

# Inhibition of Oxidative Stress in Blood Platelets by Different Phenolics From *Yucca schidigera* Roezl. Bark

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**OBJECTIVE:** We investigated the comparative effects of resveratrol (*trans*-3,4',5-trihydroxystilbene), *trans*-3,3',5,5'-tetrahydroxy-4'-methoxystilbene, and yuccaols A and C isolated from the bark of *Yucca schidigera* on oxidative stress in resting blood platelets and blood platelets activated by different agonists (thrombin or thrombin receptor activating peptide).

**METHODS AND RESULTS:** Tested phenolics (1–25  $\mu\text{g}/\text{mL}$ ) reduced, to different degrees, the level of reactive oxygen species measured by the luminol-dependent chemiluminescence and changed the production of  $\text{O}_2^-$  measured by the reduction of cytochrome c in resting blood platelets. They also inhibited the generation of free radicals in blood platelets activated by thrombin ( $P < 0.05$ ) or thrombin receptor activating peptide ( $P < 0.05$ ). Treatment of platelets with resveratrol or yuccaols A and C at the concentration of 25  $\mu\text{g}/\text{mL}$  increased (statistically non-significant) the level of thiobarbituric acid reactive substances in these cells ( $P > 0.05$ ), whereas *trans*-3,3',5,5'-tetrahydroxy-4'-methoxystilbene and the alcohol yucca extract reduced lipid peroxidation in blood platelets ( $P < 0.05$ ).

**CONCLUSIONS:** Resveratrol and other phenolic compounds from the bark of *Yucca schidigera* inhibiting free radical generation in blood platelets may be beneficial in protecting against cardiovascular diseases when hyperactivity of platelets is observed. *Nutrition* 2003;19:633–640. ©Elsevier Inc. 2003

**KEY WORDS:** resveratrol, stilbenes, yuccaols, reactive oxygen species, lipid peroxidation, blood platelets

## INTRODUCTION

Resveratrol (3, 4', 5-trihydroxystilbene) was identified as a natural phytoalexin occurring in grape skin and some medicinal plants. It also can be found in wine, especially red wine, and is recognized as a major antioxidant responsible, at least in part, for the so-called French paradox. It has a number of biological activities including anticancer and antimutagenic,<sup>1–3</sup> antiviral,<sup>4</sup> antiplatelet,<sup>5–9</sup> and antioxidant.<sup>10</sup> Our previous results showed that *trans*-resveratrol inhibits *in vitro* activation of blood platelets.<sup>11–13</sup> Blood platelets are the smallest enucleated blood cells derived from megakaryocytes. These cells are multi-responding cells with respect to a number of agonists. They can be activated by different compounds including coagulation factors (thrombin), hormones (epinephrin, vasopressin), low-molecular-weight substances (serotonin, adenosine diphosphate [ADP]), lipid derivatives (platelet aggregating factor, thromboxane  $\text{A}_2$ ), and other protein substances (collagen or immune complexes). The platelet response to different activators includes mainly adhesion, shape change, aggregation, and secretion of compounds from three different storage granules.<sup>14–17</sup> During blood platelet activation induced by thrombin, collagen reactive oxygen species (ROS) are formed.<sup>18–21</sup> We previously observed that resveratrol reduces the first step of blood platelet

activation, i.e., platelet adhesion to collagen and fibrinogen.<sup>11,22</sup> It also inhibits platelet aggregation induced by thrombin or ADP<sup>11</sup> and platelet secretion of adenine nucleotides and proteins from dense and  $\alpha$ -granules.<sup>13</sup> The mechanism of resveratrol action on the inhibition of platelet function is still unclear, and changes in ROS level may be responsible for the modification of platelet reactivity induced by resveratrol.<sup>12,23</sup>

The multifunctional activities of resveratrol encouraged the search of the action of structurally related compounds for possible pharmaceutical applications. Resveratrol (compound 2) and three other related compounds, *trans*-3,3',5,5'-tetrahydroxy-4'-methoxystilbene (compound 1) and yuccaols A (compound 4) and C (compound 3; Fig. 1), recently have been identified in *Yucca schidigera* bark. *Yucca schidigera* is a plant that grows widely in Mexico, and it is well known because of its very high content of steroidal saponins. The concentrations of different phenolics in this plant species are also extremely high.<sup>24</sup> Epidemiologic studies reported that phenolic compounds, which are present in various plants consumed by humans, may protect against cardiovascular diseases. The mechanism of this protection induces the inhibition of blood platelet activation.<sup>5–9</sup> Because *Y. schidigera* products have been certified as generally recognized as safe and approved by the U.S. Food and Drug Administration for use as food additives, we examined the influence of resveratrol and other yucca phenolics and alcohol extracts on oxidative stress in resting platelets and platelets stimulated by thrombin or thrombin receptor activating peptide (TRAP) and whether resveratrol is a "tethered" ligand domain of thrombin receptor, which begins with the sequence Ser-Phe-Leu-Leu-Arg-Asn. Our previous results indicated that these phenolics from *Y. schidigera* reduce platelet aggregation and enzymatic platelet lipid peroxidation.<sup>25</sup>

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