

# SUPERIOR EFFECTIVENESS OF CARCININE (A STABLE CARNOSINE ANALOG) ON GLYCATION-INDUCED CELL SENESCENCE, COMPARED TO CARNOSINE

L Valenti<sup>1</sup>, PG Markioli<sup>1</sup> and P Manissier<sup>2</sup>

1 Sedifa-Laboratoire, 4, av Albert II Monaco, Principality of Monaco; 2 Iontec 4, av Albert II Monaco, Principality of Monaco.

## ABSTRACT

### Objective:

Evaluate the effectiveness of Carcinine (decarboxycarnosine) on glycation-induced cellular senescence, in comparison to L-Carnosine and its metabolites.

The *in vivo* anti-glycation activity of L-Carnosine oral supplementation is well documented (reviewed in Ghodsi, 2018). However, its activity is limited by its poor resistance to carnosinase, the enzyme that degrades the dipeptide. The objective of this study was to evaluate if Carcinine, a Carnosine analog resistant to carnosinase, could be a more effective dipeptide for fighting cell senescence induced by a glycation agent (glucosone), an early product of glucose autoxidation.

### Materials and methods:

Stress-induced premature senescence was performed on cultivated human dermal microvascular endothelial cells (HDMEC) by a 3 day-treatment with glucosone. Carcinine 2HCl, Carnosine, Carnosine metabolites (L-histidine +  $\beta$ -alanine) and the anti-glycation benchmark aminoguanidine were tested on this model. Senescent cells were observed by detecting senescence-associated (SA)- $\beta$  galactosidase activity, by monitoring cell morphology changes using flow cytometry (study Sept 19).

### Results:

Firstly, Carcinine protects endothelial cells from senescence induced by the glycation agent glucosone, the efficacy is observed on all parameters.

Secondly, when tested at the same dose, Carcinine was more effective than Carnosine, itself more effective than its two products of degradation.

Regarding the inhibition of SA- $\beta$  galactosidase activity: no activity was observed for Carnosine whereas for Carcinine, a significant inhibition of 60.7% was detected. Doubling Carnosine concentration allows reaching a low significant inhibition of 18.5% vs glucosone. Carnosine metabolites had no activity.

### Conclusions:

Carcinine, thanks to its resistance to carnosinase degradation, is a superior alternative to Carnosine oral supplementation for fighting against glycation-induced cell aging.

Carcinine is approximately 7 times more effective than Carnosine in our model.

## INTRODUCTION

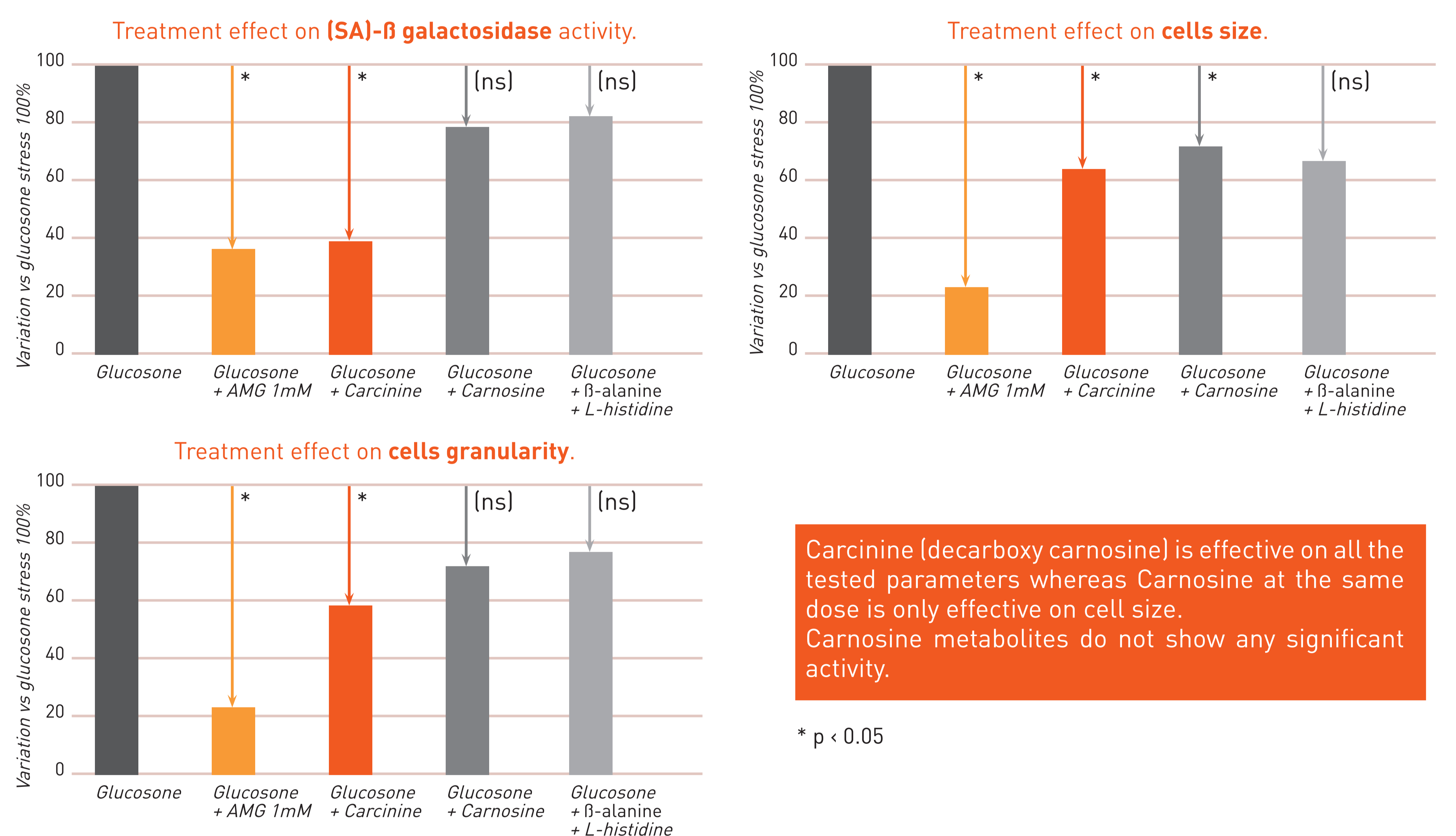
Glycation is one of the major causes of premature ageing. AGEs (Advanced Glycation End products) are formed by a reaction between sugar and proteins. Glycation in human body affects cells and protein fibres such as collagen and elastin, which induces a loss of their functionality. The accumulation of AGE can lead to complications such as atherosclerosis, osteoporosis, premature skin ageing (M.Fournet, 2018). Food supplementation with Carnosine has shown clinical benefit to prevent glycation and its consequences. Unfortunately its poor resistance to enzyme degradation can limit Carnosine efficacy (A.Boldyrev, 2013). In this context a stable analog of Carnosine (resistant to carnosinase degradation): Carcinine has been developed to optimize bioavailability to reduce the necessary doses to obtain efficacy. The objectives of the study were to validate the efficacy of Carcinine on cell senescence induced by glycation and demonstrate the superiority of Carcinine vs Carnosine.

## MATERIALS & METHODS

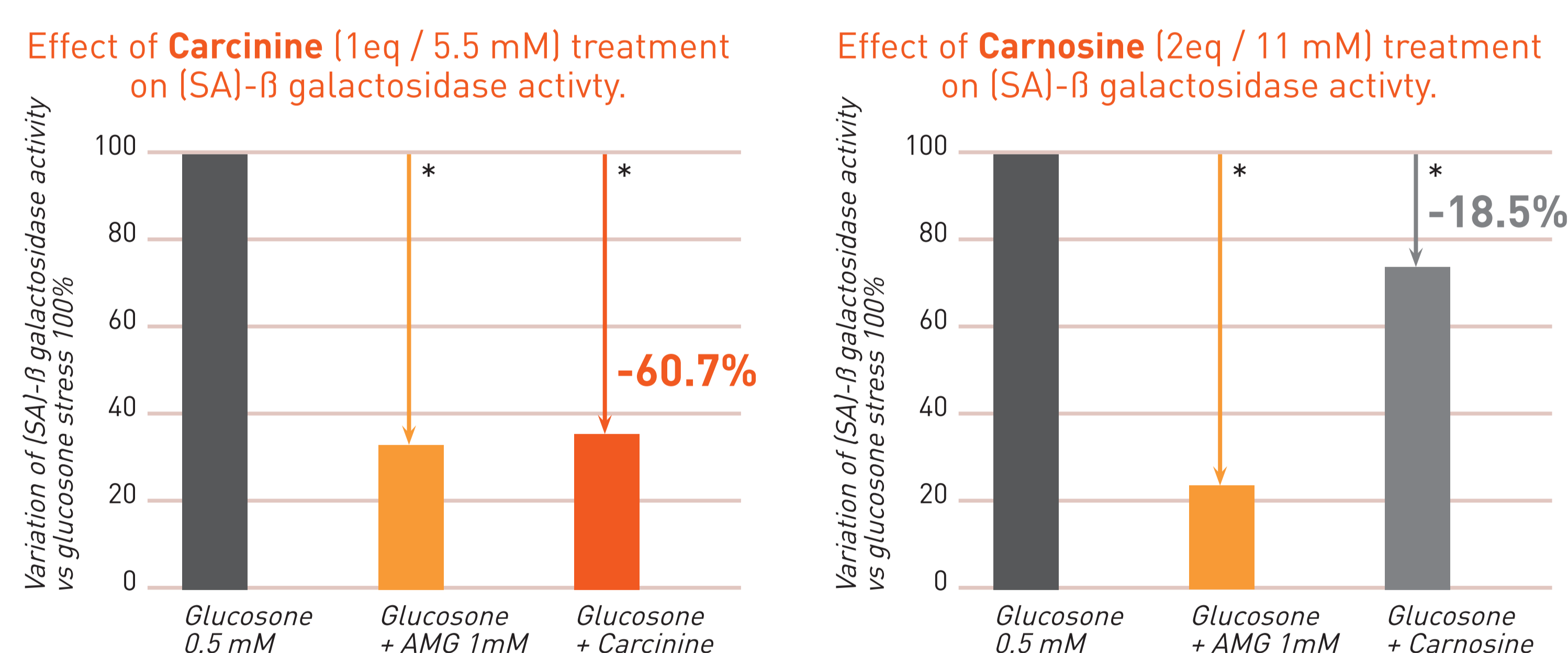
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## RESULTS

### 1/ Comparison of Carcinine vs Carnosine and its metabolites (dose 1 eq / 5.5mM):



### 2/ A second study has been conducted with increasing doses of Carnosine to try to reach an efficacy comparable to Carcinine.



## CONCLUSION

**CARCININE IS MORE EFFECTIVE THAN CARNOSINE OR ITS METABOLITES ON PREVENTION OF CELL SENESCENCE INDUCED BY GLYCATION. IN THIS STUDY CARCININE IS 7 TIMES MORE EFFECTIVE.**

This study confirms that:

- The anti-glycation activity of Carnosine is linked to the integrity of dipeptide formed by  $\beta$ -alanine and L-histidine. When the dipeptide is degraded (ex by carnosinase during the digestion process) a loss of activity is observed.
- The decarboxylation of Carnosine which optimizes bioavailability does not modify the anti-glycation activity.

**Carcinine is a more effective alternative compared to Carnosine to prevent endothelial cell ageing induced by glycation and its consequences on vascular system.**

These results allow us to hypothesize that the clinical anti-ageing benefits obtained with Carnosine supplementation could be obtained with lower doses of Carcinine.

## REFERENCES

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 A Boldyrev (2013) Physiology and pathophysiology of carnosine. Physiol Rev 93: 1803-1845.

## KEY WORDS

Carcinine; glycation; senescence; endothelial cells; Carnosine; nutrition; food supplementation.