INTRODUCTION

Close to 30% of pet owners have used or considered the use of novel ingredients (e.g., nutraceuticals and herbs/botanicals) in their animals. In the USA, approximately 90% of veterinarians sell some type of novel ingredient and the current market of veterinary novel ingredients is between $20 and $50 million per year. The American Veterinary Medical Association recognizes the importance of these medicaments through its guidelines regarding complementary or alternative medicine, which includes veterinary nutraceutical therapy. In Europe and other nations, the use of herbs/botanicals in particular enjoys a long historical use of general acceptance. However, despite the economic and medical impact of novel ingredients, their use is and should be controversial. Much more than drugs, the use of novel ingredients is complicated by issues regarding their safety, efficacy and manufacturing. The term nutraceutical is not a legal term, but was coined in the 1980’s by a physician referring to oral compounds were neither nutrients nor pharmaceuticals. The North American Veterinary Nutraceutical Council (now defunct) was formed in 1996 by interested persons in industry, practice and academia. It defined a veterinary nutraceutical as “a [non-drug] substance which is produce in a purified or extracted form and administered orally to a patient to provide agents required for normal body structure and function and administered with the intent of improving the health and well-being of animals.” The commonality among novel ingredients products is that legally they are neither food, food additives nor drugs (as recognized by the Food and Drug Administration (FDA) of the USA). As such, they undergo no premarket approval process and neither safety, efficacy nor manufacturing is assured. At least two groups in the USA have formed in North America with an interest in veterinary nutraceuticals: the Nutraceutical Alliance (www.nutraceuticalalliance.com) based in Canada, and the National Animal Supplement Council (NASC; www.nasc.ca), based in the USA. The latter group has taken an aggressive approach in trying to implement voluntary actions among nutraceutical manufacturers that will cause regulators to respond to their products in a positive fashion. Novel ingredients often are used without doctor supervision. Up to 70% of humans do not report herbal use to physicians, in part because of their failure to recognized the products as drugs. Likewise, pet owners often do not cite nutraceutical or herbal use when queried regarding drug therapy for their pet. The availability through medically recognized and trusted sources often leads the consumer to assume both their accuracy in labeling, efficacy and safety. Yet, the lack of regulations and guidelines should lead to the “buyer beware”.

LABELING

No mechanism (other than voluntary) exists to hold a manufacturer accountable for the labeling of a novel ingredient. Yet, the novel ingredient that is inappropriately labeled negatively impacts both safety and efficacy. Strong consideration should be given to purchasing those products for which assurance in manufacturing can be obtained. Manufacturers should be queried about the accuracy of their label and all aspects of their manufacturing program, with an emphasis on which “Good Manufacturing Program” they follow. The manufacturer also should be queried regarding its participation in any of the programs that offer evidence of quality assurance, such as exists in the USA: ConsumerLab’s (www.consumerlab.com) certification seal; the Institute for Nutraceutical Advancement, or trade associations (e.g., NASC when available). Several sources of scientific information indicate the need to focus on those products whose quality assurance can be verified. Chondroitin sulfates (CDS), an expensive ingredient of many “joint” targeted products, offers an example of consistent mislabeling. A study, funded in part by Nutramax Laboratories, found deviations from label claims for CDS in 84% (9 of 11) of the products studied; the amount by which products were mislabeling ranged from 0 to 115%. Further, the study found products costing less than or equal to $1 per 1200 mg CDS were seriously deficient (less than 10% of the label claim), suggesting that cheaper products should be avoided. However, expense did not guarantee accuracy. Several of the most expensive products also were found in this study to be mislabeled. Consumer Lab found similar results: at least 50% of products containing CDS are mislabeled. Two of three veterinary products contained no chondroitin despite labels that noted otherwise. In contrast to CDS, glucosamine is much more likely to be accurately labeled in regard to content. Since the time of these original studies (approximately 15 years ago), the quality of these products has markedly improved. Consumer Laboratory (www.consumerlabs.com) is a for-profit laboratory that offers a seal of “validation” for dietary supplements sold in the USA that are appropriately labeled. Products that pass analysis are allowed to place the ConsumerLab seal on the product label. The public can access selected information from the Consumer Lab web site for a fee ($20 annual at the time of this printing) for ingredients that have been tested. Criteria for passing and failing and reasons for failure for specific ingredients can be accessed, as can a list of proprietary products that have passed. Ten of the ingredients studied by Consumer Lab and listed at their web site have been used in veterinary medicine (although none of the products are veterinary). Yet, products of only four ingredients (glucosamine, co-enzyme Q, iron and methosulone [MSM]) were accurately labeled at least 80% of the time. Reasons for failure ranged from unacceptable inaccuracy in labeling of product content to contamination (with heavy metals or pesticides). Among the pass products was Cosamine®, the human version of Cosequin® DS for dogs, manufactured by Nutramax Laboratories. The presence of a “seal of verification”, unless from a recognized, reputable source, does not necessarily indicate sufficient quality in manufacturing. The presence of a lot number and expiration date offers some evidence of accuracy in labeling. Labels should contain a list of ingredients and the intended use of the product. Ingredients should be listed by their common name in decreasing order of magnitude based on weight. Note that for selected herbs, the total constituents may not be known. Additionally, the number of constituents in herbs can be overwhelming.
garlic alone contains over 200 active ingredients. Because the ingredient content can vary with the portion of the plant, the source of the plant (leaf, flower, root, stem) should be included. Labeling techniques may contribute to the advent of adverse effects. Manufacturers may improperly identify plants. Even if properly identified, the consumer may have difficulty identifying a product as potentially dangerous because an herbal agent may be referred to by many different names or an herbal name may be used in lieu of the more easily recognized chemical name (eg, guarana for ephedrine or mahuang for caffeine). The FDA has become more proactive in directing manufacturers to list generic drug names in lieu of or in addition to herbal names; however, consumers may have to look closely. Adequate directions for use also should be provided. Absence of any of this information should cause the user of the product to look for alternative products. Products whose labeling is accompanied by scare tactics, exaggerated claims and testimonials should be avoided as should products whose label includes medical claims, such as “for use in the prevention or treatment of,” or intended to changes in body structure or function.” Consumer Laboratories (www.consumerlab.com) has reviewed issues specifically related to quality assurance of a probiotic product. These include: 1. Labels should list all types of bacteria or yeast, including genus and species, and the number of colony forming units (CFU); 2; numbers of viable organisms (note the dose is generally 1 to 10 billion \[10^9\text{ to } 10^{10}\] CFU are recommended (in humans) per day. 3. Viability of organisms; 4. presence of contaminating (potentially pathogenic) organisms, including \(E.\ coli\), \(Salmonella\ sp\), \(Staphylococcus aureus\) and \(Pseudomonas aeruginosa\) (as per FDA requirements); and 5. the extent of enteric protection of selected organisms, including \(L.\ bulgaricus\), \(S.\ thermophilus\) and \(Leuconostoc\) and \(Lactococcus\) sp. Organisms which generally do not need protection include most \(Lactobacillus\), \(Bifidobacterium\) and \(Streptococcus\), or organisms present as spores, including \(Bacillus\) and some \(Lactobacillus\). Of 24 products (21 human, 3 pet) reviewed by Consumer Laboratories (October 2007), 5 (4 human, 1 pet) failed to contain the labeled amount of microbes, 6 (4 human, 2 pet) failed to provide at least \(10^9\)CFU per serving (generally those that also failed to contain labeled amount) and 1 (pet) failed due to microbial contamination (with mold). Two of the pet and 4 of the human products did not include the number of CFU on the label. Consumerlab just recently reported that up to 93% of “acidophilus”or other beneficial bacteria are missing in some supplements.

SAFETY

“Above all else, do no harm” should be the primary directive regarding the use of novel ingredients. Harm to the patient from the use of novel ingredients can reflect adverse reactions to the active ingredient, excipients, or contaminants; or therapeutic failure, particularly if traditional therapy is overlooked or not pursued in the belief that the novel ingredient will be sufficient. Of these, adverse reactions are the most likely to contribute to harm. Lack of adverse event reports in the literature for a novel ingredient should not be interpreted as evidence of safety, particularly in light of the absence of an effective adverse event reporting system. In the US and elsewhere, unlike pharmaceutical manufacturers, manufacturers of novel ingredients are not mandated to report adverse events. Studies which establish safety of novel ingredients can be implemented relatively easily. The outcome measures of adversity, or more ominously, toxicity (ie, clinical signs, clinical laboratory changes, evidence of histopathology in organs of excretion, teratogenicity etc) are more discreet and easily defined than are criteria of efficacy. However, toxicity studies can be costly, particularly if chronic dosing studies are implemented, and the cost of such studies is likely to be transferred to the consumer. None – the – less, the profession should demand and expect evidence of safety in the target species of any product marketed for animal use.

Despite their endogenous origin, nutraceuticals may be associated with adverse eventsOf the novel ingredients, herbal / botanical products may present a greater risk compared to nutraceuticals, although the incidence of adverse reactions does not appear to be as high in human medicine as that for either prescription or over-the -counter drugs. Often described in advertisements as “mild” because they are “natural,” the prudent user of herbal products will recognized that the products are natural to plants, not animals. Indeed, animals have developed sophisticated mechanisms (eg, efflux pumps, drug metabolizing enzymes) to prevent the absorption and accumulation of plant chemical products in the body. Many drugs originally were discovered because of their presence in plants. Herbal products may be unsafe for several reasons. Active ingredients, whether the intended ingredient or another chemical within the plant, may not be safe, particularly when used in excess. The risk of adverse effects to herbs is increased by the presence of many active ingredients in the same plant. Indeed, herbalists often used unpurified plant extracts because of the belief that different chemicals will interact synergistically. The portion of the plant (ie, leaf, flower, stem, root, seed) may impact safety. Herbalists often administer the whole plant in the belief that, in contrast to the purified extract, toxicity will be reduced by a buffering effect of the whole herb. During growth of the plant, environmental contaminants may become unintended residues during the manufacturing process. Microorganisms, including bacteria, fungi or molds, can either directly contaminate the product or produce contaminating toxins. Bacterial contamination is more likely with root – as opposed to flower or leaf – products. Heavy metals, such as lead, cadmium or mercury, increasingly are contaminating plants exposed to environmental pollutants. Further, unless organically grown, insecticides and pesticides can contaminate herbal products. Factors during production and storage, such as storage length and conditions can alter herbal potency and quality. Finally, herbal products might be supplemented with active ingredients (often referred to as an herb) such as benzodiazepines, ephedrine, caffeine, or fenfluramine (the latter ingredient being one of the two ingredients in the notorious Phen-Fen dietary supplements). Health Canada issued a warning to Canadians to not used selected herbal products that contain undeclared prescription drugs, including indomethacin, diethylstilbestrol and alprazolam (an anti-anxiety drug). Finally, the risk of drug interactions in persons consuming herbs has caused the American Society of Anesthesiologists to generate a brochure for its members entitled “What You Should Know About Your Patients’ Use of Herbal Medicine”. Examples of potential
interactions involving the CNS include enhanced stimulation by caffeine, ephedra, yohimbine, guarana, and ginseng; enhanced sedation by valerian, kava, and St. Johns Wort. Drug-induced hemostasis defects may be potentiated by garlic, ginger, gingko, ginseng, chamomile, feverfew and bromelain; whereas the effects of hypoglycemics may be exacerbated by bilberry, bitter melon, dandelion and garlic. Echinaacea and astragalus may offset the immunomodulatory effects of corticosteroids or other immunosuppressants. A number of other herbs have been associated with adverse effect. In 1975, the FDA reported over 30 herbs prepared as teas to be unsafe. Excessive consumption of herbal teas containing senna, aloe, buckthorn and other laxatives has been associated with the death of four women The FDA also is currently investigating the potential association of hepatotoxicity and the administration of kava (kava kava, Piper methysticum), an herbal product used for a variety of disorders, including stress and anxiety. Recent regulatory actions offer evidence of the risks that can be associated with the use of these unapproved products. Adverse events have also occurred in veterinary patients. The Animal Poison Control Center (APCC) published a report of adverse reactions in 47 dogs that ingested a popular weight loss dietary supplement containing guarana (caffeine) and ma huang (ephedrine). Seventeen percent of the dogs died following clinical signs expected from these central and cardioactive compounds.

Efficacy

Dosing of novel ingredients is often empirical and rarely, if ever, based on scientific studies. Establishing the pharmacokinetics of these products is difficult because of the multiplicity of ingredients, and, or nutraceuticals, inability to distinguish the endogenous from supplemented chemical. When assessing the validity of scientific information supporting the safety and efficacy of nutraceuticals, criteria which apply to clinical trials for drugs should apply to clinical trials for novel ingredients. The report must include a description of the study design and methods such as random assignment of treatments, placebo controls and blinding techniques that reduce the risk of scientific bias. The need for placebos in veterinary medicine can not be overemphasized. In humans, the placebo effect in studies evaluating pain can be profound, ranging from 30 to 40% or more. A similar, if not higher, placebo effect should be expected in veterinary medicine. The need for randomization, a placebo group and the avoidance of traditional therapies are examples of reasons why evidence of informed consent (not simply permission, but provision of truthful information) must be provided in the report. Other criteria of a well designed study should include methods to standardize treatment groups and appropriate statistical analysis. The larger the variability in the outcome measures, the greater the number of animals that must be studied in order to detect a significant difference. Care should be taken to not interpret the lack of a significant difference as an indication that the groups are the same unless the study investigators demonstrate that the study design provided sufficient power. Credence might be given to the results of a study that demonstrates or fails to demonstrate a clinical difference despite the lack of statistical difference. For example, products containing glucosamine and chondroitin sulfate cause significant decrease in the indices of red blood cells or platelet activity in dogs and cats, but these differences are within clinical normals and thus are not clinically relevant. Negative clinical trials also should be reported; manufacturers should be queried about their inclusion in distributed information. As with drugs, care should be taken when extrapolating information from studies in a species other than the one in which the compound is to be used. A recent systematic review of 16 clinical trials published prior to 2006 (Aragon et al, JAVMA, 2007, 230:514) in peer reviewed journals that addressed the efficacy of NSAIDS and disease modifying agents in dogs described a “moderate” comfort level regarding the claims pentosan polysulphate; green-lipped mussels; polysulfated glycosaminoglycans; and a combination of chondroitin sulfate, glucosamine hydrochloride, and manganese ascorbate. An extremely low level of comfort was described for hyaluronan.

Nutritional products were recently scientifically reviewed in human medicine. (Ameye LG, Chee WSS. Osteoarthritis and nutrition. From nutraceuticals to functional foods: a systematic review of the scientific evidence Arthritis Research & Therapy 2006, 8:R127 (doi:10.1186/ar2016; open access, July 04, 2007). Reviewed were randomized (human or animal) clinical trials that focused on OA, that were published in peer reviewed journals and were based on non-synthesized (natural) orally administered products. SAmE, glucosamine and chondroitin sulfate were excluded. Avocado soybean unsaponifiables and MSM scored highest. The science behind the use of probiotics is profoundly complicated by the following: microbiota differ with diet, different regions of the gastrointestinal tract, species, age, and state of disease. The number of CFU ingested as probiotics is minor compared to the normal microbiota. However, they transit through regions of the gastrointestinal tract that are sparsely populated and as such, may transiently become the dominant microbe.