COMPOSITIONS FOR THE TREATMENT OF LUPUS

Background of the Invention

Area of the Art

The present invention concerns a treatment for rheumatic diseases and for joint diseases.

Description of the Prior Art

Lupus Erythematosus ("Lupus") is a chronic inflammatory disease that can affect the skin, joints, blood, and kidneys as well as other parts of the body. Lupus is an "autoimmune" disease in which the immune system makes antibodies directed against parts of the body. Normally antibodies react only with bacteria, viruses and other foreign substances. When "self" antibodies are made, damage can occur either through direct antibody mediated attack on body tissues or indirectly from immune complexes. Immune complexes are the reaction products between portions of the body's tissues and the antibodies. These complexes build up in the skin or in joints or in kidneys and cause many of the symptoms of Lupus. Although many cases of Lupus are mild, the disease may cause serious life-threatening symptoms.

Lupus is one of a number of "rheumatic" diseases that generally also include an autoimmune component. Usually much of the damage of Lupus and other rheumatic diseases is mediated by inflammatory processes. Inflammation is generally a process wherein circulation to a region of tissue is increase and blood vessel walls become leaky so that white blood cells can infiltrate the region and attack foreign bodies. If autoantibodies are involved the bodies own tissues are attacked and damaged or destroyed. If the inflammation occurs in the joints, the cushioning and lubricating cartilage of the joints can be damaged. This causes frictional damage to the bones of the joint, which can result in

more inflammation and more damage. This is why anti-inflammatory drugs are often used to treat Lupus and other inflammatory joint diseases. It is generally believed that some joint diseases such as osteoarthritis are more of a "wear and tear" disease wherein the cartilage is naturally eroded. However, the end product is still inflammation (which causes further damage) so that anti-inflammatory drugs are also effective.

The most commonly used anti-inflammatory drugs are non-steroidal anti-inflammatory drugs such as ibuprofen or ketoprofen which act on the inflammatory processes downstream of the white blood cells. Steroids directly affect the white blood cells by slowing their replication or b speeding their destruction through apoptosis. Other effective drugs are cytotoxic drugs such as Imuran which suppress the immune system (and hence inflammation) by damaging rapidly dividing cells such as immune cells.

As will be appreciated, all of these drug treatments can have serous side effects. Non-steroidal anti-inflammatory drugs can cause serious damage to the digestive system and often prolong bleeding times. Steroids can be adductive and have a wide range of serious side effects including diabetes. Cytotoxic drugs can result in oversuppression of the immune system with resulting infections and even cancer. Further, many inflammatory diseases—especially Lupus—may not respond adequately to any of the treatments. Consequently, there remains an extreme need for safe and effective treatments for Lupus and other inflammatory diseases.

Summary of the Invention

The inventor has found that bioflavonoids, particularly flavnols such as Quercetin, supplemented with Bromelain and Vitamin C, (500 mg of each, in doses three times a day) completely reverse the symptoms of

Lupus and other inflammatory joint diseases. Luteolin, Myricetin and Rutin are also effective bioflavonoids in the present invention. Experimental data indicate that Luteolin is somewhat more effective than Quercetin. Luteolin, however, is currently difficult to obtain economically in quantity.

While not wishing to be bound to a single explanation for the working of the present invention, the inventor believes that a significant part of the efficacy is due to the effects of specific bioflavonoids on certain cellular ion channels. In the past it has been shown that abnormal potassium channel expression in certain autoimmune diseases is related to the abnormal immune response. (See "Abnormal K^+ channel expression in AutoImmune Diseases..." by Chandy and Cahalan published in 1990 by the University of California at Irvine and "Autoimmune diseases linked to abnormal K^+ channel expression in double-negative $CD4^-CD8^-$T cells," Eur J. Immunol, Cahalan MD, Chandy GK, Grissmer S., 1990, 20: 747-751). It was shown rats with experimental SLE (Systemic Lupus Erythematosus), Diabetes (Type I) and EAE (Experimental Autoimmune Encephalitis) were tested for the Kv1.3 channel, and it was shown found that all three have the $CD4^-$ and $CD8^-$—T-Cells (double negative T-Cells) expression that inflames the various tissues associated with the respective diseases. All of these diseases show a control of lymphocyte proliferation by the Kv1.3 channel. It has independently been demonstrated that flavonoids, especially Quercetin, are very effective at modulating the conduction by this potassium channel. This suggested to the inventor that flavonoids could be effective in controlling human Lupus.

Detailed Description of the Invention

The following description is provided to enable any person skilled in the art to make and use the invention and sets forth the best modes contemplated by the inventor of carrying out his invention. Various modifications, however, will remain readily apparent to those skilled in the art,

since the general principles of the present invention have been defined herein specifically to provide an effective treatment for Lupus and other autoimmune and inflammatory joint diseases

Flavonoids are ubiquitous secondary products found in most land plants. Flavonoids are oxygen based rather than nitrogen based like traditional pharmaceuticals plant compounds such as alkaloids. As such they are end terminus electron acceptors rather than electron donors. Flavonoids inhibit 5-lipoxygenase in the cytokine release pathways because hydroxyl groups at 4', 3, and 7 positions of the flavonoid molecules accept electrons. (*See*, Effects of FLAVONOIDS on Arachidonic Acid Metabolism, A. F. Welton, L.D. Tobias, The Biochemistry of Cell Activation Related to the Putative Action of FLAVONOIDS, S. G. Laychock, Plant Flavonoids in Biology and Medicine: Biochemical, Pharmacological, and Structure-Activity Relationships, pg 231-242, 1986 Alan R Liss, Inc.). Flavonoids modulate the immune response through sequestration of free radicals, which prevents formation of epoxide diols and subsequent attack on the DNA. Further, catalytic ion and signal transducers are sequestered by Flavonoids (*See,* Structural dependence of flavonoid interactions with $Cu2^{+}$ ions: implications for their antioxidant properties, Brown JE, Khodr H, Hider RC, Rice-Evans CA, Biochem. J. 1998 Mar 15;330 (pt 3): 1173-8).

A number of biological effects of flavonoids have been elucidated. For example, flavonoids inhibit Deiodinase, which is the enzyme that promulgates thyroid functions. Iodothyronine deiodinase is oxygen bound and directly impacts basal oxygenation. Flavonoids have the steric binding mimicry of ligands that bind the oxygen transport molecule Iodothreonine Deiodinase. ("Role of FLAVONOIDS in the Oxygen-free Radical Modulation of Immune Responses", B. Pignol, et. al., Role of Flavonoids in the Oxygen-Free Radical Modulation of the Immune Response, Plant Flavonoids in Biology and Medicine II: Biochemical, Cellular, and Medicinal

Properties, pg. 173-182, 1988 Alan R. Liss, Inc.; "Structure Activity Relationships of FLAVONOIDS Deiodinase Inhibitors and Enzyme Active Site Model", S. V. Cody, Plant Flavonoids in Biology and Medicine: Biochemical, Pharmacological, and Structure-Activity Relationships, 1986 Alan R. Liss, Inc., pg. 373-382). Flavonoids thus "turn down the thermostat" of homeostasis. ("Iodothyronine Deiodinase is Inhibited by Plant FLAVONOIDS", J. Koehrle pg. 324, Structure Activity Relationships of FLAVONOIDS Deiodinase Inhibitors and Enzyme Active Site Model, S. V. Cody, Plant Flavonoids in Biology and Medicine: Biochemical, Pharmacological, and Structure-Activity Relationships, 1986 Alan R. Liss, Inc., pg. 373-382).

It is believed that the effect of flavonoids in the present invention is mediated through the above-discussed effect on ion channels. However, the effect on the thyroid indicates that the flavonoids may be acting on more than one biological system in the present invention. The inventor included Bromelain in the present invention because there is some indication that this enzyme can aid in the regeneration of cartilage in a damaged joint. Generally, Bromelain alone is not effective in ameliorating the joint pain in either osteoarthritis or Lupus caused joint inflammation. It is logical that the compound is not effective in Lupus because continued Lupus-induced inflammation would mask any joint repairing effects of Bromelain. It also seems apparent that osteoarthritis, at least in some cases, is mediated by an inflammatory process. This may explain why Bromelain treatment of that disease has not been very effective.

However, the flavonoid component of the present invention controls inflammation through its effects on ion channels and possibly through other biological effects not yet elucidated. White blood cells are deactivated by the changes in ion channels so that inflammatory attacks on the joints are decreased. Down regulation of the immune system (as mediated by white blood cells) results in lowered production of auto-

antibodies. Under these conditions Bromelain appears to be able to help in joint repair. It does seem likely that Bromelain is in some way synergistic with the flavonoids because treatment with flavonoids but without Bromelain is clearly less effective than the combination. Many natural foods contain flavonoids; however, few, if any, contain Bromelain combined with effective flavonoids. Also, it is not known whether the combination of flavonoids in natural products might decrease the overall effectiveness of the "correct" flavonoids. For whatever reasons mere dietary treatments for Lupus and related diseases has not been successful. While the present inventor believes that the addition of vitamin C to the flavonoid/Bromelain mixture enhances the effect of the mixture, it is apparent that the mixture without vitamin C is also effective. However, because vitamin C is relatively innocuous, it has been used in the vast majority of tests.

Screening tests by experts in ion channel function have indicated that a number of flavonoids, especially certain flavonols have the correct charge structure to regulate the key ion channels. Quercetin, which has been used in the majority of tests of the present invention, is very effective in tests of ion channel function. Luteolin is even more effective than Quercetin in such tests. Limited tests have shown that replacing Quercetin with Luteolin in the inventive formula is somewhat more effective. However, at this time the inventor lacks a ready source of pharmaceutical grade Luteolin to demonstrate whether luteolin is significantly more effective overall. Quercetin and Luteolin differ by a single hydroxyl group (which Luteolin lacks as compared to Quercetin). A limited number of tests have shown that Myricetin is somewhat effective in the present; this compound varies from Quercetin in the addition of one hydroxyl. In addition, rutin is also moderately effective in the present invention. Rutin is a glycoside (rutinoside) of Quercetin so that metabolism of Rutin is likely to make Quercetin available. It is likely that other

flavonoids with structural similarities to quercetin or luteolin, or glycosides of these flavonoids, will also function in the present invention.

The results of treating actual patients with the inventive composition have been extremely dramatic. Besides the cases described herein literally dozens of patients have shown similar results when treated with the Quercetin/Bromelain/Vitamin C mixture.

One of the first tested subjects was, BZ, who had been bed ridden for nine months and could neither sit up or turn over. She showed the typical Lupus butterfly rash and was diagnosed by a blood test showing a positive ANA (anti-nucleic acid antibody) titer—criteria indicative of Lupus. The subject's mother had previously tested positive for Lupus and has been treated with several medications, including Plaquinel and Cyclosporin. A second subject, KA, had also tested positive for Lupus and had been being treated with Plaquinel and Cyclosporin.

Both of these test subjects experienced rapid relief from symptoms of fatigue and depression and pain, elimination of the associated rash and a return to normal life style within one to two months of beginning a regime of one pill (500 mg Quercetin/500 mg Bromelain/500 mg Vitamin C) three times per day at the above dosage. Kidney flares ceased and pain abrogated. Both subjects stated that they felt completely fine with no side effects and maintained a perfect state of health while on the inventive composition.

Both BZ and KA stopped taking the medication after two months, since they reported that they were "completely recovered." As might be expected, symptoms begin to reappear within two weeks. Upon reestablishment of treatment all symptoms again disappeared. This indicates that the inventive product is solely responsible for the amelioration of SLE (Systemic Lupus Erythematosus).

Additional patients have also shown similar positive results. MK was a 65-year-old woman with seropositive rheumatoid arthritis. She developed side effects from methotrexate treatment at a dose of 22.5 mg weekly. Her methotrexate was discontinued and she was started on the inventive composition. Within one month she showed a dramatic decrease in synovitis.

NM was a 37-year-old woman with an inflammatory polyarthritis and positive ANA (antinuclear antibody). She had Sjogrens syndrome with a positive SSA (anti-Ro) antibody. After three months of treatment with the inventive composition, she noticed decreased hair loss, and a lessening of joint pain and swellings. Her serologies also improved. Her initial ANA titer was 170 and SSA titer was 584, and occasionally much, much higher. Her most recent serologies show an ANA titer of 67 and SSA of 429.

DS was a 57 year old female with SLE/Sjogrens. Her disease manifestations were pulmonary infiltrates and pulmonary effusions. Despite high doses of prednisone, plaquenil, and Imuran she had continued pulmonary symptoms, fevers, joint swellings, and elevated anti-DNA antibody. After one-month treatment with the inventive composition, her Anti-DNA level decreased from 454 to 186 (normal less than 30).

LC was a 46 year old female with SLE. Her main manifestations have been joint inflammation and recurrent serositis. She has had recurrent chest pain and palpitations. Her echocardiogram in 1999 showed valvular changes with trace mitral regurgitation and mild to moderate tricuspid regurgitation. She also had pulmonary hypertension with a RV systolic pressure of 45. LC started the inventive compositions and after four months was tapered off prednisone of 20-mg qd and Plaquinel. Her recent echocardiogram shows improvement–there was no longer any evidence of pulmonary hypertension.

At this time more than 50 patients, most with some form of Lupus, but others with various inflammatory joint diseases, have been treated with the inventive composition. Virtually all patients have demonstrated a measurable amelioration of their disease state.

The following claims are thus to be understood to include what is specifically illustrated and described above, what is conceptually equivalent, what can be obviously substituted and also what essentially incorporates the essential idea of the invention. Those skilled in the art will appreciate that various adaptations and modifications of the just-described preferred embodiment can be configured without departing from the scope of the invention. The illustrated embodiment has been set forth only for the purposes of example and that should not be taken as limiting the invention. Therefore, it is to be understood that, within the scope of the appended claims, the invention may be practiced other than as specifically described herein.

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I claim:

1. A composition comprising Bromelain and a flavonoid selected from the group consisting of Luteolin, Quercetin and Myricetin.

2. The composition according to Claim 1, wherein the flavonoid comprises Quercetin.

3. The composition according to Claim 1 or Claim 2, wherein the flavonoid comprises a flavonol.

4. The composition according to Claim 1 or Claim 2, wherein the flavonoid comprises a glycoside.

5. The composition according to Claim 4, wherein the glycoside has an aglycone that is a flavonol.

6. The composition according to any one of Claims 1 to 5, wherein the flavonoid is selected to interact with lymphocyte Kv1.3 channels.

7. The composition according to Claim 3 or Claim 5, wherein the flavonol interacts with lymphocyte Kv1.3 channels.

8. A composition comprising flavonoid, Bromelain and Vitamin C.

9. The composition according to Claim 8, wherein the flavonoid is selected from the group consisting of Luteolin, Quercetin, Myricetin and Rutin.

10. The composition according to Claim 8, wherein the flavonoid comprises a flavonol.

11. The composition according to Claim 8, wherein the flavonoid comprises a glycoside.

12. The composition according to Claim 11, wherein the glycoside has an aglycone that is a flavonol.

13. The composition according to Claim 12, wherein the flavonol is selected from the group consisting of Luteolin, Quercetin, Myricetin and Rutin.

14. The composition according to any one of Claims 8 to 13, wherein the flavonoid is selected to interact with lymphocyte Kv1.3 channels.

15. The composition according any one of Claims 10, 12 or 13, wherein the flavonol interacts with lymphocyte Kv1.3 channels.

16. The composition according to Claim 8, wherein the flavonoid comprises Quercetin.

17. A composition comprising flavonoid and Bromelain said flavonoid comprises a glycoside having an aglycone that is a flavonol said flavonol being selected from the group consisting of Quercetin, Luteolin and Myricetin.

18. The composition according to Claim 27, wherein the flavonoid is selected to interact with lymphocyte Kv1.3 channels.

19. The composition according to Claim 27, wherein the flavonol interacts with lymphocyte Kv1.3 channels.

20. Use of a composition comprising flavonoid and Bromelain for the preparation of a medicament for the treatment of Lupus.

21. Use of the composition according to Claim 20, wherein the composition further comprises Vitamin C.

22. Use of the composition according to Claim 20 or Claim 21, wherein the flavonoid is selected from the group consisting of Luteolin, Quercetin, Myricetin and Rutin.

23. Use of the composition according to Claim 20 or Claim 21, wherein the flavonoid comprises a flavonol.

24. Use of the composition according to Claim 20 or Claim 21, wherein the flavonoid comprises a glycoside.

25. Use of the composition according to Claim 24, wherein the glycoside has an aglycone that is a flavonol.

26. Use of the composition according to Claim 25, wherein the flavonol is selected from the group consisting of Luteolin, Quercetin, Rutin and Myricetin.

27. Use of the composition according to any one of Claims 20 to 26, wherein the flavonoid is selected to interact with lymphocyte KV1.3 channels.

28. Use of the composition according to any one of Claims 23, 25 or 26, wherein the flavonol interacts with lymphocyte KV1.3 channels.

29. Use of the composition according to Claim 20 or Claim 21, wherein the flavonoid comprises Quercetin.

30. Use of a composition comprising Bromelain and a flavonoid selected from the group consisting of Luteolin, Quercetin and Myricetin for the preparation of a medicament for the treatment of Lupus and inflammatory joint diseases.

31. Use of the composition according to Claim 30, wherein the flavonoid comprises Quercetin.

32. Use of the composition according to Claim 30 or Claim 31, wherein the flavonoid comprises a flavonol.

33. Use of the composition according to Claim 30 or Claim 31, wherein the flavonoid comprises a glycoside.

34. Use of the composition according to Claim 33, wherein the glycoside has an aglycone that is a flavonol.

35. Use of the composition according to any one of Claims 30 to 34, wherein the flavonoid is selected to interact with lymphocyte KV1.3 channels.

36. Use of the composition according to Claim 32 or Claim 34, wherein the flavonol interacts with lymphocyte KV1.3 channels.

37. Use of a composition comprising flavonoid, Bromelain and Vitamin C for the preparation of a medicament for the treatment of Lupus and inflammatory joint diseases.

38. Use of the composition according to Claim 37, wherein the flavonoid is selected from the group consisting of Luteolin, Quercetin, Myricetin and Rutin.

39. Use of the composition according to Claim 37, wherein the flavonoid comprises a flavonol.

40. Use of the composition according to Claim 37, wherein the flavonoid comprises a glycoside.

41. Use of the composition according to Claim 40, wherein the glycoside has an aglycone that is a flavonol.

42. Use of the composition according to Claim 41, wherein the flavonol is selected from the group consisting of Luteolin, Quercetin, Myricetin and Rutin.

43. Use of the composition according to any one of Claims 37 to 42, wherein the flavonoid is selected to interact with lymphocyte Kv1.3 channels.

44. Use of the composition according to any one of Claims 39, 41 or 42, wherein the flavonol interacts with lymphocyte Kv1.3 channels.

45. Use of the composition according to Claim 37, wherein the flavonoid comprises Quercetin.

46. Use of a composition comprising flavonoid and Bromelain said flavonoid comprises a glycoside having an aglycone that is a flavonol said flavonol being selected from the group consisting of Quercetin, Luteolin and Myricetin for the preparation of a medicament for the treatment of Lupus and inflammatory joint diseases.

47. Use of a composition according to Claim 46, wherein the flavonoid is selected to interact with lymphocyte Kv1.3 channels.

48. Use of a composition according to Claim 46, wherein the flavonol interacts with lymphocyte Kv1.3 channels.

49. Use of the composition according to any one of Claims 20 to 48, wherein the medicament is an orally administered medicament.

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50. Use of the composition according to any one of Claims 20 to 49, wherein the medicament is administered at least daily.

51. Use of the composition according to any one of Claims 30 to 49, wherein the medicament is administered at least twice daily.