Broadly assessing the published literature[1] on canine and feline immunology, there are no simple significant differences between the two species. Both species have the same range of lymphoid subsets, with T helper (Th) 1, Th2, Th17 and T regulatory (Treg) cell function identified in each by expression of the same range of cytokines and key molecules. Both species express the same range of pattern recognition receptors (Toll-like receptors, nucleotide-binding oligomerization domain containing [NOD]-like receptors and others) and have the same spectrum of antigen presenting cells. Less is known about phagocytic cell function and the complement pathways, although there is little reason to suspect any significant differences.
There may, however, be subtle differences in canine and feline immunoglobulins (Igs). The dog has four IgG subclasses which are functionally equivalent to those of man. In contrast, only three IgG subclasses are recognized in the cat. Both species have IgM and IgE antibodies, although IgD has only been identified formally in the dog. There may also be differences in IgA – both species have IgA, but in the dog four genetic variants of the molecule are reported, but there have been no equivalent studies of feline IgA.

1. Glycine

Glycine is a major amino acid in mammals and other animals. It is synthesized from serine, threonine, choline, and hydroxyproline via inter-organ metabolism involving primarily the liver and kidneys. Under normal feeding conditions, glycine is not adequately synthesized in birds or in other animals, particularly in a diseased state[2].
Glycine is a major constituent of extracellular structural proteins (collagen and elastin) in animals. Glycine plays an important role in metabolic regulation, anti-oxidative reactions, and neurological function. Thus, this nutrient has been used to: (1) prevent tissue injury; (2) enhance anti-oxidative capacity; (3) promote protein synthesis and wound healing; (4) improve immunity; and (5) treat metabolic disorders in obesity, diabetes, cardiovascular disease, ischemia-reperfusion injuries, cancers, and various inflammatory diseases. These multiple beneficial effects of glycine, coupled with its insufficient de novo synthesis, support the notion that it is a conditionally essential and also a functional amino acid for mammals (including pigs and humans).

The use of glycine is reported to induce beneficial immune-modulatory and cytoprotective effects[3-5].

1. Arabinogalactan (Larch wood)

The immunostimulatory activity of larch arabinogalactan has been investigated in various in vitro and in vivo studies. These works have demonstrated activation of different components of the immune system.

In human peripheral blood mononuclear cells (PBMC), a study[6] demonstrated larch arabinogalactan's ability to enhance NK cells' activity/cytotoxicity (i.e., ability to mediate spontaneous cytotoxicity against tumor cells and virus-infected cells without prior sensitization by antigen) through a possible increase in interferon-gamma (IFN-γ). The investigators also highlighted larch arabinogalactan's ability to induce the production and/or release of pro-inflammatory cytokines such as tumor necrosis factors-alpha (TNF-α), Interleukin-1 beta (IL-1β) and Interleukin-6 (IL-6).
The role played by larch arabinogalactan on the immune system is further substantiated by an in vivo study on dogs, demonstrating that oral administration of larch arabinogalactan (at doses of 0.55 g/day or 1.65 g/day for 10 days) increases the number of circulating white blood

cell counts, namely neutrophils and eosinophils[7]. The number of lymphocytes (CD4+T helper, CD8+ cytotoxic T cells or B CD19+) was not affected by larch arabinogalactan administration. Serum IgG, IgM and IgA were also unaffected[8]. However, treatment of mice splenic lymphocytes with arabinogalactan increased their cytotoxic activity against tumor cells[9].
In humans a clinical study[10] demonstrated that larch arabinogalactan increased the body's potential to defend against common cold infection. Larch arabinogalactan decreased the incidence of cold episodes by 23 %. Improvements of serum antigen-specific IgG and IgE response to Streptococcus pneumoniae and tetanus vaccination suggesting a B cell dependent mechanism have been reported in vaccination studies with larch arabinogalactan, while the absence of response following influenza vaccination suggests the involvement of a T cell dependent mechanism. These observations suggest a role for larch arabinogalactan in the improvement of cold infections, although the mode of action remains to be further explored.

1. L-Glutamic Acid

Glutamine and glutamate are five-carbon amino acids that are structurally similar and play key metabolic roles in the citric acid cycle, transamination reactions, generation of NADPH, γ- aminobutyric acid (GABA), the antioxidant glutathione and as folic acid cofactors. The carboxyl group of glutamate is replaced by an amide nitrogen in glutamine. The two amino acids are interconverted by the enzymes glutaminase (glutamine to glutamate + ammonia) and glutamine synthetase (glutamate + ammonia to glutamine). For many years, glutamine and glutamate were considered nonessential amino acids; however, numerous studies have demonstrated that endogenous glutamine storage and synthesis may not be adequate to meet the body's needs in certain situations, such as critical illness, infection, cancer chemotherapy, low birth weight infants, diarrhea, human immunodeficiency virus infection, bone marrow transplantation and cardiac surgery. Therefore, glutamine has been reclassified as a conditionally essential amino acid.

A study[11] showed that diets containing supplemental Gln reduce intestinal injury caused by chemotherapy in animals with cancer, and this process contributes to decrease the length of hospitalization and increase the number of patient recovery.
Another study evaluated the effect of glutamine and glutamate supplementation on hematological and biochemical biomarkers in dogs with clinical enteritis[12]. A mixture of Gln + Glu along with drug treatment was capable of producing elevations in immune cells (leukocytes and lymphocytes) and biomarkers associated with improved protein metabolism and health that favor recovery of the animals without causing damage to renal and hepatic systems.
Several studies suggest that a high intake of glutamine during illness helps prevent loss of lean body mass by promoting and supporting muscle protein synthesis and decreasing muscle protein catabolism. However, the role of glutamine in the maintenance of normal gut and immune system function may be even more important for the critically ill animal. Glutamine is now considered by many investigators to be a conditionally essential nutrient during protein-calorie malnutrition, required in quantities that are greater than those that can be synthesized by the body. Based on this hypothesis and preclinical studies performed in dogs, the commercial veterinary critical care rations often recommended for cats and dogs with cancer are routinely supplemented with glutamine. Glutamine supplementation has also been suggested as a way to promote more rapid resolution of acute side effects of the oral mucosa in dogs receiving oronasal radiotherapy and to maintain gut immunity and integrity in people receiving radiotherapy or chemotherapy. Further study is needed to define the role of glutamine supplementation for cats and dogs with cancer[13].

1. Vitamin C (L-Ascorbic acid)

Because of de novo synthesis, vitamin C is not technically a vitamin for healthy dogs and cats. Vitamin C primarily functions in the body as an antioxidant and free radical scavenger. Ascorbic acid is best known for its role in collagen synthesis, where it is involved in hydroxylation of prolyl and lysyl residues of procollagen. It is also involved in drug, steroid and tyrosine metabolism and electron transport.

More recently, research into the role of ascorbic acid has shifted from prevention of deficiency to the treatment and prevention of disease. Because ascorbic acid protects against free radical damage induced by the "oxidative burst" of neutrophils and stimulates the phagocytic effect of leukocytes, it plays a role in immune function[14]. Larger doses may play a protective role against carcinogenesis. Whether the same effects as in humans can be demonstrated in species that synthesize their own ascorbate (i.e., cats and dogs) remains to be seen[15].

In a study[16], the antioxidant status in dogs with visceral leishmaniosis was evaluated. Those that were infected had significantly lower levels of plasma vitamin C compared to healthy controls. Protozoal diseases are associated with high degree of lipid peroxidation and oxidative stress, which plays an important role in the pathogenesis of hemolytic anemias seen in infected patients.

Lee et al[17] evaluated the attenuation of ischemic-reperfusion injury by vitamin C (30 mg/kg IV once) in an experimental model of canine renal transplantation. Antioxidant enzyme activity after renal transplantation was significantly increased after 72 hours in the vitamin C treated group. On histopathology, only mild tubular damage was seen in the renal grafts of the vitamin C group compared to inflammatory cell infiltration, regeneration, and congestion in the control group. Vitamin C as an exogenous antioxidant appeared to attenuate ischemic reperfusion injury by increasing antioxidant enzyme activity.

1. Echinacea extract (*Echinacea purpurea*)

A survey of clinical and pharmacology studies in man reveals that *Echinacea purpurea* both modulates and non-specifically stimulates the immune system by activating the phagocytic capacity of granulocytes and macrophages and their secretion of cytokines[18].

An open multi-centered veterinary clinical trial, comparing conditions before and after treatment with a herbal preparation, containing the powdered root of *Echinacea purpurea*, was conducted by 6 practicing veterinarians in Switzerland. The plant-based immune stimulant was administered to 41 dogs with manifestations of chronic and seasonal upper respiratory tract infections, including pharyngitis/tonsillitis, bronchitis and kennel cough. Each animal was at an individual stage of the disease, with various symptoms and different severity scores, at start of treatment. There was no control group. Echinacea powder (1:3) was administered with the food at a dose of 1.0 g/10 kg body weight once daily for 8 weeks. Overall efficacy showed significant improvement for 92% of 39 dogs after 4 weeks of treatment and this was confirmed after 8 weeks. Significant reductions of severity and resolution of typical clinical symptoms, of clear nasal secretions, enlargement of lymph nodes, dry cough, dyspnea and dry lung sounds, were evident after 4 weeks[19].

Echinacea is often recommended for chronic recurrent viral upper respiratory infection in cats, and some practitioners use Echinacea to treat patients with retroviral infection. Although some practitioners caution against the long-term use of Echinacea because toxicity or autoimmune conditions may result, this concern has not been well documented. However, immunostimulants are probably best used as pulsed treatments if they are administered on a

long-term basis, because full response to treatment is probably reached in a few weeks and does not continue to increase[20].

1. Zinc

Zinc is a constituent or activator of more than 200 enzymes, so it is involved in a number of diverse physiologic functions. Some of zinc's primary functions include: 1) nucleic acid metabolism, 2) protein synthesis, 3) carbohydrate metabolism, 4) immunocompetence, 5) skin and wound healing, 6) cell replication and differentiation, 7) growth and 8) reproduction. Zinc also interacts with hormone production, most notably testosterone, adrenal corticosteroids and insulin.

Zinc is important in a multitude of biological functions, including regulation of the immune response, modulation of keratogenesis and wound healing, maintenance of normal reproductive function, and acuity of taste and smell.

As in human medicine, veterinary medicine has reported many other therapeutic uses of zinc for specific disease entities in animals. Suggested uses in veterinary medicine include zinc therapy for burns, wound healing, seborrhea, and interdigital pyoderma in the dog' as well as for infectious pododermatitis in cattle. Most recently zinc therapy has been proposed for hypogeusia and occasional immunologic disorders[21].
Zinc-responsive dermatosis is an uncommon disease of dogs resulting from either an absolute or relative deficiency in zinc. Dermatological lesions are characterized by erythema, alopecia, scales, and crusts that primarily affect the head. Two forms of the disease exist: a familial form affecting Alaskan Malamutes and Siberian Huskies and a form that affects growing puppies fed zinc-deficient or over supplemented diets. The history, clinical signs, and skin biopsy results are typically diagnostic. Life-long zinc supplementation is usually necessary in the familial form of the disease, although dietary correction alone may be curative in the second form[22].

1. Manganese

Manganese functions as an enzyme activator or as a constituent of metalloenzymes. Although there are only a few manganese-containing metalloenzymes (e.g., arginase, pyruvate carboxylase and manganese-superoxide dismutase), many enzymes are activated by manganese, including hydrolases, kinases, decarboxylases and transferases. Manganese is also essential in bone and cartilage development because it activates glycosyltransferases (i.e., enzymes important for polysaccharide and glycoprotein synthesis). In addition, manganese is involved in reproduction and lipid metabolism (e.g., manganese is involved in the biosynthesis of choline and cholesterol). Manganese homeostasis is maintained through regulation of absorption and excretion.

Recent epidemiological and animal studies have shown that manganese increases the immune response in a wide range of vertebrates, including humans, rodents, birds, and fish. Another exciting new discovery that emerged from recent studies is the role that manganese plays in inflammatory pathways and anti-viral immunity. Manganese appears to potently increase the inflammatory response, sensitize dsDNA-driven innate immunity, and affect T cell signaling. These findings suggest that manganese metabolism could be targeted in order to treat inflammatory diseases, viral infection, and cancer (by boosting the effects of tumor immunotherapy)[23].

1. Vitamin B6, Vitamin B12, Folic acid

The eight vitamins that make up the group of B vitamins have various functions but are, however, related in that they act predominantly as co-factors to enzymes involved in energy metabolism and the synthesis of organic molecules. Through these functions, they play an essential role for the immune system that is composed of cells subject to a high turnover. This is particularly true for folic acid, cobalamin (vitamin B_{12}) and vitamin B_6 (pyridoxal, pyridoxine and pyridoxamine) that act as one carbon donors in nucleotide synthesis and the methylation of proteins and the DNA. However, these three B vitamins also have direct regulatory effects on the immune response[24].

The active form of vitamin B6, pyridoxal 5′-phosphate (PLP), serves as a co-factor in more than 150 enzymatic reactions. Plasma PLP has consistently been shown to be low in inflammatory conditions; there is a parallel reduction in liver PLP, but minor changes in erythrocyte and muscle PLP and in functional vitamin B6 biomarkers. Plasma PLP also predicts the risk of chronic diseases like cardiovascular disease and some cancers, and is inversely associated with numerous inflammatory markers in clinical and population-based studies. Vitamin B6 intake and supplementation improve some immune functions in vitamin B6-deficient humans and experimental animals. A possible mechanism involved is mobilization of vitamin B6 to the sites of inflammation where it may serve as a co-factor in pathways producing metabolites with immunomodulating effects. Relevant vitamin B6-dependent inflammatory pathways include vitamin B6 catabolism, the kynurenine pathway, sphingosine 1-phosphate metabolism, the transsulfuration pathway, and serine and glycine metabolism[25].

Vitamin B_6 shows immune-regulatory properties. Deficiency in this vitamin resulted in thymic atrophy and lower activity of thymulin in rats[26]. A negative effect on cellular T-cell-mediated immunity was also shown by the lower secretion of IL-2 in vitamin B_6-deficient mice while that of the Th2 cytokines IL-4 and IL-5 as well as of IL-10 was increased together with an enhanced reaction to sensitization with ovalbumin consistent with allergic response (IgE secretion). In turn, the production of IgG was reduced in the deficient animals. Moreover, vitamin B_6 deficiency showed a negative effect on $CD8^+$ cytotoxic cells whose number was particularly reduced. Notably, a higher dose of vitamin B_6 in excess of the required amount did not improve the immune response but on the contrary, rather impaired it. These findings were corroborated by another study in which vitamin B_6 deficiency inhibited the proliferation of lymphocytes and interfered with their differentiation. ConA-stimulated IL-2 secretion was decreased while that of IL-4 was increased and there was no effect on IFN-????. The underlying mechanism seems to be a down-regulation of the T-cell-specific transcription factor T-bet and an up-regulation of SOCS-1 (Suppressor of cytokine signalling) that attenuates cytokine signalling, in vitamin B_6 deficiency[27]. In another study, growth of FRM (Feline Mammary Tumor) cells was inhibited by the addition of pyridoxine in a dose-dependent manner[28].

Vitamin B_{12} has been shown to play a particularly important role for the cytotoxic immune response mediated by both, NK cells and $CD8^+$ T cells by upregulating these cells[29]. In old rats, vitamin B_{12} deficiency was associated with a decline of NK cell activity and also with a reduction in the B cell subset of lymphocytes. In turn, no effects on cytokine secretion and mitogen-induced lymphocyte proliferation were observed[30].

The metabolism of folate and B_{12} is closely related as methylcobalamin is required for the regeneration of tetrahydrofolate (THF) from methyltetrahydrofolate. THF plays a central role as a methyl group donor in many physiological pathways including nucleic acid synthesis and amino acid metabolism. Deficiency of vitamin B_{12} leads to trapping of THF in its methylated form and the accumulation of methyl-THF leading to a number of health impairments[31]. Maintaining the balance of the two vitamins is therefore important also with regards to the immune response. It was shown that it has particular effects on NK cells and cytotoxic

CD8+ lymphocytes. In the previously mentioned study in old rats, the vitamin B_{12}-related decline in NK cell activity and B cell numbers was most pronounced when the animals were sufficient or supplemented in folate. Moreover, NK cell activity was also found to be impaired by excessive levels of unmetabolized free folic acid.

However, folate deficiency showed negative effects on certain immune functions. Cultivating CD8+ T cells without folic acid inhibited their proliferation stimulated by PHA and IL-2 through a cytostatic mechanism rather than apoptosis. In turn, CD4+ T cells were much less affected[32]. Folate deficiency was also associated with reduced maturation of DCs, lower secretion of IL-12, TNFα, IL-6 and IL-1β by DCs stimulated with LPS and impaired differentiation of CD4+ T lymphocytes. The secretion of cytokines inducing the development of Th1 and Treg cells was reduced[33]. High constitutive expression of the folate receptor 4 was found on Treg cells distinguishing them from other naïve and activated T cell populations and its blocking depleted the number of Treg cells[34]. Additionally, oral high-dose administration of folic acid (160 µg/d to 10 mg/d) reduced the inflammatory response in mice with allergic dermatitis by suppressing T cell proliferation and the secretion of the proinflammatory and Th2 cytokines IL-4, IL-5, IL-9, IL-13, IL-17, IL-33; TNFα and TSLP in a dose-dependent manner[35].

1. Green tea (*Camellia sinensis*) extract

The effects of green tea include anti-oxidative, anti-inflammatory, anti-arthritic, anti-stress, hypolipidaemic, hypocholesterolaemic, skin/collagen protective, hepatoprotective, anti-diabetic, anti-microbial, anti-infective, anti-parasitic, anti-cancerous, inhibition of tumorigenesis and angiogenesis, anti-mutagenic, and memory and bone health-improving activities. Apart from its utilization in humans, green tea has also played a significant role in livestock production such as in dairy, piggery, goatry and poultry industries. Supplementation of animal feeds with green tea and its products is in line with the modern concepts of organic livestock production. Hence, incorporating green tea or green tea by-products into the diet of poultry and other livestock can enhance the value of the products obtained from these animals[36].

Molecular and cellular insights of green tea revealed that EGCG (Epigallocatechin gallate) has marked effect in modulating production of immunoregulatory cytokines in stimulated dendrite cells and hence acts as suppressor of T cell activation[37]. It can also prevent angiogenesis as observed in angiogenic assay in vivo and inhibits the growth of the highly angiogenic Kaposi's sarcoma tumor cells in rodent experimental modeling[38].

Green tea and EGCG effectively mitigate cellular damage by
lowering the inflammatory reaction and reduce lipid peroxidation and formation of NO radicals[39]. The anticancer perspectives of green tea catechins have been highlighted in the last few decades. It can significantly reduce the risk of cancers as revealed in experimental animal studies, human cell lines, and human clinical studies[40]. Overall, it can be used as adjunct in the treatment of bladder, breast, and colon cancer[41-42].

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