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Dietary grape poliphenols modulate oxidative stress in ageing rabbits

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RIASSUNTO – I polifenoli dell'uva regolano lo stress ossidativo nei conigli durante l'invecchiamento. *Lo studio ha avuto come obiettivo di verificare gli effetti di un'integrazione alimentare con polifenoli dell'uva sul controllo dello stress ossidativo in conigli durante l'invecchiamento. A tal fine sono stati predisposti 4 gruppi sperimentali che ricevevano diverse concentrazioni giornaliere di polifenoli (CTR: 0 mg/kg di mangime; P1: 0,03 mg/kg; P2: 0,15 mg/kg; P3: 0,30 mg/kg). I prelievi di sangue sono stati effettuati a 1 (T1), 6 (T6) e 10 (T10) mesi dall'inizio della somministrazione dei polifenoli, da settembre 2003 a luglio 2004. Come indicatori di stress sono stati utilizzati il glutatione totale (GSx), il ridotto (GSH) e l'ossidato (GSSG). I livelli di glutatione totale e ridotto sono diminuiti in T6 per poi aumentare nuovamente in T10. I livelli di glutatione ossidato non hanno subito variazioni significative nel tempo. I valori di glutatione totale, ridotto e ossidato hanno mantenuto livelli significativamente più bassi nel gruppo P3 rispetto agli altri gruppi sperimentali. Questi risultati indicano che i polifenoli dell'uva hanno, anche nei conigli, un'azione di regolazione dell'omeostasi ossido-riduttiva.*

Key words: ageing rabbits, grape poliphenols, oxidative stress, blood glutathione.

INTRODUCTION – The imbalance between reactive oxygen species (ROS) and antioxidant capacity of the organism leads to a condition of oxidative stress (Urso and Clarkson, 2003). Studies in humans and laboratory animals have reported that oxidative stress is related to some common degenerative diseases, such as cancer and cardiovascular pathologies (Pellegrini *et al.*, 2003). Oxidative stress has also been identified as causative agent for diseases, such as decline of immune function and atherosclerosis (Meydani *et al.*, 1998). In particular, reactive oxygen metabolites such as superoxide (O^{2-}), hydrogen peroxide (H_2O_2) and hydroxyl radical (OH.) have been reported to act as cytotoxic agents and damage unsaturated lipids in membranes (Girotti, 1998).

The presence of ROS in living organism is, in any case, viewed as physiological, at least until a certain level. ROS actively participate to the maintenance of the oxygen metabolite detoxification systems, which includes antioxidant compounds (uric acid, glutathione, carotenoids), and enzymes (cytochrome 450 oxidase, lipoxigenase, peroxidase, glutathione-S-transferase).

Antioxidant defences against toxic oxygen intermediates seems to be heavily influenced by nutrition in humans. For this reason, the use of nutraceutics in human and animal nutrition is considerably increased in the last decade (Young *et al.*, 2000).

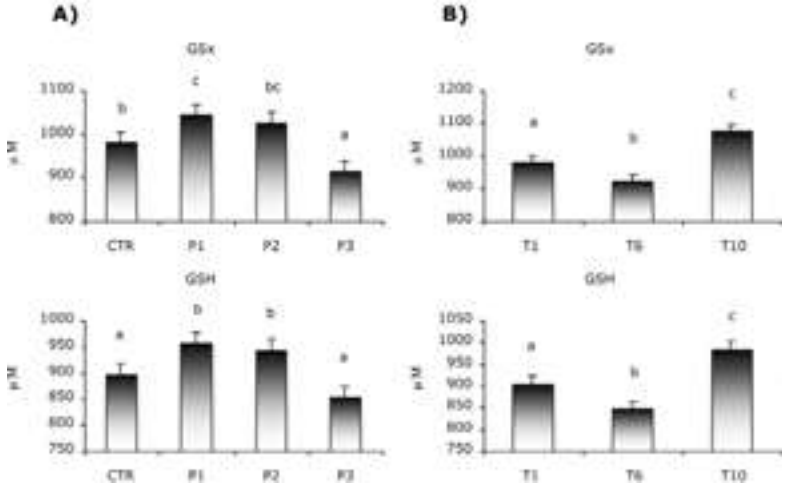
Plant-derived antioxidants can prevent ROS related damages in different ways, as interfering with the initial reactions that generate ROS, scavenging for the free oxygen molecules required to begin the production of ROS or chelating metals that speed up oxidative processes. Phenols, as flavonoids, are antioxidant compounds

derived from plants that are considered of greater interest for dietary supplementation in organisms that present an imbalanced redox state. Since ageing is the result of oxidative stress (De La Fuente *et al.*, 2004) it is important to clarify the antioxidant potential of these compounds in ageing animals.
The aim of this study was to evaluate the long-term effect of dietary grape polyphenols in ageing rabbits. This was achieved by the determination of blood glutathione concentrations and its oxidized and reduced forms.

MATERIAL AND METHODS – Eighty-eight New Zeland White rabbits, 6 months old, were reared in individual cages and were randomly assigned to the following four groups: Control (CTR), 0.03 mg of grape polyphenols (Naturex, Avignon CEDEX 9, France¸ 87% of total polyphenols; 20% of procyanidine) for kilo of feed (P1), 0.15 mg/kg (P2), and 0.30 mg/kg (P3). Blood samples were collected into heparinized tubes from the marginal ear vein. The experiment was carried out in accordance with state and local laws and ethical regulations and started on September 2003 and ended on July 2004. Blood collections were scheduled at 1, 6, and 10 months (T1, T6 and T10, respectively) after the beginning of polyphenol administration. The markers of oxidative stress analysed were total glutathione (GSx), reduced glutathione (GSH) and oxidized glutathione (GSSG). For these determinations, 100 µL of whole blood were added to 200 µL of iced 5% sulfo-salicylic acid solution, centrifuged (3000 x g/10 min) and the surnatant stored on ice until analysis. Blood GSx and GSSG content was determined by an enzymatic recycling method originally described by Tietze (1969) and adapted for microtiter plate reader. Biochemical data were analyzed with the SPSS package (release 7.0) using a factorial model with interaction, using treatment (4 levels) and time of sampling (3 levels) as fixed effects.

RESULTS AND CONCLUSIONS – Blood GSx, GSH and GSSG levels were significantly lower (respectively P=0.001, P<0.01 and P=0.006) for P3 group compared with the other experimental groups (figure 1A). This result indicates a dose-response effect of grape polyphenols, with an active dose of about tenfold higher than humans. The levels of total and reduced glutathione decreased at T6, according to the age of animals (P<0.01; figure 1B). Senescence is characterized by a spread decrease of GSH concentration (Grattagliano *et al.*, 2004) and a further reduction of GSx and GSH 10 months after the beginning of the experiment would have been expected. Instead, the levels of total and reduced glutathione significantly increased at T10 (P<0.01; figure 1B), probably as a result of heat-stress caused by the summer season. Ozturk and Gumuslu (2004) observed that in old rats exposed to a prolonged heat stress, the concentration of total and reduced glutathione showed a significant increase instead of the expected depletion.

Figure 1. Effect of grape polyphenols administration on blood GSx, GSH and GSSG contents.



The GSSG/GSx ratio did not significantly change with ageing (P=0.206), a trend that does not agree with the evidences reported in literature. De La Fuente *et al.* (2004) and many other authors have demonstrated that oxidized glutathione/reduced glutathione ratio increase with age. The absence of significant modifications of this parameter can be due to the antioxidant properties of grape polyphenols, which were able to contrast the rise of glutathione oxidation with senescence.
These results indicated that grape polyphenols are active compounds that are involved in the control of redox homostasis in rabbits during ageing, thus confirming the role reported for humans.

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