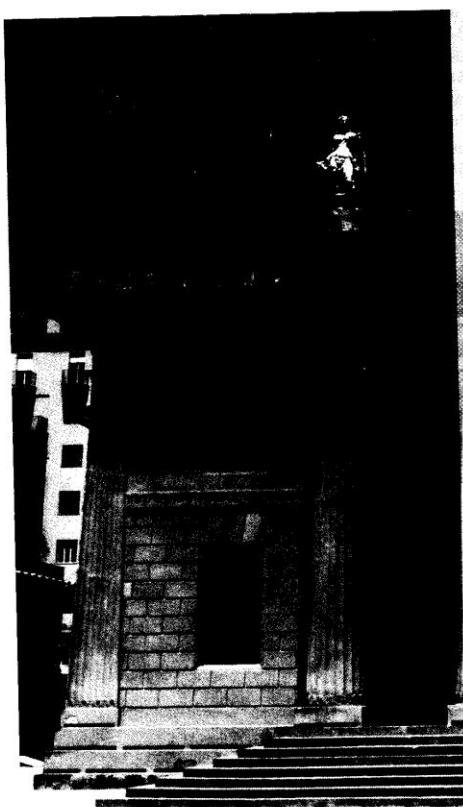
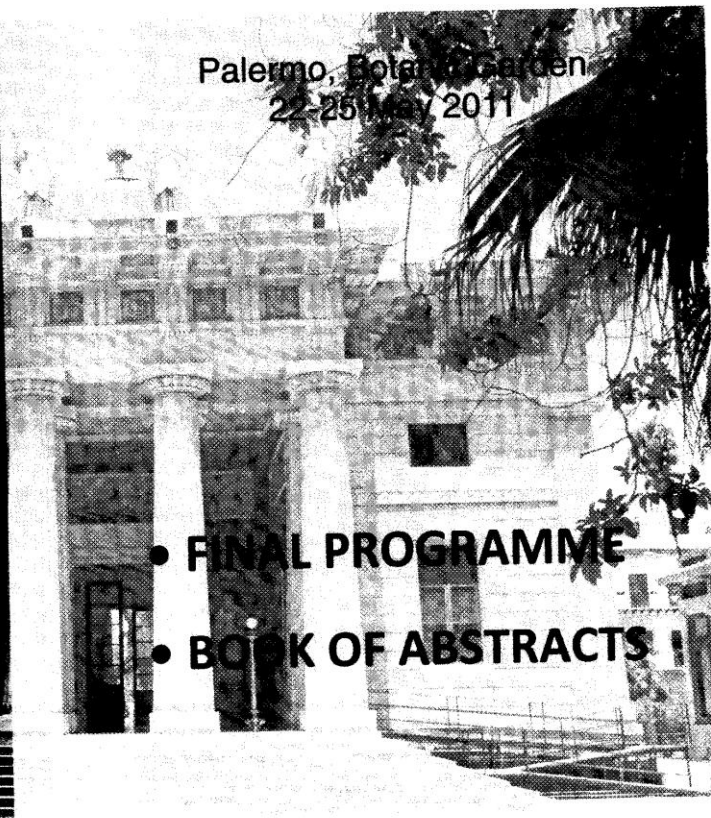


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ANTIINFLAMMATORY EFFECTS OF PISTACHIO NUT PROANTHOCYANIDINS IN Lps-STIMULATED Raw 264.7 CELLS

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It is now widely accepted that certain fruit and vegetable components can help to prevent or treat human diseases. The inflammatory response involves a innate immune signaling pathway that is controlled by the cell redox status and may implicate oxidative stress. Indeed, the inflammatory process is the driving force underlying the progression of the major chronic human diseases, including cardiovascular diseases (CVD) of multifactorial pathogenesis [1]. The effects of nut consumption on risk factors for CVD have been investigated in a number of studies and the beneficial effects are now recognized [2].

The genus *Pistacia* contains only 11 species among which *Pistacia vera* is by far the most important economically for its edible nuts. Pistachio nut consumption has been shown to have positive effects on serum lipid profile and CVD risk factors [3,4]. More recent studies in healthy subjects show that pistachio significantly improves oxidative status and reduces circulating inflammatory biomarkers, suggesting that anti-inflammatory activities of pistachio nut components may play a role in CVD prevention [5]. In previous work we showed that a hydrophilic extract from Sicilian Pistachio nuts (HPE) contains substantial amounts of polyphenols, including proanthocyanidins, and shows radical scavenging activity and antioxidative effects [6]. Proanthocyanidins, a subclass of polyphenolic compounds found in plants, have been shown to exhibit multiple biological actions, including anti-inflammatory activity [7]. Though anti-radical and antioxidant activity of these molecules may be considered [8], most of the cellular effects can rather be the result of their ability to act at several key sites of the network of signal transduction pathways [9].

Albeit triggers and mechanisms leading to overt inflammation may vary in various clinical conditions, modulation of many common pathways in endothelial cells and leukocytes results in production and/or activation of a number of pro-inflammatory mediators, including reactive oxygen and nitrogen species (ROS and RNS), transcription factors, cytokines and enzymes. In the present study, in order to rationalize the observed beneficial effects of pistachio nut diets, anti-inflammatory effects of HPE were investigated in a well-established cell model of inflammation, consisting of lipopolysaccharide (LPS)-activated RAW 264.7 macrophages, and compared to those of its proanthocyanidin fraction. Our results demonstrated that HPE pretreatment significantly inhibited LPS-induced release of nitric oxide (NO), prostaglandin E₂ (PGE₂) and tumor necrosis factor- α (TNF- α), and caused a marked inhibition of inducible NO-synthase and cyclooxygenase-2 protein amount. The inhibitory effects of HPE were observed at non toxic amounts, and were dose-dependent. HPE also caused a decrease of intracellular ROS, and interfered with the NF- κ B activation. The proanthocyanidin fraction from HPE, showed qualitative and quantitative effects comparable to those of the nut extract, when tested at the same concentrations found in the extract.

Our results provide molecular evidence of anti-inflammatory activity of pistachio nut, and indicate that proanthocyanidins can play a major role as the bioactive components. Moreover our results suggest that the observed positive effects are, at least partially, mediated by the inhibition of the NF- κ B activation pathway.

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