Latest Publications You Should Not Miss

Selected by Michael Walkenhorst, Frick

Zebeli Q. Phytochemicals in Animal Nutrition – Their Potential as Functional Feed. *Planta Med* 2019; 85(18): 1391: DOI 10.1055/s-0039-3399639.

Phytochemicals are highly versatile in plants. They are also termed secondary plant compounds, a terminology that might be outdated taking into account the primary role metabolites for plant physiology, reproduction, and protection. From the perspective of ecological mutualism between plants and animals, these compounds are of crucial importance because they not only protect but also serve as visual attraction for animals, especially herbivores, signaling nutritional and/or health-promoting values. In animal nutrition, the phytochemicals are commonly considered as phytochemical feed additives without essential nutritional value as are the primary nutritive ingredients. However, the perception of the diet has changed during the last years both in animal and human nutrition. One now expects that the diet delivers both nutritive and health-promoting values. The knowledge of the last years suggests essential nutritive and health-promoting properties of many phytochemicals, making them good functional feed candidates. Inclusion of such functional feed ingredients in the animal diet may provide precursors for synthesis, protect the animal against oxidative stress, and, most importantly, many compounds enhance key metabolic pathways both at metagenomics and host phenotypic level, being essential for animal nutrition and health. Using such examples, this talk will highlight the potentials of phytochemicals as functional feeds, particularly focusing on the promotion of animal health.

Provenza F. Let Feed and Food be Our Medicine. *Planta Med* 2019; 85(18): 1391: DOI 10.1055/s-0039- 3399640.

The health of livestock, humans, and environments is tied to plant (phytochemical) diversity. Health is enhanced when livestock forage on phytochemically rich landscapes, is reduced when

livestock forage on low-diversity pastures or eat high-grain rations in feedlots, and is greatly reduced for people who eat highly processed diets. The shift away from phytochemically and biochemically rich plant and animal foods to processed foods enabled 2.1 billion people to become overweight or obese and increased incidence of diet-related disease.

Circumstantial evidence supports the hypothesis that phytochemical richness of herbivore diets enhances biochemical richness of meat and dairy, which is linked with human health. Among many roles they play in health, phytochemicals in herbivore diets protect meat and dairy from protein oxidation and lipid peroxidation that cause low-grade systemic inflammation implicated in heart disease and cancer. Yet, epidemiological studies critical of red meat do not discriminate among meats from livestock fed high-grain rations as opposed to phytochemically rich diets.

While conventional agriculture adds 25% of greenhouse gas (GHG) emissions, regenerative agriculture can play a sizeable role in mitigating climate change. Of 80 ways to diminish these effects, regenerative agriculture—managed grazing, silvopastoralism, agroforestry, conservation agriculture, and farmland restoration—jointly rank number one as ways to sequester GHG.

We can enable human and planetary health by forsaking processed foods and by sourcing, growing, and eating wholesome foods. We must learn we are members of nature's communities. What we do to them, we do to ourselves; only by nurturing them can we nurture ourselves.

Mendel M. Pharmacological and Toxicological Insights into Veterinary Phytotherapy. *Planta Med* 2019; 85(18): 1391: DOI 10.1055/s-0039-3399641.

Increasing interest of society in natural products, disappointing and dissatisfying results of conventional therapy, as well as the "One Health" concept encouraged by authorities are only some of the causes of enhanced significance of phytotherapy in animals. Despite the long and well documented tradition of herbalism vet-

erinary medicine, some pharmacological and toxicological aspects must be carefully analyzed while considering the application of a plant-derived product into treatment protocol. In contrast to human medicine, veterinary medicine consists of various species with distinct differences in anatomy and physiology. Consequently, safe and efficient phytotherapy is a challenge for many veterinarians. Significant interspecies differences are reflected in diverse pharmacokinetics of phytomedicines. The complexity of gastrointestinal tract, various intensity of gut microorganisms' activity and the activity of enzymatic systems, predominantly CYP450, are responsible for variable bioavailability of phytocompounds in animals of different species. In cats, special attention must be paid to drugs requiring conjugation with active glucuronic acid since these animals are unable to perform this reaction. Similarly, urine excretion is species-dependent due to various urine pH which may either facilitate or decrease elimination of plant-origin substances and their metabolites. Another animal specific aspect of veterinary phytotherapy includes doping issue. Some herbal constituents are not allowed in sport animals, some other may increase the concentration of concurrently applied drugs and cause a positive result of anti-doping testing. Herb-drug and herb-nutrients interactions, as well as unconscious use of counterfeit phytomedicines are other matters to discuss. Altogether, only rational phytotherapy guarantees the safety and effectiveness people expect.

Placha I, Ocelova V, Chizzola R, Bacova K, Faix S. Effect of Sustained Dietary Application of Thyme Oil on Antioxidant Parameters and Thymol Content in Plasma and Tissues of Broilers. *Planta Med* 2019; 85(18): 1391: DOI 10.1055/s-0039-3399642.

Antioxidants are usually understood as chemicals which could eliminate oxidative stress by removing intracellular reactive oxygen species but high doses may block their beneficial effect and moreover, could be toxic. Understanding exact mechanism of action of plant components in animal organism help to propose dose, method and duration of their application. Thymol with strong antioxidant properties is the main component of thyme oil. After absorption from the intestine, thymol enters the bloodstream and is transported to the tissues. We found significant correlation between thymol levels in plasma and feed and duodenal wall, which points to the efficient thymol absorption from the digestive tract into circulation. Erythrocytes play a crucial role in the distribution of circulating polyphenols due to binding to their surface and being able to act like depots. That is why the real thymol concentration in blood could be higher than it was found in plasma. Thyme oil (0.1%, thymol 460 µg/g DM feed) significantly increased superoxide dismutase activity, had tendency to increase glutathione peroxidase activity and significantly decreased malondialdehyde as a product of lipid peroxidation in plasma which points to modulation of antioxidant enzymes activity and improvement of the oxidative stability. Obtained the lowest thymol concentrations in muscle (139 ng/g DM) in comparison with plasma (854 ng/ mL), liver (568 ng/g DM) and kidney (5541 ng/g DM) could be due to low thymol penetration or high activity of efflux transporters, hence insufficient to affect antioxidant defense system. In conclusion, thymol effectiveness depends on its systemic availability for the targeted organ.

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Hirtenlehner S, van der Klis JD, Fuller LA, Mathis GF, Müller AS. A Combination of Saponins and Essential Oils of Asteraceae, Lauraceae and Myrtaceae Plants Counteracts Coccidiosis-Related Production Losses in Fast-Growing Broilers. *Planta Med* 2019; 85(18): 1392: DOI 10.1055/s-0039-3399643.

Eimeria spp. triggered coccidiosis is a protozoal disease of the intestinal tract relevant for different avian species. Infections result in diminished nutrient absorption and cause economic losses through performance depression [1]. Frequently, they are accompanied by secondary infections with *Clostridium perfringens*. Despite rotation of chemical coccidiostats, *Eimeria* become resistant to these substances. The present study investigates how phytogetic feed additives can support health status of coccidiosis and *C. perfringens* challenged broilers. Extensive screening of EO-combinations, different saponin sources and combinations thereof [2], revealed two prototypes for testing in broiler challenge trials. Prototypes consisted of a saponin core combined with EO mixes, from Asteraceae and Lauraceae plants (PT1) or from Myrtaceae and Asteraceae plants (PT2). 1750 day-old male chickens were spray-vaccinated against coccidiosis and assigned to 5 groups of 350 birds in 7 repetitions for a 42-day feeding trial. Except non-infected non-treated group 1 (NINT), all birds were individually inoculated at days 19, 20 and 21 with *C. perfringens* to induce necrotic enteritis (NE). The further dietary groups were: 2) infected non-treated, 3) infected + Bacitracin-methylene-disalicylate, 4 and 5) infected + PT1 or PT2. Both prototypes compensated infection related growth depression. Feed Conversion Ratio was even improved compared with NINT. In an in-vitro dose response test only 208 ppm of PT2 were equally effective to 10 ppm Monensin regarding *Eimeria* sporozoite invasion (Fig. 1).

Fig. 1. Dose response effects of PT2, basing on saponins and an EO mix from Myrtaceae and Asteraceae plants, on inhibition of *Eimeria* sporozoite invasion.

In conclusion, the supplementation of phytoGENICS based on saponins and specific EO mixes can be considered as a promising and save alternative in coccidiosis and NE control.

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Biegel U, von Bodungen U, Ruess K, Reif M, Knauf Y, Stratmann N. Mistletoe in Adjuvant Cancer Treatment of Companion Animals. *Planta Med* 2019; 85(18): 1392: DOI 10.1055/s-0039-3399644.

Cancer diseases are frequent in veterinary practice and overall there is a 23% – 45 % risk for dogs to die from cancer. Oral malignant melanoma (OMM) as well as canine mammary tumor (CMT) show high malignancy and adjuvant treatment is needed. The aim of both controlled trials was to explore if *viscum album* L. extract (VAE) therapy might be a potential treatment of OMM and CTM. In OMM the adjuvant VAE treatment showed a significant longer median survival time (MST) with 236 days compared to the control (radiation only) with 49 days ($p = 0,0047$). Adjuvant VAE treatment in CMT showed not significant differences in MST compared to the control group (surgery only). A tendency ($p = 0,7$) of decrease in tumor-related death risk (TRDR) to 25% (HR 0.251, 95% CI 0.056–1.122; $p = 0.07$) was observed for the treatment group, with stable Quality of life during entire treatment.

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Axmann S, Hummel K, Nöbauer K, Razzazi-Fazeli E, Zitter-Eglseer K. Devil's Claw (*Harpagophytum Procumbens*) – Pharmacokinetics of Harpagoside in Horses. *Planta Med* 2019; 85(18): 1393: DOI 10.1055/s-0039-3399645.

Devil's claw is used for the treatment of chronic inflammatory symptoms and degenerative disorders [1] in horses since many years, but without the substantive equine pharmacokinetic data [2,3,4]. The pharmacokinetic parameters of harpagoside, the main active constituent of *Harpagophytum procumbens* DC ex Meisn., were evaluated in equine plasma after administration of *Harpagophytum* extract FB 8858 in an open, singledose, two-treatment, two-period, randomised cross-over design. Six horses received a single dose of *Harpagophytum* extract, corresponding to 5 mg/kg BM harpagoside, and after 7 days washout period, 10 mg/kg BM harpagoside via nasogastric tube. Plasma samples at certain time points (before and 0–24 h after administration) were collected, cleaned up by solid-phase extraction and harpagoside concentrations were determined by LC-MS/MS using apigenin-7- glucoside as internal standard. Plasma concentration-time data and relevant parameters were described by non-compartmental model through PKSolver software. Harpagoside could be detected up to 9 h after administra-

tion. C_{max} was found at 25.59 and 55.46 ng/ml, $t_{1/2}$ at 2.53 h and 2.32 h, respectively and t_{max} at one hour in both trials. AUC_{0-inf} was 70.46 and 117.85 ng h ml⁻¹, respectively. A proportional relationship between dose, C_{max} and AUC was observed. Distribution (V_z/F) was 259.04 and 283.83 L/kg and clearance (CL/F) 70.96 and 84.86 L h⁻¹ kg⁻¹, respectively. Treatment of horses with *Harpagophytum* extract did not cause any clinically detectable side effects. The knowledge of basic equine pharmacokinetics, based on the results of this study, will help to link results from in vitro assays and clinical studies and optimise therapeutic efficacy (Fig. 1).

Fig. 1. Mean plasma concentration-time profile of harpagoside after single intragastric dosing of *Harpagophytum procumbens* extract FB 8858 corresponding to 5 mg/kg BM harpagoside (trial 1) and 10 mg/kg BM harpagoside (trial 2) to six horses.

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Wöscher S, Coenen M, Abraham G, Kuchta K. Aloe Vera Gel and Coriandrum Sativum Seeds: Traditional Medical Plants and their Role as Anti-Diabetic Agents in Dogs. *Planta Med* 2019; 85(18): 1393: DOI 10.1055/s-0039-3399646.

This study aims to evaluate acute anti-diabetic or anti-obesity effects of Aloe vera gel and milled Coriandrum sativum L. seeds as oral treatment for several diabetes related blood parameters including glucose (G) and insulin (I) in dogs. 4 female and 5 male healthy beagle dogs were used in 2 experimental phases each 5 weeks 1 week of control diet (cd), 2 weeks of phytotherapy (cd + herbal preparation) and 2 weeks of wash-out period (cd). The herbal preparations were dosed 2g/kg body weight (BW)/day. Fasting and postprandial blood parameters were assessed after control period, first-, and second week of phytotherapy period. The BW was measured weekly and a general examination was carried out two times per week. The BW decreased 1.4% and 0.8% after two weeks of treatment with A. vera ($p=0,001$) and C. sativum ($p=0,112$), respectively. Hemogram and blood chemistry revealed no impact of herbal preparations. Blood G peaked at 160 up to 183 min after the meal containing A. vera and C. sativum respectively. Max I concentrations of 37 up to 55 $\mu\text{U/ml}$ refers to the I response on the meal and showed no treatment effect. A. vera gel and C. sativum seeds exert in a 2-week oral treatment period no significant side effects on general conditions of dogs and on blood parameters. In healthy dogs, no effect was detectable on blood G and I responses. However, significant positive effects on weight regulation could be confirmed.

Provenza F. After Ten Thousand Years of Domestication, Can Livestock still Self-Medicate? *Planta Med* 2019; 85(18): 1394: DOI 10.1055/s-0039-3399647.

To determine if livestock can self-medicate, we first showed that sheep fed high-grain diets ingest sodium bicarbonate or bentonite, substances that attenuate acidosis and restore acid-base balance. We then showed that sheep and goats regulate intake of polyethylene glycol (PEG), which alleviates the aversive effects of consuming high-tannin diets, in accord with the amount of tannin in their diet. Finally, we showed that sheep ingest dicalcium phosphate to counteract foods high in oxalic acid. To learn whether sheep make multiple illness-medicine associations, we conditioned sheep to use three medicines – bentonite, PEG, and dicalcium phosphate – and then offered them grain or food with tannins or food with oxalic acid and gave them access to the three medicines. Sheep chose the medicine that rectified the malady. Sheep and goats infected with internal parasites eat more tannin-rich forage than non-infected animals. As parasite loads increase, they increase their intake of plants with tannins, which decreases parasite loads. Livestock are less inclined to self-medicate when they are provided with anti-parasitic drugs. Parasitized sheep reduce intake of high-tannin food when their parasite infection is terminated with ivermectin. Likewise, goats treated with anthelmintic drugs eat less tannin-containing heather than do goats infected with internal parasites. Collectively, these findings show livestock self-medicate, even after 10,000 years of domestication. Biochemically mediated flavor-feedback associations, where cells and organ systems alter liking for foods as a function of needs, enable livestock to self-medicate. To do so, however, livestock must have access to phytochemically rich foods and learn to use them.

Huffman MA. Medicinal Diet of Tibetan Macaques in Southern China. *Planta Med* 2019; 85(18): 1394: DOI 10.1055/s-0039-3399648.

Dietary selection is important to assure the balance of nutrients for energy, growth, maintenance, and reproduction. The innate response of an animal is to avoid eating plants with toxic secondary metabolites, but these properties can be medicinal when ingested in appropriate amounts. It is proposed that under physical conditions that require direct intervention (health maintenance or self-medication), animals ingest even such toxic plants for their medicinal benefits to regain health homeostasis. Previous studies on primate plant food selection have found that 15~25% of the items in their diet could be classified as ‘medicinal food’ (plants with bioactive, physiology modifying properties). Here we focus on identifying prospective medicinal foods in the diet, in order to investigate the potential properties and possible roles of such items for a wild group of Tibetan macaques (*Macaca thibetana*) at Mt. Huangshan, Anhui Province, China. Using a 50 species food list of this group, a pharmacological database search was conducted. We identified 12 species (24%) with significant pharmacological potential. Across the 12-month study, medicinal foods accounted for 18~23% of the total diet in any one season. The reported activities in these items included anti-parasitic, anti-bacterial, anti-rheumatic, neuroprotective, osteoprotective, reproductive stimulant and wound healing, among others. While the actual medicinal benefits to macaques gained from ingesting these plants are yet unknown, based on the available evidence for their parasite infection ecology, reproductive behavior and possible stress reduction, we hypothesize on the possible scope of self-medication in Tibetan macaques, and suggest future avenues for research.

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Khunoana ET, Madikizela B, Erhabor JO, Nkadameng SM, Arnot LF, Wyk IV, McGaw LJ. A Survey of Plant Remedies for Livestock Diseases in the Mnisi Community, South Africa, and Investigation of their Biological Activities. *Planta Med* 2019; 85(18): 1394: DOI 10.1055/s-0039-3399649.

Ethnoveterinary medicine (EVM), although not well documented, serves as an alternative or complementary medication for infectious diseases and parasites in South African livestock. In this study, plant species and traditional remedy formulation methods used by the Mnisi community, Bushbuckridge, in EVM were documented using Rapid Rural Appraisal techniques. Three plant species were selected for evaluation of antimicrobial, antibiofilm and cytotoxic activities based on their frequency index and lack of published information on their bioactivity. Traditional methods were used for plant extraction using water. Acetone was used as an organic solvent to compare traditional and organic solvent methods of extract preparation. The extracts were tested for their antimicrobial activity and cytotoxicity. *Elephantorrhiza obliqua* acetone

extract had the best antibacterial activity with a minimum inhibitory concentration (MIC) value of 0.09 mg/ml against *Pseudomonas aeruginosa*, while *E. obliqua* water extract had the best antifungal activity with MIC of 0.02 mg/ml against *Aspergillus fumigatus*. Some extracts also inhibited biofilm formation by at least 50% and were active against mature biofilms. Only two of the nine plant extracts were relatively toxic against Vero cells. Interestingly, traditionally prepared remedies were generally more active against fungi and mycobacteria and less cytotoxic than organic solvent extracts. In vivo studies are necessary to support the traditional use and safety of the remedies against livestock diseases.

Huffman MA. The Evolution of Animal Self-Medication and Lessons for the Development of Medicine and New Medicines. *Planta Med* 2019; 85(18): 1404: DOI 10.1055/s-0039-3399675.

Parasites, viruses and other pathogens cause a variety of diseases that affect the behavior and reproductive fitness of an individual. While the study of animal self-medication as a science is relatively new, to date, research has classified health maintenance and self-meditative behaviors into four levels: 1) optimal avoidance or reduction of disease transmission; 2) the dietary selection of items with a preventative or health maintenance affect; 3) ingestion of a substance for the curative treatment of a disease or the symptoms thereof; and 4) external application of a substance to the body for the treatment or control of disease bearing insects. Of any species studied thus far, chimpanzees have provided the most details for level 2 and 3 behaviors, exemplified by such behaviors as bitter pith chewing and whole leaf swallowing used in response to parasite infection [1, 2]. This presentation will review the progress to date in primates, and compare these strategies with examples from other species to illustrate the wide and deep evolutionary origins of self-medication in the animal kingdom and show how this bio-rational approach can aid in the search for new natural plant compounds and has found new uses for well-known compounds in human and livestock health care.

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Appendino G, Pagani A, Williams C, Cullen J, Boyle G, Parsons P, Campbell J, Gordon V, Schmidt P, Reddell P. Chemistry, Mode of Action and Clinical Efficacy of the Anticancer Diterpenoid Tigilanol Tiglate (EBC-46). *Planta Med* 2019; 85(18): 1404: DOI 10.1055/s-0039-3399676.

Tigilanol tiglate (EBC-46, 1), a novel diterpene ester isolated from the seeds of the endemic Australian rainforest tree *Fontainea picrosperma* (Euphorbiaceae), is being developed for intratumoral treatment of cancers in humans and companion animals [1,2]. Here we summarise our current understanding of the chemistry

and mechanism of action of the compound, and provide results from recently completed veterinary (Phase III) and human (Phase I/II) clinical trials. Tigilanol tiglate has a multi-factorial mechanism of action. A single intratumoral injection (1) induces a rapid, highly localised and transient inflammatory response surrounding the tumour mass, (2) significantly increases permeability of the tumour vascular endothelium, and (3) causes rapid tumour cell death by oncosis. In combination, these result in tumour haemorrhagic necrosis, eschar formation and complete tumour destruction within 4 to 14 days. Localised inflammation and increasing permeability of tumour vasculature are associated directly with the activation by tigilanol tiglate of specific isoforms of protein kinase C ($-\beta I$, $-\beta II$, $-\alpha$, $-\gamma$), while tumour cell death via oncosis requires PKC/C1 domain mediated signalling. The compound also induces changes in cytokine signalling and gene expression that promote wound healing following tumour destruction. In a Phase III fully-randomised, controlled and blinded veterinary clinic trial, a single treatment with tigilanol tiglate resulted in complete and enduring tumour destruction in more than 75% of canine patients with mast cell tumours. In a clinical Phase I/II human dose-escalation study, maximum tolerated dose was not reached and signs of efficacy were observed in 9 tumour types, including complete response in 4 patients (Fig. 1).

Fig. 1. tigilanol tiglate

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