Ethnoveterinary Medicine: The Science of Botanicals in Equine Health and Disease[i]

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Introduction

"Botanicals as medicine" is not a novel concept. For the entire breadth of human culture we have used plants as our major resource for health-promoting substances, and even in contemporary society plants still offer our most valuable reservoir of new drugs. What is relatively new, however, is the ready and largely uninformed access that the horse industry has to herbal products. Though not without its benefits, this herbal revolution has faded the line between "feed" and "drug", and leaves both horse owners and veterinarians confused about the distinction between husbandry and health care. Fundamental issues of dose, efficacy, and safety are, at best, left to an educated guess and, at worst, completely ignored. Even for those wading through the scientific literature for basic and applied research, animal-based research on many herbs is difficult to come by, and research on herbs for horses is virtually non-existent.

Over the past 6 years our research laboratory has worked to generate new data on herbs for a wide variety of horse health issues, including immune function, respiratory disease, osteoarthritis, and dermatitis. Our research on Echinacea, ginseng, flaxseed, garlic and polyherbal composites has resulted in an unprecedented collection of new information on how herbs can benefit – or harm – horses. We have utilized many scientific tools familiar to pharmaceutical development and assessment to characterize the potential application of herbs to equine health. Results from these studies can provide a new basis for the utility of herbs in equine health and disease.

Material and methods

Herbs in immune function

Cellular immunity: a double-blind, placebo controlled, cross-over trial investigated the effect of Echinacea (*Echinacea angustifolia*) extract on eight healthy horses. Four animals were supplemented with standardized Echinacea extract (4% echinacoside) or placebo (USB sucrose solution) for 42 days in a cross-over manner with a 2 week washout in between. Blood was sampled weekly and screened for changes in basic haematology and biochemistry. In addition, neutrophils were isolated on a percoll gradient, and their ability to consume foreign particles was determined quantitatively by "feeding" them yeast particles.

Humoral immunity: a double-blind, placebo controlled, parallel trial investigated the effect of ginseng (*Panax quinquefolium*) extract on ten healthy horses with current vaccinations to Rhinopneumonitis. Five horses received ground ginseng once per day in their morning grain ration in a molasses/bread bolus carrier (35mg ginseng per kg body weight per day), and five received placebo (blank molasses/bread carrier) once daily in their morning grain ration for 28 days. On Day 14 all horses were vaccinated with Rhinopneumonitus vaccine (Pneumabort-K® +1b). Blood was sampled on days 0, 7, 14, 15, 16, 17, 18, 19, 20, 21, and 28 and analyzed for antigen-specific antibody concentration (serum neutralization). On days 0, 7, 14, and 21, blood was also analyzed for lymphocyte profile (flow cytometry), and changes in basic haematology and biochemistry parameters.

Herbs in respiratory disease

A double-blind, placebo controlled, cross-over trial investigated the effect of a polyherbal composite ("Breathe"; Selected Bioproducts, Guelph, Ontario, Canada) (Table 1) on six horses with naturally occurring, symptomatic COPD. Horses were housed indoors under typical management conditions for the duration of the trial. Three animals were supplemented with Breathe (1/2 cup twice daily) or placebo (equal weight of chopped alfalfa) for 21 days in a cross-over manner with a 2

week washout in between. Pulmonary microflora (tracheal lavage followed by cytospin and light microscopy quantitation) and esophageal pressure (ventigraph) were assessed on days 0, 7, 14 and 21. Blood was also analyzed for changes in basic hematology and biochemistry on days 0 and 21.

Table 1: Composition of "Breathe" herbal supplement

Common Name	Botanical Name
Garlic	*Allium sativum*
Boneset	*Eupatorium perfoliatum*
White Horehound	*Marrubium vulgare*
Black Elder	*Sambucus nigra*
Hyssop	*Hyssopus officinalis*

Herbs in osteoarthritis

A double-blind, placebo controlled, cross-over trial investigated the effect of a polyherbal composite ("Mobility"; Selected Bioproducts, Guelph, Ontario, Canada) (Table 2) on six horses with naturally occurring osteoarthritis. Three animals were supplemented with Mobility (1/2 cup twice daily) or placebo (equal weight of chopped alfalfa) for 28 days in a cross-over manner with a 2 week washout in between. Blood was sampled on days 0, 14 and 28 for serum concentration of glycosaminoglycans (GAGs) (dimethylmethylene blue – DMMB – assay). Changes in basic haematology and biochemistry were assessed on days 0 and 28. Synovial fluid was collected from the arthritic joint and corresponding opposite joint on days 0, 14 and 28, and analyzed for GAG (DMMB assay), hyaluronic acid (Alcian blue spectrophotometric assay) and prostaglandin E_2 (ELISA).

Table 2: Composition of "Mobility" herbal supplement

Common Name	Botanical Name
Dandelion	*Taraxacum officinalis*
Devil's Claw	*Harpagophytum procumbens*
Comfrey	*Symphytum officinalis*
Burdock	*Arctium lappa*
Stinging Nettle	*Urtica dioica*

Herbs in dermatitis

A double-blind, placebo controlled, cross-over trial investigated the effect of flaxseed (*Linum usitatissimum*) on six horses with naturally occurring "Sweet Itch", as determined by positive skin skin test to extract of *Culicoides*. Three animals were supplemented with flaxseed (1 lb per 1000 lb BW daily) or placebo (equal weight of wheat bran) for 42 days in a cross-over manner with a 2 week washout in between. Skin test challenges with *Culicoides* extract were conducted on days 0, 21 and 42. On the same days, blood was sampled for assessment of changes in basic haematology and biochemistry. A 6mm punch biopsy of skin and a mane-hair sample were taken for fatty acid analysis.

Toxicity of herbs

A chronic toxicity trial was conducted on four healthy horses in a randomized, placebo controlled manner. Two horses were supplemented with garlic (*Allium sativum*), as part of their normal grain ration, at gradually increasing doses up to maximum voluntary intake (5 cups freeze-dried garlic twice daily in molasses). Control horses received only molasses in their grain ration. Blood was sampled weekly for changes in basic haematology and biochemistry, and for evidence of oxidative damage to red blood cells (Heinz bodies). Duration of supplementation was 71 days. Blood was sampled weekly for a further five weeks to monitor time required for horses to return to baseline values after removal of garlic from the diet.

Results

Herbs in Immune Function

Cellular Immunity: Treatment with Echinacea increased phagocytic ability of isolated macrophages, elevated peripheral lymphocyte counts, and appeared to stimulate neutrophil migration from peripheral circulation into tissue. Echinacea supplement also increased peripheral red blood cell count, size of red blood cells, concentration of haemoglobin, and haematocrit. No adverse effects were identified through haematology and biochemistry screens (O'Neill et al., 2002a).

Humoral Immunity: Treatment with ginseng did not have statistically significant effect on immunological response to routine vaccination against rhinopneumonitis, though a trend to increased antibody response was noted (Figure 1). No adverse effects were identified through haematology and biochemistry screens (O'Neill et al., 2002b).

Herbs in Respiratory Disease

Treatment of COPD horses with Breathe resulted in a significant decline in respiratory rate (Figure 2) compared with control. This change was significant on day 7 and remained significant through day 21 ($p<0.05$). No significant changes were identified in pleural pressure, though a trend to a decrease was noted. No adverse effects were evident through haematology and biochemistry screens (Pearson unpublished).

Herbs in Osteoarthritis

Treatment of osteoarthritic horses with Mobility resulted in a decline in PGE_2 production (Figure 3). The difference between treatment and control was significant by day 28 ($p<0.05$). There was a trend to increase in GAG in synovial fluid and serum, though this did not reach significance ($p>0.05$). No changes were observed in hyaluronic acid concentration of synovial fluid. No adverse effects were identified through haematology and biochemistry screens (Pearson et al., 1999).

Herbs in dermatitis

Flaxseed supplementation resulted in a significant reduction in the area of the lesion caused by subcutaneous culicoides extract injection in treatment horses compared with control on day 42 ($p<0.05$). There was a significant increase in serum glucose across the duration of the study, and AST was lower in treatment horses on day 21 ($p<0.05$). Fatty acid profile of the hair of treatment horses differed on day 42 compared with control, due to a significantly higher concentration of lignoceric acid (C24:0) in treatment horses. No adverse effects were identified through biochemistry and haematology screens (O'Neill et al., 2002c).

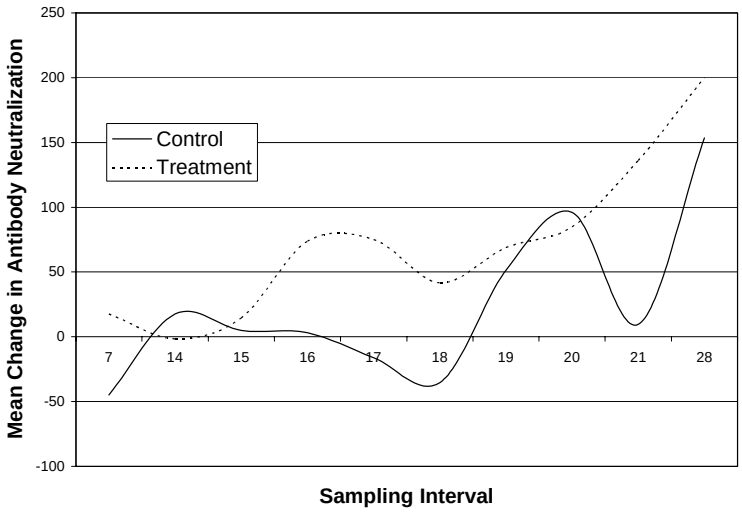

Figure 1: *change in post-vaccination antigen-specific antibody titre. Changes were not statistically significant ($p>0.05$). (O'Neill et al., 2002b)*

Figure 1: Standardized Breathing Rates (Breaths/min)

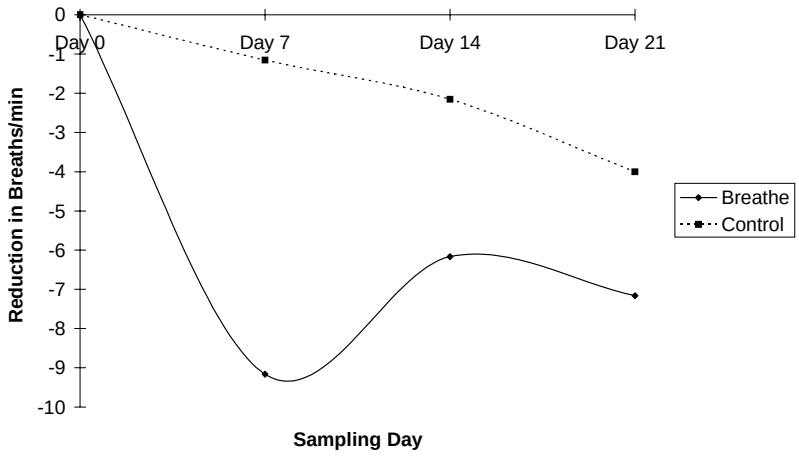

***Figure 2**: changes in respiratory rate (breaths/min). Changes in treatment horses were statistically different from control horses from days 7 through 21 ($p<0.05$). (Pearson, unpublished)*

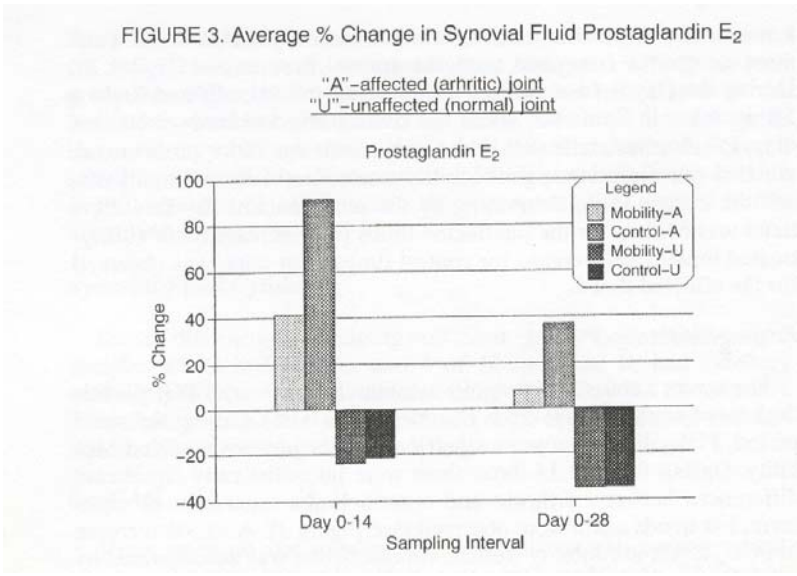

***Figure 3**: % change in prostaglandin E_2 production. Changes in treatment horses were statistically different from control on day 28 ($p<0.05$). (Pearson et al., 1999).*

Toxicity of herbs

Chronic supplementation with garlic at maximum voluntary intake resulted in Heinz body anemia, as characterized by reduced red blood cell count (Figure 4), free haemoglobin, hematocrit, and haptoglobin; and increased free bilirubin, mean red cell volume, mean red cell haemoglobin, platelets and incidence of Heinz bodies. Recovery from anemia was largely complete within 4 weeks after removal of garlic from the diet (Pearson et al., 2004).

Discussion

This series of experiments demonstrates that herbs can play an important role in maintaining health of horses through improved immune function. Studies on immunomodulation show that cellular immunity of horses can be stimulated through supplementation with Echinacea. The ability of Echinacea to stimulate isolated neutrophils to consume foreign particles has been reported previously (Melchart et al., 1995; Roesler et al., 1991), but this is the first time this result has been demonstrated in horses. Though our data on the equine humoral response to vaccination in the presence of ginseng supplementation is less compelling, it does provide some rationale for further research into this application. Further studies should employ an immunologically naive sample set, which would control for variability in response to the vaccination and may enhance differences seen between treatment and control horses.

In addition to maintaining health, our data suggest that herbs can also be used to treat symptoms of chronic equine diseases. Respiratory disease is of significant concern in the equine industry, and accounts for a significant burden on the racing industry (Rossdale et al., 1985). As research has not yet found a cure for COPD, treatment is targeted at alleviation of symptoms. Herbs have been used with some success in treating chronic respiratory disease in horses (Sommer et al., 1986) and other species (Aqel 1991), and our data support this application. An increase in respiratory rate is a fundamental symptom of COPD caused by combination of constricted airways, accumulated mucous, and smooth muscle spasms. A reduction of the resting respiratory rate may reflect improvement in any one or

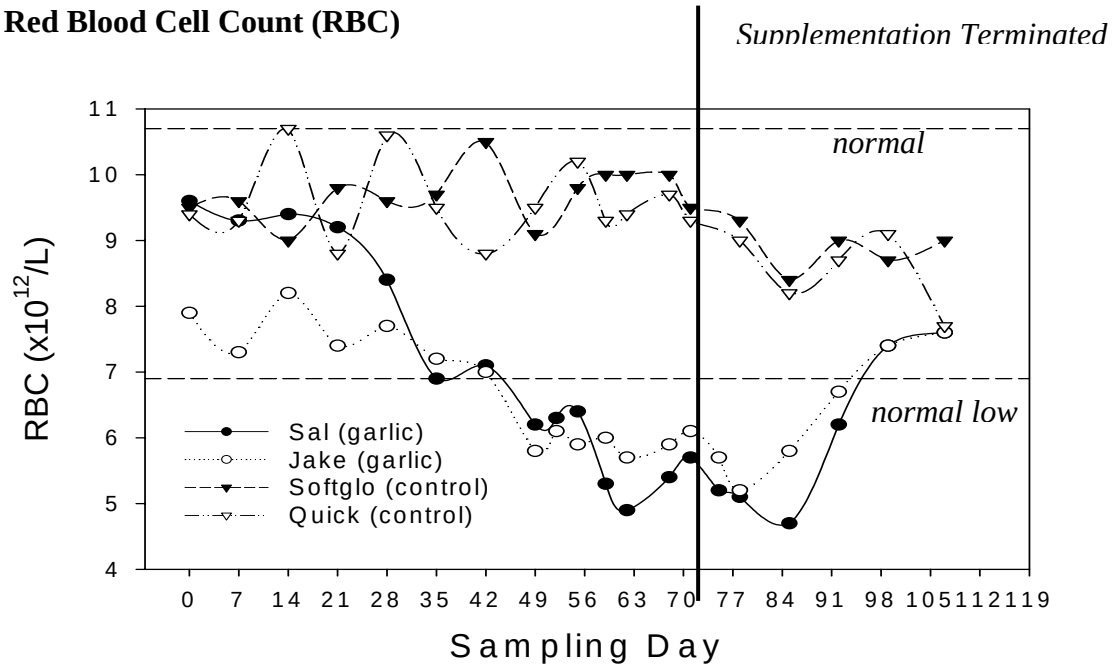

***Figure 4**: red blood cell count (x10^{12}/L). Treatment and control values are significantly different on days 35 through 71 (supplementation period). RBC for treatment horses recovered by day 99 (Pearson et al., 2004)*

combination of these causative factors. Further research is required in order to identify a mechanism for the activity of the herbal supplement as observed in our study.

Similarly, our data on the ability of herbs to reduce PGE2 in horses with osteoarthritis are in agreement with the apparent anti-inflammatory effect of some herbs in other species (Lanhers et al., 1992). PGE2 is a potent vasodilator, and enhances the neurological perception of pain. The vasodilator actions occur through synergism between PGE2 and other mediators including bradykinin and histamine, and the result is an increase in vascular permeability and erythema. This causes the characteristic hypersensitivity to pain observed in inflammatory conditions. Reduction of PGE2 is the mechanism by which anti-inflammatories such as phenylbutazone exert their efficacy (Higgins and Lees 1983), and botanicals have shown significant effect on PGE2 production in inflammatory conditions in other species (Wagner et al., 2003). It is not known which phytochemical in Mobility was responsible for the anti-inflammatory effect, or if the effect could be magnified through manipulation of the phytochemical profile of the product.

Botanicals appear to also play a role in the treatment of symptoms of dermatitis in horses. Our data suggest that feeding flaxseed can reduce the skin test response of horses that are senstive to the bite of Culicoides. The mechanism by which flaxseed exerts this effect is not known, but may be related to alterations in fatty acid profile of the sebum secreted by the sebaceous glands. Altered stereochemistry of the sebum may affect the dermal microflora, some of which are known to affect immunocompetence (Hug et al., 1999). Further research in this area should include a larger sample size, and would benefit from investigating the individual effects of isolated fatty acids and lignans on clinical endpoints.

Though much of our data suggest that botanicals can be safely used to maintain health and treat disease, the news is not all good. It was stated by Paracelsus in the early 1500s that the only difference between a medicine and a poison is the dose. The common adage that natural is synonymous with safe has led

to significant and widespread disease (Pearson 2000), and is it critical that those involved in equine husbandry and health care are aware of the potential dangers of herbal medicine. Our research with garlic demonstrates that horses will voluntarily consume enough of this botanical to cause significant adverse effects. Though this study cannot definitively describe a "toxic dose" due to the gradually increasing dosage regimen, it is clear that the combined time course and dose used in this study was toxic, causing potentially fatal Heinz body anemia. Research is currently underway in our laboratory to identify the degree of bioaccumulation of garlic metabolites in horses over an extended time course of supplementation. This will provide additional information on the potential of low-dose garlic to eventually become toxic.

Conclusions

Botanicals provide an important resource for maintaining and improving the health of horses. This series of studies demonstrates the ability of Echinacea, and possibly ginseng, to elevate immune function and protect horses from immune challenges. Further, polyherbals and flaxseed appear to be effective in treating symptoms associated with respiratory disease, osteoarthritis and dermatitis respectively. However, natural is not synonymous with safe, and horses will voluntarily consume enough garlic to cause Heinz body anaemia which, if left unchecked, can be fatal. The key to maximizing the benefit of botanicals for horses is to continue conducting species-specific research on potentially important plants, and to make this information available to those involved in their husbandry and health care.

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