

(12) STANDARD PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. **AU 2010336985 B2**

(54) Title
Compositions including pyruvate for companion animals and methods of use thereof

(51) International Patent Classification(s)
A23K 1/16 (2006.01) **A61K 31/19** (2006.01)
A23K 1/18 (2006.01) **A61K 45/06** (2006.01)

(21) Application No: **2010336985** (22) Date of Filing: **2010.12.22**

(87) WIPO No: **WO11/082080**

(30) Priority Data

(31) Number	(32) Date	(33) Country
61/290,780	2009.12.29	US

(43) Publication Date: **2011.07.07**

(44) Accepted Journal Date: **2013.09.19**

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(56) Related Art
WO2002/074301A1
DE19836450A1

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
7 July 2011 (07.07.2011)

(10) International Publication Number
WO 2011/082080 A1

(51) International Patent Classification:

A23K 1/16 (2006.01) A61K 31/19 (2006.01)
A23K 1/18 (2006.01) A61K 45/06 (2006.01)

(21) International Application Number:

PCT/US2010/061868

(22) International Filing Date:

22 December 2010 (22.12.2010)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/290,780 29 December 2009 (29.12.2009) US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: COMPOSITIONS INCLUDING PYRUVATE FOR COMPANION ANIMALS AND METHODS OF USE THERE-OF

(57) Abstract: The invention encompasses compositions and methods for treating or preventing a degenerative joint condition, wherein the compositions and methods include feeding the companion animal an edible composition including at least one pyruvate or salt thereof. The invention also encompasses methods for enhancing the palatability of an edible food composition including adding a palatability enhancing amount at least one pyruvate or salt thereof to the composition.



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COMPOSITIONS INCLUDING PYRUVATE FOR COMPANION ANIMALS AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application claims priority to U.S. Provisional Patent Application No. 61/290,780 filed on 29 December 2009, which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

[002] Virtually all joints have cartilage. Cartilage is important in the body of animals for providing flexibility, compressibility under pressure, cushion, tensile strength, range of motion and smoothness of movement within joints. Examples of joints having cartilage include fingers and toes, neck, knee, hip, shoulder and the like. Animals can suffer from a number of conditions where cartilage is negatively affected thereby bringing about a reduction in the joint's flexibility, compressibility and often times resulting in a generalized inflammation of the joint and/or tissue surrounding the joints. Such animals then have significant loss of joint function and experience pain.

[003] Cartilage is the supporting structure of the body and consists of thick bundles of fibrous protein (collagen) which are woven to form an articular surface. Proteoglycans fill extracellular spaces not occupied by collagen. Such proteoglycans are comprised of a combination of a protein and a sugar. Each proteoglycan subunit contains a protein core consisting of long chains of modified sugars known as glycosaminoglycans (GAGs). Glucosamine is the single most important component and precursor for GAGs. Synthesis of collagen by the body is dependent upon GAG synthesis. Chondrocytes in the cartilage utilize glucosamine to produce N-acetylglucosamine (NAG) and glucuronic acid, which are utilized by the body to form hyaluron. Hyaluron confers a lubricating property to the joint of the animal's body.

[004] Cartilage is important in the body of animals for providing flexibility, compressibility under pressure, cushion, tensile strength, range of motion and smoothness of movement within joints. Examples of joints having cartilage include fingers and toes, neck, knee, hip, shoulder and the like. Animals can suffer from a number of conditions where cartilage is degraded thereby bringing about a reduction in the joint's flexibility, compressibility and often times resulting in a generalized inflammation of the joint and/or tissue surrounding the joint and in

some cases the development of conditions such as osteoarthritis and rheumatoid arthritis. Such animals then have significant loss of joint function and experience pain.

[005] Arthritis is a musculoskeletal disorder. Osteoarthritis is the most common type of arthritis in animals and humans. Osteoarthritis is a degenerative joint disease commonly occurring in humans and companion animals and the disease is characterized by degenerative changes in the articular cartilage, with loss of proteoglycan and collagen and proliferation of new bone formation at articular margins. These changes are accompanied by a variable inflammatory response within the synovial membrane. A principal defect in hyaline cartilage at the articular surface of a joint is the alteration in the ratio of glycosaminoglycans to the collagen fiber content of the matrix. Bones directly underlying cartilage in the joints are called subchondral bones. These subchondral bones nourish the overlying cartilage which itself is devoid of blood vessels, nerves or lymphatic tissue.

[006] A natural erosion of cartilage occurs with age, but may also result from excessive loads placed on joints, obesity, heredity, trauma, decreased circulation, poor bone alignment and repetitive stress. It is postulated that free radical damage may contribute to the development of osteoarthritis.

[007] Large dogs may develop arthritis as they age. Large dog breeds are more susceptible to arthritis due to their increased mass and/or genetic disposition. Large dogs are not the only animals at risk of arthritis and other cartilage conditions. Arthritis and other degenerative joint diseases have been commonly recognized in dogs and such conditions have been shown to be prevalent in cats. Animals at risk of developing cartilage-affecting conditions include, but are not limited to, mammals such as canine, feline, equine, hircine, ovine, porcine, bovine, human and non-human primate species, and birds including turkeys and chickens.

[008] Diet plays an important role in disease causation and progression because it is fundamentally involved in metabolism. Biological pathways are at some level regulated by nutritional factors. Thus, dietary components present in foods as nutrients may regulate gene expression at the transcriptional and translational level, as well as in certain post-translational modifications. They may similarly be involved in degradation and enzymatic activities. Nutrient levels may influence the equilibrium of metabolic pathways. Metabolic pathways are frequently complex and may involve many redundancies and interrelationships among different metabolic pathways. Altering the concentration of a single enzyme, growth factor, cytokine or

metabolite may impact a number of metabolic pathways involved in disease-related physiology. Hormones and other cell signaling molecules are well-understood to be regulated by diet and are also known to be implicated in the development and progression of disease.

[009] The same disease phenotype may result from disturbances in different metabolic pathways, and the genetic make-up of each animal differs, thereby causing variation in responses to the same factors, including nutritional and environmental factors. The interplay of genetic, nutritional and environmental factors is important in understanding the etiology, prevention, treatment and progression of diseases in animals. Finding gene expression responses to nutrients associated with various diseases and disorders permits formulation of diets for animals susceptible to disease such as abnormal arthritic disorders, and further permits diagnosis, treatment and monitoring the prognosis of the underlying disease or disorder.

[0010] As a result, the use of biomarkers for early detection and monitoring of disease progression may enable prevention or treatment of diseases as well as new therapies to be developed for animals, particularly for companion animals. Diet is arguably the most important environmental factor affecting the phenotype of an animal, including susceptibility to disease.

[0011] The invention encompasses edible food compositions for companion animals, which have therapeutic and prophylactic efficacy and possess increased palatability over currently marketed companion food products.

[0011A] Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present disclosure as it existed before the priority date of each claim of this application.

[0011B] Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

SUMMARY OF THE INVENTION

[0012] Accordingly, the inventors have developed edible compositions, including nutritionally complete dietary compositions for a companion animal, which include pyruvate to improve palatability of the edible composition and to confer clinically beneficial properties with regard to degenerative joint conditions to such companion animal.

[0013] The invention additionally encompasses methods for the prevention, amelioration of symptoms of, or treatment of certain conditions, disorders and diseases in companion animals, for example, degenerative joint conditions. The degenerative joint condition may be osteoarthritis or cartilage damage.

[0014] In one embodiment, the invention encompasses edible compositions for companion animals including one or more pyruvate in an amount effective to prevent, ameliorate the symptoms of, or treat degenerative joint conditions in a companion animal.

[0015] Another embodiment encompasses methods for preventing, ameliorating one or more symptoms of, or treating, a degenerative joint condition in a companion animal, which includes feeding the companion animal an edible composition including one or more pyruvate in an amount effective to prevent, ameliorate one or more symptoms of, or treat, the degenerative joint condition in such companion animal.

[0016] Another embodiment encompasses methods for preventing, ameliorating one or more symptoms of, or treating, osteoarthritis in a companion animal, which includes feeding the companion animal an edible composition including one or more pyruvate in an amount effective to prevent, ameliorate one or more symptoms of, or treat, osteoarthritis in such companion animal.

[0017] Another embodiment encompasses methods for preventing, ameliorating one or more symptoms of, or treating, cartilage damage in a companion animal, which includes feeding the companion animal an edible composition including one or more pyruvate in an amount effective to prevent, ameliorate one or more symptoms of, or treat, cartilage damage in such companion animal.

[0018] Another embodiment encompasses methods for enhancing palatability of an edible composition for consumption by an animal including adding a palatability enhancing amount of one or more pyruvate to the composition.

5 [0018A] One aspect relates to a method for treating or preventing a degenerative joint condition in a companion animal, which comprises feeding the animal an edible composition comprising one or more pyruvate in an amount effective to treat or prevent the degenerative joint condition, wherein the edible composition is a food composition, and

10 wherein the one or more pyruvate is in an amount of about 3% to about 6% by weight of the composition.

[0018B] Another aspect relates to an edible pet food composition comprising at least one pyruvate, wherein the one or more pyruvate is in an amount of about 3% to about 6% by weight of the composition.

15 [0018C] Another aspect relates to a nutritionally complete dietary composition for a companion animal comprising about 0 to about 90% by weight carbohydrates, about 5 to about 70% by weight protein, about 2 to about 50% by weight fat, and about 0 to about 15% by weight of one or more nutritional balancing substances selected from the group consisting of: vitamins, minerals or antioxidants; and about 3% to about 6% by weight of one or more pyruvate.

20 [0018D] Another aspect relates to the use of one or more pyruvate in the manufacture of an edible composition for treating or preventing a degenerative joint condition in a companion animal, wherein the one or more pyruvate is in an amount of about 3% to about 6% by weight of the composition.

25 **BRIEF DESCRIPTION OF THE FIGURES**

FIGURE 1 shows the effect of calcium pyruvate on GAG release from canine chondracytes.

FIGURE 2 shows the effect of calcium pyruvate on KC production from canine chondrocytes

30 FIGURE 3 shows the effect of calcium pyruvate on IL-8 production from canine chondracytes.

FIGURE 4 shows the effect of calcium pyruvate on MCP-1 production from canine chondracytes

DETAILED DESCRIPTION OF THE INVENTION

[0023] As used throughout, ranges are used as a shorthand for describing each and every value that is within the range. Any value within the range can be selected as the terminus of the range. In addition, all references cited herein are hereby incorporated by reference in their entireties. In the event of a conflict in a definition in the present disclosure and that of a cited reference, the present disclosure controls.

[0024] Unless otherwise specified, all percentages and amounts expressed herein and elsewhere in the specification should be understood to refer to percentages by weight.

[0025] The invention generally encompasses companion animal edible compositions including one or more pyruvate in an amount effective to treat or prevent a disorder in the companion animal.

[0026] The invention additionally encompasses methods for the prevention, amelioration of symptoms of, or treatment of certain conditions, disorders and diseases in companion animals, for example, degenerative joint conditions. The degenerative joint condition may be osteoarthritis or cartilage damage.

[0027] In one embodiment the companion animal is a dog or cat.

[0028] In another embodiment, the pyruvate is present in an amount of up to about 20% by weight of the composition.

[0029] In another embodiment, the pyruvate is present in an amount of about 0.1% by weight to about 10 % by weight of the composition

[0030] In another embodiment, the pyruvate is in an amount of about 5% by weight of the composition. In another embodiment, the pyruvate is in an amount of about 1% by weight of the composition.

[0031] In another embodiment, the pyruvate is in an amount of about 0.7% by weight of the composition.

[0032] In another embodiment, the composition further includes one or more proteins, fats, carbohydrates, fibers, and combinations thereof.

[0033] In another embodiment, the composition is a food, a nutritional diet, a supplement, an animal treat, or a toy.

[0034] In another embodiment, the edible composition is in the form of a moist food, dry food, supplement or treat.

[0035] Another embodiment of the invention encompasses methods for preventing, ameliorating one or more symptoms of, or treating, a degenerative joint condition in a companion animal, which includes feeding the animal an edible composition of the invention, which includes one or more pyruvate in an amount effective to prevent, ameliorate one or more symptoms of, or treat, the degenerative joint condition. In one embodiment, the degenerative joint condition is osteoarthritis or cartilage damage in such companion animal.

[0036] Another embodiment of the invention encompasses methods for preventing, ameliorating one or more symptoms of, or treating, osteoarthritis in a companion animal, which includes feeding the animal an edible composition of the invention, which includes one or more pyruvate in an amount effective to treat or prevent the osteoarthritis in such companion animal.

[0037] Another embodiment of the invention encompasses methods for preventing, ameliorating one or more symptoms of, or treating, cartilage damage in a companion animal, which includes feeding the animal an edible composition of the invention, which includes one or more pyruvate in an amount effective to treat or prevent the cartilage damage in such companion animal.

[0038] Another embodiment of the invention encompasses methods for enhancing palatability of an edible composition for consumption by a companion animal including adding a palatability enhancing amount of one or more pyruvate to the composition.

[0039] It is contemplated that the invention described herein is not limited to the particular methodology, protocols, ingredients and reagents described as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention in any way.

[0040] Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices and materials are now described. All publications mentioned herein are incorporated by reference for the purpose of describing and disclosing the materials and methodologies that are reported in the publication, which might be used in connection with the invention.

[0041] As used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise.

[0042] The term "antioxidant" means a substance that is capable of reacting with free radicals and neutralizing them. Illustrative examples of such substances include beta-carotene, selenium, coenzyme Q10 (ubiquinone), lutein, tocotrienols, soy isoflavones, S-adenosylmethionine, glutathione, taurine, N-acetylcysteine, vitamin E, vitamin C, lipoic acid and L-carnitine. Examples of foods containing useful levels of one or more antioxidants include but are not limited to, ginkgo bilboa, green tea, broccoli, citrus pulp, grape pomace, tomato pomace, carrot spinach, and a wide variety of fruit meals and vegetable meals. It will be understood by one of skill in the art that while units of antioxidants may be provided herein as "ppm", appropriate amounts of antioxidants may also be provided as "IU/kg" where appropriate and customary for a given antioxidant such as, *e.g.*, Vitamin E.

[0043] The term "carbohydrate" as used herein includes polysaccharides (*e.g.*, starches and dextrans) and sugars (*e.g.*, sucrose, lactose, maltose, glucose, and fructose) that are metabolized for energy when hydrolyzed. Examples of carbohydrates suitable for inclusion in the compositions disclosed herein include but are not limited to, corn, grain sorghum, wheat, barley, and rice.

[0044] The term "cat" includes those cats which are companion animals known as domestic cats or house cats.

[0045] The term "companion animal" used in the present invention includes any non-human animal suitable for being kept as a pet by humans including a dog and a cat. All aspects of the present invention are preferably for the treatment of cats and/or dogs.

[0046] As used herein the term "compositions of the invention" refers to animal dietary food compositions including pyruvate. The compositions of the invention include pyruvate in an amount of about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 1.5%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 15%, or about 20% by weight. The compositions of the invention may alleviate degenerative joint conditions in animals fed such compositions. The compositions of the invention may alleviate inflammation. The compositions of the invention may relieve arthritic conditions, for example, osteoarthritis, or less

common inflammatory joint diseases in companion animals such as rheumatoid arthritis, psoriatic arthritis and other degenerative joint disorders.

[0047] The term “dog” includes those dogs which are companion animals such as *Canis familiaris*, working dogs and the like. The term dog is synonymous with the term canine.

[0048] As used herein, “an amount effective”, “an effective amount”, and like terms refer to that amount of a compound, material or composition as described herein that may be effective to achieve a particular biological result. Such effective activity may be achieved, for example, by administration of compositions of the present invention to an animal. An effective amount may be based on several factors, including an animal's ideal weight, the metabolizable energy of the composition, and frequency of feeding the animal compositions of the present invention, e.g., once, twice, or three times daily, and other compositions fed to the animal.

[0049] A “food” is a nutritionally complete diet for the intended recipient animal (e.g., domestic cat or domestic dog).

[0050] The term “inflammation” refers to a protective attempt by an organism to remove an injurious stimulus and initiate the healing processes for the tissue affected by the injurious stimulus. Inflammation can be classified as either acute or chronic. Acute inflammation is an initial response to harmful stimuli and is achieved by the increased movement of plasma and leukocytes from the blood into the injured tissues. A cascade of biochemical events propagates and matures the inflammatory response, involving the local vasculature, the immune system, and various cells within the injured tissue. Chronic inflammation, or prolonged inflammation, leads to a progressive shift in the type of cells, which are present at the site of inflammation, and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process.

[0051] As used herein, an “ingredient” refers to any component of a composition.

[0052] As used herein, the terms “pyruvate” includes, but is not limited to, for example, pyruvic acid and salts and esters of pyruvic acid, including but not limited to: calcium pyruvate, sodium pyruvate, lithium pyruvate, potassium pyruvate, magnesium pyruvate, zinc pyruvate, manganese pyruvate and combinations thereof. The term “pyruvate” also includes certain pyruvate precursor molecules in the form of pyruvamides or pyruvyl-amino acids. The term pyruvyl-amino acids includes, pyruvyl-glycine, pyruvyl-glutamine, pyruvyl-lysine, pyruvyl-valine, pyruvyl-isoleucine, pyruvyl-phenylalanine, pyruvyl-proline and their amides, esters, salts and

mixtures thereof. The term “pyruvate” also include derivatives of pyruvic acid such as ethyl pyruvate, propyl pyruvate, butyl pyruvate, carbmethoxymethyl pyruvate, carbethoxymethyl pyruvate, acetoxymethyl pyruvate, carbmethoxyethyl pyruvate, carbethoxyethyl pyruvate, methoxymethyl pyruvate and ethoxymethyl pyruvate. The term “pyruvate” also includes mixtures of any of the foregoing substances. In certain preferred embodiments, the pyruvate is calcium pyruvate.

[0053] The terms “sample” and “specimen” mean any animal tissue or fluid containing, e.g., polynucleotides, polypeptides, antibodies, metabolites, and the like, including cells and other tissue containing DNA and RNA. Examples include: blood, cartilage, connective, epithelial, lymphoid, muscle, nervous, sputum, and the like. A sample may be solid or liquid and may be DNA, RNA, cDNA, bodily fluids such as blood or urine, cells, cell preparations or soluble fractions or media aliquots thereof, chromosomes, organelles, and the like.

[0054] As used herein, “soluble fiber” refers to dietary fiber that attracts water during digestion and slows the rate of nutrient absorption and is typically found in, e.g., oat bran, seeds, beans, and certain fruits and vegetables such as beet pulp, guar gum, chicory root, psyllium, pectin, blueberry, cranberry, squash, apples, oats, beans, citrus, barley and peas. As used herein, the term encompasses any source of soluble fiber suitable for the compositions disclosed herein as would be evident to one of skill in the art.

[0055] The term “substance” means an element, compound, molecule, or a mixture thereof or any other material that could potentially be useful for diagnosing, prognosing, or modulating the onset or severity of an degenerative joint condition in an animal, including any drug, chemical entity, or biologic entity.

[0056] As used herein, the term “supplement(s)” include but are not limited to, a feed used with another feed to improve nutritive balance or performance of the total. Supplements include but are not limited to, compositions that are fed undiluted as a supplement to other feeds, offered free choice with other parts of an animal’s ration that are separately available, or diluted and mixed with an animal’s regular feed to produce a complete feed. The AAFCO guidelines, for example, contain a discussion relating to supplements in the Official Publication of The Association of American Feed Control Officials, Inc. (AAFCO), Atlanta, GA, 2005, or the National Research Council’s *Nutrient Requirements of Dogs and Cats*, The National Academy Press, Washington, D.C., 2006.

[0057] Supplements may be in various forms including, for example, powders, liquids, syrups, pills, encapsulated compositions, and the like.

[0058] The term “nutrient” refers to a substance that provides nourishment. In some cases an ingredient may comprise more than one “nutrient,” for example, a composition may comprise fish oil as an ingredient, the oil itself comprising important nutrients such as eicosapentaenoic acid and docosahexaenoic acid. The distinction in these terms is familiar to one of skill in the art.

[0059] As contemplated herein, the compositions of the present invention are meant to encompass nutritionally complete and balanced animal food compositions that additionally comprise pyruvate. A “nutritionally complete diet” is a diet that includes sufficient nutrients for maintenance of normal health of a healthy animal on the diet.

[0060] Nutritionally complete and balanced pet food compositions are familiar to one of skill in the art. For example substances such as nutrients and ingredients suitable for nutritionally complete and balanced animal feed compositions, and recommended amounts thereof, may be found for example, in the Official Publication of The Association of American Feed Control Officials, Inc. (AAFCO), Atlanta, GA, 2005, or the National Research Council’s *Nutrient Requirements of Dogs and Cats*, The National Academy Press, Washington, D.C., 2006.

[0061] For example, a nutritionally complete and balanced pet food composition of the present invention may comprise: about 0 to about 90%, preferably about 5% to 60%, by weight of carbohydrates; about 5% to about 70%, preferably about 10% to about 60%, by weight of protein; about 2% to about 50%, preferably about 5% to about 40%, by weight of fat; about 0.1% to about 40%, preferably about 1% to about 11%, by weight of total dietary fiber; about 0 to about 15%, preferably about 2% to about 8%, by weight of vitamins and minerals, antioxidants, and other nutrients which support the nutritional needs of the animal; and about 0.1% to about 20% by weight of pyruvate.

[0062] One embodiment of the invention encompasses edible compositions for companion animals including one or more pyruvate.

[0063] The compositions of the invention include pyruvate in an amount effective to prevent, ameliorate one or more symptoms of, or treat, a degenerative joint condition, including degradation to articular cartilage, to decrease release of GAG from cartilage tissue, and to prevent, ameliorate one or more symptoms of, or treat, an arthritic condition.

[0064] The compositions of the invention may alternatively include pyruvate in an amount effective to enhance palatability of an edible composition for consumption by a companion animal.

[0065] Generally, the amount effective in the composition includes one or more pyruvate in an amount of up to about 20% by weight, up to about 18% by weight, up to about 16% by weight, up to about 14% by weight, up to about 12% by weight, up to about 10% by weight, up to about 9% by weight, up to about 8% by weight, up to about 7% by weight, up to about 6% by weight, up to about 5% by weight, up to about 4% by weight, up to about 3% by weight, up to about 2% by weight of the composition, or up to about 1% by weight. In certain embodiments, the one or more pyruvate is present in an amount of 0.5 to 1.0% by weight of the composition, and in other embodiments the one or more pyruvate is present in an amount of approximately 0.7% by weight of the composition.

[0066] The invention is based upon the novel discovery that adding one or more pyruvate to a composition for consumption by a companion animal enhances palatability of the composition and increases the likelihood that an animal will consume the composition. Adding one or more pyruvate to a composition for consumption by a companion animal also increases the ingestion frequency and ingestion rate of the composition. This feature of the invention was not heretofore appreciated in designing nutritionally complete dietary compositions for companion animals, particularly compositions useful for treating the conditions or disorders disclosed and claimed in this specification, nor in designing nutritionally complete dietary compositions for companion animals that maintain or promote a healthy body composition in said animal.

[0067] The invention generally encompasses pet food compositions for a companion animal comprising an amount of protein, an amount of fat, an amount of carbohydrate, an amount of fiber and an effective amount of one or more pyruvate to prevent inflammation or an inflammatory disorder in a companion animal.

[0068] In certain embodiments, the effective amount of pyruvate is at least 0.1% by weight pyruvate. In other embodiments of the invention one or more pyruvate is present in a range of about 0.1% to about 20% by weight on a dry matter basis. In preferred embodiments the pyruvate is present in an amount of about 0.7% by weight on a dry matter basis.

[0069] In certain embodiments, the companion animal is a dog.

[0070] In certain embodiments, the companion animal is a cat.

[0071] In various embodiments, the companion animals of the invention are the domestic cat (*Felis domesticus*) or the domestic dog (*Canis domesticus*). Other companion animals include, fish, bird and horse.

[0072] In certain embodiments, the companion animal is a senior animal.

[0073] In certain embodiments, the dietary food composition can be administered to a senior animal or an animal with arthritis.

[0074] The edible compositions, in addition to one or more pyruvate, may also include at least one component suitable for consumption by a companion animal including, but not limited to, fats, carbohydrates, proteins, fibers, nutritional balancing agents such as vitamins, minerals, and trace elements, and mixtures thereof. One of ordinary skill in the art can select the amount and type of food ingredients for a typical food based upon the dietary requirements of the animal, for example, the animal's species, age, size, weight, health, and function.

[0075] A "nutritionally complete diet" is a diet that includes sufficient nutrients for maintenance of normal health of a healthy animal on the diet. The methods of this invention utilize compositions that are not intended to be restricted by any specific listing of proteinaceous or fat ingredients or product form. The compositions can be prepared in, for example, a dry, canned, wet, or intermediate moisture form using conventional pet food processes.

[0076] The food composition can include up to about 100% of any particular food ingredient or can include a mixture of food ingredients in various proportions. In certain embodiments, the food composition includes a combination of food ingredients in amounts of about 0 wt. % to 50 wt. % fat, 0 wt. % to 75 wt. % carbohydrate, 0 wt. % to 95 wt. % protein, 0 wt. % to 40 wt. % dietary fiber, and 0 wt. % to 15 wt. % of one or more nutritional balancing agents.

[0077] In one illustrative embodiment, the composition may, for example, in addition to one or more pyruvate also include at least one of the following:

- (a) about 0% to about 75% carbohydrate;
- (b) about 2% to about 50% fat;
- (c) about 0% to about 40% dietary fiber, and
- (d) about 0% to about 15% of one or more nutritional balancing agents.

[0078] In certain embodiments, the fat and carbohydrate food ingredient is obtained from a variety of sources such as animal fat, fish oil, vegetable oil, meat, meat by-products, grains, other animal or plant sources, and mixtures thereof. Grains include wheat, corn, barley, and rice. In

certain embodiments, protein may be supplied by any of a variety of sources known by those skilled in the art, including plant sources, animal sources, or both. Animal sources include, for example, meat, meat by-products, seafood, dairy, eggs, etc. Meats include, for example, the flesh of poultry, fish, and mammals (e.g., cattle, pigs, sheep, goats, and the like). Meat by-products include, for example, lungs, kidneys, brain, livers, and stomachs and intestines (freed of all or essentially all their contents). The protein can be intact, almost completely hydrolyzed, or partially hydrolyzed. Protein content of foods may be determined by any number of methods known by those of skill in the art, for example, as published by the Association of Official Analytical Chemists in *Official Methods of Analysis* ("OMA"). The amount of "crude protein" in a composition disclosed herein may be determined based on the amount of nitrogen in the composition according to methods familiar to one of skill in the art.

[0079] The compositions of the present invention may also include amino acids in amounts required to avoid deficiency and maintain health. These amounts and methods of measurement are known by those skilled in the art. For example, AAFCO provides recommended amounts of such ingredients for dogs and cats. Amino acids in the present compositions may be supplied by any number of sources, including crude protein, or addition of free amino acids to the composition.

[0080] Fat can be supplied by any of a variety of sources known by those skilled in the art, including meat, meat by-products, fish oil, and plants. Plant fat sources include wheat, flaxseed, rye, barley, rice, sorghum, corn, oats, millet, wheat germ, corn germ, soybeans, peanuts, and cottonseed, as well as oils derived from these and other plant fat sources. Fat content of foods may be determined by any number of methods known by those of skill in the art.

[0081] Carbohydrate may be supplied by any of a variety of sources known by those skilled in the art, including oat fiber, cellulose, peanut hulls, beet pulp, parboiled rice, corn starch, corn gluten meal, and any combination of those sources. Grains supplying carbohydrate include, but are not limited to, wheat, corn, barley, and rice. Carbohydrate content of foods may be determined by any number of methods known by those of skill in the art. Generally, carbohydrate percentage may be calculated as nitrogen free extract ("NFE"), which may be calculated as follows: $NFE = 100\% - \text{moisture}\% - \text{protein}\% - \text{fat}\% - \text{ash}\% - \text{crude fiber}\%$.

[0082] As used herein, "fiber blend" includes a combination of soluble and insoluble fiber at a level that is between 1-5% total dietary fiber on a dry matter basis. The sources of the fiber can

be combinations of cellulose, hemicelluloses, resistant starches, or oligosaccharides such as galactooligosaccharides, xylooligosaccharides, or fructooligosaccharides.

[0083] Dietary fiber refers to components of a plant that are resistant to digestion by an animal's digestive enzymes. Dietary fiber components of foods may be determined by any number of methods known by those of skill in the art, such as those published by the OMA. Dietary fiber includes soluble and insoluble fibers.

[0084] Soluble fiber are resistant to digestion and absorption in the small intestine and undergo complete or partial fermentation in the large intestine, e.g., beet pulp, guar gum, chicory root, psyllium, pectin, blueberry, cranberry, squash, apples, oats, beans, citrus, barley, or peas. Insoluble fiber may be supplied by any of a variety of sources, including cellulose, whole wheat products, wheat oat, corn bran, flax seed, grapes, celery, green beans, cauliflower, potato skins, fruit skins, vegetable skins, peanut hulls, and soy fiber. Soluble and insoluble fiber content of foods may be determined by any number of methods known by those of skill in the art. Crude fiber includes indigestible components contained in cell walls and cell contents of plants such as grains, e.g., hulls of grains such as rice, corn, and beans. Crude fiber content of foods may be determined by any number of methods known by those of skill in the art.

[0085] In certain embodiments, the fiber food ingredient is obtained from a variety of sources such as vegetable fiber sources, for example, cellulose, beet pulp, peanut hulls, and soy fiber.

[0086] Metabolizable energy (ME) of a diet is the energy available to an animal upon consumption of the diet after subtracting the energy excreted in feces, urine, and combustible gases. Metabolizable energy values may be determined by methods known by those skilled in the art, such as detailed in the Official Publication of The Association of American Feed Control Officials, Inc. or the National Research Council's *Nutrient Requirements of Dogs and Cats*, The National Academy Press, Washington, D.C., 2006.

[0087] "Ash" consists of compounds that are not organic or water, generally produced by combustion of biological materials. Ash may be determined by any number of methods known by those of skill in the art.

[0088] Carnitine, or L-carnitine, is a vitamin-like compound synthesized in the body from lysine and methionine. Carnitine may be naturally present in ingredients of the present invention, or carnitine may be added to the compositions.

[0089] The compositions of the present invention also may contain one or more minerals and/or trace elements, e.g., calcium, phosphorus, sodium, potassium, magnesium, manganese, copper, zinc, or iron salts. One particular trace element is manganese. Manganese is essential to a host of enzymes as a cofactor, which may regulate the metabolism of foods, including proteins, fats, and carbohydrates. Such enzymes may include oxidoreductases, transferases, hydrolases, lyases, isomerases, ligases, lectins, and integrins. Manganese also affects bone development and neurological function. Manganese may be naturally present in the components of the compositions, or it may be added to compositions. Methods of measuring manganese content in a composition are well known to those of skill in the art.

[0090] The compositions of the present invention may also include vitamins and minerals in amounts required to avoid deficiency and maintain health. These amounts and methods of measurement are known by those skilled in the art. For example, AAFCO provides recommended amounts of such ingredients for dogs and cats. As contemplated herein, useful vitamins may include, but are not limited to, vitamin A, vitamin B₁, vitamin B₂, vitamin B₆, vitamin B₁₂, vitamin C, vitamin D, vitamin E, vitamin H (biotin), vitamin K, folic acid, inositol, niacin, and pantothenic acid.

[0091] In certain embodiments, the nutritional balancing agents are obtained from a variety of sources known to skilled artisans, for example, vitamin and mineral supplements and food ingredients. Vitamins and minerals can be included in amounts required to avoid deficiency and maintain health. These amounts are readily available in the art. The Association of American Feed Control Officials, Inc. provides recommended amounts of such nutrients for dogs and cats. Vitamins generally useful as food additives include vitamin A, vitamin B₁, vitamin B₂, vitamin B₆, vitamin B₁₂, vitamin D, biotin, vitamin K, folic acid, inositol, niacin, and pantothenic acid. Minerals and trace elements useful as food additives include calcium, phosphorus, sodium, potassium, magnesium, copper, zinc, chloride, iron, selenium, iodine, and iron.

[0092] In certain embodiments, the food compositions may contain additional ingredients such as fillers, palatability enhancers, binding agents, flavors, stabilizers, emulsifiers, sweeteners, colorants, buffers, salts, coatings, and the like known to skilled artisans. Stabilizers include substances that tend to increase the shelf life of the composition such as preservatives, synergists and sequestrants, packaging gases, stabilizers, emulsifiers, thickeners, gelling agents, and humectants. Examples of emulsifiers and/or thickening agents include gelatin, cellulose ethers,

starch, starch esters, starch ethers, and modified starches. Specific amounts for each composition component, food ingredient, and other ingredients will depend on a variety of factors such as the particular components and ingredients included in the composition; the species of animal; the animal's age, body weight, general health, sex, and diet; the animal's consumption rate; the type of disease or condition being treated; and the like. Therefore, the component and ingredient amounts may vary widely and may deviate from the preferred proportions described herein.

[0093] The invention encompasses pet food compositions or supplements wherein one or more pyruvate is present in an effective amount to prevent, ameliorate one or more symptoms of, or treat, a condition in a companion animal. The effective amount of one or more pyruvate may vary depending on such factors as the patient being treated, the particular mode of administration, the activity of the particular active ingredients employed, the age, bodyweight, general health, sex and diet of the patient, time of administration, rate of excretion, the particular combination of ingredients employed, the total content of the main ingredient of the nutritional supplement or nutritionally complete diet, and the severity of the illness or symptom. It is within the skill of the person of ordinary skill in the art to account for these factors.

[0094] The food composition may further contain other ingredients such as corn, poultry meal, grease, palatability enhancers, potassium chloride, iodized salt, calcium carbonate, choline chloride, mineral premix, preservative, vitamin premix. The food may contain protein. The protein may be animal protein. Animal protein may be part of the total protein. Animal protein may be 50%, 70%, 80%, 90%, 95%, 99% or 100% of the total protein. The food may contain antioxidants, such as vitamin E. Antioxidant may be present in between about 0.0001U/g and 3.0 U/g food, such as, *e.g.*, 0.18 U/g. The food may contain eicosapentaenoic acid (EPA) at between 1% by weight and 5% weight. Fatty acids may also be included such as n-3 and n-6 fatty acids. Fatty acids may be present in about 0.05% to 5% by weight. n-3 fatty acids may be present in about 0.0001% to 2%. n-6 fatty acids may be present in about 0.5% to 5% by weight. The food may contain fiber, such as crude fiber. Fiber may be present in between 0.001% and 10% by weight.

[0095] The effective amount of the nutritional supplement will vary depending on such factors as the patient being treated, the particular mode of administration, the activity of the particular active ingredients employed, the age, body weight, general health, sex and diet of the patient, time of administration, rate of excretion, the particular combination of ingredients employed, the

total content of the main ingredient of the nutritional supplement, and the severity of the illness or symptom. It is within the skill of the person of ordinary skill in the art to account for these factors.

[0096] The pyruvate-containing dietary foods or supplements of the present invention may be formulated using a safe and effective amount of one or more pyruvate as discussed herein to provide one or more of the beneficial effects of the invention described herein, and one or more of the optional ingredients which may be obtained from slippery elm or green tea, as well as one or more of the additional optional ingredients described below. The nutritional supplement of the present invention may also be formulated with a pharmaceutically acceptable carrier.

[0097] Other materials, which may optionally be included in the nutritional supplement of the present invention include inositol, other B-complex vitamins, and anti-inflammatories. Also, ingredients such as sweeteners, flavorants, coloring agents, dyes, preservatives, emulsifying agents, suspending agents, melting agents, excipients, and solvents or diluents such as water, ethanol, propylene glycol, glycerin and various combinations thereof, may be included in the pyruvate-containing foods or supplements of the present invention.

[0098] The optional sweeteners, which may be used in the pyruvate-containing foods or supplements of the present invention include, but are not limited to, saccharin, aspartame, cyclamates, acesulfame K, neohesperidin dihydrochalcone, other sweeteners, and mixtures thereof, which may be added to the carrier in amounts sufficiently low so as not to chemically interact with the main ingredients of the nutritional supplement.

[0099] The optional flavorants which may be used in the pyruvate-containing foods or supplements of the present invention include, but are not limited to, peppermint, peppermint-menthol, eucalyptol wintergreen, licorice, clove, cinnamon, spearmint, cherry, lemon, orange lime, menthol and various combinations thereof.

[00100] Such additives are present in amounts that do not impair the purpose and effect provided by the invention. Examples of additives include, for example, substances with a stabilizing effect, processing aids, substances that enhance palatability, coloring substances, and substances that provide nutritional benefits.

[00101] Stabilizing substances include, for example, substances that tend to increase the shelf life of the composition. Potentially suitable examples of such substances include, for example, preservatives, antioxidants, synergists and sequesterants, packaging gases, stabilizers,

emulsifiers, thickeners, gelling agents, and humectants. Examples of emulsifiers and/or thickening agents include, for example, gelatin, cellulose ethers, starch, starch esters, starch ethers, and modified starches.

[00102] Additives for coloring, palatability, and nutritional purposes include, for example, colorants (e.g., iron oxide, such as the red, yellow, or brown forms); sodium chloride, potassium citrate, potassium chloride, and other edible salts; vitamins; minerals; and flavoring. Such additives are known in the art. See, e.g., U.S. Patent No. 3,202,514. See also, U.S. Patent No. 4,997,671. Flavorants include, for example, dairy product flavorants (e.g., milk or cheese), meat flavorants (e.g., bacon, liver, beef, poultry, or fish), oleoresin, pinacol, and the various flavorants identified in the trade by a FEMA (Flavor Extract Manufacturers Association) number. Flavorants help provide additional palatability, and are known in the art. See, e.g., U.S. Patent No. 4,997,672. See also, U.S. Patent No. 5,004,624, U.S. Patent No. 5,114,704, U.S. Patent No. 5,532,010, and U.S. Patent No. 6,379,727. The concentration of such additives in the composition typically may be up to about 5% by weight. In some embodiments, the concentration of such additives (particularly where such additives are primarily nutritional balancing agents, such as vitamins and minerals) is from about 0% to about 2.0% by weight. In some embodiments, the concentration of such additives (again, particularly where such additives are primarily nutritional balancing agents) is from about 0% to about 1.0% by weight.

[00103] The composition of the invention may include one or more additional ingredients to prevent or treat one or more diseases or conditions. The component in the diet, which accomplishes this, may be an antioxidant or mixture thereof. An antioxidant is a material that quenches a free radical. Examples of such materials include foods such as Ginkgo Biloba, citrus pulp, grape pomace, tomato pomace, carrot and spinach, all preferably dried as well as various other materials such as beta-carotene, selenium, coenzyme Q10 (ubiquinone), lutein, tocotrienols, soy isoflavones, S-adenosylmethionine, glutathione, taurine, N-acetylcysteine, Vitamin E, Vitamin C, alpha-lipoic acid, l-carnitine and the like. Vitamin E can be administered as a tocopherol or a mixture of tocopherols and various derivatives thereof such as esters like vitamin E acetate, succinate, palmitate, and the like. The alpha form is preferable but beta, gamma and delta forms can be included. The d form is preferable but racemic mixtures are acceptable. The forms and derivatives will function in a Vitamin E like activity after ingestion by the pet. Vitamin C can be administered in this diet as ascorbic acid and its various derivatives

thereof such as calcium phosphate salts, cholesteryl salt, 2-monophosphate, and the like which will function in a vitamin C like activity after ingesting by the pet. They can be in any form such as liquid, semisolid, solid and heat stable form. L-carnitine can be administered in the diet and various derivatives of carnitine such as the salts such as the hydrochloride, fumarate and succinates, as well as acetylated carnitine, and the like can be used.

[00104] In certain embodiments, the compositions further include an effective amount of at least one substance selected from the group consisting of glucosamine, chondroitin, chondroitin sulfate, methylsulfonylmethane ("MSM"), creatine, antioxidants, *Perna canaliculata*, omega-3 fatty acids, omega-6 fatty acids, tocopherols, ascorbate, calcium, chloride, cysteine, magnesium, manganese, methionine, phosphorous, potassium, iron, essential amino acids and mixtures thereof.

[00105] In certain embodiments, the pet food composition further comprises any of the following: vitamin E, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), other n-3 fatty acids, n-6 fatty acids, crude fiber, soluble fiber, and mixtures of the foregoing ingredients.

[00106] As contemplated herein, functional ingredients and nutrients for use in the present invention include walnut oil, sesame oil, sunflower oil, capsibilol-*T*, pomegranate, magnolia, lipoic acid, vitamin C, ginger, green and black tea, optionally together with an optimal fiber blend of soluble and insoluble fibers. Juices, extracts, pulp or other forms of formulations of said ingredients are included.

[00107] In various embodiments, the pet food composition can further include corn, poultry meal, palatability enhancers, potassium chloride, iodized salt, calcium carbonate, choline chloride, minerals, mineral premix, preservatives, vitamins, and mixtures thereof. In certain embodiments, the dietary food composition may further include L-tryptophan. The quantities administered in the diet, all as wt % (dry matter basis) of the diet, are calculated as the active material, per se, that is measured as free material. The maximum amounts employed should not bring about toxicity. At least about 100 ppm or at least about 150 ppm of Vitamin E can be used. A preferred range of 500 to 1,000 ppm can be employed. Although not necessary, a maximum of about 2000 ppm or about 1500 ppm is generally not exceeded. With respect to Vitamin C at least about 50 ppm is used, desirably at least about 75 ppm and more desirably at least about 100 ppm. A non-toxic maximum can be employed. The quantity of lipoic acid can vary from at least about 25, desirably at least about 50 ppm, more desirably about 100 ppm. Maximum quantities can

vary from 100 ppm to 600 ppm or to an amount which remains non-toxic to the pet. A preferred range is from 100 ppm to 200 ppm. For l-carnitine about 50 ppm, desirably about 200 ppm, more desirably about 300 ppm for canines are a useful minimum. For felines, slightly higher minimums of l-carnitine can be employed such as about 100 ppm, 200 ppm, and 500 ppm. A non-toxic maximum quantity can be employed, for example, less than about 5,000 ppm. For canines, lower quantities can be employed, for example, less than about 5,000 ppm. For canines, a preferred range is 200 ppm to 400 ppm. For felines, a preferred range is 400 ppm to 600 ppm. Beta-carotene at 1-15 ppm can be employed. Selenium at 0.1 up to 5 ppm can be employed. Lutein at least about 5 ppm can be employed. Tocotrienols at least about 25 ppm can be employed. Coenzyme Q10 at least about 25 ppm can be employed. S-adenosylmethionine at least about 50 ppm can be employed. Taurine at least about 1000 ppm can be employed. Soy isoflavones at least about 25 ppm can be used. N-acetylcysteine at least about 50 ppm can be used. Glutathione at least about 50 ppm can be used. Gingko Biloba at least 50 ppm of extract can be used.

[00108] In various embodiments, the pyruvate may be added to the animal's food. In various embodiments, the pyruvate may be added to the animal's food by a compounder or manufacturer at a site or by an animal's caregiver prior to feeding the animal. In various embodiments, the pyruvate may be added during the processing of an animal's food, such as during and/or after mixing of other components of the composition that is then packaged and made available to consumers. Such processing may include extrusion, canning, baking, and the like or any other method or process of producing pet foods that is known in the art. In various embodiments, the pyruvate may be contributed by a natural source like an animal or plant component or the pyruvate may be contributed by a synthetically derived source or the pyruvate may be contributed by a mixture of natural and synthetic sources.

[00109] The edible compositions of the invention may be prepared in a canned or wet form using conventional food preparation processes known to skilled artisans. Typically, ground animal proteinaceous tissues are mixed with the other ingredients such as fish oils, cereal grains, balancing ingredients, special purpose additives (e.g., vitamin and mineral mixtures, inorganic salts, cellulose and beet pulp, bulking agents, and the like) and water in amounts sufficient for processing. These ingredients are mixed in a vessel suitable for heating while blending the components. Heating of the mixture is effected using any suitable manner, for example, direct

steam injection or using a vessel fitted with a heat exchanger. When heated to the appropriate temperature, the material will typically be in the form of a thick liquid. The thick liquid is filled into cans. A lid is applied, and the container is hermetically sealed. The sealed can is then placed into conventional equipment designed to sterilize the contents. The compositions of the present invention can be added to the food compositions before, during, or after preparation.

[00110] Food compositions may be prepared in a dry form using conventional processes known to skilled artisans. Typically, dry ingredients such as animal protein, plant protein, grains, and the like are ground and mixed together. Moist or liquid ingredients, including fats, oils, animal protein, water, and the like are then added to and mixed with the dry mix. The mixture is then processed into kibbles or similar dry pieces. Kibble is often formed using an extrusion process in which the mixture of dry and wet ingredients is subjected to mechanical work at a high pressure and temperature and forced through small openings and cut off into kibble by a rotating knife. The wet kibble is then dried and optionally coated with one or more topical coatings such as flavours, fats, oils, powders, and the like. Kibble also can be made from the dough using a baking process, rather than extrusion, wherein the dough is placed into a mold before dry-heat processing.

[00111] In preparing a composition for use with the methods of the present invention, any ingredient (e.g., fish oil) generally may, for example, be incorporated into the composition during the processing of the formulation, such as during and/or after mixing of other components of the composition. Distribution of these components into the composition can be accomplished by conventional means. In one embodiment, ground animal and poultry proteinaceous tissues are mixed with the other ingredients, including fish oils, cereal grains, other nutritionally balancing ingredients, special-purpose additives (e.g., vitamin and mineral mixtures, inorganic salts, cellulose and beet pulp, bulking agents, and the like); and water that is sufficient for processing is also added.

[00112] Methods of the present invention include utilizing compositions that can be prepared in a dry form using conventional processes. In one embodiment, dry ingredients, including, for example, animal protein sources, plant protein sources, grains, etc., are ground and mixed together. Moist or liquid ingredients, including fats, oils, animal protein sources, water, etc., are then added to and mixed with the dry mix. The mixture is then processed into kibbles or similar dry pieces. Kibble is often formed using an extrusion process in which the mixture of dry and

wet ingredients is subjected to mechanical work at a high pressure and temperature, and forced through small openings and cut off into kibble by a rotating knife. The wet kibble is then dried and optionally coated with one or more topical coatings which may include, for example, flavors, fats, oils, powders, and the like. Kibble also can be made from the dough using a baking process, rather than extrusion, wherein the dough is placed into a mold before dry-heat processing.

[00113] The compositions may also be designed to be easier to chew. Canine and feline foods are typically formulated based on life stage (age), size, body composition, and breed. In the methods of this invention, some embodiments of the compositions address specific nutritional differences between senior regular or small breed dogs, large breed dogs, and cats.

[00114] All percentages expressed herein are on a weight by dry matter basis unless specifically stated otherwise.

[00115] In one embodiment, the compositions are in the form of a companion animal food composition or pet food.

[00116] Foods of any consistency or moisture content are contemplated, e.g., the compositions of the present invention may be a moist, semi-moist, or dry animal food composition. "Moist" food refers to food that has a moisture content of 60 to 90% or greater. "Dry" food refers to compositions with 3 to 11% moisture content and is often manufactured in the form of small bits or kibbles. "Semi-moist" refers to compositions with 25-35% moisture content. Also contemplated herein are compositions that may comprise components of various consistency as well as components that may include more than one consistency, for example, soft, chewy meat-like particles as well as kibble having an outer cereal component and an inner cream component as described in, e.g., U.S. Patent No. 6,517,877.

[00117] The edible composition can be a liquid or a solid food. When the composition is a liquid, the pyruvate can be admixed with other components. Where the composition is solid, the pyruvate may be coated on the composition, incorporated into the composition, or both.

[00118] In certain embodiments, the edible composition can be a supplement. Supplements include, for example, a feed used with another feed to improve the nutritive balance or performance of the total. Supplements include compositions that are fed undiluted as a supplement to other feeds, offered free choice with other parts of an animal's ration that are separately available, or diluted and mixed with an animal's regular feed to produce a complete feed. AAFCO, for example, provides a discussion relating to supplements in the Official

Publication of The Association of American Feed Control Officials, Inc. (2009). Supplements may be in various forms including, for example, powders, liquids, syrups, pills, encapsulated compositions, and the like.

[00119] In certain embodiments, the edible composition can be a treat. Treats include compositions that are given to an animal to entice the animal to eat during a non-meal time, for example, dog bones for canines. Treats may be nutritional wherein the composition includes one or more nutrients and may have a food-like composition. Non-nutritional treats encompass any other treats that are non-toxic. The composition or components are coated onto the treat, incorporated into the treat, or both. Treats of the invention can be prepared by an extrusion or baking process similar to those used for dry food. Other processes also may be used to either coat the composition on the exterior of existing treat forms or inject the composition into an existing treat form.

[00120] In certain embodiments, the edible composition can be a toy. Toys include chewable toys such as artificial bones. The at least one pyruvate can form a coating on the surface of the toy or on the surface of a component of the toy, be incorporated partially or fully throughout the toy, or both. In one embodiment, the one or more pyruvate is orally accessible by the intended user. There are a wide range of suitable toys currently marketed, for example, U.S. Pat. No. 5,339,771, U.S. Pat. No. 5,419,283, and references disclosed therein. This invention provides both partially consumable toys, for example, toys including plastic components, and fully consumable toys, for example, rawhides and various artificial bones. The invention preferably provides toys for use by a dog or a cat.

[00121] The invention also encompasses methods of preventing, ameliorating one or more symptoms of, or treating certain disorders by administering a therapeutically or prophylactically effective amount of a composition including one or more pyruvate to a companion animal in need thereof

[00122] In one embodiment the composition providing a therapeutically or prophylactically effective amount of one or more pyruvate is administered in a nutritionally complete dietary composition.

[00123] In another embodiment, the invention encompasses methods of preventing, ameliorating one or more symptoms of, or treating, a degenerative joint condition in a companion animal, which includes feeding to the animal an edible composition of the invention including one or

more pyruvate in an amount effective to prevent, ameliorate one or more symptoms of, or to treat, the degenerative joint condition. In certain embodiments of the invention, the composition and method for preventing, ameliorating one or more symptoms of, or treating a degenerative joint condition is for a canine or a feline. In other embodiments of the invention the composition providing an effective amount of one or more pyruvate to prevent, ameliorate one or more symptoms of, or to treat, the degenerative joint condition is a nutritionally complete dietary composition.

[00124] The methods or uses of the compositions of the invention include administering the composition including one or more pyruvate to a companion animal susceptible to or suffering from a degenerative joint condition or administering the compositions to an animal experiencing a decline in joint function, particularly a decline due to aging. The composition may also be fed to a healthy companion animal in order to maintain healthy joint functions and/or prevent a degenerative joint condition.

[00125] The treatment or prevention of a degenerative joint condition according to the invention includes the treatment or prevention of various cartilage affected conditions. The invention therefore includes not only the treatment of a pre-existing cartilage affecting condition but also the prevention or protection of animals against a cartilage affecting condition. The invention includes managing a cartilage affecting condition.

[00126] The term “managing a cartilage affecting condition” as used herein means to improve, treat, prevent and/or alleviate at least one cartilage affected condition and/or to provide a positive cartilage effect to an animal. The term “managing a cartilage affecting condition” includes preventative methods for an animal with a latent cartilage effecting condition, a predisposition, whether hereditary or otherwise to a cartilage affected condition or as a preventative measure at any time during an animal’s lifetime to strengthen cartilage, prevent abnormalities in cartilage, improve joint health, decrease the effects of joint degradation over age, or to prevent arthritis or other joint affected condition. Illustrative examples of a positive cartilage effect includes increasing flexibility, repairing lesions, reducing inflammation, improving mobility, strengthening cartilage, reducing abnormalities, and/or preventing any of reduced flexibility and/or mobility, weakening and/or degrading cartilage, abnormalities and/or lesions, inflammation, or a cartilage affected condition, and the like. Illustrative examples of such cartilage affected conditions include osteoarthritis, rheumatoid arthritis, osteochondrosis,

degenerative joint disease, synovitis, bacterial purulent arthritis, osteoarthropathia psoriatica and the like.

[00127] In another embodiment, the invention encompasses methods for preventing, ameliorating one or more symptoms of, or treating, osteoarthritis in companion animals, which includes feeding the animal an edible composition including at least one or more pyruvate in an amount effective to prevent, ameliorate one or more symptom of, or treat, osteoarthritis in such companion animal. In other embodiments of the invention the composition providing an effective amount of one or more pyruvate to prevent, ameliorate one or more symptoms of, or to treat osteoarthritis is a nutritionally complete dietary composition.

[00128] In another embodiment, the invention encompasses methods for preventing, ameliorating one or more symptoms of, or treating, cartilage damage in a companion animal, which includes feeding the animal an edible composition including one or more pyruvate in an amount effective to prevent, ameliorate one or more symptom of, or treat, cartilage damage in such companion animal. In other embodiments of the invention the composition providing an effective amount of one or more pyruvate to prevent, ameliorate one or more symptoms of, or to treat cartilage damage in a companion animal is administered in a nutritionally complete dietary composition.

[00129] Another embodiment of the invention is a method of preventing, ameliorating one or more symptom of, or treating, a degenerative joint disease in a companion animal, the method comprising the step of administering to said animal in need thereof a nutritionally complete dietary composition comprising one or more pyruvate at a concentration of from about 0.1% to about 10% by weight on a dry matter basis.

[00130] Yet another embodiment of the invention is a method of preventing, ameliorating one or more symptom of, or treating, an arthritic condition in a companion animal, the method comprising the step of administering to said animal in need thereof a nutritionally complete dietary composition comprising one or more pyruvate at a concentration of from about 0.1% to about 10% by weight on a dry matter basis.

[00131] Another embodiment of the invention is a method of preventing, ameliorating one or more symptoms of, or treating, osteoarthritis in a companion animal, the method comprising the step of administering to said animal in need thereof a nutritionally complete dietary composition

comprising one or more pyruvate at a concentration of from about 0.1% to about 10% by weight on a dry matter basis.

[00132] A further embodiment of the invention is a method of managing a cartilage affecting condition in a companion animal, the method comprising the step of administering to said animal in need thereof a nutritionally complete dietary composition comprising one or more pyruvate at a concentration of from about 0.1% to about 10% by weight on a dry matter basis.

[00133] Another embodiment of the invention is a method of decreasing production of one or more inflammatory cytokine in a companion animal predisposed to developing or suffering from a degenerative joint disease, comprising the step of administering to said animal in need thereof a nutritionally complete dietary composition comprising one or more pyruvate at a concentration of from about 0.1% to about 10% by weight on a dry matter basis.

[00134] Another embodiment of the invention is a method of decreasing production of one or more inflammatory cytokines in a companion animal predisposed to developing or suffering from a degenerative joint disease, comprising the step of administering to said animal in need thereof a nutritionally complete dietary composition comprising one or more pyruvate at a concentration of from about 0.1% to about 10% by weight on a dry matter basis, wherein the inflammatory cytokine is selected from the group consisting of alpha-ketocaproic acid, interleukin-8 or monocyte chemotactic protein-1.

[00135] Another embodiment of the invention is a method of reducing the severity and frequency of clinical signs and symptoms of a degenerative joint condition in a companion animal, comprising the step of administering to said animal in need thereof a nutritionally complete dietary composition comprising one or more pyruvate at a concentration of from about 0.1% to about 10% by weight on a dry matter basis.

[00136] Another embodiment of the invention is a method of reducing the severity and frequency of clinical signs and symptoms of osteoarthritis in a companion animal, comprising the step of administering to said animal in need thereof a nutritionally complete dietary composition comprising one or more pyruvate at a concentration of from about 0.1% to about 10% by weight on a dry matter basis.

[00137] Another embodiment of the invention is a method of slowing the clinical progression of an arthritic condition degenerative joint condition in a companion animal, comprising the step of administering to said animal in need thereof a nutritionally complete dietary composition

comprising one or more pyruvate at a concentration of from about 0.1% to about 10% by weight on a dry matter basis.

[00138] Another embodiment of the invention encompasses methods for enhancing palatability of an edible composition for consumption by an animal including adding a palatability enhancing amount of one or more pyruvate to the composition.

[00139] In certain embodiments, the method is for enhancing the palatability of an edible composition for consumption by a dog or cat. As shown in the results of example 2, cats preferred the food which contained one or more pyruvate compared to the control food. This suggests improved palatability with the inclusion of one or more pyruvate in the food.

[00140] The invention also encompasses methods of using one or more pyruvate as a palatability enhancer when the composition is or contains an unpalatable medication such as a drug having less than desirable palatability to an animal, for example, typical small molecule pharmaceuticals, small proteins, macromolecular proteins and molecules, and antibodies administered orally.

SPECIFIC EMBODIMENTS OF THE INVENTION

[00141] The invention is further described in the following examples. The examples are merely illustrative and do not in any way limit the scope of the invention as described and claimed.

This invention can be further illustrated by the following examples of preferred embodiments thereof, although it will be understood that these examples are included merely for purposes of illustration and are not intended to limit the scope of the invention unless otherwise specifically indicated.

EXAMPLES

[00142] Example 1: Effect of Pyruvate on GAG Release and Cytokine Production in Canine Chondrocytes

Materials and Methods:

Culture Media Compositions:

[00143] Complete Culture Media (CM): DMEM with high glucose, L-glutamine (GlutaMAX), sodium pyruvate, 10% FBS, 100 U/ml penicillin, 100 µg/ml streptomycin and 0.5 µg/ml amphotericin B.

Complete Culture Media + ascorbic acid (CM + AA): CM + 50 µg/ml ascorbic acid.

Serum Free Culture Media (SFM): DMEM with high glucose, L-glutamine (GlutaMAX), sodium pyruvate, 100 U/ml penicillin, 100 µg/ml streptomycin and 0.5 µg/ml amphotericin B.

Test Procedure

Day: 0, 1, 5

A B C

A: Test Articles added.

B: Oncostatin M added.

C: Cell culture supernatants and beads removed.

Canine Chondrocyte Cell Culture:

[00144] Cryopreserved canine chondrocytes were isolated by Cell Applications, Inc. (catalog number 402-05, lot number 2035). Cryopreserved cells were grown as monolayers for 2 passages in CM. Monolayer cultures were suspended in 1.2% sodium alginate (prepared in 155 mM sodium chloride) at 4×10^6 cells/ml. The cell solution was passed drop-wise through a 22 gauge needle into a solution of 102 mM calcium chloride. Cell beads were allowed to solidify for 10 minutes and resuspended in CM + AA. Cells beads were grown at 37°C with 5% CO₂. After 24 days of growth in CM + AA (media changed every 2 – 3 days), beads were grown for 24 hours in SFM prior to Test Article addition.

Test Article Preparation:

[00145] Calcium pyruvate (65% mixture, MW 88.06) was dissolved to 10 mM in water, heated for 15 minutes at 37°C and filter sterilized through a 0.2 micron syringe filter. 10 µM and 1 µM working calcium pyruvate solutions were prepared by diluting the 10 mM and 10 µM solutions, respectively, in SFM.

Preparation of Dexamethasone/Vehicle Control:

[00146] A 2.55 mM solution of dexamethasone prepared in ethanol was diluted to 10 μ M SFM.

[00147] Vehicle control solution 1 (0.09% ethanol) was prepared by diluting ethanol to 0.09% in SFM. Vehicle control solution 2 was SFM.

Preparation of Oncostatin M:

[00148] A 100 μ g/ml solution of oncostatin M (OSM; prepared in water) was diluted to 500 ng/ml in SFM.

Test Article Treatment:

[00149] After 24 hours in SFM, beads were transferred to 24-well plates (3 beads/well) and the appropriate Test Article and control solutions were added. Cells were incubated for 24 hours prior to oncostatin M treatment.

Oncostatin M Treatment:

[00150] 50 μ L of SFM was added to the – OSM plate. 50 μ L of the 500 ng/ml OSM solution was added to the + 50 ng/ml OSM plate. The plates were incubated for 4 days at 37°C with 5% CO₂.

Cell Culture Plate Layout:

[00151] OSM

1 2 3 4 5 6

A Vehicle 1 Vehicle 1 Ca Pyruvate (10 μ M) Ca Pyruvate (10 μ M)

B Dexamethasone Dexamethasone Ca Pyruvate (1 μ M) Ca Pyruvate (1 μ M)

+ 50 ng/ml OSM

1 2 3 4 5 6

A Vehicle 2 Vehicle 2 Ca Pyruvate (10 μ M) Ca Pyruvate (10 μ M)

B Dexamethasone Dexamethasone Ca Pyruvate (1 μ M) Ca Pyruvate (1 μ M)

Supernatant/Cell Bead Harvesting:

[00152] After 4 days of OSM treatment, cell culture supernatants were harvested and stored at -30°C until assayed. Cell beads were washed with PBS and stored at -30°C until digested.

Cell Bead Digestion:

[00153] 200 μ L of water and 250 μ L of 2 x digestion buffer (0.1 M phosphate buffer pH 6.5, 4 mM EDTA, 4 mM L-cysteine, 250 μ g/ml papain) were added to thawed cell beads (approximate cell bead volume = 50 μ L). Beads were digested for 4 hours at 65°C. Digested beads were stored at -30°C until assayed.

Glycosaminoglycan (GAG) Assay:

[00154] 100 μ L of cell culture supernatants or 10 μ L of digested cell beads with 90 μ L of 1 x digestion buffer (without papain) were added to 1.5 ml tubes. GAG standard was prepared in 1 x digestion buffer (without papain) or SFM. Samples and standards were incubated for 45 minutes with 1 ml of Blyscan Dye Reagent on an orbital shaker at 700 rpm. Samples were centrifuged at 20,817 x g for 10 minutes. Supernatants were removed and pellets were incubated with Blyscan Dye Dissociation Reagent for > 4 hours. 200 μ L of dissociated dye from each sample was transferred to 96 well plates.

[00155] Data were collected at 650 nm using a ThermoMax microplate reader (Molecular Devices). Standard curves were generated using a 4-parameter logistic curve fitting equation (SoftMax Pro 4.7.1; Molecular Devices). Each sample reading was interpolated from the appropriate standard curve. Values were corrected for the amount of GAG present in the cell beads and cell culture supernatants.

Cytokine/Chemokine Assays

[00156] Cell culture supernatants were assayed for PGE2 by ELISA following the manufacturer's instructions. Absorbance readings were detected using a ThermoMax microplate reader (Molecular Devices). Standard curves were generated using a 4-parameter logistic curve fitting equation (SoftMax Pro 4.7.1; Molecular Devices). Each sample reading was interpolated from the appropriate standard curve. Duplicate interpolated sample values were averaged and standard deviations were calculated. Calculated concentrations were multiplied by the appropriate dilution factor.

[00157] Cell culture supernatants were assayed for GM-CSF, IL-2, IL-6, IL-7, IL-8, IL-10, IL-15, IL-18, IP-10, KC and MCP-1 using a Luminex-based assay according to the manufacturer's instructions. Data were collected using a Luminex 100 (Luminex Corporation, Austin, TX). Standard curves were generated using a 5-parameter logistic curve-fitting equation weighted by 1/y (StarStation V 2.0; Applied Cytometry Systems, Sacramento, CA). Each sample

reading was interpolated from the appropriate standard curve. Calculated concentrations were multiplied by the appropriate dilution factor when necessary.

[00158] Data were analyzed using one-way ANOVA followed by Dunnett's post test (Prism V 4.0, GraphPad Software, San Diego, CA).

[00159] Figures 1 to 4 show the results of the above experiments. Figure 1 shows the effect of calcium pyruvate on % GAG release on the in vitro stimulation of canine chondrocyte cells. Figure 2 shows the effect of calcium pyruvate on KC production on the in vitro stimulation of canine chondrocyte cells. Figure 3 shows the effect of calcium pyruvate on IL-8 production on the in vitro stimulation of canine chondrocyte cells. Figure 4 shows the effect of calcium pyruvate on MCP-1 production on the in vitro stimulation of canine chondrocyte cells.

[00160] Example 2: The Effect of Pyruvate on Feline Palatability

Materials and Methods:

[00161] 21 cats were offered choice of either a control food or control + pyruvate. The control food compositions are as in Table 1. 1% Calcium pyruvate was added to the control food in place of the corn. At day 0, cats were allotted to one of two foods, the control food or the control food + pyruvate. Intakes were measured and an intake ratio was calculated based on standard palatability testing.

Table 1. Ingredients Used to make Feline Control Food

Ingredient Order	Feline Control Food
1	Corn Gluten Meal
2	Corn
3	Poultry Meal
4	Cellulose
5	Beet Pulp
6	Soybean oil
7	Pal Enhancer 1
8	Pal Enhancer 2
9	L-Lysine
10	Potassium Chloride
11	Calcium Sulfate
12	L-carnitine
13	Choline Chloride
14	DL-Methionine
15	Vitamin E
16	Glycerol Monosaturate
17	Potassium Citrate
18	Vitamin Premix
19	Taurine
20	Salt
21	L-Arginine
22	Mineral Premix

Table2. Feline Pyruvate Palatability Test

Item	Feline Control	Feline Control + Pyruvate	% preferring control	% preferring pyruvate	Intake Ratio	Probability
Intake, g	11	19	29	67	0.6335	0.0389

[00236] Example 3: The Effect of Pyruvate on Feline Arthritis Biomarkers in Felines

Materials and Methods:

[00237] Calcium pyruvate was tested in arthritic and normal cats to determine efficacy in reducing cartilage damage and inflammatory markers. Ten normal and ten arthritis cats were fed

the feline control diet enhanced with 1% by weight calcium pyruvate for 28 days. Analysis was performed on natural log transformed values. Means and SED are antilog values of log transformed data.

[00238] Results:

Calcium pyruvate reduced the concentration of serum IL-1 beta and HMGB1 in cats and also improved a marker of bone formation, BAP. This suggests that the food containing pyruvate had anti-inflammatory affects and improved bone formation that is lost in arthritic conditions.

Table 3: Senior Feline Pyruvate Biomarker Measurements

Biomarker	Control	Control + 1% Calcium pyruvate	SED	PValue
BAP	9.28	12.74	1.05	<0.0001
HMGB1	1.09	0.63	1.24	0.0198
IL-1 beta	101.0	84.6	1.08	0.0334
IL-6	84.2	77.9	1.08	0.201

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method for treating or preventing a degenerative joint condition in a companion animal, which comprises feeding the animal an edible composition comprising one or more pyruvate in an amount effective to treat or prevent the
5 degenerative joint condition, wherein the edible composition is a food composition, and
wherein the one or more pyruvate is in an amount of about 3% to about 6% by weight of the composition.
2. The method of claim 1, wherein the companion animal is a dog.
- 10 3. The method of claim 1, wherein the companion animal is a cat.
4. The method of any preceding claim, wherein the composition further comprises a component selected from the group consisting of protein, fat, carbohydrate, fiber, and
15 combinations thereof.
5. The method of any preceding claim, wherein the composition is a nutritional diet, a supplement, an animal treat, or a toy.
- 20 6. The method of any preceding claim, wherein the degenerative joint condition comprises osteoarthritis.
7. The method of any preceding claim, wherein the degenerative joint condition comprises cartilage damage.
- 25 8. An edible pet food composition comprising at least one pyruvate, wherein the one or more pyruvate is in an amount of about 3% to about 6% by weight of the composition.
- 30 9. The composition of claim 8, wherein the composition is a dog food.

10. The composition of claim 8, wherein the composition is a cat food.
11. The composition of any one of claims 8-10, wherein the one or more pyruvate is in an amount of about 5% by weight of the composition.
- 5 12. The composition of any one of claims 8-11, wherein the composition further comprises a component selected from the group consisting of protein, fat, carbohydrate, fiber, and combinations thereof.
- 10 13. The composition of any one of claims 8-12, wherein the composition is a food, a nutritional diet, a supplement, an animal treat, or a toy.
14. The composition of any one of claims 8-13, wherein said one or more pyruvate is calcium pyruvate.
- 15 15. A nutritionally complete dietary composition for a companion animal comprising about 0 to about 90% by weight carbohydrates, about 5 to about 70% by weight protein, about 2 to about 50% by weight fat, and about 0 to about 15% by weight of one or more nutritional balancing substances selected from the group consisting of: vitamins, minerals or antioxidants; and about 3% to about 6% by weight of one or more pyruvate.
- 20 16. The composition of claim 15, wherein said companion animal is a canine.
- 25 17. The composition of claim 15, wherein said companion animal is a feline.
18. The composition of any one of claims 15-17, wherein said one or more pyruvate is calcium pyruvate.
- 30 19. Use of one or more pyruvate in the manufacture of an edible composition for treating or preventing a degenerative joint condition in a companion animal, wherein

the one or more pyruvate is in an amount of about 3% to about 6% by weight of the composition.

- 5 20. The method of claim 1, the edible food composition of claim 8, the nutritionally complete dietary composition of claim 18, or the use of claim 19, substantially as hereinbefore described.

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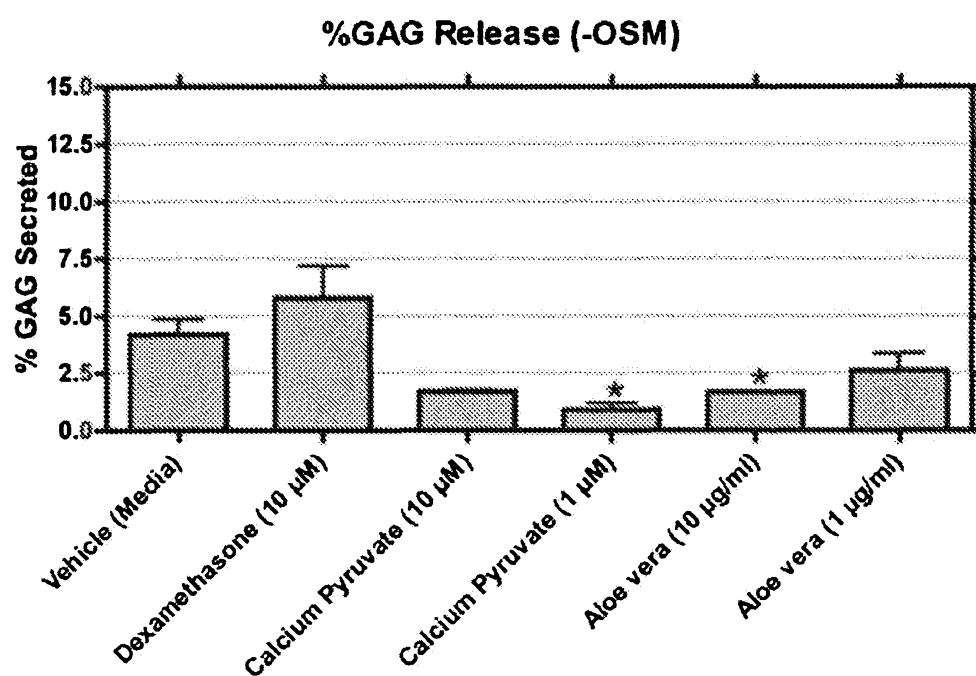


FIGURE 1

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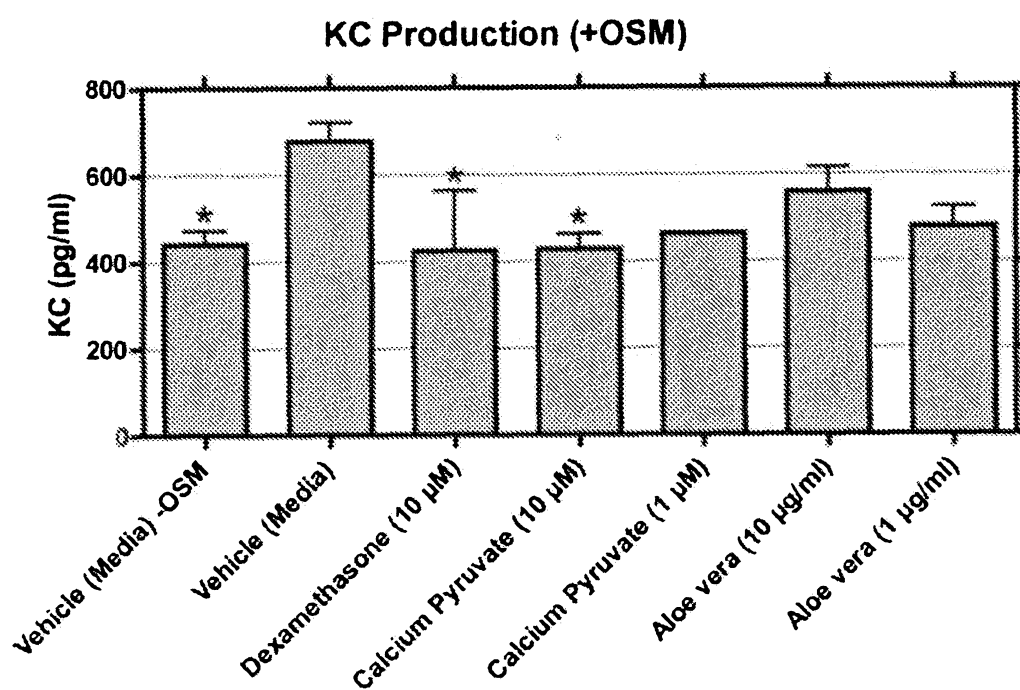


FIGURE 2

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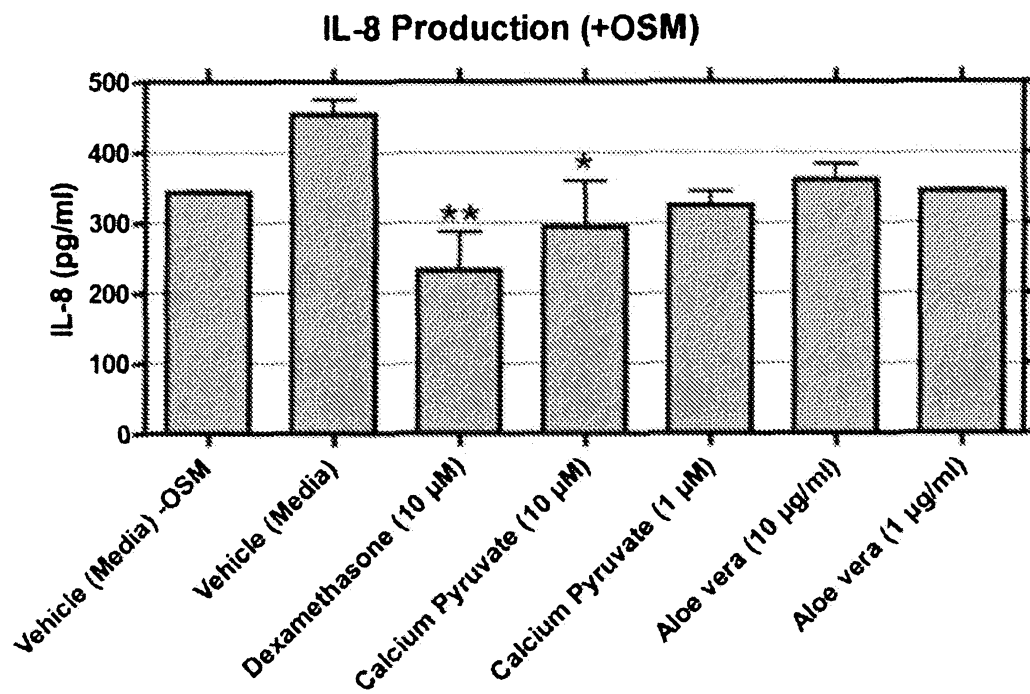


FIGURE 3

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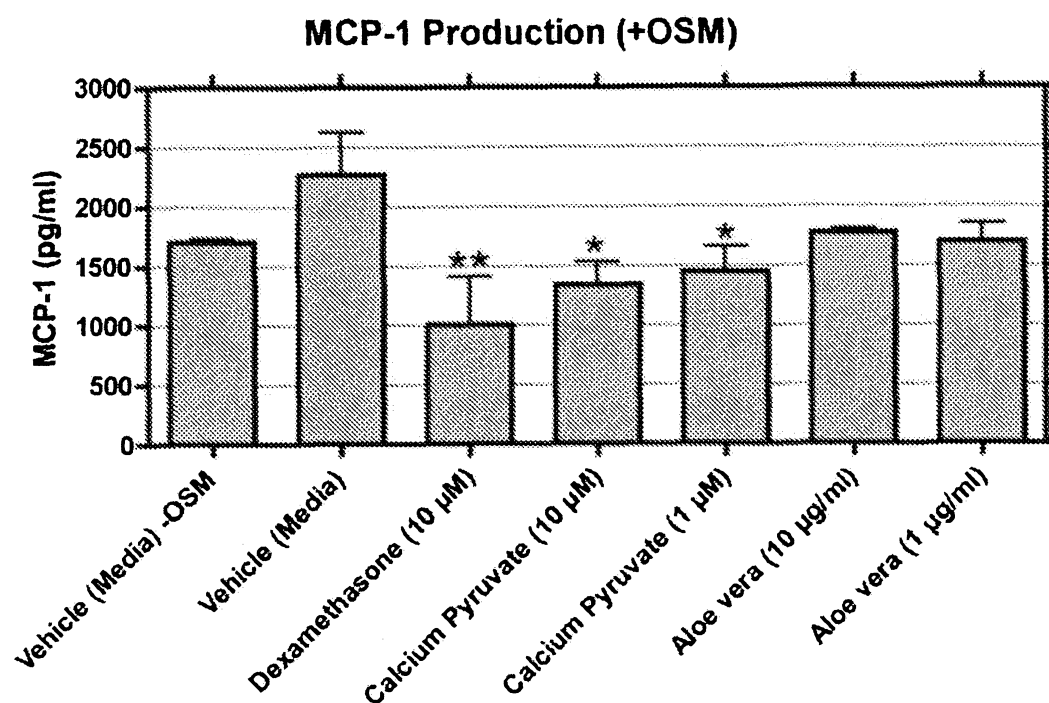


FIGURE 4