



US 20060013905A1

(19) **United States**
 (12) **Patent Application Publication** (10) **Pub. No.: US 2006/0013905 A1**
Tehoharides (43) **Pub. Date: Jan. 19, 2006**

(54) ANTI-INFLAMMATORY COMPOSITIONS FOR TREATING MULTIPLE SCLEROSIS

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(21) Appl. No.: **11/214,831**
(22) Filed: **Aug. 31, 2005**

Related U.S. Application Data

(63) Continuation-in-part of application No. 10/811,826, filed on Mar. 30, 2004.
Continuation-in-part of application No. PCT/US02/00476, filed on Jan. 3, 2002.
Continuation-in-part of application No. 09/771,669, filed on Jan. 30, 2001.
Continuation-in-part of application No. 09/056,707, filed on Apr. 8, 1998, now Pat. No. 6,689,748.

Publication Classification

(51) **Int. Cl.**
A61K 35/78 (2006.01)
A61K 31/7048 (2006.01)
A61K 31/737 (2006.01)
A61K 31/685 (2006.01)
A61K 31/225 (2006.01)
 (52) **U.S. Cl.** **424/769**; 514/27; 514/54; 514/78; 514/547

(57) **ABSTRACT**

Compositions with synergistic anti-inflammatory effects in inflammatory diseases resulting from activation and consequent degranulation of mast cells and followed by secretion of inflammatory biochemicals from the activated mast cells, the compositions containing one or more of a flavone or flavonoid glycoside a heavily sulfated, non-bovine proteoglycan, an unrefined olive kernel extract that increases absorption of these compositions in various routes of administration, a hexosamine sulfate such as D-glucosamine sulfate, S-adenosylmethionine, a histamine-1 receptor antagonist, a histamine-3 receptor agonist, an antagonist of the actions of CRH, a long-chain unsaturated fatty acid, a phospholipid, Krill oil, a polyamine, glutiramer acetate and interferon. Certain of the present compositions are useful in protecting against the neuropathological components of multiple sclerosis and similar inflammatory neurological diseases.

ANTI-INFLAMMATORY COMPOSITIONS FOR TREATING MULTIPLE SCLEROSIS

[0001] This Continuation-in-Part application takes its priority from copending Ser. No. 10/811,826, filed Mar. 13, 2004, PCT/US02/00476, filed Jan. 3, 2002, U.S. Ser. No. 09/771,669, filed Jan. 30, 2001, and U.S. Ser. No. 09/056,707, filed Apr. 8, 1998, now U.S. Pat. No. 6,689,748.

BACKGROUND OF THE INVENTION

[0002] The invention is generally related to the treatment of inflammatory conditions. More specifically, the invention is related to compositions containing inhibitors of mast cell activation and secretion such as a proteoglycan and a flavonoid compound that are designed to be used as dietary supplements or adjuvants to conventional approved medications for the relief of inflammatory conditions, e.g., in the brain as in multiple sclerosis.

[0003] There have been a number of mostly anecdotal reports that the proteoglycan chondroitin sulfate, as well as glucosamine sulfate, a product of the intestinal breakdown of proteoglycans, may be helpful in relieving the pain of osteoarthritis.—Shute N. Aching for an arthritis cure. *US News and World Report*, Feb. 10, 1997.—Cowley G. The arthritis cure? *Newsweek*, Feb. 17, 1997; Foreman J., People, and their pets, tout arthritis remedy. *The Boston Globe*, Apr. 7, 1997; Tye L. Treatment gains scientific attention. *The Boston Globe*, Sep. 25, 2000.

[0004] A meta-analysis showed potential therapeutic benefit of chondroitin sulfate and/or glucosamine in osteoarthritis [McAlindon et al. *J Am Med Assn.* 283:1469 (2000)], while a double-blind clinical trial with glucosamine showed definite benefits in osteoarthritis with respect to both pain and radiographic joint appearance [Reginster et al., *Lancet* 337:252 (2001)]. However, less than 5% of the chondroitin sulfate in commercially available preparations is absorbed orally, because the size of the molecule and the degree of sulfation impede its absorption from the gastrointestinal tract. Furthermore, such commercial preparations use chondroitin sulfate obtained from cow trachea, with the possible danger of contracting spongiform encephalopathy or “mad cow disease”. In fact, the European Union has banned even cosmetics that contain bovine-derived products.

[0005] Theoharides et al. *British Journal of Pharmacology* 131:1039 (2000) indicated for the first time how proteoglycans, such as chondroitin sulfate, may work. This paper reported that chondroitin sulfate and, to a lesser degree, glucosamine sulfate, inhibit activation of mast cells that are known to trigger allergy and asthma. This discovery is the basis for Theoharides, T C, U.S. Pat. No. 6,689,748 and Ser. No. 09/773,576, filed Feb. 2, 2001.

[0006] Mast cells are also now recognized as important causative intermediaries in many painful inflammatory conditions [Galli, *N Eng J. Med.* 328:257 (1993); Theoharides, *Int J Tissue Reactions* 18:1 (1996)], such as interstitial cystitis and irritable bowel syndrome [Theoharides, T C, *Ann NY Acad. Sci.* 840:619 (1998)], as well as in migraines [Theoharides, T C, *Brain Res. Rev.* 49:65 (2005) and possibly multiple sclerosis [Theoharides, T C *Pers Biol Med.* 26:672 (1983), Theoharides, *Life Sci* 46:607 (1996), and J. *Neuroimmunol.* 146:1 (2004)

rheumatoid arthritis, through activation of local mast cells by, for example, neuropeptides, such as Substance P. Additional indirect evidence also supports the involvement of mast cells in bone resorption: (a) systemic mastocytosis is invariably associated with osteoporosis; (b) inhibition of mast cell mediator release reversed lytic bone changes; (c) depletion of mast cells inhibited bone resorption in organ culture; (d) human synovial mast cells were shown to secrete in response to allergic and non-immunologic stimuli; (e) human mast cells release the cytokine IL-6 and (f) IL-6 has been definitively linked to bone resorption and osteoporosis.

[0008] It was shown that chondroitin sulfate’s ability to inhibit the activation of mast cells compliments the inhibitory effects on mast cell activation of another class of naturally occurring compounds, the flavonoids [Middleton et al. *Pharm Rev* 52:1 (2000)]. Certain plant flavones (in citrus fruit pulp, seeds, sea weed) are now recognized as anti-allergic, anti-inflammatory, anti-oxidant and cytoprotective with possible anti-cancer properties. Only some flavonoids, especially those belonging to the subclass of flavonols, e.g., quercetin, inhibit mast cell activation.

[0009] Quercetin inhibits secretion from human activated mast cells [Kimata et al. *Allergy* 30:501(2000)], and has also been used effectively for the treatment of chronic prostatitis [Shoskes et al., *Urology* 54:960 (1999)]. However, other flavonoids may have opposite effects. Use of the term “bioflavonoids” or “citrus flavonoids” in certain commercial products, therefore, provides little information, and may include molecules that have detrimental effects; for example, soy contains isoflavones that have estrogen-like activity that worsens inflammatory conditions.

[0010] U.S. Pat. No. 6,689,748, and divisional application Ser. No. 09/773,576 claim the oral use of proteoglycans, without and with flavonoids, for the treatment of mast cell activation-induced diseases. Absorption of these compositions from the gastrointestinal tract and synergism with other treatment modalities were not addressed in these applications.

[0011] Applicant has described the use of antagonists of the action of Corticotropin Releasing Hormone (“CRH”) (also known as Corticotropin Releasing Factor) in inhibiting myocardial mast cell activation in myocardial ischemia, in treating stress-induced skin disease (U.S. Pat. No. 6,020,305) and stress-induced migraine headaches (U.S. Pat. No. 5,855,884), the contents of which are incorporated herein by reference. The synergistic effects of the compositions of the present invention that include antagonists of the actions of CRH on mast cells were not recognized at the time of the previous studies. The word “antagonists” in connection with CRH is intended herein to include any molecule that prevents the actions of CRH on target cells, and includes, but is not limited to, anti-CRH neutralizing antibodies or binding proteins, or molecules preventing the release of CRH at local sites (see below for details).

[0012] Applicant has also described a method for treating patients with mast cell derived molecules-induced interstitial cystitis with certain histamine-I receptor antagonists (Theoharides, U.S. Pat. No. 5,994,357). Treatment of mast cell molecules-induced migraines with histamine-3 receptor agonists is the subject of Theoharides U.S. Pat. No. 5,855,

U.S. Pat. No. 5,831,259. The contents of these three patents are incorporated herein by reference. At the time of this invention the synergistic effects of the present compositions with such antagonists had not yet been recognized.

[0013] An important need therefore exists for compositions for administration to human patients being treated for mast cell-induced inflammatory diseases by various modalities, that are synergistic in that they have stronger effects than the sum of the effects of the individual components, and also synergistic with conventional clinical treatments of inflammatory conditions. "Synergistic" is also intended to mean: "coordinated or correlated action by two or more structures or drugs"[Stedman's Medical Dictionary, 23rd edition, Williams & Wilkins, Baltimore, 1976]. An important need also exists for formulations that increase the absorption from the gastrointestinal tract, nasal passages and skin surface of the compositions of the invention. Such formulations have been discovered, and are described below.

SUMMARY OF THE INVENTION

[0014] The invention comprises compositions for human use containing one or more of a flavonoid compound, a non-bovine heavily sulfated proteoglycan, an unrefined olive kernel extract, a sulfated hexosamine, S-adenosylmethionine ("SAM"), histamine-1 receptor antagonists, histamine-3 receptor agonists, antagonists of the actions of CRH, folic acid, a straight chain polyunsaturated fatty acid, a phospholipid, a polyamine, an interferon and glutiramer acetate, together with appropriate excipients and carriers, said compositions having improved absorption from the gastrointestinal tract, skin surface, and nasal and pulmonary surfaces, and anti-inflammatory effects synergistic with each other and synergistic with available conventional clinical treatment modalities.

[0015] In one embodiment, the sulfated glucosamine is D-glucosamine sulfate, the proteoglycan is non-bovine chondroitin sulfate, and the flavonoid is quercetin (3,3',4',5,7-pentahydroxy flavone), the quercetin glycoside rutin, myricetin, genistein, kaempferol, luteolin, apigenin, (-)-epigallocatechin-3 gallate, kaempferol or the kaempferol glycoside astragaline, or hesperitin or its glycoside hesperidin.

[0016] In another embodiment, compositions may also contain antagonists of the effects of CRH on mast cells or other target cells of the myocardium, gastric mucosa, urinary bladder, skin, meningeal membranes, blood-brain barrier, and brain structures.

[0017] In still another embodiment, the inventive compositions are used against superficial vasodilator flush syndromes.

[0018] In still another embodiment, the inventive compositions may be used as coatings on medical devices, not only to protect surrounding tissues from inflammation due to the devices, but also to treat innate inflammation in surrounding tissues.

[0019] In another embodiment, the inventive compositions are used against the inflammatory processes of endometriosis.

hormonally-related cancers, such as breast, ovarian, uterine, prostate and testicular cancers, and when supplemented with chemotherapeutic agents are used against the cancer itself.

[0021] In still another embodiment, the inventive compositions may be used in the treatment of the neuroinflammatory aspects of multiple sclerosis.

[0022] In another embodiment, the inventive olive kernel extract is used to improve the absorption of biochemicals across membrane barriers in the body, such as those of the intestine, skin, oral mucosa, blood-brain barrier, and pulmonary alveoli.

[0023] In yet another embodiment, the inventive compositions may be used in the treatment of fibromyalgia or chronic fatigue syndrome.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS OF THE INVENTION

[0024] It has been discovered that various combinations of a sulfated proteoglycan, unrefined olive kernel extract, a flavone (a.k.a. flavonoid compound), a sulfated D-hexosamine, a phospholipid, a long chain unsaturated fatty acid, a CRH antagonist, a histamine-1 receptor antagonist, a histamine-3 receptor agonist, glutiramer acetate, an interferon, and a polyamine have synergistic anti-inflammatory effects when used as a dietary supplement, a topical product or an aerosol for nasal or pulmonary administration, without or with a conventional clinical treatment for inflammatory diseases. Within the present context, such inflammatory diseases result from the activation, degranulation and consequent secretion of inflammatory biochemicals from mast cells, and the resultant inflammatory diseases include the group consisting of: allergic inflammation, arthritis (to include osteoarthritis and rheumatoid arthritis), fibromyalgia, chronic fatigue syndrome, inflammatory bowel disease, interstitial cystitis, irritable bowel syndrome, migraines, atherosclerosis, coronary inflammation, ischemia, chronic prostatitis, eczema, multiple sclerosis, psoriasis, sun burn, periodontal disease of the gums, superficial vasodilator flush syndromes, hormonally-dependent cancers, and endometriosis. The olive kernel extract alone may be used to improve the transmembrane transport of difficultly-absorbable biomolecules in the intestine, skin and pulmonary alveoli.

[0025] In a highly preferred embodiment, the sulfated proteoglycan is non-bovine chondroitin sulfate, preferably from shark cartilage, which blocks mast cell activation, degranulation and consequent secretion of inflammatory biochemicals from the mast cells. Other natural sulfated proteoglycans suitable for practicing this invention include keratan sulfate, dermatan sulfate and hyaluronic acid sodium salt (sodium hyaluronate). The preferred biological source of the chondroitin sulfate is shark cartilage which is more highly sulfated than the common commercial chondroitin sulfate isolated from cow trachea; the shark cartilage source also avoids the potential dangers associated with bovine sources.

[0026] A highly preferred flavonoid is quercetin which inhibits secretion of inflammatory molecules from mast cells

(2000), Kempuraj et al. *Br. J. Pharmacol.* 145:934 (2005)]. In addition to quercetin, other flavonoids suitable in carrying out the invention include: the quercetin glycoside rutin, myricetin, genistein, luteolin, apigenin, (-)-epigallocatechin-3 gallate, kaempferol and the kaempferol glycoside astragaline, hesperitin and its glycoside hesperidin.

[0027] The olive kernel extract product component of the inventive compositions is preferably an unrefined (first pressing, filtered, oleic acid-related acidity <3%, water content <1%) extract product produced, for one source, on the island of Crete in Greece. This kernel extract product is especially prepared by applicant's process consisting essentially of: (1) harvesting first collection ripe olives, preferably in December; (2) compressing the oil from the flesh of the ripe olives; (3) washing the kernels remaining after step (2) with water to remove debris; (4) drying the washed kernels with a stream of hot air; (5) crushing the dried kernels to produce an extract; (6) extracting the extract from step (5) with an organic solvent (e.g., hexane, heptane, octane) plus steam; (7) removing particulate matter from the organic extract by centrifugation or microfiltering through 1-2 micron pore size filters; (8) evaporating the organic solvent and water from the clarified extract of step (7) by maintaining the extract at 86-100 degrees C. while percolating helium (to avoid oxidation) through the fluid, which process reduces the water content to <1%, the acidity (as oleic acid) to <3%; and, the organic solvent to <1%; and (8) storing the final kernel extract product in the absence of air.

[0028] The inventive olive kernel extract surprisingly has the unique property of increasing absorption of the other components of the anti-inflammatory compositions through the intestinal mucosa or skin, and also adds its own content of important anti-oxidants, such as omega fatty acids (e.g., eicosapentanoic acid) and alpha tocopherol. The polyphenols found in such olive kernel extracts also have anti-inflammatory effects in, for example, arthritis [Martinez-Dominguez et al., *Inflamm. Res.* 50:102 (2001)]. E.B.E.K., Inc., Commercial, Industrial Enterprises of Crete, 118 Ethnikis Antistasecos, Heraklion, Crete, 71306, Greece, or MINERVA S.A. Edible Oil Enterprises, 31 Valaoriton St., Metamorphosis, Attizes, Greece will prepare the extract product according to applicant's above-described procedure for commercial users.

[0029] In addition to its usefulness in increasing the absorption of the inventive macromolecular compositions across the intestinal wall and the skin, the inventive olive kernel extract product is useful in aiding the dissolution of other drugs prior to administration to a patient, and is useful in promoting the absorption of other difficultly-absorbable drugs, e.g., the HDL-increasing drug torcetrapib across intestinal mucosa, oral mucosa, nasal mucosa, and skin of patients.

[0030] Supplementation of the compositions described above with the methylation reagent S-adenosylmethionine ("SAM") adds antioxidant, anti-inflammatory and cytoprotective properties, particularly in inflammatory joint and cardiovascular diseases. Addition of SAM also accelerates metabolism of homocysteine, which amino acid has been implicated in coronary disease, to cysteine, which is harmless. Folic acid may be added to certain of the present formulations for similar reasons.

hydroxyzine, merelastine, azelastine, azatadine, rupatadine, and cyproheptadine. Other histamine-1 receptor antagonists are described in Table 25-1 in Goodman and Gilman's *The Pharmaceutical Basis of Therapeutics*, 9th ed., New York, 1996. Histamine-3 receptor agonists are described in the Theoharides patents listed above.

[0032] Inhibitors of mast cell activation and secretion of inflammatory biochemicals may be used in the treatment of inflammatory processes such as superficial vasodilator syndrome, such as occurs in menopausal-associated flush, carcinoid flush, MSG-associated flush, and niacin-associated flush.

[0033] Hormone-dependent cancers, including the estrogen/progestin linked ovarian, uterine, breast, and endometrial cancers, and the androgen-linked prostate and testicular cancers, are associated with tissue inflammation. These conditions can be treated with chondroitin sulfate, quercetin, genistein, rutin, phenoxodiol isoflavone, (-)-epigallocatechin-3-gallate, olive kernel extract, and, optionally, chemotherapeutic agents such as tomoxifen or raloxifen.

[0034] Pelvic inflammatory conditions, such as present in endometriosis, can also be treated with the inventive compositions. Particularly useful in this regard are compositions delivering 50-300 mg/day of rutin, quercetin, kaempferol, myricetin, or hesperitin.

[0035] The inventive compositions may also be used as coatings on implanted medical devices, which devices may lead to or be associated with inflammation of surrounding tissues, in order to provide protection against such inflammations. Not only can the coating of such medical devices inhibit or protect against inflammation caused by the device itself, but the coated devices can also be used to deliver the inventive compositions to innately inflamed tissues due to other causes. Such medical devices include artificial skins (scaffolding such as naturally occurring polymers, e.g., collagen; man-made polymers, e.g., PTFE, Dacron, PET or polyethylene; self-degrading man-made polymers, e.g., PLA or PGA; biopolymer matrices from animal tissues including fetal and neonatal tissues to be used as tissue engineering scaffolds (cf. Bell et al., U.S. patent application Pub. No. 20020146393)), artificial joints, band-aids, stents for blood vessels, artificial blood vessels, pacemakers, stents for abdominal support in hernia repair, tissue transplants, prostheses, breast implants, etc. Particularly useful in this regard are compositions containing heavily sulfated, non-bovine proteoglycans (e.g., chondroitin sulfate) and a flavonoid.

[0036] Oral flavonoids, such as those listed above, are reported to influence the course of experimental autoimmune encephalomyelitis in mice, a model for multiple sclerosis (Verbeck, R. et al., *Biochem. Pharm.* 70(2):220 (Jul. 15, 2005); Hendriks, J J et al *J Exp Med.* 200(12):1667 (Dec. 20, 2004). In preferred embodiments of the inventive compositions, flavonoids or flavonoid glycosides plus one or more of a proteoglycan, olive kernel extract, Krill oil, hydroxyzine, (-)-epigallocatechin-3-gallate, and a long chain fatty acid plus injections of interferon and/or glutiramer acetate (Copolymer I) (Copaxone, TEVA Pharmaceuticals, Israel; Avonex, Biogen., USA) are used in treatment of the chronic inflammation of the central nervous system in multiple sclerosis. The glutiramer acetate is of particular

5:451 (2005); Schwartz, M. et al. J. Neurol. Sci. 233:163(2005); Amon, R., et al., Proc. Nat. Acad. Sci. USA 102 Suppl. 2:14593 (2004)].

[0037] Sources of CRH antagonists include, in addition to the Theoharides patents listed in the Background section above: Neurocrine Biochem. Inc.'s D-Phe 12 Nle Ala32,21, 38hCRH(12-41)NH2, cat no. 1P-36-41; Pfizer non-peptide CP-154,526-1; Sigma Chem., St. Louis anti-CRH polyclonal antiserum; and Pfizer, NY patents and applications: U.S. Pat. No. 6,211,195, U.S. Pat. No. 5,795,905, PCT/IB95/00573, PCT/IB95/00439, U.S. Ser. No. 08/448,539, U.S. Ser. No. 08/481,413, U.S. Ser. No. 09/735,841, and in Owens et al. *Pharm. Rev.* 43:425 (1991).

[0038] The preferred concentration range of the proteoglycan, hexosamine sulfate, flavonoid, polyunsaturated fatty acid, phospholipid components of the oral formulations are 10-3,000 mg per tablet or capsule. The preferred concentration range for SAM is 3-1,000 mg per capsule or tablet. Generally, where present, the amounts of the unrefined olive kernel extract are at least twice those of the other active ingredients, preferably 300-1200 mg. The number of capsules or tablets to be taken per day is determined by the nature and severity of the medical condition, and is readily determinable by the patient's health provider. Other representative formulations are described in the examples below.

[0039] The compositions of the invention may be formulated in any standard means of introducing pharmaceuticals into a patient, e.g., by means of tablets or capsules. The compositions of the invention include ointments and creams for skin conditions, mouth washes and toothpaste for periodontal diseases, and solutions for nasal aerosols. Standard excipients and carriers for the active ingredients of the inventive compositions are described in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa.

[0040] Although not bound by any particular mechanism of action of the components of the claimed compositions, the inventor contemplates that they inhibit the activation and degranulation of the relevant mast cells, and inhibit the secretion of inflammatory biomolecules from these mast cells. "Activation" and "degranulation" of mast cells are defined herein as is standard and well known in this art, that is, to mean synthesis and secretion from the activated mast cell of any type of molecule(s) that alone or in combination triggers inflammation.

EXAMPLES

Example 1

[0041]

TABLE 1

Table 1 compares chondroitin sulfate-containing commercial products to the present compositions. Comparison of Chondroitin Sulfate-Containing Products to Present Invention

Product	Most Available Compositions	Present Invention
Main ingredient	Mixture of chondroitins	Non-bovine chondroitin sulfate, preferably the C

TABLE 1-continued

Table 1 compares chondroitin sulfate-containing commercial products to the present compositions. Comparison of Chondroitin Sulfate-Containing Products to Present Invention

Product	Most Available Compositions	Present Invention
Source	Cow trachea	Shark cartilage
Amount per capsule or tablet	100-300	10-3000 mg
Degree of sulfation	Low, if any	High
Absorption from g.i. tract	<5%	>15%
Target	Unknown	Mast cells, inflammatory cells
Other ingredients	Vitamins, fish oils (some preparations)	Flavones, unrefined olive kernel extract, SAM, histamine-1 receptor antagonists, histamine-3 receptor agonists, CRH antagonists, polyamines, caffeine, folic acid
Advantages	None known	Anti-allergic, anti-inflammatory, anti-oxidant, cytoprotective
Adverse effects	Risk of mad cow disease, spongiform encephalopathy, stomach upset, allergy to fish products	None known
Relevant conditions	Osteoarthritis	Allergic inflammation, angina, asthma, coronary artery disease, arthritis (osteoarthritis or rheumatoid arthritis), chronic prostatitis, eczema, fibromyalgia, interstitial cystitis, irritable bowel syndrome, inflammatory bowel disease, migraines, multiple sclerosis, psoriasis, periodontal disease, flush syndrome, cancer (including hormonally-dependent forms).
Scientific publications	None found	Theoharides et al. Br J Pharm 131: 1039 (2000) Middleton et al. Pharm Rev 52: 673 (2000)

[0042] In all examples, chondroitin sulfate is to assumed to be of a non-bovine variety.

Example 2

[0043]

Composition For Protecting Against Inflammatory Diseases Two capsules to be taken orally 2-3 times daily, at least one hour before meals

Ingredients, per capsule,	mg:
*Chondroitin sulfate	150-300
*D-Glucosamine sulfate	150-300
*Quercetin	150-300
*Olive kernel extract	350-1200

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