



Hepatoprotective effects of *Hibiscus*, *Rosmarinus* and *Salvia* on azathioprine-induced toxicity in rats

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Abstract

As an anti-metabolite, Azathioprine inhibits the de novo and salvage pathways of purine synthesis. Intraperitoneal injection of this drug results in not only lymphocyte suppression but also toxicity to bone marrow, gastrointestinal tract, and liver. This Azathioprine-induced hepatotoxicity was found to be associated with oxidative damage. Plants with antioxidative properties have been traditionally used to prevent diseases associated with free radicals. In this report, we used water extracts of three herbal plants that have been commonly used for treating many illnesses (*Hibiscus sabdariffa*, *Rosmarinus officinalis* and *Salvia officinalis*). Here we show their novel hepatoprotective effects against Azathioprine-induced hepatotoxicity in rats. Typically, administration of Azathioprine induces oxidative stress through depleting the activities of antioxidants and elevating the level of malonaldehyde in liver. This escalates levels of alanine aminotransferase, and aspartate aminotransferase in serum. Pretreatment with any of the three herbal plants used in this investigation proved to have a protective effect against Azathioprine-induced hepatotoxicity. Animals pretreated with water extracts from any of the three herbs under investigation not only failed to show necrosis of the liver after azathioprine administration, but also retained livers that, for the most part, were histologically normal. In addition, these herbs blocked the induced elevated levels of alanine aminotransferase and aspartate aminotransferase in serum. The Azathioprine-induced oxidative stress was relieved to varying degrees by the examined herbal extracts. This effect was evident through reducing malonaldehyde levels and releasing the inhibitory effect of Azathioprine on the activities of glutathione, catalase and superoxide dismutase. To our

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knowledge, this report is the first that shows hepatoprotective effects of *Hibiscus*, *Rosmarinus* and *Salvia species* against Azathioprine-induced acute liver damage.

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Introduction

Azathioprine (AZP), a 6-(1-methyl-4-nitro-5-imidazolyl) thiopurine, is common immunosuppressant that has been used in the treatment of hematological malignancies, solid organ transplantation and inflammatory bowel disease (Maltzman and Koretzky, 2003). However, its use has been complicated by a high incidence of serious adverse drug reaction such as myelosuppression, hepatotoxicity, pancreatitis and gastro intestinal disturbances (Rulyak et al., 2003; Sinico et al., 2003; Ziegler et al., 2003). The hepatotoxicity of AZP was also documented in rats (Raza et al., 2003).

The mechanism of AZP toxicity to rat hepatocytes involves elevation of reactive oxygen species (ROS) leading to mitochondrial injury and cell death by necrosis. This AZP-induced injury was prevented by potent antioxidants (Lee et al., 2003). Several plants have been reported to be effective in the treatment of liver diseases. The therapeutic effect and molecular mechanism of most of these plants are still unclear (Lupper, 1999).

Salvia officinalis (SO), a plant endemic to the Mediterranean region, is the most popular herbal remedy in the Middle East to treat common health complications such as cold and abdominal pain (Gali-Muhtasib et al., 2000). *Salvia species* (*Labiatae*) are generally known for their multiple pharmacological effects including their antibacterial (Miski et al., 1983), hypoglycemic (Perfumi et al., 1991), antianoxic (Wu et al., 1997), antitumor (Liu et al., 2000), antioxidative (Wang et al., 2003) and anticholestatic (Oh et al., 2002) effects. Phytochemically, the whole plant contains several antioxidants that prevent peroxidative damage to hepatocytes such as water-soluble compounds; salvianolic acid A, salvianolic acid B, and rosmarinic acid (Huang and Zhang, 1992), tanshinone IIA (Cao et al., 1996) and several phenolic glycosides (Wang et al., 1999).

Dried flower extract of *Hibiscus sabdariffa* L (HS) (*Malvaceae*), a common local drink (Karkade) and medicinal herb, has been used in folk medicines against hypertension (Wang et al., 2000). *Hibiscus* anthocyanins, a group of phenolic natural pigments present in the dried flower of HS and *Hibiscus rosa sinensis*, have been found to have cardioprotective (Jonadet et al., 1990), hypocholesterolemic, antioxidative and hepatoprotective (Wang et al., 2000) effects in animals. Anthocyanin pigments and other phenolic compounds (*Hibiscus* pterocatechuic acid), also isolated from dried flowers of HS, demonstrate protective effect against tert-butyl hydroperoxide (t-BHP)-induced oxidative damage and hepatotoxicity both in vitro and in vivo (Wang et al., 2000; Liu et al., 2002).

Rosemary (*Rosmarinus officinalis* L) (RO) (*Lamiaceae*) is a native Mediterranean plant that has been commonly used against asthma, eczema and rheumatism (Fahim et al., 1999). RO extracts are found to exhibit different protective effects in rats such as hepatoprotective (Sotelo-Felix et al., 2002), anti-mammary tumorigenesis and mutagenesis (Fahim et al., 1999), anti-hyperglycemic (Al-Hader et al., 1994) and anti ulcerogenic (Dias et al., 2000). The extract of RO has been shown to have potent hepatoprotective effects against a variety of hepatotoxic agents including CCl₄ (Fahim et al., 1999), t-BHP (Joyeux et al., 1990) and cyclophosphamide (Fahim et al., 1999). RO was also

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