Thujone, a component of medicinal herbs, rescues palmitate-induced insulin resistance in skeletal muscle

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Alkhateeb H, Bonen A. Thujone, a component of medicinal herbs, rescues palmitate-induced insulin resistance in skeletal muscle. Am J Physiol Regul Integr Comp Physiol 299: R804–R812, 2010. First published June 23, 2010; doi:10.1152/ajpregu.00216.2010.—Thujone is thought to be the main constituent of medicinal herbs that have antidiabetic properties. Therefore, we examined whether thujone ameliorated palmitate-induced insulin resistance in skeletal muscle. Soleus muscles were incubated for $\leq 12$ h without or with palmitate (2 mM). Thujone (0.01 mg/ml), in the presence of palmitate, was provided in the last 6 h of incubation. Palmitate oxidation, AMPK/ acetyl-CoA carboxylase (ACC) phosphorylation and insulin-stimulated glucose transport, plasmalemmal GLUT4, and AS160 phosphorylation were examined at 0, 6, and 12 h. Palmitate treatment for 12 h reduced fatty acid oxidation (−47%), and insulin-stimulated glucose transport (−71%); GLUT4 translocation (−40%); and AS160 phosphorylation (−26%), but it increased AMPK (51%) and ACC phosphorylations (+44%). Thujone (6–12 h) fully rescued palmitate oxidation and insulin-stimulated glucose transport, but only partially restored GLUT4 translocation and AS160 phosphorylation, raising the possibility that an increased GLUT4 intrinsic activity may also have contributed to the restoration of glucose transport. Thujone also further increased AMPK phosphorylation but had no further effect on ACC phosphorylation. Inhibition of AMPK phosphorylation with adenine 9-β-d-arabinofuranoside (Ara) (2.5 mM) or compound C (50 μM) inhibited the thujone-induced improvement in insulin-stimulated glucose transport, GLUT4 translocation, and AS160 phosphorylation. In contrast, the thujone-induced improvement in palmitate oxidation was only slightly inhibited (≤20%) by Ara or compound C. Thus, while thujone, a medicinal herb component, rescues palmitate-induced insulin resistance in muscle, the improvement in fatty acid oxidation cannot account for this thujone-mediated effect. Instead, the rescue of palmitate-induced insulin resistance appears to occur via an AMPK-dependent mechanism involving partial restoration of insulin-stimulated GLUT4 translocation.

Activation of AMPK promotes FA oxidation by phosphorylating acetyl-CoA carboxylase (ACC) which, in turn, prevents the production of malonyl-CoA, thereby releasing the inhibitory effect exerted by malonyl-CoA on carnitine-palmitoyl-CoA trans- ferase 1. However, this role of AMPK has recently been questioned. Nevertheless, many insulin-sensitizing agents such as, metformin and thiazolidinediones (TZDs), exert their antidiabetic effect, in part, through activation of AMPK. Yet, many of TZD therapies have either limited efficacy or may have undesirable side effects, including body weight gain, enhancement of gastrointestinal problems, and an increased cardiovascular risk. There is considerable interest in seeking alternative therapeutic approaches, with minimal or no side effects, to activate AMPK. Selected herbal preparations have the ability to ameliorate or delay the progression of insulin resistance or type 2 diabetes. For example, Allium cepa (garden onion) and Momordica charantia (bitter melon) have hypoglycemic effects (13, 17, 24) and improved insulin action in rats fed a high-fat diet (17), while the medicinal plant, Galega officinalis, led to discovery of a hypoglycemic mechanism (64). Essential (volatile) oils of herbs and medicinal plants have long been known to have antimicrobial, anti-fungal, and antioxidant properties (10, 60), as well as exerting hypoglycemic effects in animal models of type 1 diabetes (54, 55), type 2 diabetes (Zucker fatty rats), and insulin resistance (59). Thus, it appears that essential oils offer therapeutic
potential for the treatment of insulin resistance, although their mechanism of action remains unknown.

Thujone, a monoterpene, which exists as two stereo isomers (α- and β-thujone), is an ingredient of essential oils of a great many different herbs, including Salvia spp, Thuja spp, Artemisia spp, and many others (22, 39, 40, 48). Thujone oil has long been used in beverages, food additives, and herbal medicine (26, 57), and it is thought to be the main constituent of several medicinal herbs that have antidiabetic properties (1, 5, 21, 38). Despite the use of these herbs for the treatment of diabetes, the use of thujone per se for the treatment of insulin resistance has not been examined. Thus, given that thujone is the principal constituent of antidiabetic herbal medicine and that thujone belongs to the family of essential oils, some of which have therapeutic antidiabetic properties, we speculated that thujone could be a naturally occurring agent responsible for improving skeletal muscle insulin sensitivity. Therefore, in the present study, we examined whether thujone is an insulin-sensitizing agent that acts by increasing the phosphorylation/activation of AMPK. To examine this question, we rapidly induced insulin resistance with a high concentration of palmitate, as we have recently reported (4). Subsequently, we attempted to restore insulin sensitivity with thujone, while maintaining high concentrations of palmitate. During this last 6 h of incubation, some muscles were treated with thujone 0.01 mg/ml or with thujone 0.01 mg/ml + AMPK inhibitors adenoine 9-β-D-arabinofuranoside (Ara) (2.5 mM) or compound C (50 μM). The doses of thujone (0.01 mg/ml) and compound C (50 μM) were established in pilot studies, as these concentrations provided the optimal effects (data not shown).

Glucose transport. [3H]-3-O-methyl-d-glucose (3-O-MG) transport was determined according to previously described procedures in our laboratory (4). Briefly, at the end of the specified incubation periods, soleus muscles were incubated (30°C, 30 min, 95% O2-5% CO2) in 2 ml of palmitate-free Krebs-Henseleit buffer [8 mM glucose, 32 mM mannitol, and 0.1% BSA with (20 μM/ml) or without insulin]. Subsequently, muscles were washed (2 × 10 min, 30°C, glucose-free Krebs-Henseleit buffer, 40 mM mannitol, 0.1% BSA, with [20 μM/ml] or without insulin). Glucose transport was then determined in palmitate-free Krebs-Henseleit buffer (2 ml) supplemented with 0.5 μCi [3H]-3-O-MG, 1.0 μCi [14C]-mannitol, 32 mM 3-O-MG, 4 mM mannitol, 4 mM pyruvate, and 0.1% BSA, in the presence (20 μM/ml) or absence of insulin for 20 min, as previously reported (3, 4). Thereafter, muscles were blotted, weighed, and solubilized followed by scintillation counting of muscle extracts.

Palmitate oxidation. To determine the rate of FA oxidation, our previously described method was used (4). Briefly, at the end of the incubation periods (0, 6, and 12 h), isolated soleus muscles that had been incubated with and without palmitate were transferred to other glass vials containing 2 ml of pregassed (95% O2-5% CO2) medium 199 supplemented with 4% BSA and palmitate (2 mM, 0.5 μCi/ml [1-14C]-palmitate). Palmitate oxidation occurred at 30°C for 40 min, and the 14CO2 released was captured in a benzothiohydroxide trap (400 μl, 1.0 M). In addition, at the end of the 40-min incubation period, dissolved CO2 was released by adding sulfanilic acid (1.0 ml, 1 M) to a 1.0-ml aliquot of the incubating medium and capturing the 14CO2 in a benzothiohydroxide trap. Finally, water-soluble 14C-labeled intermediates were extracted from muscles homogenized after their incubation (4). After scintillation counting, the palmitate oxidation rate was determined as we have done previously (4), by summing the three sources of [14C]palmitate.

Plasma membrane preparation. The plasmalemmal content of GLUT4 protein was determined in soleus muscles incubated in medium 199 for 0, 6, and 12 h with or without palmitate. At these time points, the muscles were treated with insulin (20 μU/ml) for 70 min to mimic the time course in the foregoing glucose transport experiments. Thereafter, giant vesicles were prepared in which plasma membrane content of GLUT4 was measured, as we have previously reported (3, 4). To obtain sufficient plasma membrane, 10 incubated solei were pooled for each independent experiment. In total, 40 such independent preparations were performed. Giant vesicle plasma membranes were obtained, as we have previously reported in detail (8, 9). Briefly, soleus muscles were cut into thin layers (~1–3 mm thick) with a scalpel. The scored muscles were then incubated for 75 min at 34°C in 140 mM KCl-10 mM MOPS (pH 7.4), collagenase (150 U/ml), and aprotinin (1 mg/ml). Thereafter, the incubating medium was collected, and the remaining muscle debris as washed with 10 mM EDTA in KCl/MOPS until 7 ml had been collected. Percoll (final concentration 16%) and aprotinin (1 mg/ml) were added to the collected medium. The resulting mixture was placed at the bottom of a density gradient consisting of a 3-ml middle layer of 4% Nycodenz (w/vol) and a 1-ml KCl-MOPS upper layer. The samples were spun at 60 g for 45 min at room temperature. After centrifugation, the vesicles were harvested from the interface of the two upper solutions and centrifuged at 12,000 g for 5 min. The supernatant fraction was aspirated and the resulting pellet was resuspended in KCl/MOPS. Vesicles were stored at −80°C for subsequent analysis.

Protein analysis. The expression of selected proteins was determined in soleus muscle incubated in medium 199 for 0, 6, and 12 h without or with palmitate. Thereafter, muscles were rapidly blotted, frozen in liquid nitrogen, and stored at −80°C until analyzed. To
measure the phosphorylation of AS160, muscles were incubated for the various experiments, as described above, followed by incubation with insulin (20 mU/ml) for 10 min, the time in which maximal phosphorylation was observed (4). Thereafter, the muscles were rapidly blotted, frozen, and stored at −80°C for later analysis.

Muscle protein extraction and Western blot analysis. For whole muscle protein determination, frozen soleus muscle was homogenized in 2 ml of buffer. Muscle homogenate and plasma membrane protein concentrations were determined using the bichinchoninic acid assay. Proteins were separated using SDS-polyacrylamide gel electrophoresis and were detected using Western blot analysis. We (4, 6) have reported these procedures previously.

Statistics. Data were analyzed using two-way ANCOVA. For some experiments, the data were analyzed with a one-way ANOVA, when this was warranted, and when appropriate, a Fisher’s LSD post hoc analysis was used. All data are reported as means ± SE.

RESULTS

Effect of thujone on insulin-stimulated glucose transport. In the absence of palmitate, basal glucose transport was not altered during the 12-h incubation period (P > 0.05; Fig. 1). In the palmitate-treated muscles, the basal glucose transport was reduced slightly by 0.25 μmol·g·min⁻¹ within the first 6 h (P < 0.05; Fig. 1). Thereafter (6–12 h), basal glucose transport remained unaltered (P > 0.05; Fig. 1).

In control muscle, insulin-stimulated glucose transport was not altered over the 12-h incubation period (P > 0.05; Fig. 1). In contrast, palmitate induced a progressive reduction in insulin-stimulated 3-OMG transport over 12 h. After 6, and 12 h, glucose transport was reduced by 39% (P < 0.05), and 71% (P < 0.05), respectively.

Treatment with thujone (0.01 mg/ml) for 6 h restored insulin-stimulated glucose transport to normal despite the continued presence of palmitate (2 mM) (Fig. 1). In palmitate-treated muscles, the thujone-induced increase in basal glucose transport (Δ = +0.31 μmol·g·min⁻¹) cannot account for the much larger, thujone-induced increase in insulin-stimulated glucose transport (Δ = 1.47 μmol·g·min⁻¹) (Fig. 1).

Effect of thujone on insulin-stimulated plasmalemmal GLUT-4. The expression of GLUT4 protein was not altered with any of the experimental treatments (data not shown). In control muscles, insulin stimulation induced similar increases in the levels of plasmalemmal GLUT4 at 0, 6, and 12 h (P > 0.05; Fig. 2A). In contrast, in palmitate-treated muscles, the insulin-stimulated GLUT4 translocation was markedly reduced by 40% within the first 6 h (P < 0.05, Fig. 2A). Thereafter, palmitate treatment did not further reduce the insulin-stimulated GLUT4 content at the plasma membrane at 12 h (P > 0.05; Fig. 2A).

In control muscles treated with thujone, the insulin-stimulated appearance of GLUT4 at the plasma membrane was increased (+27%, P < 0.05, Fig. 2A). In muscles treated with palmitate for 12 h, the addition of thujone for the last 6 h increased insulin-stimulated GLUT4 appearance at the plasma membrane, although not to the levels in control muscle. Specifically, the net increase in the insulin-stimulated plasma membrane GLUT4 was similar in the thujone-treated control and thujone + palmitate-treated muscles. However, the insulin-stimulated plasma membrane GLUT4 was 22% (P < 0.05) lower in the thujone + palmitate-treated muscles than in untreated control muscles (Fig. 2A).

Effect of thujone on AS160 phosphorylation. The protein expression of AS160 was not altered during (0–12 h) incubation in either the control or palmitate-treated muscles, or in the thujone treated muscles (data not shown). In control muscles, insulin-stimulated AS160 phosphorylation was not altered (P > 0.05; Fig. 2B). In contrast, palmitate treatment reduced insulin-stimulated AS160 phosphorylation by 26% after 6 h (P < 0.05; Fig. 2B), and AS160 remained at this reduced level of activation until 12 h (Fig. 2B). In control muscles treated with thujone, the insulin-stimulated AS160 phosphorylation did not change (Fig. 2B). However, in palmitate-treated muscles thujone fully rescued the insulin-stimulated phosphorylation of AS160 (P < 0.05, Fig. 2B), despite the continued presence of palmitate (2 mM).

Effect of thujone on palmitate oxidation. The rate of palmitate oxidation was not altered in control muscles (P > 0.05; Fig. 3). In contrast, in the palmitate-treated muscles, palmitate oxidation was markedly decreased by 40% at 6 h (P < 0.05; Fig. 3) and remained reduced (~50%) up to 12 h of incubation. In palmitate-treated muscles, thujone increased the palmitate oxidation rate (P < 0.05) to the levels observed in the untreated control muscles (Fig. 3).

Effect of thujone on AMPK phosphorylation. The total expression of AMPK did not change during 12-h incubation in
control, palmitate-, or thujone-treated muscles (data not shown). Incubating soleus muscles without palmitate (0–12 h) increased AMPK phosphorylation (+30% at 6 h; +31% at 12 h) ($P < 0.05$, Fig. 4A). This was also observed in the palmitate-treated muscles, although compared with the control muscle, the increases at 6 h (+50%) and at 12 h (+51%) were somewhat greater ($P < 0.05$). In control muscles, AMPK phosphorylation was not increased further by thujone treatment. In contrast, in the palmitate-treated muscles, thujone treatment increased AMPK phosphorylation an additional 48% beyond the increase observed in palmitate-treated muscles at 6 h ($P < 0.05$, Fig. 4A).

**Effect of thujone on ACC phosphorylation.** The total expression of ACC did not change during the 12-h incubation in control, palmitate-, or thujone-treated muscles (data not shown). Incubating muscles without palmitate (0–12 h) increased ACC phosphorylation (+26% at 6 h; +21% at 12 h; $P < 0.05$, Fig. 4B). This also occurred in the palmitate-treated muscles, although ACC phosphorylations were greater at 6 h (+48%) and at 12 h (+44%) ($P < 0.05$). Thujone treatment did not alter ACC phosphorylation either in control or palmitate-treated muscles ($P > 0.05$, Fig. 4B).

**Effect of ara and compound C on ACC phosphorylation.** To establish whether the effect of thujone on insulin action was attributable to AMPK activation, we performed independent experiments with inhibitors of AMPK phosphorylation. In control, palmitate-, or thujone-treated muscles (data not shown). Incubating muscles without palmitate (0–12 h) in control, palmitate-, or thujone-treated muscles (data not shown). Incubating muscles without palmitate (0–12 h) in control, palmitate-, or thujone-treated muscles (data not shown). Incubating muscles without palmitate (0–12 h) in control, palmitate-, or thujone-treated muscles (data not shown). Incubating muscles without palmitate (0–12 h) in control, palmitate-, or thujone-treated muscles (data not shown). Incubating muscles without palmitate (0–12 h) in control, palmitate-, or thujone-treated muscles (data not shown). Incubating muscles without palmitate (0–12 h) in control, palmitate-, or thujone-treated muscles (data not shown). Incubating muscles without palmitate (0–12 h) in control, palmitate-, or thujone-treated muscles (data not shown). Incubating muscles without palmitate (0–12 h) in control, palmitate-, or thujone-treated muscles (data not shown). Incubating muscles without palmitate (0–12 h) in control, palmitate-, or thujone-treated muscles (data not shown). Incubating muscles without palmitate (0–12 h) in control, palmitate-, or thujone-treated muscles (data not shown). Incubating muscles without palmitate (0–12 h) in control, palmitate-, or thujone-treated muscles (data not shown). Incubating muscles without palmitate (0–12 h) in control, palmitate-, or thujone-treated muscles (data not shown). Incubating muscles without palmitate (0–12 h) in control, palmitate-, or thujone-treated muscles (data not shown).
C and Ara inhibited AS160 phosphorylation only in the palmitate-treated muscles (P < 0.05; Fig. 6B), not in control muscles (P > 0.05; Fig. 6B).

The addition of AMPK inhibitors Ara or compound C largely failed to strongly inhibit the restorative effects of thujone on the rate of palmitate oxidation. Specifically, the thujone-mediated increases in palmitate oxidation were only inhibited by 20% (Ara) and 18% (compound C) (P < 0.05; Fig. 6C).

DISCUSSION

Thujone is a monoterpenic present in essential oils of several medicinal plants and herbs that have antidiabetic properties (1, 5, 21, 38). Therefore, we examined whether thujone was able to rescue palmitate-induced insulin resistance in skeletal muscle. Our study has provided novel information on the therapeutic effects of thujone on insulin resistance and on its mechanism of action. Specifically, we found that thujone completely recovered insulin sensitivity of insulin-resistant muscles, despite the continued presence of palmitate. This marked improvement in insulin action was closely associated with the complete restoration of AS160 phosphorylation and palmitate oxidation, but only a partial restoration of insulin-stimulated GLUT4 translocation to the plasma membrane. Although thujone activated AMPK, only some of the restorative effects of thujone were associated with the concurrent activation of AMPK, namely insulin-stimulated AS160 phosphorylation and glucose transport, but not palmitate oxidation. These studies have shown that thujone, a naturally occurring plant product, can rescue palmitate-induced insulin resistance in muscle.

GLUT-4 mediated changes in glucose transport induced by palmitate and by thujone. It is now well known that the impaired recruitment of GLUT4 to cell surface plays an essential role in the induction of insulin resistance (35, 65). In agreement with our previous work (4) and others (47, 56, 66),
glucose transport was measured in intact muscle, in which and plasma membrane GLUT4 might reflect the fact that the discord between insulin-stimulated glucose transport respectively, the discord between insulin-stimulated glucose transport from 6 to 12 h in insulin-stimulated palmitate-treated muscles, insulin-stimulated GLUT4 translocation was not further reduced during this time period. This may reflect a reduction in the intrinsic activity of plasma and by possibly also improving the intrinsic activity of plasmalemmal GLUT4. Thujone rescued insulin-stimulated glucose transport, despite maintaining a high concentration of palmitate. These thujone-induced improvements were not attributable to changes in the basal rates of glucose transport, as these were only altered minimally by thujone. The thujone-induced improvements in insulin-stimulated glucose transport and GLUT4 translocation did not completely parallel each other. This may suggest that thujone treatment exerted an insulin-sensitizing effect in muscle by other mechanism(s), in addition to altered GLUT4 translocation, possibly an improved intrinsic activity of GLUT4. This interpretation, as we have noted above, is complicated by the fact that glucose transport was measured in the intact muscle, while plasma membrane GLUT4 was determined in giant vesicles. Nevertheless, we suggest that the thujone treatment rescued insulin resistance by partially restoring the insulin-stimulated GLUT4 translocation and by possibly also improving the intrinsic activity of plasmalemmal GLUT4. AS160 phosphorylation restoration does not fully restore GLUT4 translocation. AS160, a downstream target in the insulin signaling pathway, plays a critical role in insulin-stimulated GLUT4 translocation, and hence in glucose uptake (15, 49). In agreement with previous work (3), induction of insulin resistance by palmitate treatment, reduced insulin-stimulated AS160 phosphorylation, and this was associated with the reduction in plasma membrane content of GLUT4 at 6 h, and their continued reduction to the same levels until 12 h. Thus, the impaired insulin-stimulated GLUT4 translocation appears to be due to the reduced activation of AS160 in palmitate-treated muscle. In contrast, while thujone fully restored insulin-stimulated AS160 phosphorylation, this did not fully restore insulin-stimulated plasma membrane GLUT4 content. This implies that other signals may also be required to fully restore GLUT4 translocation. Effect of thujone on palmitate oxidation and AMPK/ACC phosphorylation. Numerous studies have shown that reductions in FA oxidation are associated with reduced insulin sensitivity in skeletal muscle, as this can lead to an intramuscular accumulation of bioactive lipids that interfere with insulin signaling (4, 34, 63). As in our previous work (4), we again observed that prolonged (0–12 h) incubation with palmitate reduced the oxidation rate of this substrate. Importantly, we demonstrate for the first time, that thujone fully rescued palmitate oxidation, despite the maintenance of high concentrations of palmitate.

It has been widely thought that AMPK activation in skeletal muscles stimulates FA oxidation via the inhibition of ACC activity (14, 29, 43). However, the necessity for AMPK acti-
vation to stimulate FA oxidation has recently been called into question by several groups (20, 23, 45), as well as in the present study. For example, incubating muscle with or without palmitate increased AMPK and ACC phosphorylations, although, for unknown reasons, this effect was somewhat greater in the palmitate-treated muscles. Yet, despite the increase in AMPK phosphorylation, palmitate oxidation was unaltered in control muscles and was suppressed by 40–50% in the palmitate-treated muscles [present study and (3)]. Similar observations have also been reported in palmitate-treated L6 myotubes (45). On the other hand, in palmitate + thujone-treated muscles, AMPK phosphorylation was associated with the increase in palmitate oxidation, although the basis for this thujone-mediated effect is not known. Nevertheless, in the present study and others (20, 23, 45), the relationship between AMPK phosphorylation and fatty acid oxidation has been questioned, especially as ACC phosphorylation can be maintained, despite a lack of AMPKα2 activation in muscle (20), heart (18), or hepatocytes (30). In addition, in the present study, the thujone-induced palmitate oxidation was only slightly reduced, when AMPK phosphorylation was inhibited. This observation, as well as others (18, 20, 23, 30, 42, 45), suggest that palmitate oxidation may be regulated in an AMPK-independent manner, by as yet unknown kinases that remain to be identified.

Fatty acid oxidation and insulin sensitivity. Many studies (3, 4, 19, 28, 34) have found a positive association between the increase in palmitate oxidation and insulin-stimulated glucose transport. In the present study, a similar association appeared to be present, as the palmitate-induced reduction and the thujone-stimulated rescue of insulin-stimulated glucose transport were accompanied by concurrent changes in fatty acid oxidation. However, it seems unlikely that thujone-stimulated improvement in palmitate oxidation is the direct cause of improved insulin sensitivity, for the following reason: AMPK inhibitors only inhibited thujone-stimulated fatty acid oxidation slightly, while completely blocking the thujone-mediated rescue of insulin-stimulated glucose transport. We acknowledge that we cannot entirely rule out the possibility that the “AMPK-sensitive” component of fatty acid oxidation was still present and was able to reverse the effects of palmitate-induced insulin resistance. Nevertheless, on balance, our observations would seem to suggest that the restorative action of thujone on insulin-stimulated glucose transport is largely attributed to the activation of AMPK, rather than an increase in fatty acid oxidation.

Conclusion. The present study has shown that thujone, a major component of several medicinal herbs, had an effective insulin-sensitizing action, which rescues insulin-stimulated glucose transport by restoring insulin-stimulated AS160 phosphorylation, which partly normalized insulin-stimulated GLUT4 translocation to the cell surface. In addition, it appears that thujone also enhanced the GLUT4 intrinsic activity. Additionally, thujone completely restores palmitate oxidation. However, this restoration in the rate of palmitate oxidation could not easily be attributed to the activation of AMPK, as inhibition of AMPK phosphorylation provoked only a partial inhibition in palmitate oxidation.

Perspectives and Significance

Selected herbal preparations have the ability to ameliorate or delay the progression of insulin resistance or type 2 diabetes, as these can have hypoglycemic effects. While a similar therapeutic potential is also provided by essential (volatile) oils of herbs and medicinal plants, their mechanism of action remains unknown. Our work has identified thujone, a naturally occurring compound and the main constituent of several medicinal herbs that have antidiabetic properties, as a compound that can improve insulin sensitivity in skeletal muscle. With further study as to its exact mechanism of action and its safety in humans, thujone may in the long term prove to be a low-cost therapeutic agent. Thus, our present findings may be significant in the development of novel therapies.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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