



## **Effects of N-acetylcysteine, oral glutathione (GSH), and a novel sublingual form of GSH on oxidative stress markers: a comparative study**

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**Background:** A cross-over study was carried out to evaluate the effectiveness of Sublinthion®, a patented, reduced sublingual glutathione stabilized with punicalagins from pomegranate, on different oxidative stress markers in comparison with reduced glutathione (GSH) and the precursor N-acetylcysteine (NAC).

**Materials & Methods:** Study was carried out on 25 subjects with signs of metabolic syndrome (overweight together with at least one of the two following criteria: glucose intolerance, high blood pressure, and hypertriglyceridemia). The subjects consumed the following products in a random order:

- Sublinthion®
- GSH
- N-acetylcysteine

Each product was taken for 21 days on the basis of a daily dose equivalent to 450 mg of GSH, which equates to:

- 3 tablets daily of Sublinthion
- 3 capsules daily of the GSH
- 1 sachet daily of NAC

Between each product, a washout period of 21 days was observed to ensure unbiased results. For each period, the subjects had blood samples taken on D0, D11, and D21.

### **Results:**

#### **1. Effect on the level of endogenous reduced glutathione (GSH)**

- a. Supplementation with the unprotected GSH resulted in a reduction of GSH levels.
- b. Supplementation with N- acetylcysteine results in moderate increase in GSH levels.

- c. Supplementation with Sublinthion results in a greater and more rapid increase in GSH levels than is observed with NAC

**2. Effect on the ratio of reduced (active) glutathione (GSH) to oxidized (inactive) glutathione (GSSG):** The ratio of reduced to oxidized glutathione (GSH/GSSG) reflects degree of significant oxidative stress. The ratio of reduced to oxidized glutathione in the blood stream also has strong correlations to risk factors for several diseases and metabolic inefficiencies. Effective supplementation will lead to an increase in the GSH/GSSG ratio. The evolution of the GSH/GSSG ratio in the 25 subjects was measure between D0 and D21 during comparative supplementation with each product.

- a. A decrease in the GSH/GSSG ratio was observed with supplementation of the reference GSH.
- b. NAC stimulated *de novo* synthesis of GSH, which is reflected in an increase in the GSH/GSSG ratio.
- c. Supplementation with Sublinthion<sup>®</sup> demonstrates a more significant increase in the GSH/GSSG ratio that other forms of glutathione or precursors (+65% in relation to N-Acetylcysteine, +230% in relation to reference GSH).

**3. Recycling of vitamin antioxidants:** the regeneration of vitamin E levels was measured among the 25 subjects between D0 and D21 in response to each of the 3 products.

- a. A decrease in vitamin E levels was observed with reference GSH supplementation.
- b. NAC supplementation was observed to increase vitamin E levels.
- c. The greatest increase in vitamin E levels was observed with Sublinthion<sup>®</sup> supplementation (+57% in relation to NAC and +277% in relation to reference GSH).

**4. Effects on Triglyceride and HDL levels**

- a. A decrease in triglyceride levels and an increase in HDL levels were observed with Sublinthion<sup>®</sup> supplementation, higher that those obtained with either the NAC or reference glutathione. Neither NAC nor reference GSH increased HDL levels, whereas Sublinthion increased baseline HDL levels by approximately 5% after 21 days of supplementation. Reference glutathione reduced HDL levels, and NAC showed no change. Sublinthion was shown to reduce triglycerides after 21 days of use by approximately 10%.

**Discussion:**

Glutathione is generally agreed to be the most significant endogenous antioxidant, though it plays many metabolic roles beyond arresting oxidative damage. Glutathione is important to genetic preservation via

protective effects on telomeres; preserves DNA integrity; is essential for liver detoxification; recycles oxidized vitamin E; and regulates the mechanisms essential to homeostasis, which includes enzymatic activity, protein synthesis, gene expression, and mitochondrial integrity. The ratio of reduced glutathione to oxidized glutathione has been documented as a noted factor in many diseases and chronic health issues. The ability to create reduced glutathione diminishes with age. At age 40, the loss is approximately 30%, and increases to as much as 50% reduction by age 65. Other factors, including tobacco smoke, pollution, unbalanced diet, genetic inefficiencies, and use of prescription and/or over the counter drugs (most notably acetaminophen) can further compound this loss. While intravenous administration of reduced glutathione has been shown to significantly impact this ratio (GSH:GSSG), oral supplementation has been ineffective because the reduced glutathione is either a) broken down to simple amino acids during digestion or b) are oxidized and no longer active when absorbed, or a combination of a and b. Glutathione precursors provide unpredictable results, as they rely upon the ability of the patient to synthesize reduced glutathione, an ability which decreases with age and certain physical challenges. We describe here a novel process utilizing reduced glutathione, further stabilized with punicalagins from pomegranate, delivered to the sublingual mucous membrane. This sublingual administration bypasses both the intestine and the liver, and the glutathione enters the body in its reduced (active) form, significantly improving the ratio of GSH to GSSG, 230% more than reference glutathione, and 65% more than the precursor N-acetylcysteine.