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P. R. Cheeke

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Actual and potential applications of *Yucca schidigera* and *Quillaja saponaria* saponins in human and animal nutrition

P. R. Cheeke

Department of Animal Sciences, Oregon State University, Corvallis 97331

Abstract

Saponins are natural detergents (surfactants) found in a variety of plants. The two major commercial sources of saponins are desert plants: *Yucca schidigera* from Mexico and *Quillaja saponaria* from Chile. Yucca saponins have a steroid nucleus, whereas *Quillaja* saponins are triterpenoid in structure. Saponins contain a lipophylic nucleus (steroid or triterpenoid) and one or more water-soluble carbohydrate side chains. Thus, the surfactant activity is a result of both fat-soluble and water-soluble moieties in the same molecule. There are several current and potential applications of yucca and *Quillaja* products in animal nutrition. Yucca extract is used as a feed additive to reduce ammonia and fecal odors in animal excreta. Saponins, by virtue of their surfactant properties, have antiprotozoal activity. Saponins have membranolytic properties; they complex with cholesterol in protozoal cell membranes, causing cell lysis. They have antibacterial activity and modify ruminal fermentation by suppressing ruminal protozoa and selectively inhibiting some bacteria. Ruminal ammonia concentrations are reduced. Yucca extract is used for prevention and treatment of arthritis in horses, although convincing evidence of its efficacy has not been reported. Saponins influence absorption of lipids, through formation of micelles with bile salts and cholesterol in the intestine. *Quillaja* saponins are used as adjuvants in veterinary vaccines. They are effective in both injected and orally administered vaccines, through saponin effects on cell membranes. There is evidence that oral administration of saponins may stimulate the immune system and increase resistance to a disease challenge. Yucca extract has been shown to reduce neonatal pig mortality when fed to sows in late pregnancy. Thus, dietary saponin sources have several beneficial properties in animal production.

Key Words: Yucca schidigera, Quillaja saponaria, *Saponins, Protozoa, Surfactants*

Introduction

Saponins are natural detergents found in many plants. Saponins have detergent or surfactant properties because they contain both water-soluble and fat-soluble components. They consist of a fat-soluble nucleus, having either a steroid or triterpenoid structure, with one or more side chains of water-soluble carbohydrates (Figure 1). Certain desert plants are especially rich in saponin content. The two major commercial sources of saponins are *Yucca schidigera*, which grows in the arid Mexican desert, and *Quillaja saponaria*, a tree that grows in arid areas of Chile. The actual and potential applications of saponins from these plants in human and animal health and nutrition will be described in this paper.

Production of Yucca and Quillaja Extracts

Yucca schidigera is native to the southwestern United States and Mexico. Currently, most commercial production of yucca products takes place in Mexico. The yucca plants are harvested by Mexican farmers and transported to processing plants. The trunk of the plant (yucca logs) is the part used. The logs are mechanically macerated and either dried and ground to produce 100% yucca powder, or the macerated material is subjected to mechanical squeezing in a press, producing yucca juice. The juice is concentrated by evaporation, with the concentrated product referred to as yucca extract. The term "yucca extract" is slightly misleading, in that the plant juice is removed by mechanical means, rather than by solvent extraction.

Quillaja saponaria is a tree native to Chile. Traditionally, the bark has been used as a source of saponins. Newer processing techniques use the wood as well (San Martin and Briones, 1999). The wood and bark are boiled in large tanks, the water extract is drawn off, and the extract is concentrated by evaporation.

As a consequence of their surface-active or detergent properties, saponins are excellent foaming agents, forming very stable foams. Yucca and *Quillaja* extracts are used in beverages in which a stable foam is desirable. Because of their surfactant properties, they are used industrially in mining and ore separation, preparation of emulsions for photographic films, and in cosmetics such as lipstick and shampoo. Their antifungal and antibacterial properties are also important in cosmetic applications, in addition to their emollient effects. *Quillaja* saponins have even been used in bioremediation of PCB-contaminated soil (Fava and Di Gioia, 1998).

Saponins, Nitrogen Metabolism, and Odor Control

Yucca and *Quillaja* saponin-containing extracts are currently used as dietary additives for livestock and companion animals, primarily for ammonia and odor control. Although the mode of action is not certain, the effects of yucca extract on reducing air ammonia concentrations in livestock buildings are probably not attributable to the saponin components (Killeen et al., 1998a). These authors determined that the

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effects of yucca extract on nitrogen metabolism are caused by the non-butanol-extractable fraction, which contains mainly carbohydrates and has no saponins. The saponin fraction is butanol-extractable. The active ammonia-reducing constituent in yucca extract has not been conclusively identified. Besides carbohydrate components, stilbenes may also be involved. Kong (1998) isolated a urease-inhibiting polyhydroxy stilbene (*trans*-tetrahydroxy-methoxystilbene). Yucca bark is especially rich in stilbenes (Oleszek et al., 1999), which have antioxidant activity. Makkar et al. (1999) reported that yucca extract was more effective than *Quillaja* in binding ammonia.

Effects of yucca extract (**YE**) on nitrogen metabolism include reductions in serum urea and ammonia (Hussain and Cheeke; 1995; Hussain et al., 1996; Killeen et al., 1998a). Killeen et al. (1998a) suggested that non-butanol-extractable YE components may alter kidney function to increase the rate of urea clearance, thus lowering blood urea and ammonia concentrations. In ruminants, feeding YE reduces rumen ammonia concentrations (Wallace et al., 1994; Hristov et al., 1999). As discussed in a following section of this paper, Saponins and Rumen Fermentation, this effect is a consequence of the suppression of ruminal protozoa by saponins.

Reductions in serum urea concentrations in cattle, as noted by Hussain and Cheeke (1995), may have some practical implications, especially in dairy cattle. Milk production and conception rates of dairy cattle can be adversely affected by high blood urea levels (Visek, 1984). The effects on reproduction may be a consequence of elevated ammonia levels in the reproductive tract; an ammonia-induced elevation in pH may reduce motility and survival of sperm. Elrod and Butler (1993) found changes in uterine pH when cows were fed high levels of fermentable protein, increasing blood urea nitrogen (**BUN**). The BUN and milk urea nitrogen (**MUN**) can be monitored to evaluate possible negative impacts of elevated blood urea and ammonia on reproduction of dairy cows (Hof et al., 1997). In Europe, it is widely believed that consumption of spring-grass pasture has adverse effects on reproduction in dairy cows, as a consequence of production of large quantities of ammonia in the rumen, and subsequently high levels of plasma ammonia nitrogen (**PAN**) and BUN (G. Demaegdt, INOBIO, Romilly-sur-Andelle, France, personal communication). It can be speculated that dietary YE fed to cattle on spring-grass pasture may have favorable effects on reproduction by way of reducing ruminal ammonia concentrations. However, Trevaskis and Fulkerson (1999) in Australia found no evidence that high MUN levels are associated with poor reproductive performance in dairy cows grazing tropical grass pastures. Wilson et al. (1998) found no effect of dietary yucca extract on plasma and milk ammonia and urea concentrations.

Recent research (Lowe and Kershaw, 1997; Lowe et al., 1997) has shown that feeding YE to dogs and cats reduces fecal odor, as assessed by a human test panel, and alters the chemical array of fecal volatiles. Several possible modes of action were postulated by these authors, including direct binding of odiferous compounds to some component of the YE. They also noted that addition of YE to dilute aqueous solutions of odiferous compounds such as dimethyl disulfide, dimethyl sulfide, indole, and skatole ameliorated the perception of odor by humans. Killeen et al. (1998a) found that the saponin fraction of YE when fed to rats significantly reduced concentrations of indoles in the hindgut. These effects may be a result of saponin inhibition of microbial fermentation of protein (Killeen et al., 1998b).

Saponins and Ruminal Fermentation

A consistent finding when YE is administered to ruminants is a reduction in ruminal ammonia concentrations (Wallace et al., 1994). A major source of ruminal ammonia is proteolysis of bacterial protein, occurring as a result of ingestion of ruminal bacteria by protozoa. Saponins have pronounced antiprotozoal activity. The mechanism of the antiprotozoal effects is that saponins form irreversible complexes with cholesterol. Cholesterol and other sterols are components of the cell membranes of all organisms except prokaryotes (bacteria). Thus, reductions in ruminal protozoa numbers observed when saponins are fed (Lu and Jorgensen, 1987; Wallace et al., 1994; Klita et al., 1996) and within in vitro ruminal fermentation systems (Makkar et al., 1998; Wang et al., 1998) are caused by reaction of saponins with cholesterol in the protozoal cell membrane, causing breakdown of the membrane, cell lysis, and death. The antiprotozoal activity requires the intact saponin structure with both the nucleus and side chain(s) present. Saponins may have potential as natural ruminal defaunating agents. However, a complicating factor is that saponins are hydrolyzed by ruminal bacteria that remove the carbohydrate side chains (Makkar and Becker, 1997; Wang et al., 1998). Because there may be an adaptation of ruminal bacteria for metabolism of saponins, one approach for retaining antiprotozoal activity would be to feed saponins intermittently. Such a regimen might suppress protozoa, but without the continuous presence of saponins bacterial adaptation might also be suppressed. Thalib et al. (1995) found that administering saponins to sheep every 3 d was effective in suppressing protozoa and reducing ruminal ammonia concentrations. Primarily as a result of suppression of ruminal protozoa, dietary saponins increase the outflow of bacterial protein from the rumen (Wallace et al., 1994; Makkar and Becker, 1996).

Makkar and Becker (1997) observed that quillaja saponins were stable in the rumen for up to 6 h after administration. It is possible that this time period may be adequate for the saponins to have antiprotozoal activity. Thus, the fact that saponins are rapidly degraded in the rumen may not necessarily eliminate their capacity to suppress ruminal protozoa. The practicality of using yucca extract to suppress rumen protozoa has been questioned (Killeen et al., 1998b), because effective concentrations (1,000 to 10,000 mg/L) are much higher than those commonly applied to livestock feeds (60 to 250 mg/kg).

Although the most obvious effect of saponins on ruminal microbes is the suppression of protozoa, there are effects on ruminal bacteria (Wallace et al., 1994). Using pure cultures of ruminal bacteria, Wallace et al. (1994) observed that YE

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stimulated growth of *Prevotella ruminicola*, whereas the growth of *Streptococcus bovis* was suppressed. The antibacterial properties were most pronounced against Gram-positive bacteria, similar to the action of ionophores. It would be interesting to determine whether there is an interaction between saponins and ionophores in ruminal fermentation. Both saponins and ionophores suppress Gram-positive bacteria and protozoa, so synergistic effects would not be surprising. In the antiprotozoal activity, they act via different mechanisms: saponins cause cell lysis by interacting with cholesterol in the protozoal cell membrane, whereas ionophores disrupt ion transport. Ruminal protozoa are unable to adapt to or detoxify saponins (Newbold et al., 1997).

The mode of action of antibacterial effects of saponins seems to involve membranolytic properties, rather than simply altering the surface tension of the extracellular medium (Killeen et al., 1998b). Thus, their inhibitory activity is associated with adsorption to microbes and is, therefore, influenced by microbial population density. Sen et al. (1998) observed a concentration-dependent growth response of *E. coli* K-12 to *Quillaja* and yucca saponins, with growth-promoting activity at low concentrations and inhibition at higher levels. Thus, the impact on a mixed bacterial population such as in the rumen is difficult to predict.

Saponins and Protozoal Diseases

As discussed above, saponins suppress ruminal protozoa by the action of complexing with cholesterol in protozoal cell membranes. Antiprotozoal activity against ruminal protozoa raises the question of whether saponins would be effective against protozoal diseases that afflict humans, livestock, and poultry. Those protozoal diseases in which part of the life cycle occurs in the gastrointestinal tract would be expected to be responsive to antiprotozoal activity of saponins. An example is the disease giardiasis, caused by the protozoan *Giardia lamblia* (also known as *G. duodenalis*). It is one of the most common intestinal pathogens in humans and animals throughout the world (Olson et al., 1995). Yucca saponins are effective in killing the giardia tropozoites in the intestine (McAllister et al., 1998). The effect of saponins on other common livestock protozoal diseases such as coccidiosis is an area that should be investigated.

In horses, various ciliated protozoa cause colitis and diarrhea (Manahan, 1970; Love, 1992; Gregory et al., 1986; French et al., 1996). There may be potential for use of yucca saponins to control protozoal diseases in horses. In the United States, yucca products are used in the horse feed industry to relieve symptoms of arthritis in horses. This use is based on work with humans (Bingham et al., 1975), suggesting that yucca saponins have antiarthritic effects, which Bingham (1976) speculated were due to antiprotozoal activity. Citing evidence from other researchers that protozoa in the intestine may contribute to arthritis, Bingham (1976) suggested "that a reduction in protozoal infestation of patients' intestines may be a yucca extract action." He quotes Roger Wyburn-Mason of England on the "protozoal theory of the cause of rheumatoid arthritis." Bingham (1976) states that "in 1964, Dr. Wyburn-Mason discovered a free living protozoan, an amoeba of the *Naegleria* genus of parasites in cases of active rheumatoid arthritis. It is a very fragile amoeba organism which can live indefinitely in the tissues of its host. He found it in all living tissues in patients with rheumatoid arthritis." Bingham (1976) further states: "Along with treatment using the antiprotozoal drugs it is important to carry out an intensive routine of nutritional vitamin and mineral therapy to help the body restore the damaged joints as much as possible."

These comments are very interesting in view of what we now know about yucca saponins. They are very effective in killing protozoa (Wallace et al., 1994; Klita et al., 1996; Wang et al., 1997, 1998). If the hypothesis of Bingham is correct, then yucca extract may have beneficial effects on arthritis in horses by way of its antiprotozoal activity. As previously discussed, saponins react with cholesterol in protozoal cell membranes, causing the membrane to break down and the protozoal cell to lyse and die.

There are well-known interactions between rheumatoid arthritis, chronic inflammatory disease, and food and nutrition (Parke et al., 1996; Martin , 1998). Of particular importance are nutrients that stimulate 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 (fish oils), which protect against autooxidation. Yucca saponins are known to reduce iron absorption (Southon et al., 1988) and may reduce fatty acid absorption by sequestering bile acids that are necessary for micelle formation and fat absorption (Oakenfull and Sidhu, 1989).

An interesting possibility is that yucca saponins may control the protozoa that cause the fatal disease equine protozoal myeloencephalitis (**EPM**). This disease has been reported from throughout North America (Bentz et al., 1997; Blythe et al., 1997; Saville et al., 1997). The protozoal organism involved has been isolated and named *Sarcocystis neurona* (Dubey et al., 1991). The protozoa invade the tissues of the central nervous system (**CNS**), causing fatal neurologic damage. Horses ingest the protozoal sporocysts in contaminated feed and pasture. The sporocysts sporulate in the intestine, producing sporozoites that enter the intestinal epithelial cells, where they undergo asexual reproduction to produce merozoites. These invade CNS tissue, causing disruption of function and, ultimately, fatal neurologic disease. Clinical signs include weakness, lameness, muscle atrophy, blindness, and seizures. A major source of infection is opossum feces, contaminating feed and pasture (Fenger et al., 1995).

Lending support to the saponin suppression of intestinal protozoa theory is that saponins have been investigated as potential antiprotozoal agents against human disease. Saponin-containing plant extracts have protective activity against the human disease leishmaniasis (McClure and Nolan, 1996), which is second in importance only to malaria among the protozoal diseases of humans. Another significant point is that saponins stimulate the immune system (Maharaj et al., 1986) and produce an array of antigen-specific and nonspecific immune responses (Chavali and Campbell, 1987). Saponins are used as adjuvants in antiprotozoal vac-

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cines (Bomford, 1989). Thus, it is possible that dietary yucca saponins will not only have protective effects against EPM by killing sporozoites in the intestine, but they may also stimulate the immune system to give horses increased resistance against any protozoa that do invade their tissues.

As discussed in a later section (Saponins, Surfactants, and Intestinal Function), saponins increase intestinal permeability by causing microlesions of the intestinal mucosa. It is possible, regarding interactions with gut protozoa, that high doses of saponins could increase the ability of infective protozoal life stages (e.g., sporozoites, tropozoites, and merozoites) to invade the intestinal mucosa. Much research is needed on saponin effects on protozoal diseases.

Cholesterol-Saponin Interactions

It has been known for many years that saponins form insoluble complexes with cholesterol (Lindahl et al., 1957). Saponins form micelles with sterols, such as cholesterol and bile acids. The hydrophobic portion of the saponin (the aglycone or sapogenin) associates (lipophilic bonding) with the hydrophobic sterol nucleus, in a stacked micellar aggregation (Oakenfull and Sidhu, 1989).

Interactions of saponins with cholesterol and other sterols account for many of the biological effects of saponins, particularly those involving membrane activity. Implications of the roles of saponins in reducing blood cholesterol levels in humans will be discussed later. Oakenfull and Sidhu (1989) reviewed the effects of dietary saponins on blood and tissue cholesterol levels in poultry. It was demonstrated over 40 yr ago that dietary saponin reduces blood cholesterol levels in chickens (Newman et al., 1957; Griminger and Fisher, 1958). This effect is likely a result of saponins binding to cholesterol in the bile in the intestine, and preventing its reabsorption. Efforts to reduce egg cholesterol levels by feeding sources of saponins to laying hens have generally not been successful (Nakaue et al., 1980; Sim et al., 1984). The main source of egg cholesterol is endogenous synthesis in the ovary, so reductions in blood cholesterol in laying hens do not result in lowered egg cholesterol.

Dietary saponins also reduce blood cholesterol levels in mammals (Oakenfull and Sidhu, 1989). In livestock species, a possible application might be the use of dietary saponin to reduce meat cholesterol levels. However, because cholesterol in meat is an integral component of muscle cell membranes, it is not likely to be possible to lower meat cholesterol levels by dietary manipulations.

Cholesterol-lowering properties of saponins in humans are of obvious interest. There is little clinical trial information. Bingham et al. (1978) observed a reduction in serum cholesterol levels in human patients receiving yucca tablets for arthritis relief. This seems to be the only study reported in which a saponin product has been given directly to human subjects.

The Masai people of East Africa have low serum cholesterol levels despite a diet rich in animal fat. Chapman et al. (1997) attribute the low cholesterol levels to the Masai diet, in which saponin-rich herbs are added to milk and meat-based soups.

A number of studies, such as those of Malinow et al. (1977), have shown that alfalfa saponins have hypocholesterolemic activity in nonhuman primates. A number of synthetic saponins have been shown to be cholesterol absorption inhibitors (Harwood et al., 1993; Morehouse et al., 1999), causing reduction in plasma non-high-density-lipoprotein cholesterol fractions.

Although it is generally accepted that the principal action of saponins on blood cholesterol is by sequestration of cholesterol and bile acids in the intestine, another possible mode of action is via increased intestinal cell turnover rate. An increased rate of exfoliation of intestinal cells caused by the membranolytic action of saponins could result in increased loss of cell membrane cholesterol contained in the exfoliated cells (Gee and Johnson, 1988; Milgate and Roberts, 1995).

Saponins, Surfactant Activity, and Intestinal Function

Saponins affect the permeability of intestinal cells by forming addition complexes with sterols (e.g., cholesterol) in mucosal cell membranes (Johnson et al., 1986). These authors found that saponins increase the permeability of intestinal mucosal cells, inhibit active nutrient transport, and may facilitate the uptake of substances to which the gut would normally be impermeable. This was confirmed in a more recent study (Gee et al., 1997), in which it was demonstrated that exposure of rats to saponin increased the transmucosal uptake of the milk allergen β-lactoglobulin. Saponin-exposed rats developed antigen-specific antibody responses to administration of ovalbumin (Atkinson et al., 1996), indicating that saponins may increase the sensitivity of animals to dietary antigens. A purified *Quillaja* saponin has effectiveness as an agent to enhance absorption of orally administered drugs (Chao et al., 1998). Saponins from various food sources, such as oats (Onning et al., 1996) and quinoa (Gee et al., 1993), increase intestinal cell permeability. Feeding 0.15% and 0.30% *Quillaja* saponin to rainbow trout caused significant intestinal damage (Bureau et al., 1998).

Saponins, being both fat- and water-soluble, have surfactant and detergent activity. Thus, they would be expected to influence emulsification of fat-soluble substances in the gut, including the formation of mixed micelles containing bile salts, fatty acids, diglycerides, and fat-soluble vitamins.

Saponins form micelle-like aggregates in water (Oakenfull and Sidhu, 1989). They have a critical micelle concentration (**CMC**); below the CMC the molecules remain unassociated and make an abrupt change in physical properties as they make the transition to the micellar state at the CMC. Increased temperature or pH increases the CMC, and increased salt concentration decreases it (Mitra and Dungan, 1997). In the digestion and absorption of fats, both emulsification and micelle formation are involved. Dietary lipids, mainly triglycerides, are emulsified by bile acids in the duodenum. Free fatty acids, released by lipase action, form mixed micelles with bile acids, transporting the fatty acids

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through an aqueous medium to the intestinal mucosal surface for absorption. Saponins would be expected to influence both fat emulsification and micelle formation.

Formation of micelles containing bile acids and saponins has been described by Oakenfull and Sidhu (1989). Bile acids and saponins form a stacked structure with the hydrophobic nuclei stacking together like a pile of coins, with the hydrophilic carbohydrate side chains of the saponin molecules extending out from the interior core. Many hundreds of saponin and bile acid molecules may aggregate in this manner, with the physical characteristic determined by the particular chemical structure of the saponin involved. For example, yucca and *Quillaja* saponins differ in the number of side chains (yucca is monodesmosidal and *Quillaja* saponins are bidesmosidal) and the charged groups (e.g. carboxyl groups) in the side chains.

Saponins act as emulsifiers, stabilizing the oil/water interface (Barla et al., 1979; Oakenfull and Sidhu, 1989). Saponins have a high capacity for solubilizing monoglycerides (Barla et al., 1979). Based on these activities, it can be speculated that dietary saponins could improve fat emulsification and digestion. However, the opposite seems to be true, with several studies finding that dietary saponin reduces fat digestibility. For example, Reshef et al. (1976) found that dietary alfalfa saponins reduced fat digestibility in mice, although there was no effect in quail.

The major effect of saponins on lipid digestibility seems to be exerted via effects on bile acids. Saponins form micelles with bile acids (Oakenfull and Sidhu, 1989), reducing availability of bile acids for formation of micelles with fatty acids. The bioavailability of vitamins A and E may also be reduced by saponins, probably because of sequestration of bile acids (Jenkins and Atwal, 1994).

Primary bile acids are those excreted in the bile, and secondary bile acids are the result of microbial metabolism of primary bile acids. For example, cholic acid is a primary bile acid that is converted to deoxycholic acid by microbial activity in the hindgut. Saponins bind to primary bile acids, protecting them from bacterial action. Thus, with dietary saponin, formation of secondary bile acids is reduced in rats (Oakenfull et al., 1979), in pigs (Topping et al., 1980), and in humans (Potter et al., 1980).

The binding of primary bile acids by saponins may be significant in preventing colon cancer (Rao and Sung, 1995), by reducing their availability to form secondary bile acids via hindgut microbial activity. Secondary bile acids are cytotoxic and tumor-promoting. In addition to the bile acids, saponins also bind to cholesterol and prevent cholesterol oxidation in the colon. Oxidized cholesterol products are promoters of colon cancer (Koratkar and Rao, 1997). Thus, dietary saponins may have beneficial effects against two major human health problems: coronary heart disease (by hypocholesterolemic activity) and colon cancer (by sequestering bile acids).

Digestibility of fats in ruminants is limited by the lack of emulsifying agents in the rumen. Ramirez et al. (1998) investigated whether the inclusion of yucca extract in a high-fat diet for feedlot cattle would improve fat utilization. However, there were no effects on ruminal or postruminal digestion of fatty acids, although there was a tendency toward reduced postruminal digestibility of fatty acids.

Feed grains such as barley, wheat, and oats contain nonstarch polysaccharides (**NSP**) such as β-glucans, which are viscous gums that are poorly water-soluble. They cause a "plugging-up" of the intestinal mucosa in poultry because of their high viscosity. Speculatively, saponins via their surfactant activity might be effective in improving the water-solubility of NSP, improving the feeding value of barley, wheat, and oats for poultry. However, preliminary studies (H. L. Classen, Univ. of Saskatchewan, personal communication; A. Skrede, Agricultural Univ. of Norway, As, personal communication) have not shown an improvement from the feeding of yucca extract with NSP-containing grains.

Yucca saponins are used for their surfactant activity in a commercial product for tempering grains (Salinas et al., 1999). Tempering is a chemically facilitated process by which moisture is added to grains prior to further processing.

Saponins may influence the absorption of minerals and vitamins. Southon et al. (1988) found that saponins reduce iron absorption in rats. They suggested that the mode of action involves an effect on iron transport into or across the mucosal cell, rather than a chemical binding of iron to saponin in the intestinal lumen. Formation of mineral-saponin complexes in vitro was reported by West et al. (1978), including complexes with iron. Presumably, saponin structure, with functionalities such as carboxyl groups, would influence metal binding capacities of saponins.

Effects of saponins on vitamin metabolism might be anticipated. For example, by binding bile acids, saponins impair micelle formation in the intestine. Fat-soluble vitamins form mixed micelles, necessary for their absorption. Lowered plasma and liver concentrations of vitamins A and E have been noted in chicks fed fairly high levels (0.9%) of *Quillaja* saponin (Jenkins and Atwal, 1994). Vitamin D is a sterol similar to cholesterol in structure. However, Birk and Peri (1980) found that two forms of vitamin D, ergosterol and cholecalciferol, did not precipitate with alfalfa triterpenoid saponins.

Saponins and the Immune System

Saponins are of interest in terms of their effects on the immune system and their applications in vaccines. Saponins have the following implications in immunology: 1) *Quillaja* saponins are widely used as adjuvants in oral and injected vaccines, 2) saponins improve the effectiveness of orally administered vaccines by facilitating the absorption of large molecules, and 3) oral administration of saponins increases the resistance of animals to a disease challenge, suggesting that saponins have immunostimulatory effects. These properties will be briefly discussed.

Quillaja saponins have been used for many years as veterinary vaccine adjuvants (adjuvants are substances that improve the effectiveness of a vaccine). Their adjuvant activity was first reported many years ago by French scientists (Thibault and Richou, 1936), and they have subsequently

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been widely employed in veterinary vaccines, especially those for foot-and-mouth disease (Dalsgaard, 1978). The saponin adjuvants most widely used are a type called Quil A, which is a purified *Quillaja saponaria* saponin fraction (Dalsgaard, 1978). Quil A has been used to prepare an immunostimulating complex (**ISCOM**). The ISCOM are prepared by solubilizing viral proteins in detergent, removing the detergent and adding Quil A. The resulting structure is a micelle, with Quil A saponin surrounded by a layer of viral protein (Morein et al, 1987). Apparently the mode of action of ISCOM involves binding of the Quil A saponin to cholesterol in membranes of macrophages or antigen-presenting cells of the immune system, facilitating uptake of the complex by the cells (Bomford, 1988). The ISCOM have been evaluated against a number of viruses, including feline leukemia virus (Osterhaus et al., 1985) and HIV (Wu et al., 1992). The Quil A saponin fraction has been further purified to increase its adjuvant potentials while minimizing side effects (Kensil et al., 1991). These purified *Quillaja* saponins generate increased immune responses by upregulating T-helper (Th-1 and Th-2) cells (Sjolander et al., 1997), as well as potentiating antigen-specific antibody responses. One of these purified *Quillaja* saponins is currently undergoing human clinical trials as a component of an influenza vaccine (Sjolander et al., 1997). Fractionation of the saponin components has shown that the immune responses generated by ISCOM can be manipulated by altering the triterpenoid saponin composition and that the triterpenoids can determine whether a T-Helper cell response occurs (Dotsika et al., 1997).

Saponins are particularly effective as adjuvants in antiprotozoal vaccines (Bomford, 1989). This is of interest because of the direct antiprotozoal activity of saponins in the gut. Saponins could thus be used in a two-pronged attack on pathogenic protozoa. This would seem to be a very promising area for further research.

In a study of *Quillaja* saponin as an adjuvant for a rabies vaccine, Chavali and Campbell (1987) noted that dietary administration of saponin increased the subsequent resistance of mice to a challenge of rabies virus. The enhanced resistance to viral infection was induced by promotion of nonspecific immune functions. One mode of action includes increased permeability of the intestinal mucosa, allowing increased uptake of viral antigen (Maharaj et al., 1986). The natural killer cell activity in mice fed *Quillaja* saponin alone was greatly enhanced and persisted for an extended period of time (Chavali and Campbell, 1987).

Saponins increase the effectiveness of oral vaccines by altering the permeability of the intestinal mucosa. Johnson et al. (1986) determined that some saponins increase the permeability of intestinal mucosal cells, facilitating the uptake of substances to which the gut would normally be impermeable. They proposed that saponins react with cholesterol in the membranes of the microvilli, causing structural lesions, a phenomenon that has subsequently been demonstrated (Gee et al., 1997). It should also be acknowledged that this effect of saponins could have negative consequences. Increased gut permeability to large molecules could increase the risk of sensitization to dietary antigens that would not normally be absorbed. Saponins also cause depolarization of intestinal membranes, altering permeability (Oleszek et al., 1994). Similar effects have been noted with oat saponins (Onning et al, 1996).

The involvement of saponins with the immune system could have numerous practical applications. One area of interest would be to determine whether administration of saponins to baby pigs could increase the passive immunization response by facilitating absorption of maternal antibodies by the young animal. The direct immunostimulatory effects noted with mice challenged with rabies virus suggest that feeding saponin to pigs and poultry under confinement conditions could be a means of enhancing resistance to disease. As Sjolander and Cox (1998) have pointed out, it is important to note that the only data on immune stimulation by saponins have been obtained with mice; there is a definite need for more research with livestock species.

Stillbirths in Swine

Cline et al. (1996) found that feeding a yucca extract-containing commercial feed additive to sows prior to farrowing resulted in a significant reduction in numbers of pigs born dead (stillbirths). Blood oxygen levels were higher in piglets at birth from sows fed the yucca extract. Cline et al. (1996) suggested that the reduction in stillbirths was a result of improved blood oxygen supply to the fetuses during birth. Preweaning mortality was also reduced. Piglets suffering from oxygen deprivation during birth are less viable and more likely to succumb to stress of postuterine life (Herpin et al., 1996). The results of Cline et al. (1996) were later confirmed (Herpin, unpublished observations), observing that dietary inclusion of whole yucca plant powder in sow diets caused a reduction in stillbirths and increased viability of neonatal pigs. However, there were no differences in blood oxygenation between control and yucca-fed pigs. Litters with stillbirths have a higher preweaning mortality than litters without stillbirths (Leenhouwers et al., 1999). The number of litters with no stillbirths was greater with the yucca treatment than in the control group (Herpin, unpublished observations).

Implications

Saponin-containing yucca extracts are currently used in the feed industry for control of ammonia and odor. The active components in this function are probably carbohydrates, rather than saponins. Specific roles of saponins in yucca and *Quillaja* products may involve modification of gut microbes, particularly in ruminants. Saponins suppress ruminal protozoa by binding to cholesterol in the protozoal cell membrane, causing the organism to lyse and die. Saponins inhibit Gram-positive bacteria and have antifungal properties. Antiprotozoal activity against pathogenic protozoa such as giardia by saponins has been observed. *Quillaja* saponins are used as adjuvants in vaccines, and when used as dietary additives they have immunostimulatory properties. When used as feed additives, saponins have multifaceted beneficial properties.

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Notes

1. Correspondence: phone (541)737-1917; FAX (541)737-4174; E-mail Peter.R.Cheeke@orst.edu.

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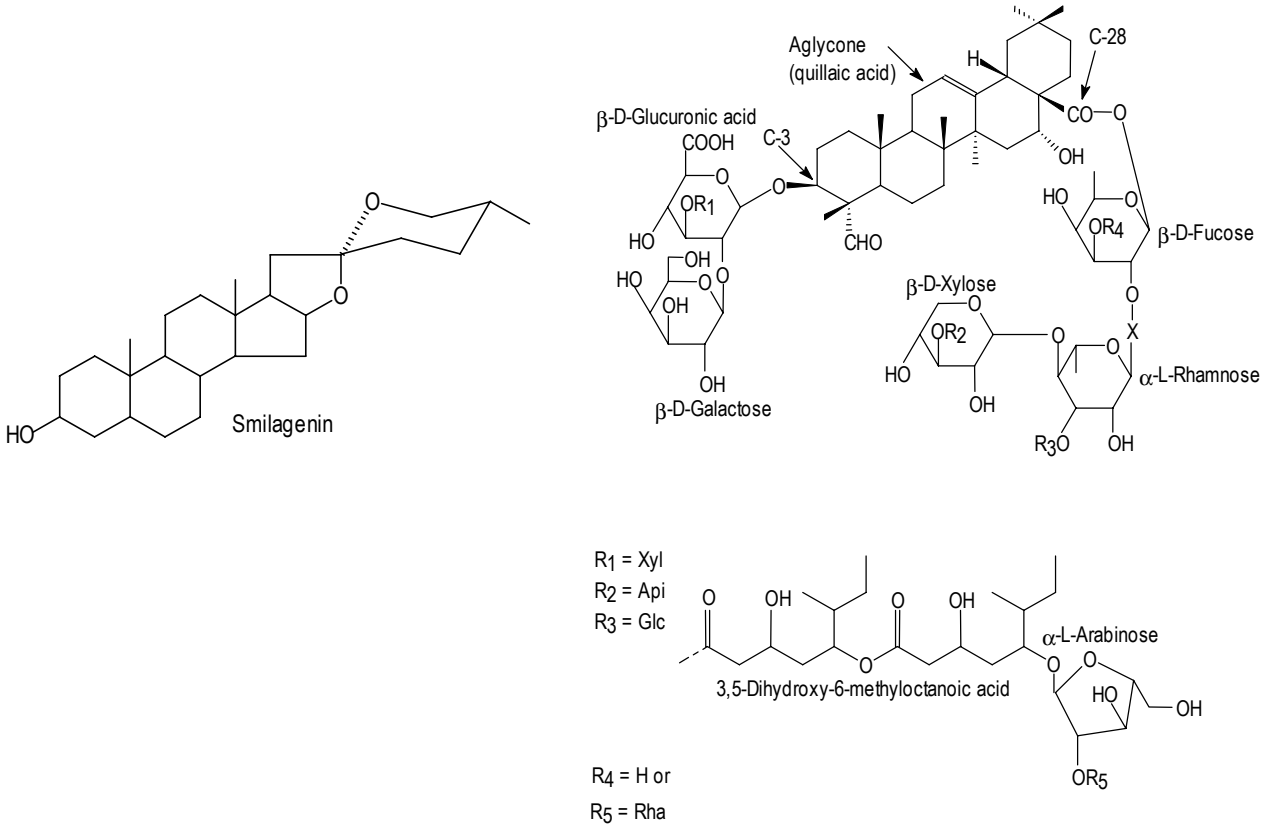

Figure 1. Structures of yucca (left) and quillaja (right) saponins, showing the steroidal (yucca) and triterpenoid (quillaja) sapogenin nuclei, and the bidesmosidal (two carbohydrate side chain) nature of quillaja saponins. The side chain on the yucca saponin is attached to the hydroxyl group.

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