Effects of Trans-Resveratrol, Isolated from Smilax Aspera, on Smooth Muscle, Blood Pressure, and Inflammation in Rats and Nociception in Mice

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Abstract

Smilax aspera (Liliaceae) has been used in herbal medicine for the treatment of many disorders. Chemical analysis of this plant resulted in the isolation of the stilbene trans-resveratrol. The effects of this compound on rat isolated ileum and urinary bladder, blood pressure and inflammation, and nociception in mice have been examined. Resveratrol (3x10^-7 - 4.4x10^-4 M) caused a concentration-dependent relaxation in both ileal longitudinal segments and urinary bladder rings. Intravenous doses of resveratrol (0.026-8.5 mg/kg) caused a dose-dependent fall of systolic and diastolic blood pressure of anesthetized rats. Oral administration of this compound (1.3, 4.0, 13 and 40 mg/kg) decreased carrageenan-induced paw edema in rats. Furthermore, oral administration of resveratrol (3, 10, 30 and 100 mg/kg) decreased the number of writhes induced by i.p. injection of 0.8% acetic acid in mice. These effects of resveratrol and its potential as a medicinal source were discussed in the light of the reported effects of resveratrol on nitric oxide and prostaglandin synthesis.

1. Introduction

Smilax aspera is an evergreen, creeping, extremely tough shrub that belongs to the Liliaceae family (Longo and Vasapollo, 2006) and has been used in herbal medicine for muscle relaxation, skin ailments, rheumatic pain, deparative, diuretic, diaphoretic, antidouleur, dropsy stimulant and for its tonic properties (Longo and Vasapollo, 2006; Aburjai et al., 2007). S. aspera has also been used traditionally for the treatment of syphilis (Vernani and Garg, 2002), diabetes (Fukunaga et al., 1997), rheumatism (Ageel et al., 1989), as an antioxidant (Demo et al., 1998) and to treat symptoms of menopause in women (Weil et al., 2000). In fact, several species of the genus Smilax are well-known Chinese traditional medicines, and are used as anti-inflammatory, antinecancer and analgesic agents (Shu et al., 2006). Chemical and pharmacological studies were carried out on this species (e.g. Ageel et al., 1989; Ruan et al., 2005; Selenu et al., 2005; Xu et al., 2005; Longo and Vasapollo, 2006). In an attempt to isolate chemical ingredients from the local Smilax aspera, we have been able to isolate the known stilbene trans-resveratrol.

Resveratrol is a non flavonoid polyphenolic compound found in a large number of plant species (at least 72 species), a number of which are human diet components, including mulberries, peaches, grapes, and red wines (Lastra and Villegas, 2005). Resveratrol has been proposed as an effective agent in the prevention of pathologic processes such as inflammation, atherosclerosis, oxidative stress and carcinogenesis (Miatello et al., 2005; Baur and Sinclair, 2006). It has also been reported as neuroprotective, cardioprotective and to modulate lipoprotein metabolism (Martin et al., 2004; Baur et al., 2006). The interest in resveratrol was rekindled after reports that it extends life span in the yeast Saccharomyces cerevisiae (Howitz et al., 2003) and the worm Caenorhabditis elegans and the fruit fly Drosophila.

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melanogaster (Wood et al., 2004). In spite of reports to the contrary (Bass et al., 2007; Pearson et al., 2008), the debate on the biological effects of resveratrol continued to generate scientific interest (Valenzano et al., 2006). This communication is a contribution to evaluate other potential effects of resveratrol such as its effects on isolated smooth muscle preparations, blood pressure, and inflammation in rats and on pain in mice.

2. Materials and Methods

2.1. Effect of Resveratrol on Isolated Ileum and Urinary Bladder

Male and female albino rats weighing 250-300gm were used. Animals were lightly anesthetized with ether, and then sacrificed in compliance with the university adopted guidelines for animals’ use in research. A mid piece of the ileum was excised, flushed with aerated physiological salt solution (PSS) and cut into several pieces (1-2cm long each) (Hammad and Abdalla, 1997). Urinary bladder was also isolated, and cut into 2-3mm rings taken from the middle region of the bladder (Khattab and Al-Hrasen, 2006). The preparations were placed in 10-ml water-jacketed glass tissue baths containing aerated PSS at 37°C and gassed with a mixture of 95% O₂-5% CO₂ and mounted for isometric recording using force transducers (Grass FT03C) connected to a physiograph (Graphtec Thermal Arraycorder, WR5000) under a tension of 1g (Abdalla et al., 1994).

After an equilibration period, cumulative concentration-response curves of resveratrol were established by addition of 3-fold increasing concentration of resveratrol. When the maximum response to resveratrol was achieved, a strong non-specific relaxant agent (10⁻⁵ M papaverine HCl) was added to the tissue bath. The response to resveratrol was expressed as percent of the maximum effect of papaverine (Onwukaeme et al., 1999).

2.2. Effect of Resveratrol on Blood Pressure

Male albino rats (250-350 gm body weight) were anesthetized with sodium thiopental (50mg/kg body weight; i.p.). The right common carotid artery was exposed and a catheter was introduced for the recording of blood pressure using P23AA Statham pressure transducer situated at the level of the heart and connected to a Gilson polygraph (Abdalla et al., 1994). The right femoral vein was also catheterized for intravenous injection of resveratrol. After a steady baseline of blood pressure was obtained (about 15 minutes), resveratrol was injected intravenously in doses of 0.028, 0.085, 0.28, 0.85, 2.8, and 8.5 mg/kg body weight. The changes in systolic and diastolic blood pressure were observed and expressed as percent of their respective control values obtained before resveratrol injection.

2.3. Anti-Inflammatory Effect of Resveratrol

Male albino rats, weighing 130-200 gm were used. Animals were fasted for 24 hours before the beginning of the experiment with free access to water (Amanlou et al., 2005). Animals were divided into 6 groups each of eight animals as follow:

1. Control group: Received 0.9% NaCl.
2. Four treated groups: Received 1.3, 4, 13, and 40 mg/kg of resveratrol.
3. Positive control group: Received 10 mg/kg of indomethacin, a reference anti-inflammatory drug.

All doses were administered orally at a dose volume of 0.5ml/100 g animal. One hour later, acute paw edema was induced by plantar injection of 0.1ml of 1% freshly prepared carrageenan suspension in normal saline into the right hind paw of each rat. The paw volume was measured before (0 h) and at intervals of 1, 2, 3, 4, 5, and 6 hrs after carrageenan using a plethysmometer (Type 7140 Ugo Basile, Italy) (Wu et al., 2006).

2.4. Antinociceptive Effect of Resveratrol

Male and female albino mice, weighing 20-30g were used. Animals were deprived of food, but with free access to drinking water for 12 hours prior to the experiments (Costa-Lotufo et al., 2004). The animals were divided into 6 groups each of eight animals as follows:

1. Control group: received 0.9% NaCl.
2. Four treated groups: received 3, 10, 30, and 100 mg/kg of resveratrol.
3. Positive control group: received 10 mg/kg of indomethacin, a reference analgesic drug.

Animals were pretreated orally with resveratrol 60 minutes prior to i.p. injection with 0.1ml/10g body weight of 0.8% (v/v) acetic acid solution in 0.9% NaCl (Rabelo et al., 2003). The number of writhes was counted during a 30-min period following the injection of acetic acid. A writhes was defined as a contraction of the abdominal muscles accompanied by an extension of the forelimbs and elongation of the body (Choi et al., 2005).

2.5. Solutions

The composition of PSS in mM was: NaCl 118.0; KCl 4.7; CaCl₂·2H₂O 2.5; MgCl₂ 0.5; NaH₂PO₄ 1.0; NaHCO₃ 24.0; and glucose 11.1. Trans-resveratrol was isolated from Smilax aspera and was identified by comparison of its spectral data with literature (Vitrac et al., 2005). Stock solution of resveratrol was prepared daily by dissolving resveratrol in minimal amount of 1N NaOH, the volume was then completed to 1ml with 0.9% NaCl (final concentration of NaOH was 0.075%). Papaverine HCl (Acros Organics, New Jersey) solution (10⁻³M) was prepared by dissolving papaverine hydrochloride in distilled water. Indomethacin (Sigma-Aldrich Chemie, Germany) was prepared by dissolving in 0.5% carboxymethylcellulose sodium. Carrageenan (Fluka Biochemika, Switzerland) was prepared by dissolving 0.1 g of carrageenan in 10 ml 0.9%NaCl.

2.6. Statistical Analysis

Data are presented as means ± the standard error of means (SEM). One way-analysis of variance (ANOVA) and Student t-test for independent samples were used to screen for differences between the means of the samples. The differences were considered significant if P < 0.05. The median effective concentration producing 50% of the maximum response (EC50) was calculated from the plot. Experimental data were analyzed by a computer fitting treatment using GraphPad Prism 5.0 software.
3. Results

3.1. Effect of Resveratrol on Isolated Smooth Muscle Preparations

Figure 1 shows that $3 \times 10^{-5} - 1 \times 10^{-1}$ mg/ml resveratrol ($=1.3 \times 10^{-7} - 4.3 \times 10^{-4}$ M), caused concentration-dependent relaxation in the rat isolated ileal longitudinal segments. The EC50 of resveratrol for relaxation of ileal longitudinal segments was $(8.0 \pm 2.3) \times 10^{-7}$ mg/ml (n=4).

Figure 1. Cumulative concentration-response curves of resveratrol on rat isolated ileal longitudinal segments.

Figure 2 shows that resveratrol ($3 \times 10^{-5} - 1 \times 10^{-1}$ mg/ml) caused a concentration-dependent relaxation of the urinary bladder rings. The maximum relaxation induced by resveratrol reached $(82.0 \pm 4.1)\%$ and $(43.0 \pm 6.5)\%$ for ileal longitudinal segments and urinary bladder rings, respectively.

Figure 2. Cumulative concentration-response curves of resveratrol on rat isolated urinary bladder rings.

3.2. Hypotensive Effect of Resveratrol

Intravenous injection of resveratrol at doses ranging from 0.028 to 8.5 mg/kg induced dose-dependent fall of both systolic and diastolic blood pressure of the anesthetized rats (Figs. 3 and 4).

Figure 3. Typical responses of blood pressure to intravenous injections of resveratrol in the doses indicated (A-F). A-F were obtained from the same preparation. The solid line above the traces is a reference baseline.

Figure 4. Dose-response curves of resveratrol on systolic (solid squares) and diastolic (solid triangles) blood pressure of anesthetized rats.

doses did not reach the level of statistical significance when compared to the control group. At concentrations of 13 and 40 mg/kg, there was a significant decrease in the hind paw volume, when compared to the control group. The positive control group also showed reduction of the volume of the hind paw and this inhibition reached the level of statistical significance 4, 5 and 6 hours after carrageenan administration.

3.3. Anti-Inflammatory Effect of Resveratrol

Table 1 shows that resveratrol in doses of 1.3 and 4.0 mg/kg caused an inhibition in the hind paw volume over time although the decrease in the volume at these two

Table 1. The effects of resveratrol and indomethacin on the hind paw volume.

3.4. Analgesic Effect of Resveratrol

Figure 5 shows that resveratrol-treated groups showed a dose-dependent decrease in the number of writhes counted in 30 minutes after injection of acetic acid. The highest reduction was obtained at a dose of 100 mg/kg (76.6 % of inhibition). This effect is comparable to that induced by indomethacin (71.3 % of inhibition) albeit a higher dose of resveratrol. Other resveratrol-treated groups (3, 10, and 30 mg/kg) showed intermediate inhibition values of 39.3 %, 54.0 %, and 56.6 %; respectively. This inhibition in the number of writhes reached the level of statistical significance at all doses of resveratrol-treated groups.
Table 1. Hind paw volumes in male rats observed over a period of six hours after oral administration of 0.9% NaCl, 1.3, 4, 13, and 40 mg/kg resveratrol, and indomethacin.

<table>
<thead>
<tr>
<th>Experimental group</th>
<th>0h</th>
<th>1h</th>
<th>2h</th>
<th>3h</th>
<th>4h</th>
<th>5h</th>
<th>6h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (0.9% NaCl)</td>
<td>1.00±0.05</td>
<td>1.24±0.02</td>
<td>1.29±0.03</td>
<td>1.35±0.04</td>
<td>1.37±0.09</td>
<td>1.37±0.06</td>
<td>1.40±0.06</td>
</tr>
<tr>
<td>Resveratrol (1.3 mg/kg)</td>
<td>1.10±0.05</td>
<td>1.26±0.05</td>
<td>1.30±0.06</td>
<td>1.32±0.05</td>
<td>1.35±0.04</td>
<td>1.36±0.05</td>
<td>1.35±0.05</td>
</tr>
<tr>
<td>Resveratrol (4 mg/kg)</td>
<td>1.09±0.04</td>
<td>1.21±0.05</td>
<td>1.26±0.05</td>
<td>1.30±0.04</td>
<td>1.25±0.05</td>
<td>1.27±0.05</td>
<td>1.25±0.05</td>
</tr>
<tr>
<td>Resveratrol (13 mg/kg)</td>
<td>0.99±0.04</td>
<td>1.10±0.03</td>
<td>1.14±0.04</td>
<td>1.14±0.03*</td>
<td>1.12±0.02*</td>
<td>1.13±0.02*</td>
<td>1.06±0.03*</td>
</tr>
<tr>
<td>Resveratrol (40 mg/kg)</td>
<td>0.94±0.03</td>
<td>1.03±0.03*</td>
<td>1.01±0.03*</td>
<td>1.03±0.03*</td>
<td>1.05±0.03*</td>
<td>1.07±0.02*</td>
<td>1.06±0.03*</td>
</tr>
<tr>
<td>Indomethacin (10 mg/kg)</td>
<td>1.08±0.04</td>
<td>1.12±0.04</td>
<td>1.13±0.02</td>
<td>1.13±0.02</td>
<td>1.15±0.03*</td>
<td>1.14±0.02*</td>
<td>1.13±0.01*</td>
</tr>
</tbody>
</table>

*All values represent means of the volume ± SEM for 8 experiments.
*P < 0.05 compared to the control group.

Figure 5: Number of writhes induced by acetic acid in mice treated with: 0.9% NaCl (control), 3, 10, 30, and 100 mg/kg resveratrol, and with 10 mg/kg indomethacin. Number of writhes is given as the means ± SEM of 8 animals. Asterisks indicate that P < 0.05 compared to the control group (0.9% NaCl).

4. Discussion

The growing interest in the use of herbs and their bioactive compounds is attributed largely to the fact that most herbs are relatively inexpensive and are easily available, yet have fewer adverse effects (Kim et al., 2006). *Smilax aspera*, a member of the Liliaceae family, is well known for its medicinal uses and has been used for many disorders. Many constituents have been isolated from this plant including flavonoids, tannins, asperoside, sapogenins, β-sitosterol and essential oils (Ayengar and Rangaswami, 1967; Petricic and Radosevic, 1969; Tschesc et al., 1974; Bruno et al., 1985; Long and Vassapollo, 2006). The current study on the whole plant material of *Smilax aspera* yielded resveratrol (0.0067% yield) which has been isolated from the genus *Smilax* previously (Zhang et al., 2006).

Resveratrol has been proposed as an effective agent in the prevention of pathologic processes such as inflammation, atherosclerosis, oxidative stress, and carcinogenesis (Miatello et al., 2005). Resveratrol, a polyphenolic compound found in many edible plant species, is satisfactorily absorbed from the intestine and distributed in the blood stream and can be detected in significant concentrations in the blood and a number of organs. Little is known about the transport and the distribution of resveratrol through the body but it must be bound to proteins and/or be conjugated to remain at high concentration in the serum as a consequence of its relatively low water solubility (Lastra and Villegas, 2005). Therefore, its pharmacological effects and its pharmacokinetics are of paramount importance to human health.

4.1. Resveratrol Spasmolytic Effects

In the current study, resveratrol has been found to cause concentration-dependent relaxation in both rat ileal longitudinal segments and urinary bladder rings. This observation is consistent with other studies which showed relaxant effects for resveratrol on isolated smooth muscles preparations. The relaxant effect of this compound was documented in many vascular beds including rat aorta, porcine coronary arteries, guinea pig mesenteric and uterine arteries and sheep coronary arteries (Naderali et al., 2000; El-Mowafy, 2002; Slater et al., 2003; Campos-Toimil et al., 2005; Buluc and Demirel-Yelmaz, 2006; King et al., 2006).

The mechanism of resveratrol relaxation cannot be deduced from the current experiments but observations made by other workers are suggestive of such mechanism. In one hand, several studies showed that nitric oxide relaxes ileum and urinary bladder via increasing cGMP synthesis (Hedlund, 2005; Gharib-Naseri et al., 2007) and that resveratrol relaxed endothelium-intact rat aortic rings constricted by phenylepherine and KCl via NO release (King et al., 2006). On the other hand, resveratrol stimulates the endothelium-dependent vasorelaxation through the stimulation of the NO/cGMP cascade in rat aortic rings (Fitzpatrick et al., 1993; Slater et al., 2003), and it was shown that resveratrol upregulates the GC/cGMP system in coronary artery smooth muscle and to...
trigger a vasorelaxant response (El-Mowafy, 2002). The GC/cGMP system plays a key role in spasmyolytic signaling mechanisms (Song et al., 2006). NO, synthesized by the enzyme NO synthase, is released by peripheral nerves and mediates relaxant effect on vascular and non-vascular smooth muscles (Capasso et al., 2004). NO produces smooth muscle relaxation by activating the soluble guanylate cyclase (sGC) and thereby increasing tissue levels of cGMP, which in turn interacts with various intracellular components that regulate activities of the contractile proteins (Hedlund, 2005). Other effects of resveratrol pertain to variable effects on Ca in various tissues and cells are also possible and may play a role in the mechanism of action of resveratrol (Buluc and Demirel-Yilmaz, 2006; Wang and Scherer, 2008).

4.2. Resveratrol Effect on Blood Pressure

In this study, resveratrol was found to reduce arterial blood pressure of anesthetized normotensive rats when administered intravenously, indicating that it has a hypotensive effect. Although one component of the effect of resveratrol on both systolic and diastolic pressure was transient, blood pressure, in general, did not return to the original baseline. The present work is consistent with the recent studies that demonstrated the effects of resveratrol on blood pressure in various hypertensive rat models. It has been shown that resveratrol decreased systolic and diastolic blood pressure in ovariecтомized rats (Li et al., 2006), and in the partially nephrectomized rats (Liu et al., 2005). It is likely that the hypotensive effect of resveratrol in the present study is due to an increase in NO production from the vascular endothelium. This suggestion stems from the observations that resveratrol administration prevented blood pressure elevation and reduced both vascular and myocardial endothelial NO synthase (eNOS) activity in fructose-fed rats (Miatiello et al., 2005). Moreover, resveratrol was shown to restore the eNOS activity in the rat aorta and to normalize blood pressure of rats with modeled arterial hypertension (Gumanova et al., 2007). NO generated in endothelial cells by eNOS is known to play a major role in blood pressure control (Minuz, 2006).

4.3. Resveratrol Effect on Inflammation

Among the several models of acute inflammation, carrageenan-induced inflammation has been well established as a valid model to study free radicals generation in paw tissue after inflammatory states. The cellular and molecular mechanism of carrageenan-induced inflammation is well characterized, and this model of inflammation is a standard model to screen the anti-inflammatory activity of various experimental compounds (Bilici et al., 2002). Carrageenan-induced edema is caused by the release of a number of inflammatory mediators and is initiated by dilation of arterioles and an eventual increase in permeability of postcapillary venules resulting in exudation of inflammatory cells and fluids at the site of injury. Inhibition of this acute phase of inflammation will therefore ultimately abort the inflammatory process (Duwiejua et al., 2002). In this study, the edema induced in the rat hind paw by carrageenan was maximal at the 6th hour of its plantar injection. This time course of edema is consistent with that reported by Zakaria et al., (2006) but longer than that observed by Koo et al., (2006) who showed progressive paw volume reaching a maximum at 4 hrs, or that reported by Vasudevan et al., (2006) who showed maximum swelling after 3 hrs. Our results showed that resveratrol caused a dose-dependent decrease in the rat hind paw volume and this inhibition was statistically significant after 3h and 1h for doses of resveratrol of 13 and 40 mg/kg respectively. This observation is consistent with the finding that resveratrol isolated from Smilax china in a dose of 0.2 mg/kg/day inhibited the cotton pellet-induced granuloma in rats (Ruan et al., 2005). Resveratrol has also a significant suppressive effect on hind paw edema induced by egg albumin in bilateral adrenalectomized rats. The anti-inflammatory effects of resveratrol was found independent of adrenal gland but might be related to inhibition of inflammatory mediators and free radicals (Liu et al., 2006). Contrary to our observation, another study failed to demonstrate any anti-inflammatory effect of resveratrol using the carrageenan-induced paw edema model in which the administration of resveratrol at doses of 0.4, 2, 10, and 50 mg/kg did not reverse the swelling and edema, although they reversed the hyperalgesia induced by local tissue injury provoked by carrageenan (Gentilli et al., 2001). This contradiction might be attributed to differences in the route of resveratrol administration (oral vs. i.p.), the time between injection of resveratrol and injection of carrageenan (1hr vs. 30 min), differences in the instrument used for measurements (plethysmometer vs. analgesiometer) and the parameter measured (paw volume vs. paw circumference).

Several possibilities could account for the anti-inflammatory effects of resveratrol: i) inhibition of cyclooxygenase activity, since resveratrol has been shown to inhibit the induced production of PG_E2 in a dose-dependent manner in human peripheral blood leukocytes (Richard et al., 2005), and it decreased significantly the elevated levels of rat PG_D2 in vivo. In the in vitro and in vivo models, resveratrol decreased the expression of cyclooxygenase-2 (COX-2) (King et al., 2006). Because COX-2 is the key enzyme catalyzing the rate-limiting step in PG biosynthesis, it is likely that at least part of the anti-inflammatory activity of resveratrol can be attributed to inhibition of COX-2 expression, ii) inhibition of the NO-generating pathway, since resveratrol has been shown to inhibit both the generation of NO and the expression of inducible nitric oxide synthase (iNOS) in activated macrophages and in cultured cells (Tsai et al., 1999). The expression of inducible isofrom of NO synthase has been proposed as an important mediator of inflammation (Bilici et al., 2002). Resveratrol is known to inhibit the synthesis and release of pro-inflammatory mediators, inducible nitric oxide synthase (iNOS) and COX-2 via its inhibitory effects on nuclear factor – (kappa)B (NF-κB) (Sharma et al., 2007a). Tsai et al. (1999) showed that resveratrol protected against endotoxin-induced inflammation by preventing the NF-κB activation. In addition, resveratrol has been shown to be a potent and specific inhibitor of tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) and consequently the induced NF-kB activation (Fulgenzi et al., 2001).
4.4. Resveratrol Analgesic Effects

In this study, resveratrol was also shown to decrease the number of writhes in a dose-dependent manner. We used the acetic acid-induced mice abdominal writhing model to study the antinociceptive effect. Contortions induced by intraperitoneal injections of acetic acid originate from the pain of inflammation mediated by prostaglandins (Oliveira et al., 2001). When the tissues and cells suffer harmful stimulation, they release compounds such as H⁺, prostaglandin E₂ (PGE₂) or 5-hydroxytryptamine (5-HT) which cause pain at the location. Acetic acid H⁺ itself may cause pain; at the same time it can stimulate the tissue to produce PGE₂ which causes further pain. Thus, acetic acid is widely used to screen compounds for antinociceptive activity and is accepted as a suitable model for antinociception (Shu et al., 2006). Levels of prostaglandins were reported to be high during the first 30 min after intraperitoneal injection of acetic acid (Neto et al. 2005). Our observations are consistent with those by Torres-Lopez et al. (2002) which showed that resveratrol has peripheral antinociceptive effect since it reduced nociception in a dose-dependent manner in the second phase of formalin test which is dependent on many mediators including prostaglandins (Sayyah et al., 2002). In addition, resveratrol has been shown to prevent streptozotocin-induced thermal hyperalgesia in diabetic mice (Sharma et al., 2007b). Although we have not investigated the mechanism of action of resveratrol as antinociceptive in the present work, we postulate that resveratrol causes this effect through inhibition of prostaglandin synthesis through an action on COX enzyme since there is evidence that resveratrol produces antinociception through the selective inhibition of COX-1 and COX-2 (Grandos-Soto et al., 2002). Other workers showed that resveratrol has the ability to disrupt arachidonic acid metabolism by inhibiting COX-1 and hyperperoxidase activity of COX-1. Furthermore, resveratrol has been reported to inhibit COX-2 expression induced by carcinogens in human breast and oral epithelial cells (Tang et al., 2006) and to inhibits potent PGE₂ production and free radical scavenging in activated microglial cells (Candelario-Jalil et al., 2007). Other mechanisms of analgesia include the reduction of prostaglandin production at the primary afferent neurons by resveratrol thus diminishing the depolarization of nerve terminals otherwise observed during the nociception process. Alternatively, the opening of Ca²⁺-activated K⁺ channels by resveratrol would further reduce the depolarization leading to antinociception (Grandos-Soto et al., 2002). Also, resveratrol in doses of 5, 10, 20, and 40 mg/kg i.p. caused dose-dependent analgesia in the hot plate test and this effect was suggested to be mediated via an opioidergic mechanism (Gupta et al., 2004).

In conclusion, our results demonstrated that trans-resveratrol has spasmylic, hypotensive, anti-inflammatory effects on rats and analgesic effects when tested in mice, and this compound could represent a source for the development of plant-based therapy useful in the control of arterial blood pressure, inflammation and pain. Further work is needed to elucidate the mechanism of action of this compound.

References


