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Influence of Phenolic Constituents from *Yucca schidigera* Bark on Arachidonate Metabolism in Vitro

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Yucca schidigera Roezl. (Agavaceae) has been traditionally used to treat a variety of diseases including arthritis and rheumatism. Phenolic constituents isolated from yucca bark, such as resveratrol, *trans*-3,3′,5,5′-tetrahydroxy-4′-methoxystilbene, and the yuccaols, have been shown to possess various activities in vitro, such as antioxidant, radical scavenging, iNOS expression inhibitory, and platelet aggregation inhibitory effects. In the present study, the influence of a phenolic-rich fraction from yucca bark and of its main phenolic constituents on key enzymes of arachidonate metabolism was investigated. The fraction and the pure phenolics were shown to inhibit COX-1, COX-2, and LTB_4 formation by 5-LOX in vitro to different extents. The degree of COX-1 inhibition was found to be strongly dependent on the substitution pattern of ring B of the stilbenic moiety. The same trend was observed for the COX-2 inhibitory potential, which was, however, in general much lower for the yuccaols as compared with resveratrol. Resveratrol was also the only compound possessing an LTB_4 formation inhibitory activity. The inhibitory activity on key enzymes of arachidonate metabolism observed in this study might contribute to the explanation of the anti-inflammatory and antiplatelet effects observed for *Y. schidigera* and its phenolic constituents.

KEYWORDS: ***Yucca schidigera*; yuccaols; resveratrol; cyclooxygenase; lipoxygenase**

INTRODUCTION

Yucca schidigera Roezl. (Agavaceae) is native to the southwestern United States and Mexico. The plant was used in traditional medicine of the Native Americans against a variety of diseases including arthritis and rheumatism (*1*). Nowadays, from the trunk of the plant (yucca logs) either yucca powder or yucca sap is produced. Yucca extract, which is produced by mechanical squeezing and subsequent evaporation of the sap, is widely used as an additive in food, cosmetics, and pharmaceutics (*2*). Yucca products have GRAS (generally regarded as safe) status and are therefore accepted by the U.S. FDA for use in humans. Yucca powder and extract are also used as animal feed additives due to their beneficial effects in livestock such as increased growth rate and feed conversion efficiency, reduction in atmospheric ammonia, and antiprotozoal and antiarthritic activities (*2*).

The main constituents of the plant are steroidal saponins, which make up around 10% of dry weight, and considerable amounts of phenolic compounds that are enriched in the stem bark. These phenolics comprise the stilbenes resveratrol and *trans*-3,3′,5,5′-tetrahydroxy-4′-methoxystilbene (THMS) as well as the spirobiflavonoid larixinol and a series of unique compounds containing a *spiro* structure named yuccaols A−E (**Figure 1**). In the latter compounds, a C_{15} unit probably derived from a flavonoid skeleton is linked to a C_{14} stilbenic unit (either resveratrol or THMS) via a γ-lactone ring (*1*).

Resveratrol (3,5,4′-trihydroxystilbene) is a phytoalexin, which has been found so far in at least 72 plant species. Its main dietary sources for humans are peanuts, peanut butter, grapes, and wine. The compound is known to possess antioxidant, cardioprotective, anticancer, anti-inflammatory, and phytoestrogenic properties and to interact with various signal transduction pathways (for review, see refs *3* and *4*).

Yucca phenolics were shown to possess antioxidant (*5, 6, 15*) and antiplatelet (*7, 8*) activity. Furthermore, yuccaol C was shown to inhibit the expression of inducible NO synthase (iNOS) by preventing NF-κB activation in vitro, an effect that is thought to contribute to the anti-inflammatory properties attributed to *Y. schidigera* (*9*).

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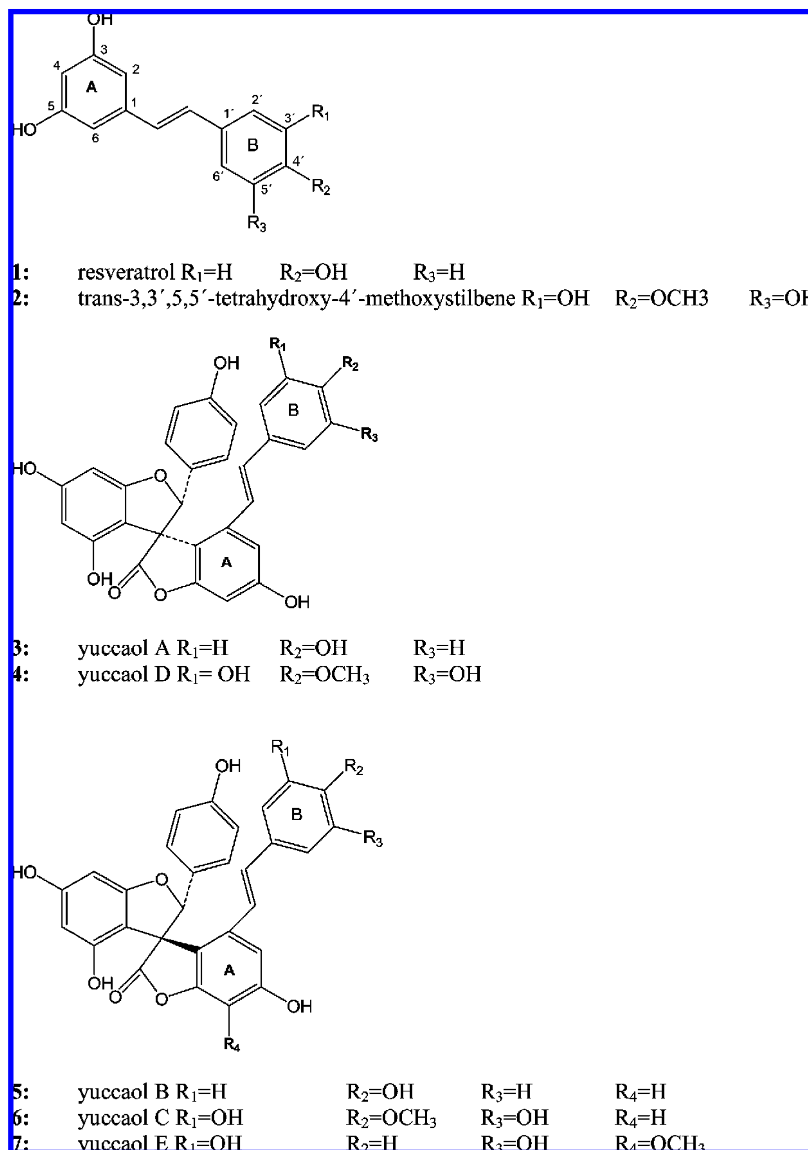

Figure 1. Compounds **1**–**7** from *Y. schidigera* bark.

Cyclooxygenases (COX)-1 and -2 and 5-lipoxygenase (5-LOX) are key enzymes in the metabolism of arachidonic acid. COX isoenzymes catalyze the first step in the production of prostaglandins. These compounds play an important role in many physiological processes such as vascular homeostasis, but they are also important mediators of inflammation. As COX-1 is the constitutive isoform and COX-2 is mainly expressed as a reaction to external stimuli, COX-1-derived prostaglandins have been associated with housekeeping functions. Inhibition of COX-1 has been thought to be responsible for side effects of NSAIDs such as gastrointestinal bleeding, whereas inhibition of COX-2 has been associated with their anti-inflammatory properties. Therefore, selective COX-2 inhibitors have been developed to treat inflammatory disorders (*10*). However, several selective COX-2 inhibitors have been found to cause side effects such as cardiovascular problems (*11*), and it was found that also COX-2 is expressed constitutively in some tissues (*12*). As various COX products also have an impact on vascular homeostasis, inhibition of COX enzymes also influences the cardiovascular system (*10, 13*).

5-LOX catalyzes the first step of the leukotriene pathway of the arachidonic acid cascade. Leukotrienes are potent mediators of inflammatory and allergic reactions. 5-LOX inhibitors are therefore considered to possess therapeutic potential in a range of allergic and inflammatory disorders (*10*).

It has been shown that the anti-inflammatory effects of resveratrol are partly due to an influence on various steps of arachidonate metabolism (*3, 4*). Furthermore, resveratrol, THMS, and yuccaols A and C have been found to inhibit platelet aggregation, and it was postulated that this effect might be mediated by inhibition of prostanoid synthesis (*7, 8*).

The aim of the present study therefore was to investigate the influence of a phenolic-rich fraction from yucca bark and of purified yucca phenolics on arachidonate metabolism by examining their COX-1, COX-2, and LTB_4 formation inhibitory activities in vitro.

MATERIALS AND METHODS

Plant Material. Yucca (*Y. schidigera* Roezl.) bark was obtained from Desert King Int., Chula Vista, CA. A voucher specimen of the material is kept at the Institute Soil Science Plant Cultivation, Pulawy, Poland.

Extraction Procedure and Isolation of Test Compounds. *Extraction.* Powdered yucca bark (10 g) was extracted with 80% MeOH at room temperature. After 72 h, the extract was filtered and the residues were extracted two times with 80% MeOH by boiling for 2 h. The

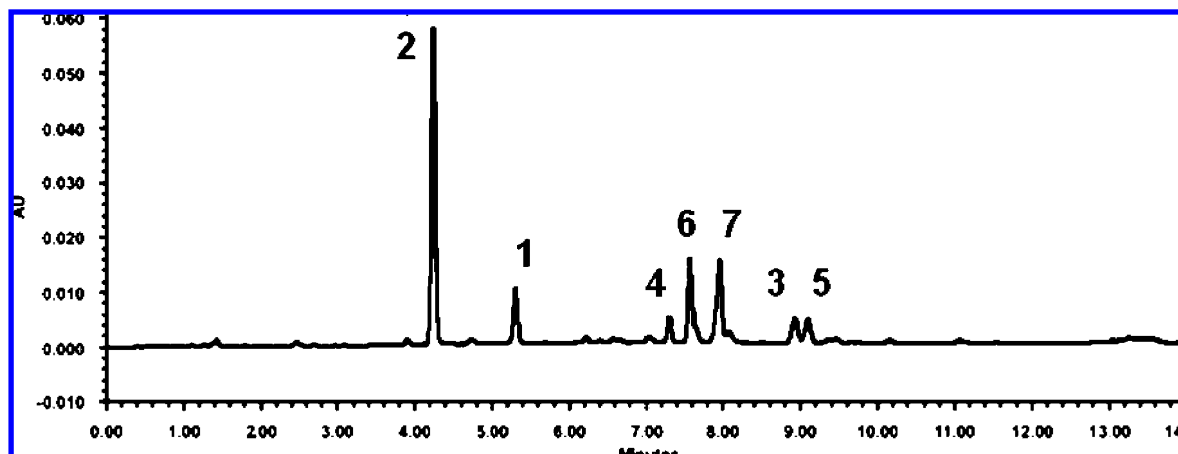

Figure 2. UPLC chromatogram of PRF (**1**, resveratrol; **2**, THMS; **3**, yuccaol A; **4**, yuccaol D; **5**, yuccaol B; **6**, yuccaol C; **7**, yuccaol E).

extracts were combined, and the solvent was removed under reduced pressure (yield = 3.4 g).

Preparation of the Phenolic-Rich Fraction (PRF). The crude extract was suspended in water, and the solution was applied to a 10 cm × 6 cm, 40−63 μm LiChroprep RP-18 (Merck, Warsaw, Poland) preparative column previously preconditioned with water. The column was washed first with water to remove sugars (0.48 g) and then with 40% MeOH to elute the PRF (0.51 g), which was dried in vacuo. This fraction (PRF) was used for in vitro testing, UPLC analysis, and isolation of pure compounds.

Compound Isolation. Compounds **1**−**3**, **5**, and **6** (**Figure 1**) were isolated from PRF as previously described (*14*). For isolation of compounds **4** and **7**, PRF (40 mg) was subjected to semipreparative HPLC on a LiChrosorb RP 18 (7 μm) LiChroCART 250-10 column (Merck, Darmstadt, Germany), using the following gradient: 0−40 min, MeCN/MeOH 4/3: H_2O 37:63; 40−50 min, 37:63−52:48; 50−51 min, 52:58−100:0; 51−60 min, 100:0; 10 min, reequilibration; flow rate, 2.5 mL/min. Fraction 5 (retention time = 19.5 min) yielded 2.5 mg of compound **7**. Fraction 7 (8 mg, retention time = 21.5 min) was further purified on the same column using a mixture of MeCN/tetrahydrofuran 95/5:H_2O 26:74 (50 min, isocratically, flow rate = 2.5 mL/min) as a mobile phase. Fraction 7/3 (retention time = 41.5 min) yielded 2 mg of compound **4**. Structures were verified by comparison of their 1D and 2D NMR data with literature data (*14, 15*).

UPLC-DAD Determination of Phenolics in the Yucca Extract. An Acquity ultraperformance liquid chromatograph (Waters) consisting of binary solvent manager, sample manager, PDA detector, and Empower Pro 2.0 software was used. Chromatographic separation was performed on a 50 mm × 2.1 mm i.d., 1.7 μm, UPLC BEH C_{18} column (Waters) utilizing a mobile phase consisting of 0.1% acetic acid in water (solvent A) and 40% MeCN in 0.1% acetic acid (solvent B) and the following gradient profile: 0−1 min, 80% A (isocratic); 1−3 min, 70% A (linear gradient); 3−7 min, 40% A (linear gradient); 7−8 min, 40% A (isocratic); 8−12 min, 30% A (linear gradient); 12−13 min, 100% B (linear gradient). The column was maintained at 50 °C, and the flow rate was kept constant at 0.35 mL/min. The methanolic solution of 0.1 mg/mL of dried PRF was used for determination of compounds **1**−**7**.

Standard curves for 3,3′,5,5′-tetrahydroxy-4′-methoxystilbene (**2**), resveratrol (**1**), yuccaol C (**6**), yuccaol A (**3**), and yuccaol B (**5**) were prepared for the concentration range of 6.25−100 μg/mL (R^2 ranged between 0.9942 and 0.9984). The concentrations of yuccaols D (**4**) and E (**7**) were determined using the calibration curve of yuccaol C.

In Vitro Assay for COX-1, COX-2, and LTB_4 Formation Inhibitory Activities. COX-1 and COX-2 inhibition assays were performed in a 96-well plate format with purified prostaglandin H synthase (PGHS)-1 from ram seminal vesicles for COX-1 and purified PGHS-2 from sheep placental cotyledons for COX-2 (both Cayman Chemical Co., Ann Arbor, MI) as previously described (*16, 17*). The concentration of PGE_2, the main arachidonic acid metabolite in the reaction, was determined by a competitive PGE_2 EIA kit (Assay Designs Inc., Ann Arbor, MI). Indomethacin (ICN, Aurora, OH; IC_{50} COX-1 = 0.9 μM) and NS-398 (Cayman Chemical Co., IC_{50} COX-2 = 2.6 μM) were used as positive controls.

The bioassay for inhibition of 5-LOX-mediated LTB_4 formation was carried out using stimulated polymorphonuclear leukocytes (PMNLs) with 5-LOX activity in a 96-well plate format as described earlier (*18, 19*). Briefly, PMNLs were isolated from venous human blood based on sedimentation rates and lysis tolerance. The cell suspension (4500 cells/mL) was incubated with the sample, $CaCl_2$, Calcimycin A23187, and arachidonic acid in a shaking water bath at 37 °C. After 10 min, incubation was stopped by the addition of 10% formic acid. After centrifugation, samples were diluted, and the concentration of LTB_4 formed during incubation was determined by means of a competitive LTB_4 EIA kit (Assay Designs Inc.). Zileuton (Sequoia, Oxford, U.K.; IC_{50} = 5.0 μM) was used as positive control.

Test samples were dissolved in absolute ethanol (final ethanol concentrations of 3.5% in the COX assays and 1.9% in the LTB_4 formation assay). Extracts were tested at a final concentration of 50 μg/mL in the assay mixture and pure compounds at 50 μM. Inhibition was expressed in percent in relation to a blank run with absolute ethanol instead of sample. Samples were tested in at least three independent experiments run in duplicate. Results are given as means ± SD.

For IC_{50} determination, active samples were tested in at least three concentrations in at least three independent experiments, each time in duplicate. Calculation of IC_{50} values was performed by semilogarithmic presentation of dose versus activity and logarithmic regression analysis.

RESULTS AND DISCUSSION

PRF was characterized by UPLC analysis, and the main compounds present in the fraction were quantified. The employed UPLC method was very efficient for the analysis of phenolic yucca constituents; the seven major constituents could be baseline separated within 10 min (**Figure 2**). This is a remarkable improvement as compared with the method of Montoro et al. (*20*), which required >40 min for the same separation using a conventional HPLC system. Yuccaols C (**6**) and E (**7**) were found to be the most abundant constituents of the fraction, whereas resveratrol (**1**) was found only at low concentration (**Table 2**). Together, the seven constituents made up about 89% of PRF. Our findings correspond quite well to the results published by Montoro et al. (*20*), except for yuccaol A (**3**), which was less abundant in our fraction, and yuccaol E (**7**), which was more concentrated in our fraction.

In the in vitro assays, PRF showed good inhibitory activity against COX-1 and moderate activity against COX-2 and against LTB_4 formation at the screening concentration of 50 μg/mL assay mixture (**Figure 3**). These findings were confirmed when the IC_{50} values of the extract were determined in the three test systems (**Table 1**).

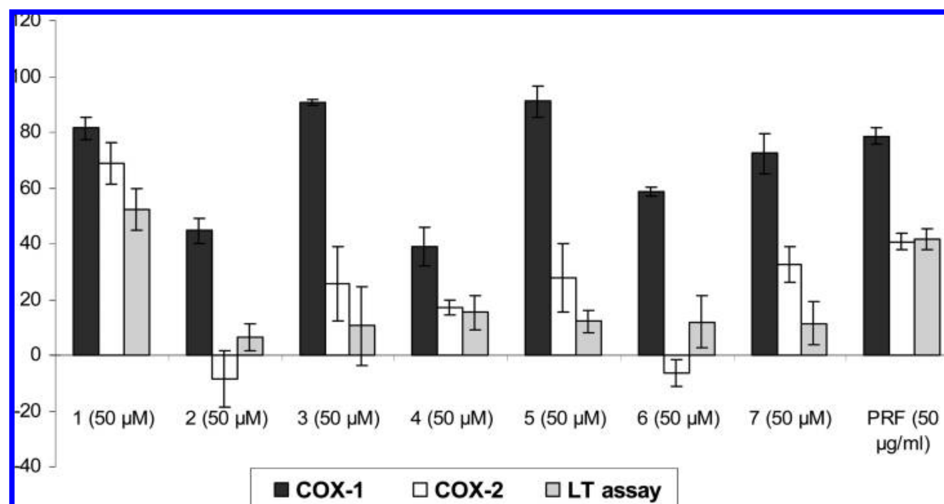

Figure 3. COX-1, COX-2, and LT formation inhibitory activity of *Y. schidigera* constituents **1**−**7** and *Y. schidigera* phenolic-rich fraction (PRF). Results are the means of three independent experiments and are expressed as mean ± SD. Positive controls: COX-1 indomethacin (IC_{50} = 0.9 μM/0.3 μg/mL); COX-2 NS-398 (IC_{50} = 2.6 μM/0.8 μg/mL); LT assay zileuton (IC_{50} = 5.0 μM/1.2 μg/mL).

Table 1. IC_{50} Values of the Phenolic-Rich Fraction (PRF) and of the Main Constituents of PRF

compd	IC_{50} COX-1	IC_{50} COX-2	IC_{50} LT assay
1	11.50 μM	14.6 μM	52.7 μM
2	52.5 μM	>125 μM	>125 μM
3	12.5 μM	75.5 μM	>125 μM
4	87.7 μM	>125 μM	>125 μM
5	10.3 μM	71.5 μM	>125 μM
6	33.8 μM	>125 μM	>125 μM
7	14.2 μM	86.2 μM	>125 μM
extract			
PRF	18.5 μg/mL	65.9 μg/mL	42.2 μg/mL
positive control			
indomethacin	0.9 μM (0.3 μg/mL)		
NS-398		2.6 μM (0.8 μg/mL)	
zileuton			5.0 μM (1.2 μg/mL)

Table 2. Concentrations of the Main Phenolics Present in PRF

compd	concn (mg/g of dry PRF)
1	15.2
2	112.5
3	60.7
4	87.7
5	93.1
6	273.3
7	247.2

Therefore, the COX-1, COX-2, and LTB_4 formation inhibitory activities of compounds **1**−**7**, which had been identified as the main constituents of PRF by UPLC analysis, were investigated. Resveratrol (**1**) exhibited activity in all three test systems (**Figure 3**; **Table 1**). Resveratrol has already been described as an inhibitor of arachidonate metabolism. The compound has been shown to decrease the expression of COX-2 in vitro and in vivo (*21, 22*). Furthermore, resveratrol was shown to target COX enzymes in vitro. The compound was found to discriminate between the two isoforms: In COX-1, both the cyclooxygenase and the hydroperoxidase reaction are inhibited, whereas in COX-2, only the hydroperoxidase but not the cyclooxygenase activity is blocked (*23*−*25*). Concerning the 5-lipoxygenase pathway, resveratrol has been found to inhibit the leukotriene release in stimulated polymorphonuclear leukocytes in vitro (*26*). In the present study, resveratrol inhibited COX-1 and COX-2 to similar extents, showing a slight tendency toward higher COX-1 inhibition. 5-LOX-mediated LTB_4 formation was also moderately inhibited (**Table 1**). These findings are consistent with other data from the literature (*26, 27*).

THMS (**2**), possessing two additional hydroxyl groups in positions 3′ and 5′ and a methoxy instead of a hydroxyl group in position 4′, was much less active against COX-1 than resveratrol and showed no activity at all in the COX-2 and in the LT formation assays. This activity profile does not correlate with the antioxidative and free radical scavenging activity found for these two compounds, as THMS had shown to be a more effective antioxidant and radical scavenging agent than resveratrol (*5, 15*). This finding suggests that different structural features are required for good in vitro antioxidant and anti-inflammatory activity of such compounds.

The activities found for resveratrol and THMS correlate well with the COX-1 inhibitory activities found for the yuccaols: Yuccaols A (**3**) and B (**5**), which contain resveratrol as stilbenic moiety, inhibit COX-1 to about the same extent as resveratrol, whereas this activity is significantly decreased in yuccaols C (**6**) and D (**4**), in which THMS makes up the stilbenic portion. In yuccaol E (**7**), in which THMS is linked to the C_{15} moiety the other way round, only a slight decrease of COX-1 inhibitory activity is found. The configuration of the *spiro* carbon did not significantly influence the COX-1 inhibitory activity of these molecules. These findings indicate that the substitution pattern of ring B of the stilbenic moiety plays a pivotal role for the COX-1 inhibitory activity of the yuccaols: Hydroxylation in position 4′ or in positions 3′ and 5′ of the stilbene moiety allows good inhibitory activity, whereas hydroxylation in positions 5′ and 3′, together with methoxylation in 4′, strongly decreases the activity.

In contrast to COX-1 inhibition, COX-2 inhibitory activity was found to be much lower in all yuccaols as compared with resveratrol. This might be caused by higher sensitivity of this isoenzyme toward the increased molecule size and the decreased flexibility of the stilbenic moiety due to steric hindrance in the yuccaols. The different mechanism of COX-1 and COX-2 inhibition, which has been reported for resveratrol (*23*−*25*), might also be relevant for these compounds. Nevertheless, as observed for COX-1, compounds **3**, **5**, and **7** were somewhat stronger COX-2 inhibitors than compounds **4** and **6**, indicating that the substitution pattern of ring B of the stilbenic moiety also influences COX-2 activity.

Taken together, the selectivity toward COX-1 is obviously increased in the yuccaols as compared with resveratrol. This is also reflected by the activity profile of the extract (PRF), which was shown to contain high amounts of yuccaols and only a low concentration of resveratrol.

None of the yuccaols was found to be active in the LTB_4 formation assay. This activity was shown only by resveratrol (**1**). As the concentration of resveratrol in PRF is rather low (**Table 2**), the LTB_4 formation inhibitory activity observed for PRF cannot be fully explained by the presence of this compound. Obviously, other yet unidentified constituents or synergistic effects contribute to this activity.

Arachidonic acid metabolites are known to play an important role in the regulation of vascular homeostasis: Thromboxane A_2 (TXA_2) is a potent vasoconstrictor and platelet aggregator that is produced in activated platelets, and prostacyclin (PGI_2) is an antiplatelet aggregator and vasodilator produced in endothelial cells. Both mediators are derived from prostaglandin H_2. However, platelets only contain COX-1. This is therefore the isoform responsible for formation of TXA_2, whereas COX-2 can act as a major source of PGI_2 in the endothelium. Selective COX-1 inhibition can therefore lead to cardioprotective effects by shifting the TXA_2/PGI_2 ratio in favor of PGI_2 (*13, 23*). Taking this into consideration, the fact that predominantly COX-1 was inhibited by PRF and its main constituents might contribute to a further elucidation of the inhibitory effect on platelet aggregation which has been observed for yucca phenolics (*7, 8*).

The anti-inflammatory and antiarthritic activities, which are ascribed to *Y. schidigera* due to its use in traditional medicine, have been associated with the in vitro antioxidant and radical scavenging effects as well as the inhibition of iNOS expression observed for yucca phenolics, on the one hand, and with the antiprotozoal activity of yucca saponins, on the other hand (*1, 5, 6, 9, 15*). The inhibitory activity on key enzymes of arachidonate metabolism, which has been observed for PRF as well as for its main constituents in the present study, possibly further contributes to the explanation of the anti-inflammatory activity of *Y. schidigera*. However, it has to be considered that studies existing on the anti-inflammatory activity of yucca phenolics are based on in vitro data. This is also the case for the present work. Concerning pharmacokinetics of these compounds, there exists some evidence that resveratrol is bioavailable at least to a certain degree; however, pharmacokinetics of resveratrol in humans are not yet fully elucidated, and the data existing so far are still inconclusive (*4*). A study in humans investigating the absorption, bioavailability, and metabolism of ^{14}C-resveratrol after oral and intravenous administration came to the conclusion that the compound is readily absorbed after oral administration; however, only trace amounts of the oral dose could be detected in the plasma. Rapid sulfatation and glucuronidation by the intestine and liver seem to limit the systemic bioavailability of resveratrol (*28*). In a study investigating the bioavailability of resveratrol after oral ingestion of grape juice preparations and of the pure aglycone, Meng et al. found that the resveratrol glycosides present in grape juice are absorbed to a lesser extent than the aglycone (*29*). Concerning the bioavailability of yuccaols, no data at all are available in the literature so far.

Therefore, before a statement can be made on a clinically relevant effect of these compounds or a beneficial effect can be derived from the dietary intake of yucca products, the performance of in vivo studies and the investigation of pharmacokinetics of yucca phenolics are required.

In conclusion, it could be shown that PRF from *Y. schidigera* bark and some of its main phenolic constituents are good inhibitors of COX-1 and moderate inhibitors of COX-2 and 5-LOX product formation. The good COX-1 inhibitory activity might play a role in the antiplatelet effect observed for yucca phenolics. Furthermore, the inhibitory activity on enzymes of arachidonate metabolism possibly also contributes to the explanation of the traditional use of yucca products as anti-inflammatory agents. However, in vivo and pharmacokinetic studies with yucca phenolics are needed to obtain more evidence on the therapeutic relevance of this effect.

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