

Review

Open Access

Anti-inflammatory and anti-arthritic effects of *yucca schidigera*: A review

PR Cheeke*^{1,2}, S Piacente³ and W Oleszek⁴

Address: ¹Department of Animal Sciences, Oregon State University, Corvallis, OR 97333, USA, ²Desert King International, 7024 Manya Circle, San Diego, CA 92154, USA, ³Department of Pharmaceutical Sciences, University of Salerno, via Ponte Don Melillo-84084, Fisciano, Salerno, Italy and ⁴Department of Biochemistry, Institute of Soil Science and Plant Cultivation, ul. Czartoryskich 8, 24100 Pulawy, Poland

Email: PR Cheeke* - peter.r.cheeke@oregonstate.edu; S Piacente - piacente@unisa.it; W Oleszek - wo@sybilla.iung.pulawy.pl

* Corresponding author

Published: 29 March 2006

Received: 16 November 2005

Journal of Inflammation 2006, **3**:6 doi:10.1186/1476-9255-3-6

Accepted: 29 March 2006

This article is available from: <http://www.journal-inflammation.com/content/3/1/6>

© 2006 Cheeke et al; licensee BioMed Central Ltd.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

Yucca schidigera is a medicinal plant native to Mexico. According to folk medicine, yucca extracts have anti-arthritic and anti-inflammatory effects. The plant contains several physiologically active phytochemicals. It is a rich source of steroidal saponins, and is used commercially as a saponin source. Saponins have diverse biological effects, including anti-protozoal activity. It has been postulated that saponins may have anti-arthritic properties by suppressing intestinal protozoa which may have a role in joint inflammation. Yucca is also a rich source of polyphenolics, including resveratrol and a number of other stilbenes (yuccaols A, B, C, D and E). These phenolics have anti-inflammatory activity. They are inhibitors of the nuclear transcription factor NFκB. NFκB stimulates synthesis of inducible nitric oxide synthase (iNOS), which causes formation of the inflammatory agent nitric oxide. Yucca phenolics are also anti-oxidants and free-radical scavengers, which may aid in suppressing reactive oxygen species that stimulate inflammatory responses. Based on these findings, further studies on the anti-arthritic effects of *Yucca schidigera* are warranted.

Introduction

Yucca schidigera is an herbaceous plant of the lily family, native to the deserts of the south-western United States and northern Mexico. This plant was used in traditional medicine by Native Americans to treat a variety of ailments including arthritis. Yucca products are currently used in a number of applications. Yucca powder and yucca extract are used as animal feed additives, as discussed in detail by Cheeke and Otero [1]. Beneficial effects in livestock and poultry production include: increased growth rate and improved feed conversion efficiency, reduction in atmospheric ammonia in confinement animal and poultry facilities, anti-protozoal and nematocidal activity, modification of ruminal microbe populations, inhibition of Gram-positive bacteria, reductions in still-

births in swine, reduction in egg and tissue cholesterol contents, and anti-arthritic activity in horses and dogs. Other applications include the use of yucca extract as a foaming agent in beverages, and use in crop production as nematode and fungi-control agents, as a soil wetting agent, and crop growth stimulant. Yucca products have GRAS status, so are FDA-approved for use in humans.

Yucca saponins

Yucca contains a number of phytochemicals which contribute to these effects. The best known are the steroidal saponins. Saponins are natural detergents [2] that form stable foams. Saponins contain a lipophilic nucleus (the sapogenin) and one or more side chains of hydrophilic carbohydrate (Fig. 1). Thus the intact saponin molecule is

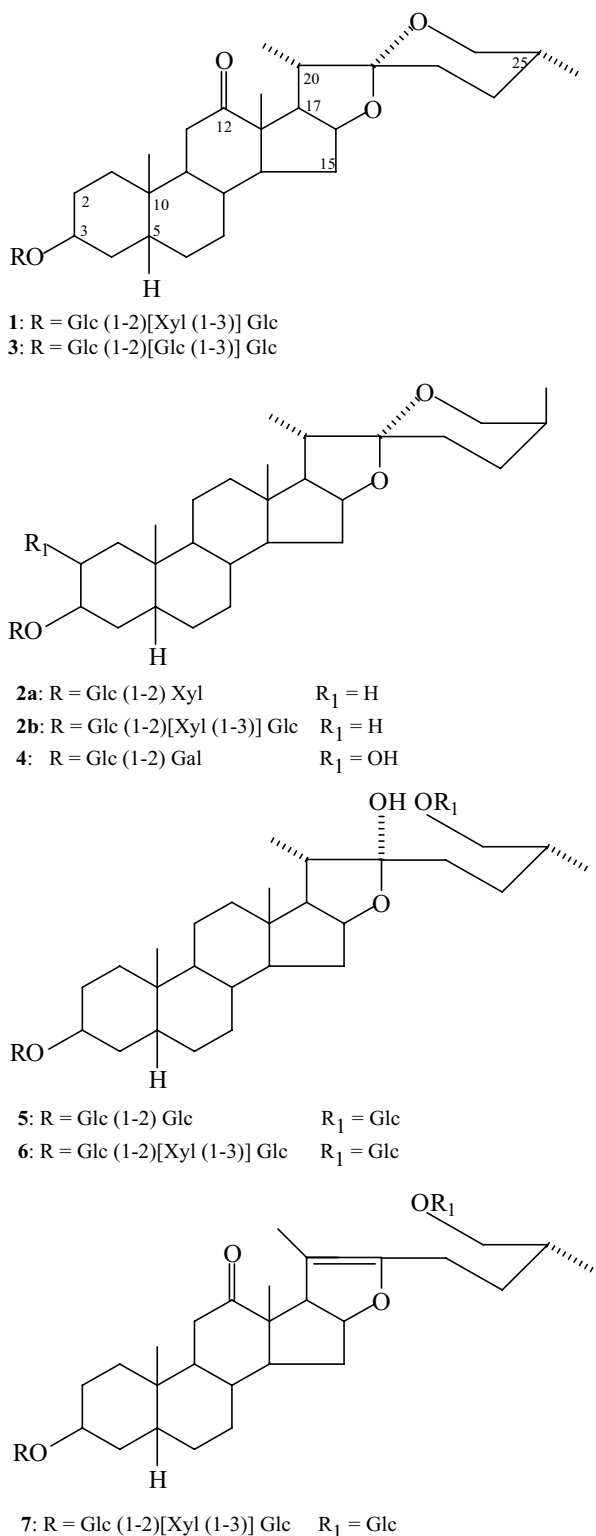


Figure 1
Chemical structures of saponins identified in *Yucca schidigera* bark [17]. Compounds 1–4 represent monodesmosidic and 6–7 bidesmosidic structures.

a surfactant, with both fat-soluble and water-soluble moieties. It has been known for many years [3] that saponins form insoluble complexes with cholesterol. The hydrophobic portion of the saponin (the aglycone or saponogenin) associates (lipophilic bonding) with the hydrophobic sterol nucleus of cholesterol in a stacked micellar aggregation [4].

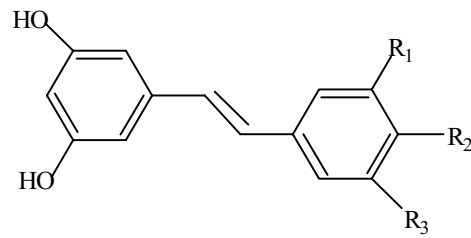


Interactions of saponins with cholesterol and other sterols account for many of their biological effects, particularly those involving membrane activity. It was demonstrated more than 45 years ago that dietary saponin reduces blood cholesterol levels [5,6]. This effect is a result of the saponins binding to cholesterol excreted in bile, thus inhibiting entero-hepatic cholesterol recycling. Dietary yucca extracts lower total and LDL cholesterol levels in hypercholesterolemic humans [7]. Saponins affect the permeability of intestinal cells by forming complexes with cholesterol in mucosal cell membranes [8]. In a similar manner, saponins have anti-protozoal activity by complexing with cholesterol in protozoal cell membranes, causing damage to the integrity of the membrane, and cell lysis. This has been well demonstrated with rumen protozoa *in vivo* [9-11]; and *in vitro* [12,13]. The antiprotozoal (cholesterol-binding) activity requires the intact saponin structure with both nucleus and side chain present.

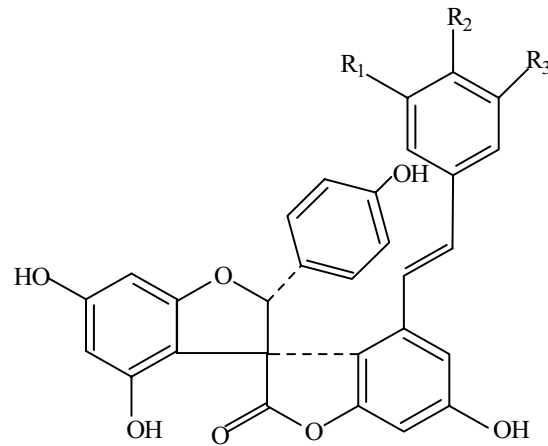
Protozoal diseases in which part of the life cycle occurs in the gastrointestinal tract respond to the anti-protozoal activity of saponins. For example, yucca saponins are as effective as the drug metronidazole in killing trophozoites of *Giardia lamblia* in the intestine [14]. *Yucca schidigera* contains as much as 10% of steroidal saponins in its stem dry matter, making this plant one of the richest commercial sources of saponins. Acid hydrolysed fractions of yucca contain both furostanol and spirostanol aglycones. These include sarsapogenin, markogenin, smilagenin, samogenin, gitogenin and neogitogenin [15]. In the plant they can be found in a multi-component mixture of glycosides [16,17]. They can be found both as monodesmosides with one sugar chain attached at 3-O- and bidesmosides with two sugar chains at 3-O- and 26-O-positions (Fig. 1). Tanaka and co-workers identified as many as 13 structurally different saponins, but all of them were monodesmosides, given trivial names YS-I-XIII [16]. In the work of Oleszek and co-workers, eight individual saponins were isolated and identified out of which five were known spirostanol and three new furostanol structures [17]. However, monodesmosides made up about 93% of total saponins present.

Yucca phenolics

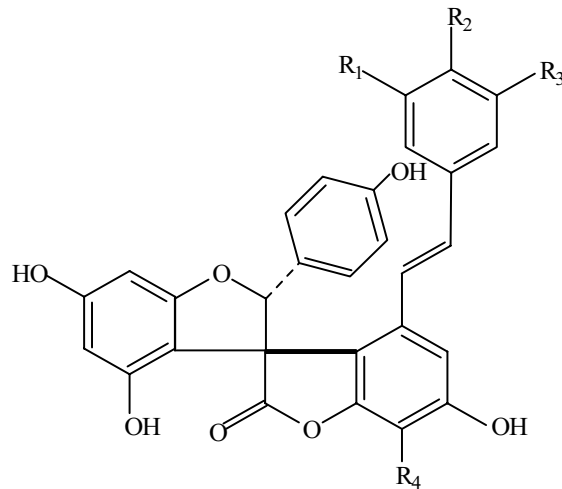
Recently it has been recognized that yucca contains other physiologically-active constituents, particularly polyphenols. Two stilbenes, including trans-3,3',5,5'-tetrahy-



resveratrol	$R_1 = H$	$R_2 = OH$	$R_3 = H$
tetrahydroxymethoxystilbene	$R_1 = OH$	$R_2 = OMe$	$R_3 = OH$



yuccaol A	$R_1 = H$	$R_2 = OH$	$R_3 = H$
yuccaol D	$R_1 = OH$	$R_2 = OMe$	$R_3 = OH$



yuccaol B	$R_1 = H$	$R_2 = OH$	$R_3 = H$	$R_4 = H$
yuccaol C	$R_1 = OH$	$R_2 = OMe$	$R_3 = OH$	$R_4 = H$
yuccaol E	$R_1 = OH$	$R_2 = H$	$R_3 = OH$	$R_4 = OMe$

Figure 2
Structures of yucca phenolics.

Table 1: Concentrations of phenolics in different fractions of yucca [28].

Item	Resveratrol (mg/g)	Yuccaols (mg/g)
Yucca bark	21.7	72.6
Yucca whole plant powder	3.2	10.0
Yucca extract	NP*	NP

*NP = not present.

droxy-4'-methoxystilbene and trans-3,4',5-tetrahydroxystilbene (resveratrol) were identified in yucca bark. Also, some unique compounds with *spiro* confirmation were isolated and characterized. These included the spiroflavonoid, larixinol, biosynthesized by combining two C₁₅ units of flavonoid origin, previously identified in *Larix gmelini* and a number of novel spirostructures, which were given trivial names of yuccaols A-E [18,19] (Fig. 2). These compounds are composed of a C₁₅ unit probably originating from the flavonoid skeleton and a C₁₄ stilbenic compound linked via γ -lactone ring. Resveratrol makes up the stilbenic portion of yuccaols A and B and trans-3,3',5,5'-tetrahydroxy-4'-methoxystilbene is the stilbene in yuccaols C, D and E. By the analogy to the biosynthesis of larixinol it was presumed that most probably these compounds are synthesized by the attachment of the stilbenic derivative to the carbocationic intermediate occurring during the oxidation of flavanone to flavanol and subsequent rearrangement of this intermediate. Resveratrol was identified previously in grapes and is believed to be a phytoalexin produced by the plant to fight fungal colonization [20]. In yucca, this compound as well as its methoxyderivative and yuccaols can be found exclusively in yucca bark (Table 1), which is a dead tissue; it is not clear how these compounds are accumulated in this plant organ. Since yucca bark is a component of commercially available yucca powder, these compounds are present exclusively in this product; they are not present in yucca extract obtained by mechanical extraction.

The chemistry and bioactivity of yucca saponins and phenolics have recently been reviewed by Piacente et al. [21].

Anti-arthritis effects of yucca

Yucca products have been used for many years for reputed anti-arthritis effects, both by Native Americans and more recently by the nutraceutical industry. Whole yucca plant powder in tablet form is a common nutraceutical. The only direct studies of anti-arthritis effects of yucca are those of Bingham [22-24], who reported that symptoms of pain and swelling in arthritic human patients were relieved by consumption of yucca tablets. Bingham's work was reported in an obscure journal, and has apparently not been recognized as valid by the arthritis research community. Nevertheless, Bingham's reports have led to the widespread use of yucca products for treatment and pre-

vention of arthritis not only in humans but also in horses and dogs.

Bingham [22] proposed that yucca saponins have anti-protozoal activity, which suppresses protozoal infection of the intestine. Bingham [22] reported that R. Wyburn-Mason had observed a free-living protozoan, *Naegleria*, universally present in the joints of arthritic patients [25]. Trophozoites of the organism reportedly were found in the intestine. Support for this theory was provided by the effectiveness of metronidazole, an anti-protozoal drug, in arthritis treatment. Saponins are also effective anti-protozoal agents. Yucca saponins are as effective as metronidazole in killing giardia trophozoites in the intestine [14]. Thus, if the protozoal theory of causation of arthritis has any merit, a role of yucca in arthritis treatment can be advanced on the basis of the anti-protozoal activity of yucca saponins.

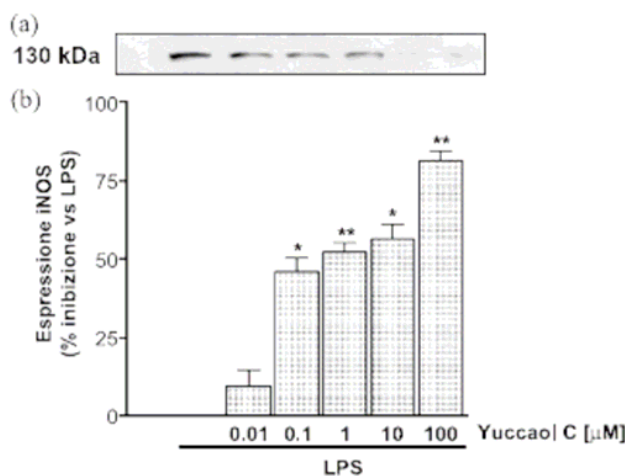


Figure 3

Representative blot of iNOS expression (a). Densitometric analysis of concentration-dependent effect of Yuccaol C (0.01–100 μ M) on LPS-induced iNOS expression in J774.A1 macrophages (b). Yuccaol C was added 1 h before and simultaneously with LPS challenge. Values, mean \pm s.e.m., are expressed as %inhibition of at least 6–9 independent experiments with 3 replicates each. Comparisons were made using one way ANOVA test. *P < 0.05, and **P < 0.01 [34]

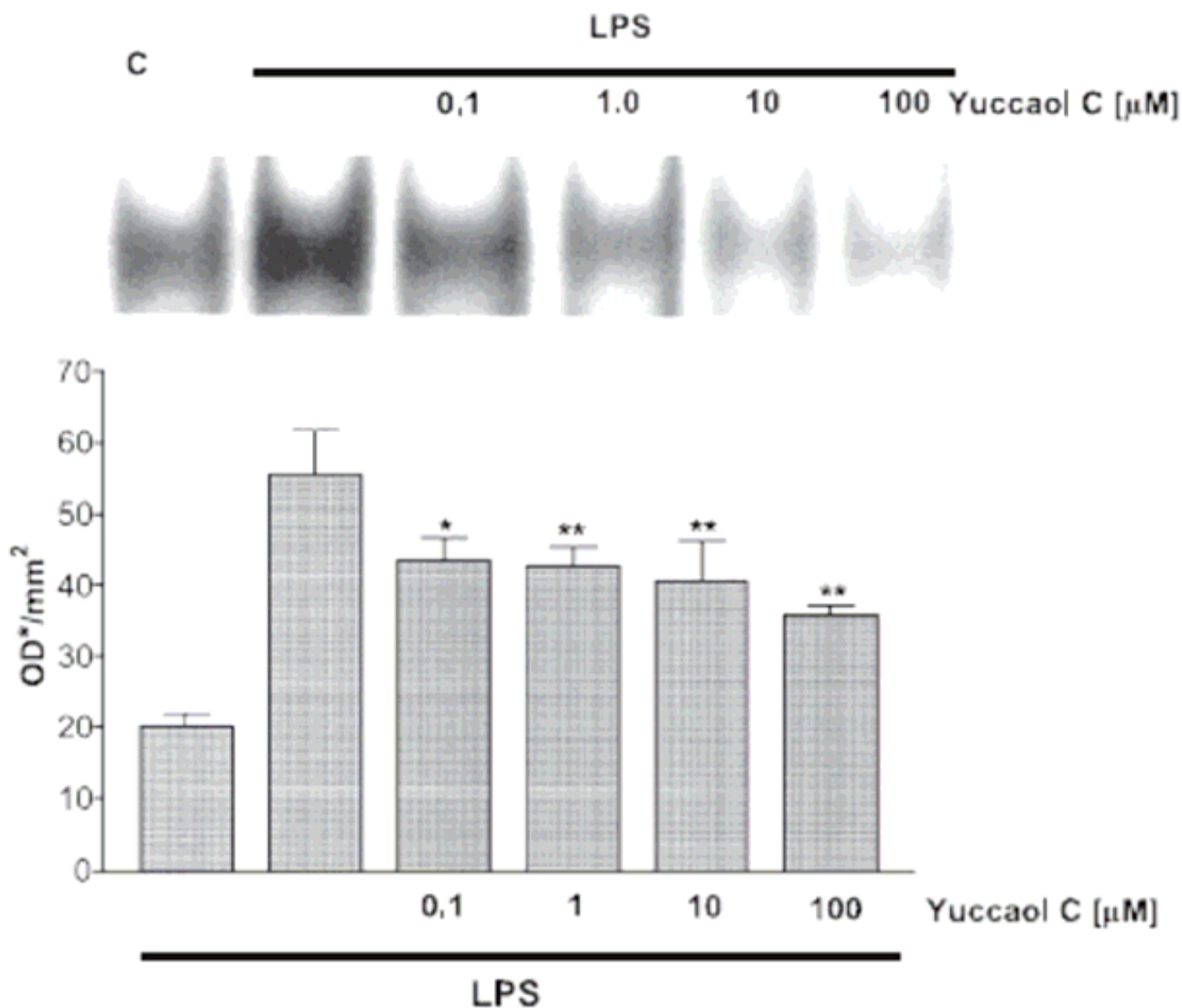


Figure 4
 Effect of yuccaol C (0.01–100 μM) on NF-κB in LPS-stimulated J774.A1 macrophages. Values, mean ± s.e.m., are expressed as optical density/mm² of at least 3 independent experiments with 3 replicates each. Comparisons were performed using one way ANOVA test. *P < 0.05, and **P < 0.01 [34]

There are well-known interactions between rheumatoid arthritis, chronic inflammatory disease, and food and nutrition [26,27]. Of particular importance are nutrients that stimulate the formation of oxidants and peroxides (e.g. unsaturated fatty acids, iron), which promote inflammatory disease, and antioxidants (e.g. vitamin E) and omega-3 fatty acids, which protect against auto-oxidation. Yucca compounds may have roles in these effects. Yucca polyphenols are potent antioxidants [18,21,28]. Yucca saponins are known to reduce iron absorption [29] and may reduce fatty acid absorption by sequestering bile

acids necessary for micelle formation and fat absorption [4].

Cordain [30] stated, "Despite the almost universal clinical observation that inflammation of the gut is frequently associated with inflammation of the joints and vice-versa, the nature of the relationship remains elusive." These authors reported that arthritis is associated with intestinal bacterial overgrowth of *Escherichia coli* and *Lactobacillus lactis*. Yucca saponins have antibacterial properties [31,32], although *Lactobacillus* spp. and *E. coli* may be tol-

erant of yucca extract and yucca saponins [31]. Thus, a beneficial effect of yucca on arthritis could involve anti-protozoal, anti-oxidant and anti-bacterial activities. As previously mentioned, the drug metronidazole attenuates gastrointestinal inflammation and can prevent activation of arthritis in animal models [30]. Yucca saponins are as effective as metronidazole in control of intestinal protozoa [14].

Recent research suggests another possible mode of action of yucca in preventing arthritis by anti-inflammatory activity. Yucca contains anti-inflammatory polyphenolics such as resveratrol and yuccaols A, B, C, D and E [18,19]. Yucca bark and whole yucca plant powder contain resveratrol (Table 1), well known for its anti-inflammatory activity [20,33]. Marzocco [34] demonstrated that yuccaols inhibit inducible nitric oxide synthase (iNOS) expression (Fig. 3). Nitric oxide is an inflammatory agent, and its content in tissues increases during inflammatory responses. The expression of iNOS is controlled by NFκB (NFκB), a transcription factor that regulates gene expression. Resveratrol and yucca phenolics strongly inhibit NFκB [34]. Yuccaol C is particularly effective (Fig. 3 and 4). Thus, whole plant yucca powder has powerful anti-inflammatory activity, mediated via inhibition of NFκB activation.

The generation of reactive oxygen species (free radicals) is an important factor in the development and maintenance of rheumatoid arthritis in humans and animal models [35]. One source of free radicals is nitric oxide produced within the synoviocytes and chondrocytes, giving rise to the highly toxic radical peroxynitrite [35]. The study of experimental arthritis in animals has demonstrated an increased activity of iNOS [36,37]. Thus the NFκB inhibitory and anti-oxidant effects of yucca polyphenolics may aid in prevention of reactive oxygen species (ROS) induction of arthritis by inhibiting the induction of iNOS.

Platelet aggregation is characteristic of inflammation. Yucca phenolics have inhibitory activity against platelet aggregation [38-40]. Yucca phenolics also have antioxidant activity [19] and free-radical scavenging effects [18]. Blood platelets participate in allergic inflammation responses [41]. Yuccaols inhibit the generation of free radicals in blood platelets [39]. One of the yucca phenolics, *trans*-3,3',5,5'-tetrahydroxy-4-methoxystilbene, showed the highest anti-platelet action.

Another botanical product with anti-inflammatory activity is cat's claw [42]. As reviewed by Miller et al. [42], cat's claw (*Uncaria guianensis*) "is a remarkably potent inhibitor of NFκB activity and tumor necrosis factor production." Evaluation of the anti-inflammatory activity of a combination of yucca and cat's claw would be of interest.

The evidence presented in this review indicates that yucca has potential in vivo anti-inflammatory activity, and warrants more in-depth investigation.

Conclusion

Yucca schidigera is a medicinal plant which may have beneficial effects in the prevention and treatment of arthritis. Active components of yucca include steroidal saponins and polyphenolics such as resveratrol and yuccaols. Saponins may have anti-arthritic effects associated with their anti-protozoal activity. Yucca polyphenolics may have several roles in anti-arthritic activity. They inhibit NFκB, a transcription factor which stimulates iNOS, an inducible enzyme which produces the inflammatory agent nitric oxide. Yucca phenolics also are antioxidants and free-radical scavengers, which may aid in suppressing reactive oxygen species (ROS) that stimulate inflammatory responses. Folk medicine and anecdotal reports suggest that whole yucca plant powder aids in prevention and treatment of arthritis. Further studies on the anti-arthritic effects of yucca are warranted.

Competing interests

PRC is a consultant to Desert King International (DKI), a privately-held company which produces and markets yucca extracts and yucca powder as commodities. He has no equity interest in this company. SP and WO have no relationships with DKI.

Authors' contributions

PRC wrote the paper.

SP provided Figures 3 and 4, and the discussion in the paper associated with these figures.

WO provided Figures 1 and 2, and the discussion in the paper associated with these figures. He also developed the collaboration with SP, and collectively they demonstrated the role of yucca phenolics as inhibitors of NFκB and iNOS production.

References

1. Cheeke PR, Otero R: **Yucca, quillaja may have role in animal nutrition.** *Feedstuffs* 2005:11-14 [<http://www.feedstuffs.com/ME2/Default.asp>].
2. Cheeke PR: *Natural Toxicants in Feeds, Forages and Poisonous Plants* Upper Saddle River, NJ: Prentice-Hall; 1998.
3. Lindhal IL, Shalkop WT, Dougherty RV, Thompson CR, Van Atta GR, Bickoff EM, Walter ED, Livingston AG, Guggolz J, Wilson RH, Sideman MB, DeEds F: **Alfalfa saponins: Studies on their chemical, pharmacological and physiological properties in relation to ruminant bloat.** In *USDA Technical Bulletin No. 1161* Washington, D.C; 1957.
4. Oakenfull D, Sidhu GS: **Saponins.** In *Toxicants of Plant Origin Volume 2*. Edited by: Cheeke PR. Boca Raton, Fla: CRC Press; 1989:97-141.
5. Newman HA, Kummerow FA, Scott HH: **Dietary saponin, a factor which may reduce liver and serum cholesterol levels.** *Poult Sci* 1957, **37**:42-46.
6. Griminger P, Fisher H: **Dietary saponin and plasma cholesterol in the chicken.** *Proc Soc Exp Biol Med* 1958, **99**:424-426.

7. Kim S-W, Park S-K, Kang S-I, Kang H-C, Oh H-J, Bae C-Y, Bae D-H: **Hypocholesterolemic property of *Yucca schidigera* and *Quillaja saponaria* extracts in human body.** *Arch Pharm Res* 2003, **26**:1042-1046.
8. Johnson IT, Gee JM, Price KR, Curl C, Fenwick GR: **Influence of saponins on gut permeability and active nutrient transport in vitro.** *J Nutr* 1986, **116**:2270-2277.
9. Lu CD, Jorgensen NA: **Alfalfa saponins affect site and extent of nutrient digestion in ruminants.** *J Nutr* 1987, **117**:919-927.
10. Wallace RJ, Arthaud L, Newbold CJ: **Influence of *Yucca schidigera* extract on ruminal ammonia concentrations and ruminal microorganisms.** *Appl Environ Microbiol* 1994, **60**:1762-1767.
11. Klita PT, Mathison GW, Fenton TW, Hardin RT: **Effects of alfalfa root saponins on digestive function in sheep.** *J Anim Sci* 1996, **74**:1144-1156.
12. Makkar HPS, Sen S, Blummel M, Becker K: **Effects of fractions containing saponins from *Yucca schidigera*, *Quillaja saponaria* and *Acacia auriculoformis* on rumen fermentation.** *J Agric Food Chem* 1998, **46**:4324-4328.
13. Wang Y, McAllister TA, Newbold CJ, Rode LM, Cheeke PR, Cheng K-J: **Effects of *Yucca schidigera* extract on fermentation and degradation of steroidal saponins in the rumen simulation technique (RUSITEC).** *Anim Feed Sci Tech* 1998, **74**:143-153.
14. McAllister TA, Annett CB, Cockwill CL, Olson ME, Yang Y, Cheeke PR: **Studies on the use of *Yucca schidigera* to control giardiasis.** *Vet Parasit* 2001, **97**:85-99.
15. Kaneda N, Nakanishi H, Staba J: **Steroidal constituents of *Yucca schidigera* plants and tissue cultures.** *Phytochemistry* 1987, **26**:1425-1429.
16. Tanaka O, Ikeda T, Ohtani K, Kasai R, Yamasaki K: **Antiyeast steroidal saponins from *Yucca schidigera* (Mohave Yucca), a new anti-food-deteriorating agent.** *J Nat Prod* 2000, **63**:332-338.
17. Oleszek W, Sitek M, Stochmal A, Piacente S, Pizza C, Cheeke P: **Steroidal saponins of *Yucca schidigera* Roezl.** *J Agric Food Chem* 2001, **49**:4392-4396.
18. Oleszek W, Sitek M, Stochmal A, Piacente S, Pizza C, Cheeke P: **Resveratrol and other phenolics from the bark of *Yucca schidigera* Roezl.** *J Agric Food Chem* 2001, **49**:747-752.
19. Piacente S, Montoro P, Oleszek W, Pizza C: ***Yucca schidigera* bark: Phenolic constituents and antioxidant activity.** *J Nat Prod* 2004:882-885.
20. Bertelli AA, Migliori M, Panichi V, Origlia C, Das Filippi DK, Giovannini L: **Resveratrol, a component of wine and grapes, in the prevention of kidney disease.** *Ann NY Acad Sci* 2002, **957**:230-238.
21. Piacente S, Pizza C, Oleszek W: **Saponins and phenolics of *Yucca schidigera* Roezl: Chemistry and bioactivity.** *Phytochem Rev* 2005, **4**:177-190.
22. Bingham R: **New and effective approaches to the prevention and treatment of arthritis.** *J Appl Nutr* 1976, **28**:38-47.
23. Bingham R, Bellow BA, Bellow JG: ***Yucca* plant saponin in the management of arthritis.** *J Appl Nutr* 1975, **27**:45-51.
24. Bingham R, Harris DH, Laga T: ***Yucca* plant saponin in the treatment of hypertension and hypercholesterolemia.** *J Appl Nutr* 1978, **30**:127-136.
25. Wyburn-Mason R: ***Naegleria* in rheumatoid and malignant disease.** *SA Med J* 1983, **63**:31.
26. Parke AL, Parke DV, Jones FA: **Diet and nutrition in rheumatoid arthritis and other chronic inflammatory diseases.** *J Clin Biochem Nutr* 1996, **20**:1-26.
27. Martin RH: **The role of nutrition and diet in rheumatoid arthritis.** *Proc Nutr Soc* 1998, **57**:231-234.
28. Oleszek W, Sitek M, Stochmal A, Cheeke P: **Antioxidant properties of *Yucca schidigera* products.** In *Biologically-active Phytochemicals in Food. Analysis, Metabolism, Bioavailability and Function* Edited by: Pfannhauser W, Fenwick GR, Khokhar S. Royal Society of Chemistry; 2001:303-306.
29. Southon S, Wright AJA, Price KR, Fairweather-Tait SJ, Fenwick GR: **The effect of three types of saponin on iron and zinc absorption from a single meal in the rat.** *Brit J Nutr* 1988, **59**:389-396.
30. Cordain L, Toohey L, Smith MJ, Hickey MS: **Modulation of immune function by dietary lectins in rheumatoid arthritis.** *Brit J Nutr* 2000, **83**:207-217.
31. Katsunuma Y, Nakamura Y, Toyoda A, Minato H: **Effect of *Yucca schidigera* extract and saponins on growth of bacteria isolated from animal intestinal tract.** *Anim Sci* 2000, **71**(2):64-170.
32. Wang Y, McAllister TA, Yanke L-J, Cheeke PR: **Effect of steroidal saponin from *Yucca schidigera* extract on ruminal microbes.** *J Appl Microbiol* 2000, **88**:887-896.
33. Bhat KP, Pezzuto JM: **Cancer chemopreventive activity of resveratrol.** *Ann NY Acad Sci* 2002, **957**:210-229.
34. Marzocco S, Piacente S, Pizza C, Oleszek W, Stochmal A, Pinto A, Sorrentino R, Autore G: **Inhibition of inducible nitric oxide synthase expression by yuccaol C from *Yucca schidigera* roezl.** *Life Sci* 2004, **75**:1491-1501 [<http://www.sciencedirect.com>].
35. Darlington LG, Stone TW: **Antioxidants and fatty acids in the amelioration of rheumatoid arthritis and related disorders.** *Brit J Nutr* 2001, **85**:251-269.
36. McCartney-Francis N, Allen JB, Mixel DE, Xie Q-W, Nathan CF: **Suppression of arthritis by an inhibitor of nitric oxide synthase.** *J Exp Med* 1993, **178**:749-754.
37. Sakurai HG, Kohsaka H, Liu M-F, Higashiyama H, Hirata Y, Kanno K, Saito I, Miyasaka N: **Nitric oxide production and inducible nitric oxide synthase expression in inflammatory arthritides.** *J Clin Investigation* 1995, **96**:2357-2363.
38. Olas B, Wachowicz B, Stochmal A, Oleszek W: **Anti-platelet effects of different phenolic compounds from *Yucca schidigera* roezl. bark.** *Platelets* 2002, **13**:167-173.
39. Olas B, Wachowicz B, Stochmal A, Oleszek W: **Inhibition of oxidative stress in blood platelets by different phenolics from *Yucca schidigera* roezl. bark.** *Nutrition* 2003, **19**:633-640.
40. Olas B, Wachowicz B, Stochmal A, Oleszek W: **Inhibition of blood platelet adhesion and secretion by different phenolics from *Yucca schidigera* Roezl. bark.** *Nutrition* 2005, **21**:199-206.
41. Levy-Toledano S: **Platelet signal transduction pathways: could we organize them into a hierarchy?** *Haemostasis* 1999, **29**:4-15.
42. Miller MJS, Mehta K, Kunte S, Raut V, Gala J, Dhumale R, Shukla A, Tupalli H, Parikh H, Bobrowski P, Chaudhary J: **Early relief of osteoarthritis symptoms with a natural mineral supplement and a herbomineral combination: A randomized controlled trial [ISRCTN38432711].** *J Inflammation* 2005, **2**:11.

Publish with **BioMed Central** and every scientist can read your work free of charge

"BioMed Central will be the most significant development for disseminating the results of biomedical research in our lifetime."

Sir Paul Nurse, Cancer Research UK

Your research papers will be:

- available free of charge to the entire biomedical community
- peer reviewed and published immediately upon acceptance
- cited in PubMed and archived on PubMed Central
- yours — you keep the copyright

Submit your manuscript here:
http://www.biomedcentral.com/info/publishing_adv.asp

