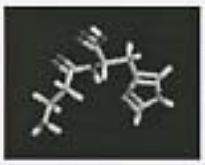
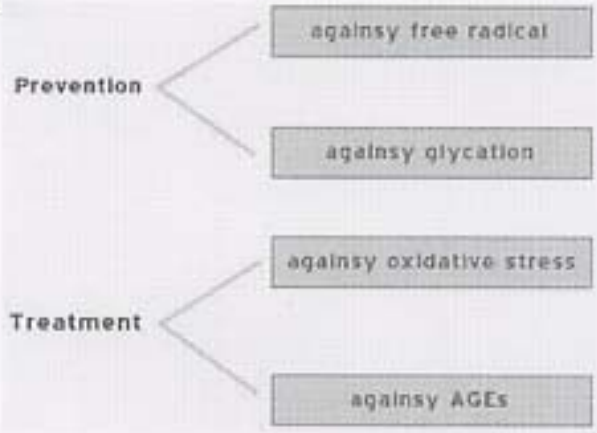
:: A free radical scavenger and anti-glycation dipeptide to prevent skin aging

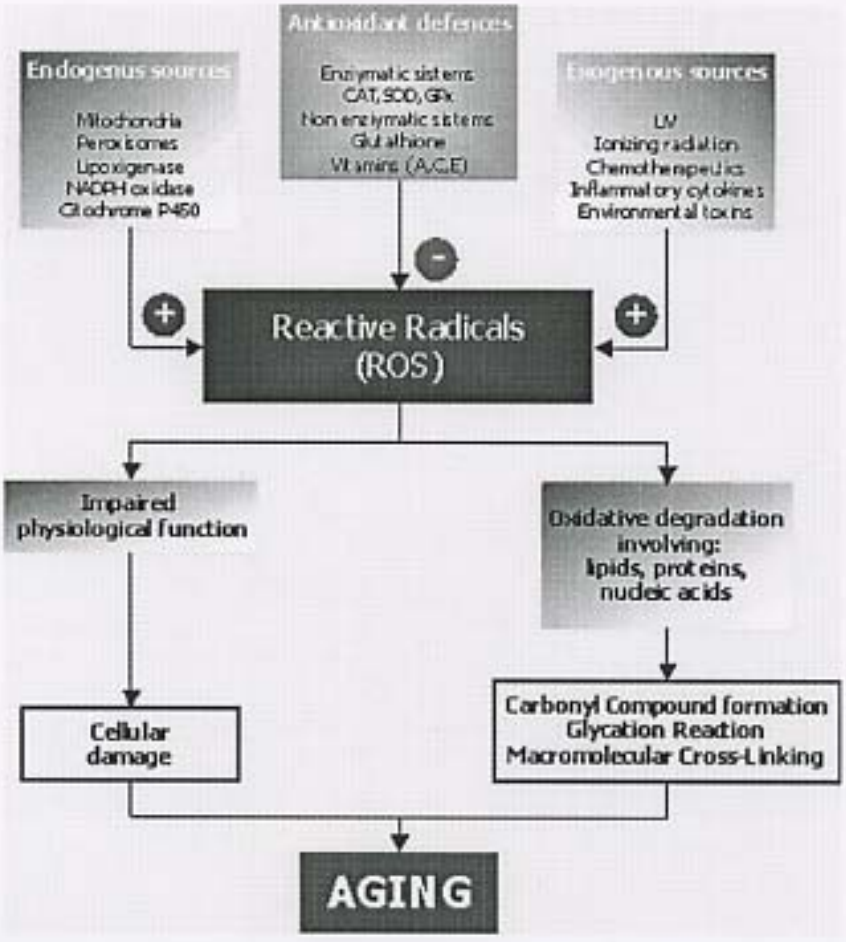


Carnosine is a new cosmetic and nutraceutical raw material against skin senescence, a non toxic molecule, design by Nature and **produced by Flamma.**

Carnosine performes its anti-aging efficacy at two different levels of action:



:: Biology of the aging process
In this section the aging process is considered from the biochemical point of view. The current knowledge about the mechanisms involved in the aging process and the defence mechanisms are described.



Particularly two phenomena are of particular concern: the deleterious effects of **reactive oxygen species (ROS)** and the formation of **reactive carbonyl compounds** related to the **glycation reaction**, involved in the acceleration of molecular and tissue aging processes

:: Oxidative stress

Numerous studies have been carried out in the last decades to elucidate the biochemical and molecular mechanism of aging. The general consensus appears to be that the aging process is multifactorial and that reactive oxygen species (ROS) are a contributing factor, even though the extent of their contribution remains uncertain. Substantially, the more reliable theory of aging remain the "free radical theory", articulated in the mid-1950s by Denham Harman, which speculates that endogenous oxygen radicals were generated in cells and resulted in a pattern of cumulative damage.

ROS action

All the biological structures undergo the detrimental action of ROS. Cytoplasmic and the other membranes are very easily attacked: the unsaturated fatty acids of the phospholipidic and proteic bilayer loose an hydrogen from their molecules because of the action of ROS and this turns in the formation of lipoperoxides leading to a considerable membrane alteration (membrane permeability increases, fluidity of the lipids and proteins mosaic changes, all the active transport process and enzymatic activity are modified). Structural proteins and enzymes undergo the alteration of lateral chains, that's turns into aggregation phenomena, fragmentation, cross-linking. Sugars react immediately with ROS giving result to the formation of toxic and unstable products. Nucleic acids are not excluded from the ROS action, even though they are a quite sheltered target. Whatever is the substrate of ROS action, the outcome is the oxidation of intracellular and extracellular components, resulting into phenomena such as cytoxicity, macromolecular depolimerization, alteration of the structure and function of cell proteins and proteins of the extracellular matrix (collagen, elastin).

:: Carbonyl compounds

The balance between ROS production and antioxidant defences determines the degree of oxidative stress. Unfortunately, the activity of these systems declines during aging, so the consequences of this stress include modification to cellular components.

Carbonyl compounds formation

The most widely studied oxidative stress-induced process is the formation of carbonyl compounds (also known as carbonyl derivatives). Carbonyl derivatives formation can occur, following the ROS-mediated oxidation of sugar and membrane lipids through a complex and still unclear cascade of reactions. Carbonyl compounds are very reactive small molecules which can be considered a key

point in the propagation and amplification of the aging process.
Carbonyl compounds damage
All these catabolic products are potent proteins and nucleic acid modifying agents at physiological concentrations and under physiological conditions.

Carbonyl reactive compounds are able to form adducts commonly known as CO-proteins (proteins bearing carbonyl groups) with structural proteins, lipoproteins, enzymes and with DNA, causing alterations in their biological activity through a whole of chemical reaction steps in all known as Glycation Reaction.

:: Glication reaction
Namely it is a reaction between reducing sugars, or other carbonyl group bearing molecules, and free amino groups of protein, leading to the formation of abnormal products (Advanced Glycation End Products-AGEs, cross-linked proteins).
We can distinguish three kind of glycation reaction:
1) Glycation itself or direct glycation
in which sugars attack directly protein substrate, without any intermediate, to form CO-proteins and AGEs
2) Glycoxidation
in which CO-proteins and AGEs can be formed through sugars oxidation products
3) Pseudo-glycation or lipid oxidation reaction
CO-proteins and AGEs are produced by the conjugation with reactive carbonyl compounds resulted from polyunsaturated fatty acids oxidation through a Michael addition.

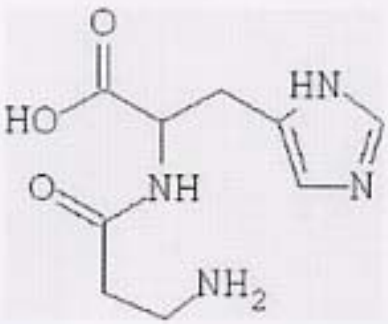
AGEs are very toxic for the cells, as they are very rich in double bonds which can react irreversibly with biological substrates leading to a loss of their physiological function.

:: Cross-linking phenomena
Cross-linking is one of the various phenomena that can be found in an aged tissue. Literally, it is the setting up of chemical links between macromolecular chains, found in proteins or DNA. Because of the generation of new abnormal links, proteins loose their biological functions. Carbonyl compounds such as toxic aldehydes are further involved in protein cross-linking typical of the senescence. Cross-linking could be an intra- or inter-molecule reaction between toxic aldehydes or CO-proteins and a lysine residue on a normal protein.

The result is a loss of physiological function, loss of cell division capacities and genome information, and consequently senescence.

:: Skin Agingss
The skin ages because of damage to proteins and DNA, induced by both chemical and physical means and because of the formation of toxic products, such as CO-proteins and cross-linked macromolecules.
Modified proteins and cross-linking are irreversible phenomena responsible for the permanent, deep wrinkling in the dermis.
Those structural and functional changes turn into a senescent appearance. Skin is mottled and gray to yellow with red spots and dilated veins, and it becomes thin. So any stress could cause permanent damage.

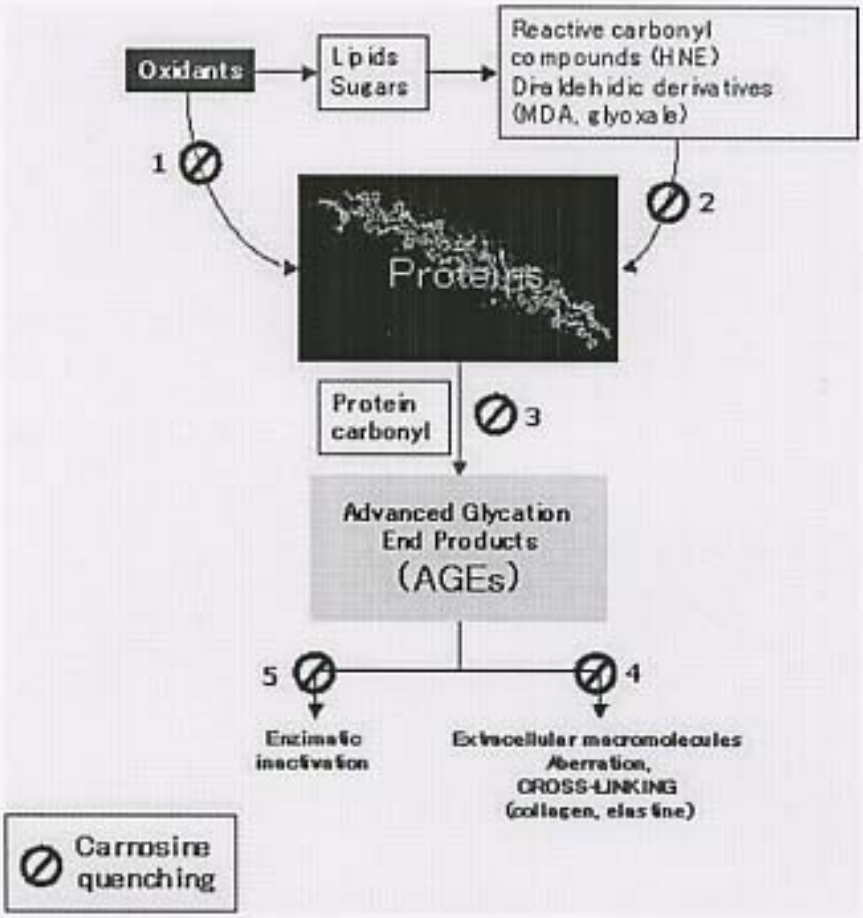
Flamma presents CARNOSINE, a non toxic molecule, able to dam the aging process and its unwanted effects



Carnosine (b-alanyl-L-histidine) is an endogenous dipeptide and exists at millimolar concentrations in muscle tissues. Its presence in muscle tissue has been known for 100 years, but its exact functions are only recently becoming unrevealed.

:: Carosine against the aging process
The powerful and effective action of CARNOSINE is performed against all the elements that triggered the aging process and against all the phenomena that contribute to its propagation and amplification.
In the following scheme are summarized the sites of intervention of L-carnosine as anti-aging

molecule:



Carnosine can claim different properties performed at different steps of the whole aging process:

:: 1 It **stops** the **oxidative damage** acting as an antioxidant agent, a ROS scavenger agent, metal ions chelating agent and by expressing a SOD-like activity.

:: 2 It **inhibits the Glycation reaction,** by quenching carbonyl compounds.

:: 3 It **inhibits the Glycation reaction,** by quenching AGEs .

:: 4 It **prevents** the macromolecules **cross-linking.**

:: 5 It promotes modified protein degradation enzyme- mediated