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The role of natural plant products in modulating the immune system: An adaptable approach for combating disease in grazing animals☆

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ABSTRACT

Plants provide herbivores with an array of chemicals with the potential to improve health and well-being. For instance, phytochemicals, known as secondary compounds, which protect plants from consumers and pests can adversely affect cellular and metabolic processes in herbivores, but at low doses and in appropriate mixtures, they can have beneficial effects on animal nutrition and health, though the latter has not been explored in great breadth or depth. In this review, we summarize the potential impact of natural plant products on immunomodulation and other therapeutic effects in herbivores. Development of preventative strategies to help animals resist disease would be a more economical, ecological and socially effective long-term healthcare strategy than treating diseases. In this realm, immunomodulation promoted by forages emerges as an interesting alternative and complement to chemotherapy. The challenge for feeding systems will be to incorporate mixes of plants with bioactive properties in ways that enhance health without compromising animal production and well-being. A solution to this challenge may involve developing management programs that acknowledge the ability of animals to learn about the beneficial effects of diverse foods.

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1. Introduction

Over a 30-year period beginning in the early-1970s researchers became increasingly aware of the importance of structurally diverse compounds not directly involved with the essential or "primary" roles of photosynthesis, respiration, growth and development of plants (Rosenthal and Janzen, 1979; Cozier et al., 2006). Phytochemicals, many of which accumulate in surprisingly high concentrations in plants, not belonging to this "primary" category were considered "secondary" and waste products of plant metabolism (Rosenthal and Berenbaum, 1992). We now know these compounds protect plants from consumers and pests, and they serve as attractants for pollinators and seed-dispersing animals, as allelopatic agents, and as filters for UV radiation. They also help plants recover from injury, persist and adapt (Rosenthal and Janzen, 1979; Palo and Robbins, 1991; Cozier et al., 2006).

From the standpoint of defense, plants that produce compounds that quickly induce satiety in foragers stand a better chance of surviving. Most secondary compounds limit how much of a particular species an herbivore can eat, which spreads the burden of herbivory across species in a plant assemblage (Freeland and Janzen, 1974; Foley et al., 1999). At high doses, secondary compounds can adversely affect cellular and metabolic processes, reduce forage intake, and cause weight loss and even death (Cheeke and Shull, 1985; Cheeke, 1988). However, secondary compounds can also adversely affect the harmful bacteria, parasites and fungi that inhabit herbivores' bodies and cause decreases in health (Lozano, 1998). Thus, at certain concentrations and in appropriate mixtures,

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secondary compounds can have beneficial effects on herbivores (Provenza, 2008). The nature of this dual action (i.e., toxin/medicine) is merely a matter of dosage and a consequence of the animal's tolerance and current physiological state (Plotkin, 2000).

Secondary compounds are increasingly recognized as important in animal health and nutrition, though historically they were thought by agriculturalists and ecologists alike to adversely affect herbivores (Robbins et al., 1987; Dawson et al., 1999). However, eating plants high in tannins is a way for herbivores to reduce internal parasites and alleviate bloat by binding to proteins in the rumen (Waghorn, 1990; Min and Hart, 2003). Tannins also enhance nutrition providing high-quality protein to the small intestines by making plant protein unavailable for digestion and absorption until it reaches the more acidic abomasum (Barry et al., 2001). Plant-derived alkaloids, terpenes and phenolics also have antiparasitic properties (Kayser et al., 2003; Hocquemiller et al., 1991), and sesquiterpene lactones have anti-tumorigenic, anti-amoebic, anti-bacterial, anti-fungal and cardiotonic properties (Picman, 1986; Robles et al., 1995; Huffman et al., 1998).

Thus, secondary compounds at certain doses have the potential to benefit herbivores in ways that may be more consequential than their negative effects. Unfortunately, the notion of herbivores using secondary compounds as medicines has been overshadowed by the inherent, even if erroneous, perception of their negative effects at high doses. Reviews in the 1960s and 1970s considered plant phenolics as toxic in general, despite reports that many phenolics have very low toxicities and that humans have enjoyed tannins in food and drink for thousands of years (Mueller-Harvey, 2006).

Certain plant biochemicals considered to be "primary" also have the potential to function as medicines. For instance, certain polysaccharides, polymers of glucose (glucans), mannose (mannans), xylose (hemicellulose), and fructose (levans) provide immune-stimulating and antineoplasic activity (Tizard et al., 1989). The importance of proteins and their building blocks, amino acids, has long been recognized in immune function and nutritional immunology is emerging as a new discipline exploring the role of nutrients in the metabolism and function of cells of the immune system (Li et al., 2007).

The effects of plant compounds on pathogens have been addressed by others (Hutchings et al., 2003; Kayser et al., 2003; Jackson and Miller, 2006). Here, we synthesize emerging information on how natural plant products may indirectly, through immunomodulatory effects, help to prevent and combat disease in livestock. Developing preventative strategies to resist disease would be a more effective long-term healthcare strategy than treating disease (Schepetkin and Quinn, 2006). We explore how health benefits may be enhanced by understanding the interplay between natural plant products and foraging behavior. Plant-derived immunomodulatory compounds have been used in traditional remedies for both humans and animals (Plotkin, 2000; Engel, 2002), but critically assessing their effectiveness and understanding their mechanisms of action are in their infancy, particularly in the realm of livestock health. Thus, our aim is to provoke discussion and spur readers into new ways of studying the relationships among foraging behavior, natural plant products and immune responses in herbivores.

2. An overview of the immune system

The immune system is organized in layers of systems of increasing specificity designed to protect the host from pathogens. It is typically divided into two categories, innate (natural, non-specific) and adaptive (acquired, specific), although these categories overlap. Innate immunity is most universal and most rapidly acting. The first line of defense is the physical barrier, including skin and endothelial cells. The next line of defense, the myeloid cells, involves mononuclear phagocytes (e.g., monocytes, macrophages, and dendritic cells), natural killer (NK) cells, and polymorphonuclear phagocytes (e.g., mast cells, eosinophils, basophils) that release inflammatory mediators and humoral factors including collectins, C-reactive proteins and interferons (Beutler, 2004; Li et al., 2007).

Macrophages are critical in innate and adaptive immune responses. These ancient and phylogenetically conserved cells in all multicellular organisms are the first line of host defense after the epithelial barrier is breached. They can engulf and kill microbes and through the elaboration of chemotactic cytokines (signaling proteins), macrophages recruit other myeloid cells to the site of infection. Macrophages can also function as antigen-presenting cells and interact with T lymphocytes to modulate adaptive immune responses (Birk et al., 2001; Beutler, 2004). Natural killer cells produce and secrete very potent immunoregulatory cytokines, particularly interferon-γ, which increases cell reactivity and activates macrophages (Justo et al., 2003). The ability of the macrophages and other monocytic cells to phagocytize an invading organism and present a small portion of it to the T cell is critical in immunocompetence which links the innate and adaptive immune responses.

Most organisms survive through innate immune mechanisms alone, but vertebrates have evolved an additional system for pathogen recognition and elimination that consists of T and B lymphocytes and humoral factors called the adaptive immune system (Calder, 2006). The two classes of lymphocytes originally derived their names from research in birds. Differentiation of one class of lymphocytes is influenced by the bursa of Fabricius (B cells) and the thymus is required for T-cell development (Glick et al., 1956; Miller, 2002). The T helper type 1 (Th1) lymphocytes secrete cytokines such as interferon and interleukin-2 and stimulate type 1 (cellular) immunity characterized by intense phagocytic activity by cytotoxic T lymphocytes and other myeloid cells. Conversely, Th2 cells secrete different kinds of signaling proteins (e.g., interleukins 4, 5, 9) that stimulate type 2 (humoral) immunity characterized by high antibody production by B lymphocytes. These antibodies can neutralize microorganisms or toxins by binding to them; activate complement proteins in plasma for the destruction of microorganisms by phagocytes; immobilize bacteria; and opsonise various pathogens (Spellberg and Edwards, 2001; Li et al., 2007). Innate and adaptive immune systems are regulated by a complex network of chemical sig-