly, it is a risk factor for cardiovascular disease (CVD) regardless of other risk factors
- Functional and structural changes in heart and arterial system
- Endothelial dysfunction is associated with an important cause of mortality and morbidity
- Increased levels of oxidative stress

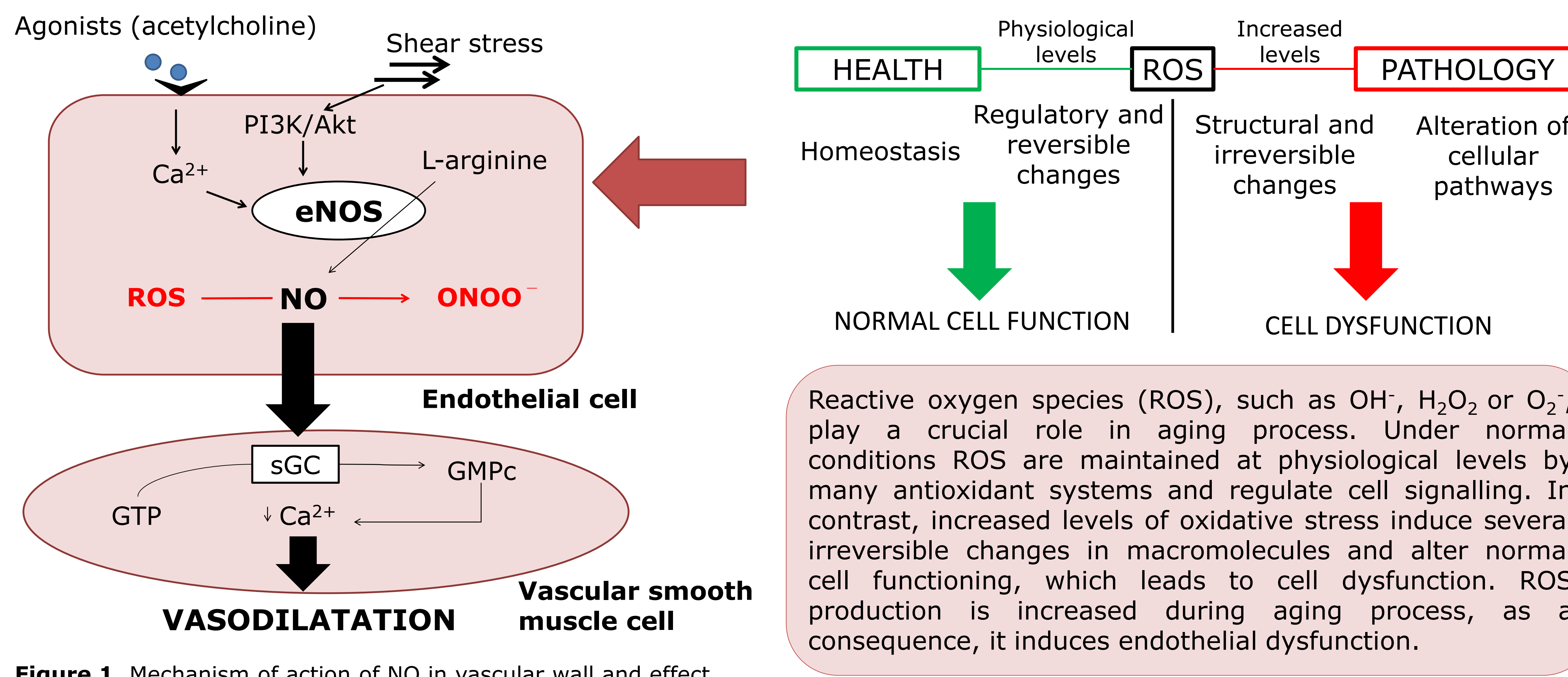
## 2. Aims

- To evaluate the effect of oxidative stress to the main triggers of CVD in elderly.
- To analyze the scientific evidences of a non-pharmacological treatment which provides antioxidant and cardioprotective properties.

## 3. Materials and Methods

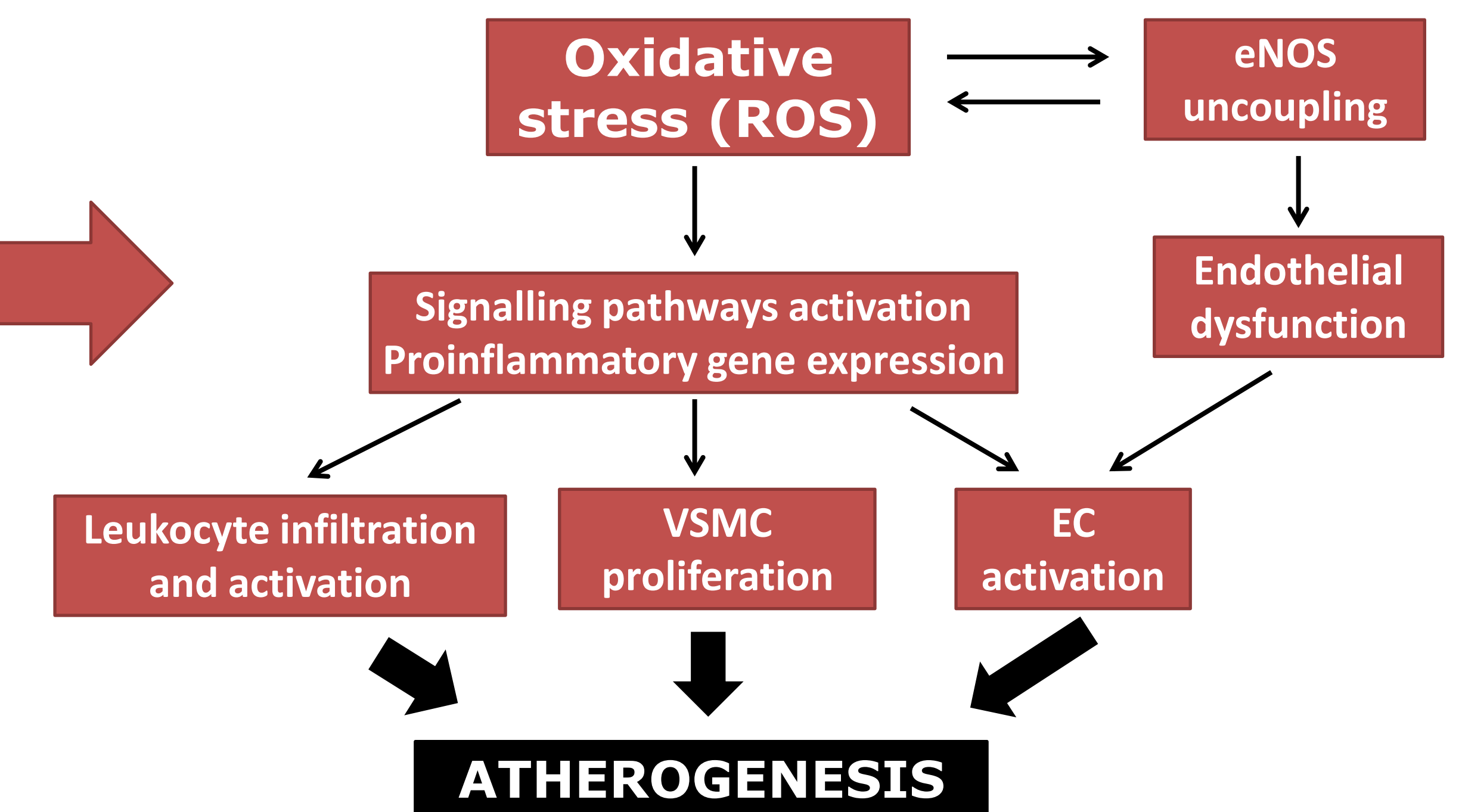
- Search for articles in Pubmed database. Keywords used: "cardiovascular aging", "oxidative stress", "nitric oxide", "atherosclerosis", "Hibiscus sabdariffa AND hypertension", "Hibiscus sabdariffa AND atherosclerosis". 43 articles collected.
- Search in PubChem database.

## 4. ROS, NO and Atherosclerosis



**Figure 1.** Mechanism of action of NO in vascular wall and effect of ROS in NO bioavailability. Adapted from Vigorito et al. [1].

Nitric oxide (NO) is the main contributor to blood vessels vasodilatation. ROS induce NO degradation; as a result, NO-dependent vasodilatation is reduced. This process not only triggers arterial hypertension, but also induce cellular damage through ONOO<sup>-</sup>.



**Figure 2.** Oxidative stress activates specific signalling pathways that lead to atherosclerosis. VSMC, vascular smooth muscle cells; EC, endothelial cells. Adapted from Li et al. [2].

Atherosclerosis is a trigger of several CVD. ROS contribute to generation of atheromatous plaques in a number of ways. Oxidative stress activates a chronic low degree of inflammatory response that leads to atherosclerosis. Furthermore, ROS oxidise LDL lipoproteins (ox-LDL). In the native state LDLs are not atherogenic, whereas modified (ox-LDL) can be internalized by macrophages and contribute to plaque formation.

## 5. Hibiscus sabdariffa

### IN VITRO, EX VIVO AND ANIMAL STUDIES

#### ANTIOXIDANT CAPACITY

- Strong dose-dependent antioxidant effect in *in vitro* assays
- Increased ability to scavenge ROS in plasma of HS-treated rats
- HS induced antioxidant enzymes activity
- Probably polyphenols are the main generators of the effect

#### LDL

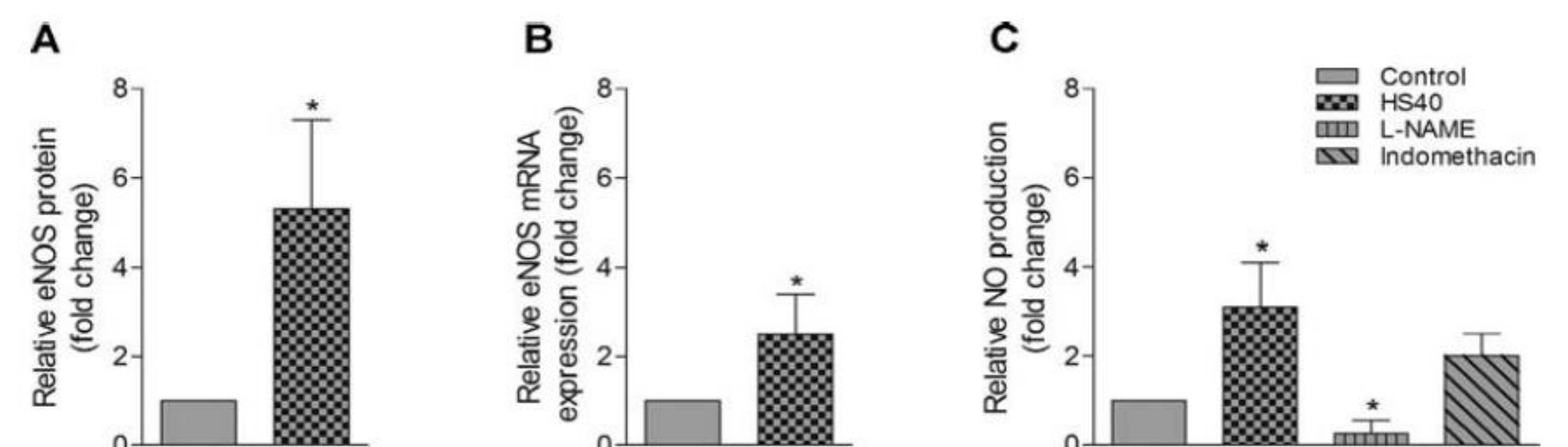
- Prevention of LDL oxidation and lipid accumulation *in vitro*
- Hypolipidemic effects in HS-treated animals
- Decreased atherosclerotic levels and foam cell formation in HS-treated rabbits
- Total cholesterol, LDL and triglycerides have been lowered in the majority of animal studies. In contrast, HDL was generally not affected

#### ENDOTHELIAL NO

- Induction of eNOS protein, eNOS mRNA and NO production in HS-treated endothelial cell cultures
- Vasorelaxant responses in HS-treated aorta rings of hypertensive rats, whereas eNOS and cGMP inhibition decreased relaxations
- Ethyl-acetate extract (containing anthocyanins) had the strongest vasorelaxant effects in isolated aorta of male Wistar rats

#### TOXICITY

- Low degree of acute toxicity
- Few studies to evaluate toxicity



**Figure 3.** Endothelial cells incubated with 40 µg/ml of HS extract increased the production of eNOS enzyme (A), eNOS mRNA (B) and NO production (C). L-NAME, an inhibitor of eNOS decreased NO production. Indomethacin effects, a cyclooxygenase inhibitor, were not significant [3].

### HUMAN STUDIES

#### HYPOTENSIVE

- 5 studies analyzed:
- 31 patients with metabolic syndrome
  - 65 pre- and mildly hypertensive patients
  - 60 mildly hypertensive diabetic patients
  - 75 mildly and moderately hypertensive patients
  - 193 stage 1-2 hypertensive patients

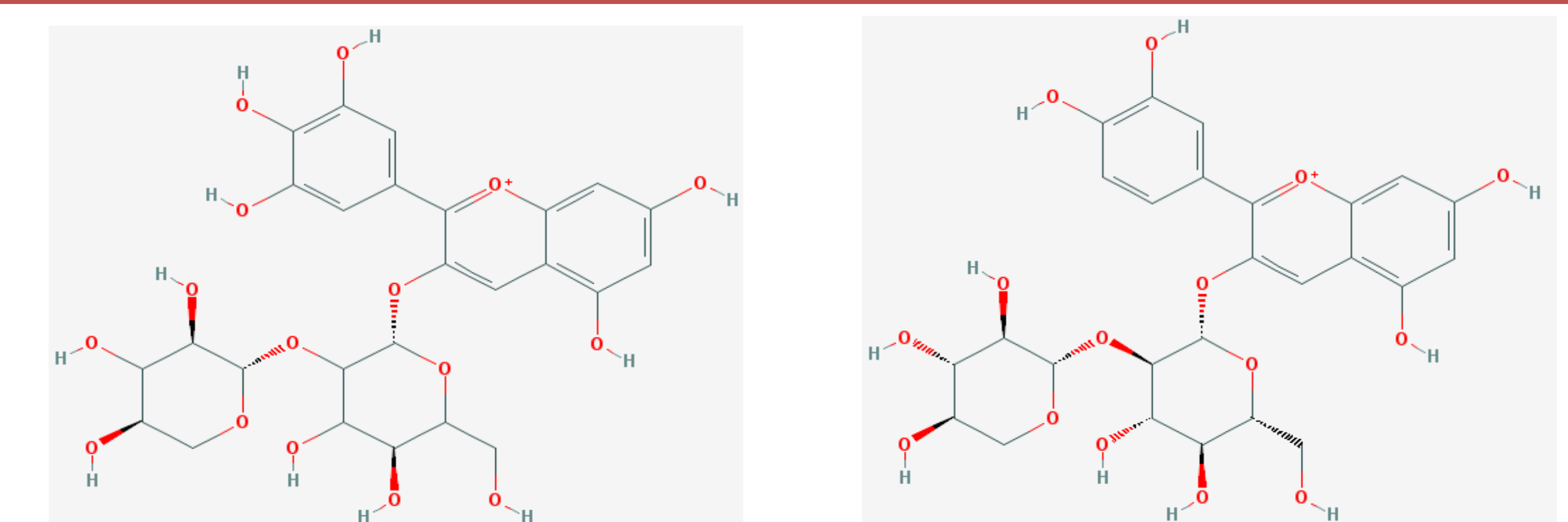
Decline in systolic and diastolic blood pressure in HS-treated patients

#### HYPOLIPIDEMIC

- Not concluding results
- Some studies showed an improvement of lipid profile, others demonstrated no difference in total cholesterol, LDL and triglycerides in HS-treated group

### BIOACTIVE COMPOUNDS

- Anthocyanins, a group of flavonoids (polyphenols), are considered to be the phytochemicals responsible for the beneficial effects of HS
- Particularly delphinidin 3-sambubioside and cyanidin 3-sambubioside are believed to be the major bioactive compounds
- Anthocyanin metabolites may also contribute to the effects of HS
- Some scientific evidences of anthocyanin-rich extracts: prevent loss of NO-mediated relaxation, oxidative stress protection in endothelial cells, upregulation of eNOS, increased serum antioxidant capacity



**Figure 4.** Left: Delphinidin 3-sambubioside. Right: Cyanidin 3-sambubioside [4].

## 6. Future Research

- To find all the bioactive compounds and the molecular pathways of its action
- To standardize the studies: large-scale studies controlled in dose, bioactive compounds, bioavailability and other important variables
- To analyze the influence of HS on lipid profile
- To analyze pharmacological interactions with drugs and adverse effects
- To find an effective dose

## 7. Conclusions

- ROS levels increase in aging and contribute to cardiovascular risk
- HS increases antioxidant capacity and ROS scavenging
- HS improves endothelial function by increasing NO production and preventing LDL oxidation *in vitro*
- HS may have an effect on lipid profile
- Studies in hypertensive patients have demonstrated HS is an hypotensive agent
- Anthocyanins are probably the main contributors to the observed effects

## 8. References

- Vigorito C, Giallauria F. Effects of exercise on cardiovascular performance in the elderly. *Front Physiol.* 2014 Jan; 5:51.
- Li H, Horke S, Förstermann U. Vascular oxidative stress, nitric oxide and atherosclerosis. *Atherosclerosis.* 2014 Nov; 237(1): 208-219.
- Joven J, March I, Espinel E, Fernández-Arroyo S, Rodríguez-Gallego E, Aragonès G, et al. Hibiscus sabdariffa extract lowers blood pressure and improves endothelial function. *Mol Nutr Food Res.* 2014 Jun; 58(6): 1374-1378.
- PubChem. <https://pubchem.ncbi.nlm.nih.gov/search/>