PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/355, 31/60

A1

(11) International Publication Number: WO 99/25336

(43) International Publication Date: 27 May 1999 (27.05.99)

(21) International Application Number: PCT/US98/24606

(22) International Filing Date: 17 November 1998 (17.11.98)

(30) Priority Data:
08/971,703 17 November 1997 (17.11.97) US

(71) Applicant: LIPOGENICS, INC. [US/US]; Suite 650, 2425 East Camelback Road, Phoenix, AZ 85016 (US).

(72) Inventors: LANE, Ronald, H.; 14624 N. Seventh Place, Phoenix, AZ 85022 (US). SCHNEIDER, Frederick, H.; 21 Center Street, Yarmouthport, MA 02675 (US).

(74) Agents: ROSE, Bernard, F. et al.; Lyon & Lyon LLP, Suite 4700, 633 West Fifth Street, Los Angeles, CA 90071–2066 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: METHODS FOR PREVENTING RESTENOSIS USING TOCOTRIENOLS

(57) Abstract

This invention relates to the prevention of restenosis using tocotrienols. Specifically, this invention relates to the use of individual tocotrienols (such as P_{25} tocotrienol), mixtures of tocotrienols and mixtures of one or more tocotrienols with other substances (such as the TRF_{25} mixture). The methods of this invention include a method for administering a pharmaceutically acceptable composition comprising a tocotrienol to a patient in need of restenosis prophylaxis and a method for preventing restenosis in a patient undergoing an arterial angioplastic procedure comprising the steps of: (a) coating the exterior surface of an angioplastic balloon with a composition comprising a tocotrienol; and (b) performing the arterial angioplastic procedure such that a prophylactically effective amount of the composition is transferred to the interior surface of the artery.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

METHODS FOR PREVENTING RESTENOSIS USING TOCOTRIENOLS

TECHNICAL FIELD OF THE INVENTION

This invention relates to the prevention of restenosis using tocotrienols. Specifically, this invention relates to the use of individual tocotrienols (such as P_{25} tocotrienol), mixtures of tocotrienols and mixtures of one or more tocotrienols with other substances (such as the TRF_{25} mixture). The methods of this invention are particularly well suited for preventing restenosis in patients having undergone or prior to undergoing angioplasty or arterial bypass surgery.

BACKGROUND OF THE INVENTION

An estimated 905,000 patients are at high risk for restenosis. An artery that is constricted or narrowed is referred to as being stenosed. The artery may be clogged by the buildup over time of fat, cholesterol and other substances that adhere to the interior of arterial walls. Procedures designed to unblock such clogged arteries result in localized arterial trauma. The result of such damage to the artery is an increased risk for atheroma formation at the site of trauma (restenosis).

One procedure for widening blocked coronary arteries is percutaneous transluminal coronary angioplasty (PTCA), also known as balloon angioplasty. PTCA involves the use of a balloon-tipped catheter that is inserted directly into the heart's vessels to open partially blocked, or stenotic, coronary arteries. Over 400,000 PTCA procedures were performed in 1994 alone in the United States. The average cost of the PTCA procedure well exceeds $20,000. Unfortunately, PTCA often does not yield long term success in unblocking clogged arteries. About one-third of patients undergoing PTCA develop restenosis of the widened segment within about six months of the procedure. Patients suffering from restenosis may have to undergo additional procedures to reduce the

blockage, including repeated angioplasties, atherectomies or the insertion of stents (collapsible supports placed inside the arteries). Collectively, these additional procedures add billions of dollars to the cost of health care. For example, in 1994, repeat angioplasty alone was responsible for about $2.4 billion of additional health costs in the United States.

Restenosis can also occur following other procedures that cause damage or trauma to an artery, such as arterial bypass operations (including coronary artery bypass procedures). Arterial bypass surgery reroutes the flow of blood around clogged arteries via an arterial transplant or graft to improve the supply of blood and oxygen to the heart and other vital organs. In such cases, stenosis sometimes occurs in the transplanted blood vessel' segment. Like other stenosed arteries, angioplasty or atherectomy may be required to widen the passage. Because of the arterial trauma associated with arterial bypass surgery, restenosis is a substantial risk after such procedures.

A variety of approaches to restenosis prevention are being explored. These include administration of antibodies against platelet antigen, use of an epidermal growth factor fusion protein, gene therapy, nitrogen oxide based therapy, acyclovir therapy and use of sulfated cyclodextrins. In addition, use of catheter-based intracoronary radiotherapy has been shown to reduce the intimal hyperplasia that is a part of restenosis in a preliminary, short term study (P.S. Teirstein et al., The New England Journal of Medicine, 336(24), pp. 1697-703). The efficacy of antioxidants in preventing restenosis has also been preliminarily explored. There is some evidence to suggest that oxidizing metabolites generated at the site of coronary angioplasty induce a chain reaction that can lead to restenosis. Orally administered alpha-tocopherol (vitamin E) has been shown to reduce restenosis after angioplasty in rabbits (A.M. Lafont et al., J. Clin. Invest., 95(3), pp. 1018-25 (1995)). However, a more recent study debates the efficacy of antioxidants in preventing restenosis (J.C. Tardif et al., New England Journal of Medicine, 337(6), pp. 365-72 (1997)). The Tardif et al. article notes that although one antioxidant (probucol (Lorelco, Merrell, Kansas City, Mo.)) was somewhat effective in preventing restenosis, other antioxidants did not prevent restenosis. Furthermore, the combination of probucol with other antioxidants was shown to be less effective than probucol alone in preventing restenosis. Finally, Tardif et al. propose that the antioxidant properties of probucol may not be related to its prophylactic activity with respect to restenosis (as is the case with its atherosclerosis and vascular reactivity profile).

Notwithstanding extensive research conducted in this area, there is still a well-recognized and unmet need for effective therapy to prevent restenosis.

SUMMARY OF THE INVENTION

The present invention satisfies the need for therapeutic agents effective in the prevention of restenosis. Specifically this invention provides methods for preventing restenosis in a patient comprising the step of administering to the patient a prophylactically effective amount of a composition comprising a tocotrienol, a mixture of tocotrienols or a mixture of one or more tocotrienols with other substances.

This invention also provides a method for preventing restenosis in a patient undergoing an arterial angioplastic procedure comprising the steps of:

(a) coating the exterior surface of an angioplastic balloon with a composition comprising a tocotrienol; and

(b) performing the arterial angioplastic procedure such that a prophylactically effective amount of the composition is transferred to the interior surface of the artery.

The tocotrienols useful in the methods of this invention include those compounds possessing the following three structural characteristics: (1) a hydrogen donor group (or a group that can be hydrolyzed to a hydrogen donor group) attached to an aromatic ring system; (2) a side chain attached to the aromatic ring system comprising one or more isoprenoid or isoprenoid-like units and (3) a methylene unit or a functional group having at least one lone pair of electrons positioned adjacent to the atom to which the side chain is attached to the aromatic ring, said electrons being conjugated to the aromatic ring system. Specific preferred tocotrienols useful in the methods of this invention include desmethyl-tocotrienol, α- tocotrienol, β- tocotrienol, γ- tocotrienol, δ- tocotrienol, P_{18} tocotrienol and P_{25} tocotrienol.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the effects of γ- tocotrienol (GT301) on superoxide production in human peripheral blood neutrophils.

DETAILED DESCRIPTION OF THE INVENTION

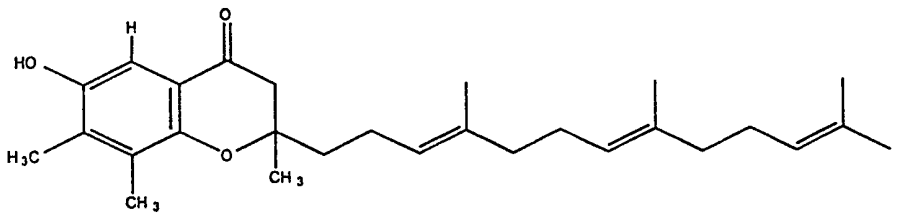
As used herein, the following definitions apply (unless expressly noted to the contrary):

"Composition" as used herein refers to a preparation for administration via any acceptable route known to those of ordinary skill in the art. Such routes include, but are not limited to oral, parenteral, intravenous or topical administration. "Composition" encompasses pharmaceutical compositions as well as dietary supplements, foodstuffs, food additives and the like.

"Desmethyl-tocotrienol" refers to the compound 3,4-dihydro-2-methyl-2-(4,8,12-trimethyltrideca-3'(E), 7'(E), 11'-trienyl)-2H-benzopyran-6-ol. This specific tocotrienol has been referred to as "tocotrienol" in some of the published literature cited herein.

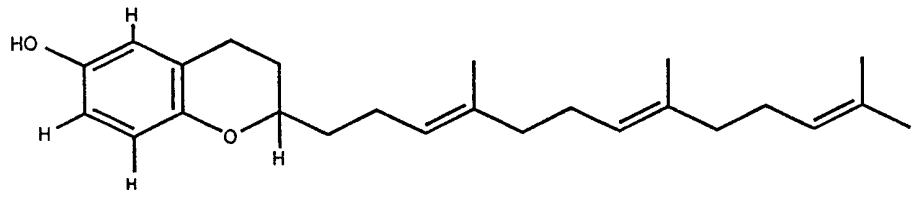
"Patient" refers to a warm-blooded mammal and preferably, a human. Patients in need of prophylactic therapy to prevent restenosis are those patients possessing one or more risk factors for the development of restenosis. For example, patients who have undergone angioplasty or arterial bypass surgery are at particular risk for the development of restenosis. Advantageously, patients may also receive prophylactic restenosis therapy according to this invention (short or long-term) prior to undergoing angioplasty or arterial bypass surgery.

"P_{18} tocotrienol" refers to a tocotrienol having the formula



P_{18} tocotrienol and P_{18} are trademarks of Bionutrics, Inc. (Phoenix, Arizona).

"P_{25} tocotrienol" refers to the tocotrienol 3,4-dihydro-2-(4,8,12-trimethyltrideca-3'(E),7'(E), 11"-trienyl)-2H-1-benzopyran-6-ol) which has the formula

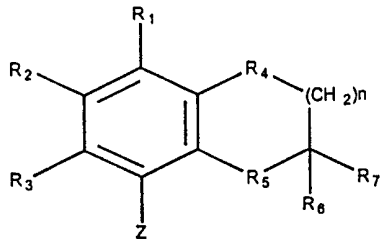


This compound is also known as didesmethyl-tocotrienol. P_{25} tocotrienol and P_{25} are trademarks of Bionutrics, Inc. (Phoenix, Arizona).

"Prophylactically effective amount" refers to an amount of active ingredient sufficient to prevent restenosis or the symptoms of restenosis in a patient for a period of at least about six months. "Prophylactically acceptable means" refers to means effective to impart a prophylactic effect.

"Tocotrienol" refers to compounds possessing the following three structural characteristics: (1) a hydrogen donor group (or a group that can be hydrolyzed to a hydrogen donor group) attached to an aromatic ring system; (2) a side chain attached to the aromatic ring system comprising one or more isoprenoid or isoprenoid-like units and (3) a methylene unit or a functional group having at least one lone pair of electrons positioned adjacent to the atom to which the side chain is attached to the aromatic ring, said electrons being conjugated to the aromatic ring system (preferably CH_2, C=O, CHOH, O, S or NH). Preferred tocotrienols for use in the methods of this invention are those which are naturally occurring. These naturally occurring tocotrienols may be conveniently isolated from biological materials or synthesized from commercially available starting material. Preferably, the tocotrienols for use in the methods of this invention are obtained from biological materials that have been stabilized and extracted, such as by the processes described in PCT publication WO 91/17985 (the entire disclosure of which is hereby incorporated by reference). Examples of preferred biological materials, tocotrienols and methods for obtaining tocotrienols synthetically and from biological materials are referred to in co-owned US patent 5,591,772 and PCT publication WO 91/17985 (the entire disclosures of which are hereby incorporated by reference). Preferred biological materials from which the tocotrienols of this invention may be obtained include stabilized brans and especially, stabilized rice bran.

Specific preferred tocotrienols of this invention include those of formula (I):



wherein

R_1 and R_3 are each independently selected from the group consisting of H, halogen, OH, OCH_3 and C_1-C_6 branched or unbranched alkyl (preferably, H, halogen and C_1-C_3 branched or unbranched alkyl and more preferably, H and methyl);

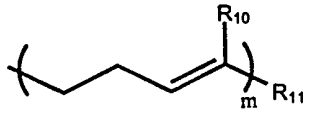
R_2 is a hydrogen donor group selected from the group consisting of OH, NHR_8, CO_2Y, $C(R_8)_2CO_2H$ and C_1-C_8 branched or unbranched alkyl substituted with OH, NHR_8, CO_2Y or $C(R_8)_2CO_2H$ (preferably, OH and C_1-C_3 branched or unbranched alkyl substituted with OH and more preferably, OH);

R_4 is selected from the group consisting of O, NH, CH-R_9, C=O and CH-OH (preferably, O, CH_2 and C=O);

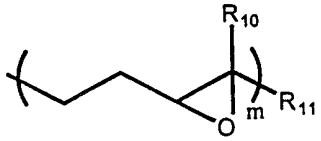
R_5 is selected from the group consisting of CH_2, C=O, CHOH, O, S and NH (preferably, O, CH_2 and C=O and more preferably, O and C=O);

R_6 is selected from the group consisting of H and C_1-C_6 branched or unbranched alkyl (preferably, H and C_1-C_3 branched or unbranched alkyl and more preferably, H and methyl);

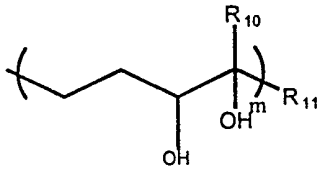
R_7 is selected from the group consisting of isoprenoid and isoprenoid-like side chains, and more preferably from the group consisting of side chains of formulas (a)-(c):



(a)



(b) and



(c)

wherein each R_{10} is independently selected from the group consisting of H, NH_2 and C_1-C_6 branched or unbranched alkyl and R_{11} is selected from the group consisting of H, C_1-C_6 branched or unbranched alkyl, CH_2OH, CO_2H and OH (preferably, R_7 is a side chain of formula (a), wherein R_{10} and R_{11} are each independently is selected from the group consisting of H and C_1-C_3 branched or unbranched alkyl and more preferably, H and methyl);

each R_8 and R_9 is independently selected from the group consisting of H and C_1-C_6 branched or unbranched alkyl (preferably, H and C_1-C_3 branched or unbranched alkyl and more preferably, H and methyl);

Y is H or and C_1-C_{18} branched or unbranched alkyl (preferably H and C_1-C_6 branched or unbranched alkyl and more preferably, H and C_1-C_4 branched or unbranched alkyl);

Z is selected from the group consisting of H, halogen, OH, CH_2OH, CH_3, OCH_3 and $COCH_3$ (preferably H and CH_3);

n is an integer selected from the group consisting of 0, 1, 2, 3 and 4 (preferably 0 and 1); and

m is an integer selected from the group consisting of 1-30 (preferably 1-20, more preferably 3-10 and most preferably, 3-7).

More preferred tocotrienols of this invention include desmethyl-tocotrienol, α-tocotrienol, β- tocotrienol, γ- tocotrienol, δ- tocotrienol, P_{18} tocotrienol and P_{25} tocotrienol.

This invention expressly encompasses the prodrug form of tocotrienols. Upon administration to a patient, such a prodrug undergoes biotransformation to their active form. Prodrugs include the esterified form of the tocotrienols used in this invention which comprise a carboxylic acid functionality.

The tocotrienols for use in the methods of this invention may be in their isomerically pure form or be present as mixtures of isomers. For example, the tocotrienols of this invention

may exist as the d- or l-isomer or the d,l-racemic mixture. The naturally occurring isomer (usually the d-isomer) and the d,l-racemic mixture are preferred.

"TRF" refers to a tocotrienol rich fraction obtained by the stabilization and extraction of a biological source. TRF typically contains varying amounts of desmethyl-tocotrienol,. α-tocotrienol, β- tocotrienol, γ- tocotrienol and δ- tocotrienol and may also contain quantities of the newly discovered tocotrienols, P_{18} tocotrienol and P_{25} tocotrienol. Most commonly, TRF will be comprise at least about 50% to about 90% tocotrienols w/w (preferably, at least about 60% to about 90% and more preferably, at least about 70% to about 90%).

"TRF_{25}" refers to a TRF comprising a significant weight percentage of P_{25} tocotrienol. Preferably, TRF_{25} comprises at least about 5% P_{25}, more preferably, at least about 10% P_{25}, and even more preferably, at least about 15% P_{25} w/w. An example of the preparation of a specific TRF_{25} is set forth in A.A. Qureshi et al., Nutr. Biochem., 8, pp. 290-98 (1997). TRF_{25} is a preferred component of the compositions and methods described herein. TRF_{25} is a trademark of Bionutrics, Inc. (Phoenix, Arizona).

One embodiment of this invention provides a method for preventing restenosis in a patient comprising the step of administering to the patient a prophylactically effective amount of a composition comprising a tocotrienol, a mixture of tocotrienols or a combination of one or more tocotrienols with one or more additional substances. This embodiment of the invention provides an effective means for administering tocotrienols systemically or locally to a patient in need of restenosis prophylaxis.

An alternate embodiment of this invention provides a method for preventing restenosis in a patient comprising the steps of:

(a) coating the exterior surface of an angioplastic balloon with a composition comprising a tocotrienol; and

(b) performing the arterial angioplastic procedure such that a prophylactically effective amount of the composition is transferred to the interior surface of the artery.

Such a coating also may be applied to implantable and non-implantable vascular instruments (*e.g.*, stents).

This alternate embodiment of the invention provides an effective means for delivering tocotrienols directly to the site of damage where restenosis is likely to develop without necessitating further invasive procedures. Delivery of the tocotrienols in this way reduces the severity of endothelial damage caused as a result of the trauma and also reduces further damage resulting from the subsequent inflammatory response.

The methods described herein may be used alone or in conjunction with conventional prophylactic methods (such as those described above). Accordingly, the methods of this invention, used alone or together with other methods, provide a safe and effective means for reducing or eliminating the risk of restenosis in a patient in need of such prophylactic treatment.

Without wishing to be bound by theory, tocotrienols are useful in preventing restenosis due to their unique combination of antioxidant, antiinflammatory and antithrombotic properties. As opposed to conventional therapeutics that target a single mechanism, tocotrienols target multiple mechanisms leading to restenosis. For example, the tocotrienols of this invention inhibit the production of free arachidonic acid (a major mediator of inflammatory response). This inhibition is believed to occur by either the inhibition of phospholipase A_2 or alternatively, through the increase in corticosterone levels in the blood. Phospholipase A_2 cleaves at C-2 of phosphate head groups, resulting in the release of free arachidonic acid. Free arachidonic acid can then be converted to a variety of biologically important molecules, such as prostaglandins and thromboxanes (via the cyclooxygenase pathway) and the leukotrienes (via the lipoxygenase pathway). These factors are associated with the increased platelet aggregation and vasoconstriction in restenosis.

Furthermore, tocotrienols inhibit the production of a variety of cytokines (including TNF, IL-1 and growth factors). These cytokines contribute to the proliferation of smooth muscle and propagation of the inflammatory response associated with restenosis. Furthermore, tocotrienols reduce the levels of superoxide production. Superoxide and nitric oxide react to form peroxynitrite, which is a causative factor in endothelial damage and arteriosclerosis. By reducing superoxide and cytokine production, tocotrienols reduce the cell proliferation, chemotaxis, inflammation and endothelial damage that are

responsible for restenosis. As a result of their unique combination of properties, tocotrienols are capable of combating the root causes and lessen the severity of the arterial response to injury that often leads to restenosis.

Compositions of this invention are prepared by combining one or more tocotrienols with an acceptable carrier. For pharmaceutical compositions of this invention, the carrier must be pharmaceutically acceptable (i.e., a carrier which is non-toxic to the patient at the administered level and which does not destroy the activity of the active component(s) of the composition). Acceptable carriers, including pharmaceutically acceptable carriers, are well known to those of ordinary skill in the art.

The compositions of this invention may be used or administered by any prophylactically acceptable means to a patient in need of restenosis prophylaxis. For example, pharmaceutical compositions of this invention may be administered orally, topically, transdermally, parenterally, intravenously or by inhalation. These compositions may be formulated so as to impart a time-released benefit. Oral compositions may take the form of tablets, capsules, caplets, emulsions, liposomes, suspensions, powders and the like. Topical compositions include, but are not limited to, gels, lotions and creams. Parenteral compositions take the form of sterile solutions and emulsions and the like. Intravenous compositions include, but are not limited to sterile solutions. The preferred routes of administration are parenteral injection of a sterile solution or emulsion (if being administered to a patient immediately prior to undergoing angioplasty or arterial bypass surgery) and oral or transdermal administration (if being administered to patients who have already undergone angioplasty or arterial bypass surgery or who will be treated for a prolonged period of time prior to any such procedure).

Suitable carriers for use in the alternate embodiment of this invention are pharmaceutically acceptable carriers that are sufficiently viscous to adhere to the exterior surface of an angioplastic balloon but that are readily transferred to the interior surface of the treated artery upon inflation during the angioplastic procedure. The exterior surface of the angioplastic balloon can be pretreated or altered (such as by mechanical or chemical roughening or increasing the surface porosity) to enhance the ability of the tocotrienol composition to adhere to the surface. Suitable carriers include glycols, such as propylene glycol, parabens (such as methyl and propyl), glycerin, alcohols, petrolatum, oils (including rice bran and other bran oils) and waxes. Propylene glycol and rice bran oil are preferred carriers for this method. Other suitable carriers (including additives and

adjuvants) are well known to those of ordinary skill in the art. Typically, a formulation comprising about 0.1 - 5000 mg of a tocotrienol composition (comprising from about 0.1% to about 50%, preferably from about 1% to about 25% and more preferably, about 5% to about 15% w/w tocotrienol) and about 0.1 to about 100 g of a suitable carrier (preferably about 1 to about 50 g and more preferably, from about 1 to about 25 g of a suitable carrier) is used to coat the balloon prior to the angioplastic procedure. The balloon may be coated immediately preceeding surgery or may be pre-coated and stored for later use.

Dosage levels and requirements are well-recognized in the art and may be chosen by those of ordinary skill in the art from publicly available sources. Typically, dosage levels will range between about 0.1 and about 10,000 mg of tocotrienol or mixture of tocotrienols per dose. Preferably, the range is between about 0.1 and about 5,000 mg of active ingredient per dose. If being administered to patients who have undergone angioplasty or arterial bypass surgery, multiple doses may be required over a period of time to obtain maximum benefit. For example, a patient may receive oral administration of between about 0.1 and about 5000 mg/day for a period of several weeks to several months following angioplasty or bypass surgery. Patients receiving prophylactic treatment prior to undergoing angioplasty or arterial bypass surgery may be administered, for example, one or more doses of between about 0.1 and about 5000 mg/day by parenteral injection for one or more days or weeks prior to the procedure. For the alternate embodiment of this invention, a concentration should be selected such that a prophylactically effective amount of the tocotrienol composition is transferred to the interior surfaces of the treated artery. Specific dosage and treatment regimens will depend upon factors such as the patient's overall health status, the severity and course of the patient's disorder or disposition thereto and the judgment of the treating physician. Higher or lower doses may be employed as needed.

Tocotrienols and mixtures thereof may be used in combination with conventional therapeutics in the methods described herein. The conventional therapeutics may be administered separately from the tocotrienols and mixtures thereof, or they may be formulated together in a single dosage form. Such combination therapy advantageously utilize lower dosages of those conventional therapies and reduce or avoid possible toxicity incurred when those agents are used as monotherapies. For example, the tocotrienols used in the methods of this invention may be used in conjunction with any anti-inflammatory or anti-oxidative agent. Preferably, in combination therapy, the

tocotrienols are used in conjunction with non-steroidal anti-inflammatory agents (NSAIDS) or with one or more of the following restenosis prophylactic agents: ReoPro (Centacor, Inc.), DAB389EGF (Seragen, Inc.), gene-based anti-restenosis agents (such as those being developed by Antivirals, Inc.), nitrogen oxide based anti-restenosis agents (such as those being developed by NitroMed, Inc.), acyclovir, acyclovir with the thymidine kinase gene (CardioGene Therapeutics, Inc.) or cyclodextrins (such as the sulfated cyclodextrins being developed by Atlantic Pharmaceuticals, Inc.). Particularly preferred combination therapies employ the co-administration of the tocotrienol compositions of this invention with aspirin, naproxen salts and ibuprofen (and more preferably, aspirin).

EXAMPLES

In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

The methods used for obtaining and purifying tocotrienols and mixtures thereof (including TRF) useful for the methods of this invention are described in the Examples section of US patent 5,591,772. Stabilization of rice bran follows Example 1 of US patent 5,591,772. Purification of TRF, P_{25} tocotrienol and P_{18} tocotrienol follow Examples 2-4 of US patent 5,591,772.

All assays conducted on chicken or swine were done following the protocols described in A.A. Qureshi et al., Am J. Clin. Nutr., 53, pp. 1021S-26S (1991). All enzymatic assays were conducted following the protocols described in A.A. Qureshi et al., Lipids, 17, p. 924 (1982). TRF levels were measured using the radioimmunoassay kit available from Genzyme Corp. (Cambridge, MA).

The following specific protocols are used in the subsequent examples herein:

Protocol I: Dry Heat Stabilization

Extruder: Wenger Model X-25

Standard Screw/Barrel Setup

Barrel No.	Standard Port	Screw No.	Standard Port
5	28714-9	5	28320-1
4	28318-1	4	8326-9
3	28372-9	3	28326-1
2	28318-1	2	28326-1
1	28350-1	1	28387-9

Standard Die Setup

Die/Spacer	Measurement	Standard Port
Spacer	0.375	28340-11
Back Plate	0.625	28361-51
Intermediate Plate	0.218	28316-723
Front Plate	0.235	28389-507

Operating Conditions

Feed Rate:	1000 lbs/hr
Temperature:	170°C at exit die
Pressure:	975-1025 psi
Moisture Feed:	12%
Moisture Discharge:	9.6%
Residence Time:	15 seconds
Run Duration:	8 hours
Sample Size:	50 lbs

Protocol II: Dry Heat Followed By Wet Heat Stabilization

Dry Heat Stage: Protocol I

Wet Heat Stage:

Extruder: Anderson 4 inch

Screw Barrel Configuration: Standard Cut Flight

Die Setup:

Diameter: 0.1875 inches

Length: 0.75 inches

Operating Conditions:

Feed Rate:	378 lbs/hr
Shaft Speed:	279 rpm
Steam Injection:	36 lbs/hr (32 psi at #8 hole)
Mechanical Pressure:	750 psi (ast.)
Moisture Feed:	11.4%
Discharge Moisture:	15%
Discharge Rate:	450 lbs/hr
Discharge Temp.:	121°C

Protocol III: Drying/Cooling Procedure

The wet heat stabilized product of protocol II (15% moisture) was discharged onto aluminum trays and placed in a tray oven at 101.1°C until the moisture content was 8-10% (approximately 1.5 hrs). The trays were then placed on tray racks and allowed to cool at ambient temperature (approximately 20°C).

Protocol IV: Oil Extraction

Oil to Hexane Ratio:	1:4
No. of Washings:	3
Extraction Temperature	40°C

The hexane was removed from the extract by mild heating (40°C) under a mild vacuum.

Protocol V: Dewaxing

20 lbs of crude oil were refrigerated for 24 hrs at -15.6°C. The supernatant (containing the dewaxed oil) was decanted from the solidified waxes. The waxes were then centrifuged to removed entrained oil, yielding 0.59 lbs of waxes and 19.41 lbs of dewaxed oil.

Evaluation of Activity of Tocotrienols

Example 1

The effects of tocotrienols (in the form of the TRF mixture and individual tocotrienols) on plasma levels of thromboxane B_2 and platelet factor 4 in chickens were determined. These levels are known to correlate with the levels of inflammatory cytokines. The following feeding conditions were used:

Each group of six chickens (6-week old female white leghorn chickens) was administered a chick mash control diet or a control diet containing one or more additives. The amount of feed consumed by all groups was comparable to the control group. The feeding period was 4 weeks. The birds were fasted for a period of 14 hours prior to sacrifice (at 0800 hours).

The chicken mash control diet contained the following ingredients:

Ingredient	Weight (g)
Corn (8.8% protein)	615.0
Soybean Meal	335.0
Corn Oil	10.0
Calcium Carbonate	10.0
Dicalcium Phosphate	20.0
Iodized Salt	5.0
Mineral Mixture	2.5
Vitamin Mixture	2.5

The mineral mixture contained per kg feed: zinc sulfate • H_2O, 110 mg; manganese sulfate • $5H_2O$, 70 mg; ferric citrate • H_2O, 500 mg; copper sulfate • $5H_2O$, 16 mg; sodium selenite, 0.2 mg; DL-methionine, 2.5 g; choline chloride (50%), 1.5 g; ethoxyquin (1,2-dihydro-6-ethoxy-2,2,4-trimethylquinoline), 125 mg; and thiamine HCl, 1.8 mg. The vitamin mixture contained per kg feed: vitamin A, 1,500 units; vitamin D_3, 400 units; vitamin E, 10 units; riboflavin, 3.6 mg; calcium panthothenate, 10 mg; niacin, 25 mg; pyridoxine HCl, 3 mg; folacin, 0.55 mg; biotin, 0.15 mg; vitamin B_{12}, 0.01 mg; and vitamin K_1, 0.55 mg.

Results are reported as mean ± standard deviation. Percentages of control are reported in parentheses. The following results were obtained:

EXPERIMENT 1

Diet	Thromboxane B_2 (mg/100 ml)	Platelet Factor 4 (ng/ml)
1)control diet + 5% corn oil	16.7 ± 1.69 (100.0)	7.2 ± 0.48 (100.0)
2) control diet + 5% corn oil + waxes (50 ppm)	15.8 ± 1.29 (94.6)	7.5 ± 0.42 (104.2)
3) control diet + 5% corn oil + TRF (50 ppm)	12.4 ± 1.42 (74.3)	5.7 ± 0.64 (79.2)

Significant decreases of thromboxane B_2 and platelet factor 4 plasma levels were observed in the chickens fed a control diet supplemented with TRF.

EXPERIMENT 2

Diet	Thromboxane B_2 (pg/ml)	Platelet Factor 4 (ng/ml)
1)control diet	25.84 ± 0.84 (100.00)	13.9 ± 0.49 (100.00)
2) control diet + TRF (50 ppm)	20.55 ± 0.95 (79.53)	9.67 ± 0.43 (73.87)
3) control diet + α-tocotrienol (50 ppm)	21.63 ±0.89 (83.71)	8.78 ± 0.72 (67.07)
4) control diet + γ-tocotrienol (50 ppm)	19.22 ± 0.78 (74.38)	8.36 ± 0.79 (63.87)
5) control diet + δ-tocotrienol (50 ppm)	18.65 ± 0.99 (72.17)	8.23 ± 0.77 (62.87)
6) control diet + desmethyl-tocotrienol (50 ppm)	16.74 ± 1.62 (64.78)	7.76 ± 1.67 (59.28)
7) control diet + P_{25} tocotrienol (50 ppm)	16.42 ± 1.36 (63.54)	7.27 ± 0.74 (55.54)
8) control diet + Geraniol (100 ppm)	25.46 ± 1.52 (98.53)	12.38 ± 1.26 (94.57)
9) control diet + Lovastatin (100 ppm)	24.89 ± 0.88 (96.32)	12.24 ± 1.49 (93.51)
10) control diet + Geraniol (50 ppm) + Lovastatin (50 ppm)	24.95 ± 0.97 (96.56)	12.19 ± 1.15 (93.12)

Significant decreases of thromboxane B_2 and platelet factor 4 plasma levels were observed in the chickens fed a control diet supplemented with TRF and individual tocotrienols.

Example 2

The effects of tocotrienols (in the form of the TRF mixture and individual tocotrienols) on plasma levels of thromboxane B_2 and platelet factor 4 in swine were determined. These levels are known to correlate with the levels of inflammatory cytokines. The following feeding conditions were used:

Each group of three swine (5-month old swine carrying Lpd^5 and Lpu^1 mutant alleles) were administered a control diet or a control diet supplemented with one or more additives. After a 12 hour fast, plasma samples were taken at 42 days from the start of the feeding period.

The swine control diet contained the following ingredients:

Ingredient	Weight Percentage
Corn (9.3% protein)	78.37
Soybean Meal (44.0% protein)	15.42
Lard	3.00
Calcium Carbonate	0.95
Dicalcium Phosphate	0.96
Mineral Mixture	0.30
Vitamin Mixture	1.00

The mineral mixture contained per kg feed: zinc sulfate • H_2O, 110 mg; manganese sulfate • $5H_2O$, 70 mg; ferric citrate • H_2O, 500 mg; copper sulfate • $5H_2O$, 16 mg; sodium selenite, 0.2 mg; DL-methionine, 2.5 g; choline chloride (50%), 1.5 g; ethoxyquin (1,2-dihydro-6-ethoxy-2,2,4-trimethylquinoline), 125 mg; and thiamine HCl, 1.8 mg. The vitamin mixture contained per kg feed: vitamin A, 1,500 units; vitamin D_3, 400 units; vitamin E, 10 units; riboflavin, 3.6 mg; calcium panthothenate, 10 mg; niacin, 25 mg; pyridoxine HCl, 3 mg; folacin, 0.55 mg; biotin, 0.15 mg; vitamin B_{12}, 0.01 mg; and vitamin K_1, 0.55 mg.

The gain in body weight in all groups was comparable to the control.

Results are reported as mean ± standard deviation. Percentages of control are reported in parentheses. The following results were obtained:

Diet	Thromboxane B_2 (pg/100 ml)	Platelet Factor 4 (ng/ 100 ml)
1)control diet	75.93 ± 1.45 (100.00)	24.12 ± 1.75 (100.00)
2) control diet + TRF (50 ppm)	64.55 ± 1.18 (95.23)	20.32 ± 1.70 (84.30)
3) control diet + γ-tocotrienol (50 ppm)	62.54 ± 1.39 (92.25)	20.65 ± 1.15 (85.28)
4) control diet + desmethyl tocotrienol (50 ppm)	60.48 ± 1.46 (87.66)	19.85 ± 1.27 (82.59)
5) control diet + P_{25} tocotrienol (50 ppm)	57.03 ± 1.95 (83.02)	19.15 ± 1.45 (79.36)

Significant decreases of thromboxane B_2 and platelet factor 4 plasma levels were observed in the swine fed a control diet supplemented with TRF and individual tocotrienols.

Example 3

The effects of γ-tocotrienol on the release of superoxide in human peripheral blood neutrophils were determined. Neutrophils are an extracellular source of oxygen free radicals and, together with nitric oxide, form peroxynitrite (responsible for endothelial damage). Activated neutrophils attach to endothelial tissue, where they release the potent toxin, superoxide. Superoxide amplifies the inflammatory response and impairs local blood circulation.

The neutrophils tested were isolated by density centrifugation on Ficoll-Hypaque gradients using conventional methods (see E. Serbinova et al., Free Rad. Bio. and Med., 10, pp. 263-75 (1991)). The neutrophils were then placed in a 96-well plate. γ-tocotrienol and phorbol myrstate acetate were added to the wells at the same time. The secretion of superoxide was measured as the superoxide dismutase-inhibitable reduction of ferricytochrome C. The results of this study are displayed in Figure 1.

The amount of released superoxide was reduced from 19.7 nmole ($5x10^5$ cells/hour) in the control to 8.0 and 0.0 nmole at γ-tocotrienol concentrations of 10^{-6} and 10^{-5}, respectively.

Efficacy of Tocotrienols in Restenosis Animal Models

The following restenosis animal models can be used to evaluate the efficacy of tocotrienols:

A.M. Lafont et al., J. Clin. Invest., 95(3), pp. 1018-25 (1995) and I.A. Guzman et al., Arteriosclerosis, Thrombosis & Vascular Biology, 16(3), pp. 479-87 (1996) describe rabbit models in which angioplasty was performed on established atherosclerotic lesions.

R. Bonan et al., Catheterization & Cardiovascular Diagnosis, 38(1), pp. 44-49 (1996) describe a balloon injury/reinjury (plaque of dilation) protocol in swine.

ApoE deficient mice develop atherosclerotic lesions that are similar to those in humans. Using apoE deficient (-/-) C57BL/6 mice, atherosclerotic lesions develop after about 16 weeks when fed a standard low fat mouse diet. ApoE heterozygous (+/-)C57BL/6mice only develop atherosclerotic lesions when fed an atherogenic high fat diet. Once atherosclerosis has developed, the mice can be subjected to angioplasty and the effects of tocotrienols can then be measured by administering unsupplemented feed or feed supplemented with between about 5 and about 100 ppm of tocotrienols and tocotrienols mixtures (such as P_{18}, P_{25} and TRF_{25}). The effect of the tocotrienols on the prevention of restenosis can be measured using a standard low fat mouse feed or a high fat atherogenic diet. Feeding protocols can be carried out for a period of about 4 to about 40 weeks.

One or more of these models can be used to establish the efficacy of tocotrienol compositions useful in the methods of this invention to prevent restenosis.

While we have described a number of embodiments of this invention, it is apparent that our basic constructions may be altered to provide other embodiments which utilize the compositions and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims, rather than by the specific embodiments that have been presented hereinabove.

What is claimed is:

1. A method for preventing restenosis in a patient comprising the step of administering to the patient a prophylactically effective amount of a composition comprising a tocotrienol.

2. The method according to claim 1, wherein the composition comprises a mixture of tocotrienols.

3. The method according to claim 2, wherein the composition comprises TRF_{25}.

4. The method according to claim 1, wherein the composition comprises one or more tocotrienols and one or more non-steroidal anti-inflammatory agents.

5. The method according to claim 4, wherein the non-steroidal anti-inflammatory agent is aspirin.

6. The method according to claim 1, wherein the composition comprises one or more tocotrienols selected from the group consisting of desmethyl-tocotrienol, α-tocotrienol, β- tocotrienol, γ- tocotrienol, δ- tocotrienol, P_{18} tocotrienol and P_{25} tocotrienol.

7. The method according to claim 6, wherein the tocotrienol is P_{25} tocotrienol or P_{18} tocotrienol.

8. The method according to claim 1, wherein the patient has undergone angioplasty or is being administered the composition prior to undergoing angioplasty.

9. The method according to claim 1 wherein the patient has undergone arterial bypass surgery or is being administered the composition prior to undergoing arterial bypass surgery.

10. The method according to claim 8 or 9, wherein the angioplasty or arterial bypass surgery is conducted on a coronary artery.

11. The method according to claim 10, wherein the coronary artery is selected from the group consisting of the left anterior descending coronary artery, the left circumflex coronary artery and the right coronary artery.

12. The method according to claim 1, wherein the composition is administered parenterally.

13. The method according to claim 12, wherein the composition is in the form of a sterile solution or emulsion.

14. The method according to claim 13, wherein the composition comprises between about 0.1 and about 5000 mg of tocotrienol/dose.

15. The method according to claim 1, further comprising the step of administering to the patient an anti-steroidal anti-inflammatory agent.

16. A method for preventing restenosis in a patient undergoing an arterial angioplastic procedure comprising the steps of:

(a) coating the exterior surface of an angioplastic balloon with a composition comprising a tocotrienol; and

(b) performing the arterial angioplastic procedure such that a prophylactically effective amount of the composition is transferred to the interior surface of the artery.

17. The method according to claim 16, wherein the composition comprises a mixture of tocotrienols.

18. The method according to claim 17, wherein the composition comprises TRF_{25}.

19. The method according to claim 16, wherein the composition comprises one or more tocotrienols and one or more non-steroidal anti-inflammatory agents.

20. The method according to claim 19, wherein the non-steroidal anti-inflammatory agent is aspirin.

21. The method according to claim 16, wherein the composition comprises one or more tocotrienols selected from the group consisting of desmethyl-tocotrienol, α-tocotrienol, β- tocotrienol, γ- tocotrienol, δ- tocotrienol, P_{18} tocotrienol and P_{25} tocotrienol.

22. The method according to claim 21, wherein the tocotrienol is P_{25} tocotrienol or P_{18} tocotrienol.

23. The method according to claim 16, wherein the arterial angioplasty is conducted on a coronary artery.

24. The method according to claim 23, wherein the coronary artery is selected from the group consisting of the left anterior descending coronary artery, the left circumflex coronary artery and the right coronary artery.

25. The method according to claim 16, wherein the composition further comprises a pharmaceutically acceptable carrier.

26. The method according to claim 25, wherein the pharmaceutically acceptable carrier is rice bran oil.

27. The method according to claim 25, wherein the composition comprises between about 0.1 and about 5000 mg of tocotrienol/dose.

28. A method for treating restenosis, comprising:

a) diagnosing a patient at risk for developing restenosis; and

b) administering to said patient a therapeutically effective amount of a pharmaceutical composition comprising a tocotrienol.

29. The method of claim 28, wherein the composition comprises a mixture of tocotrienols.

30. The method of claim 29, wherein the composition comprises TRF_{25}.

31. The method of claim 28, wherein the composition comprises one or more tocotrienols and one or more non-steroidal anti-inflammatory agents.

32. The method of claim 31, wherein the non-steroidal anti-inflammatory agent is aspirin.

33. The method according to claim 28, wherein the composition comprises one or more tocotrienols selected from the group consisting of desmethyl-tocotrienol, α - tocotrienol, β - tocotrienol, γ - tocotrienol, δ - tocotrienol, P_{18} tocotrienol and P_{25} tocotrienol.

34. The method according to claim 33, wherein the tocotrienol is P_{25} tocotrienol or P_{18} tocotrienol.

35. The method according to claim 28, wherein the patient has undergone angioplasty or is being administered the composition prior to undergoing angioplasty.

36. The method according to claim 28, wherein the patient has undergone arterial bypass surgery or is being administered the composition prior to undergoing arterial bypass surgery.

37. The method according to claim 35 or 36, wherein the angioplasty or arterial bypass surgery is conducted on a coronary artery.

38. The method according to claim 37, wherein the coronary artery is selected from the group consisting of the left anterior descending coronary artery, the left circumflex coronary artery and the right coronary artery.

39. The method according to claim 28, wherein the composition is administered parenterally.

40. The method according to claim 39, wherein the composition is in the form of a sterile solution or emulsion.

41. The method according to claim 40, wherein the composition comprises between about 0.1 and about 5000 mg of tocotrienol/dose.

42. The method according to claim 28, further comprising the step of administering to the patient an anti-steroidal anti-inflammatory agent.

43. A method for preventing restenosis in a patient undergoing an arterial procedure for implanting a stent, comprising the steps of:

a) coating the stent with a composition comprising a tocotrienol; and
b) radially expanding the stent at a region of interest within an artery.

44. The method of claim 43, wherein the composition comprises a mixture of tocotrienols.

45. The method of claim 44, wherein the composition comprises TRF_{25}.

46. The method of claim 43, wherein the composition comprises one or more tocotrienols and one or more non-steroidal anti-inflammatory agents.

47. The method of claim 46, wherein the non-steroidal anti-inflammatory agent is aspirin.

48. The method according to claim 43, wherein the composition comprises one or more tocotrienols selected from the group consisting of desmethyl-tocotrienol, - tocotrienol, - tocotrienol, - tocotrienol, - tocotrienol, P_{18} tocotrienol and P_{25} tocotrienol.

49. The method according to claim 48, wherein the tocotrienol is P_{25} tocotrienol or P_{18} tocotrienol.

50. The method according to claim 43, wherein the arterial angioplasty is conducted on a coronary artery.

51. The method according to claim 50, wherein the coronary artery is selected from the group consisting of the left anterior descending coronary artery, the left circumflex coronary artery and the right coronary artery.

52. The method according to claim 43, wherein the composition further comprises a pharmaceutically acceptable carrier.

53. The method according to claim 52, wherein the pharmaceutically acceptable carrier is rice bran oil.

54. The method according to claim 52, wherein the composition comprises between about 0.1 and about 5000 mg of tocotrienol per dose.

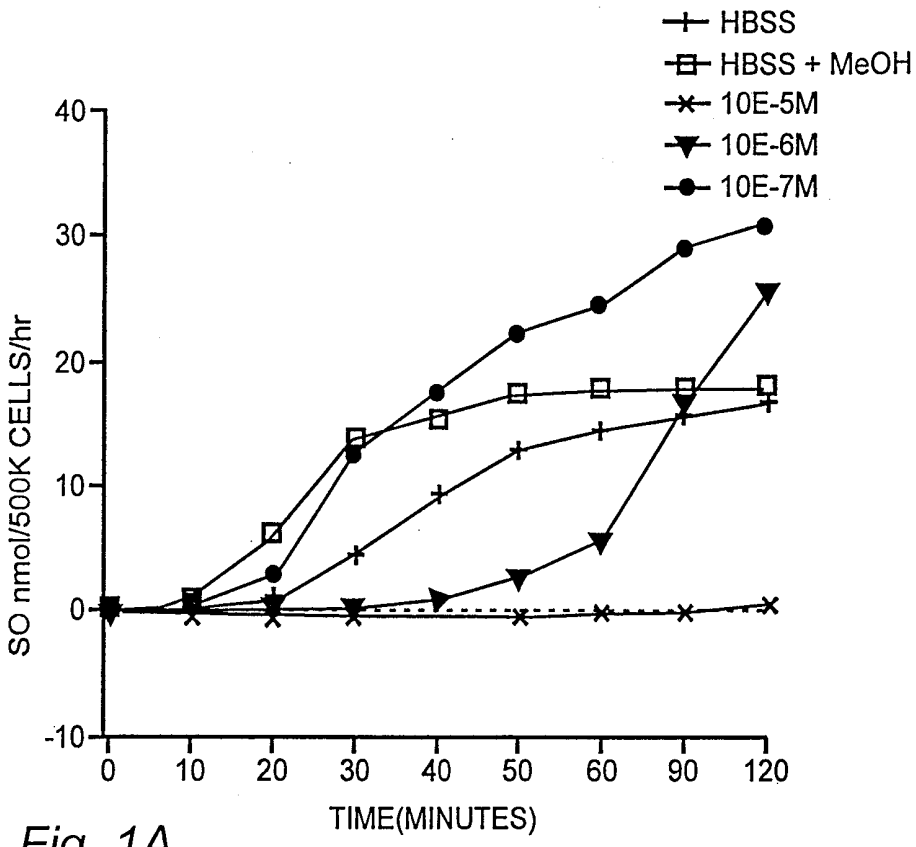

HBSS
HBSS + MeOH
10E-5M
10E-6M
10E-7M
SO nmol/500K CELLS/hr
40
30
20
10
0
-10
0
10
20
30
40
50
60
90
120
TIME(MINUTES)

Fig. 1A

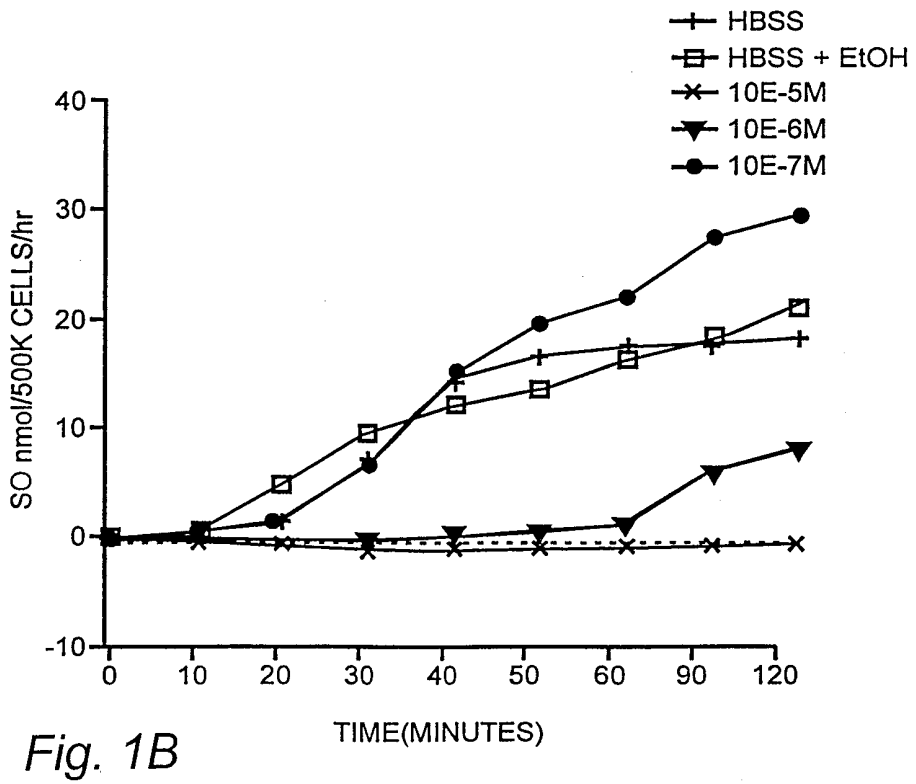

HBSS
HBSS + EtOH
10E-5M
10E-6M
10E-7M
SO nmol/500K CELLS/hr
40
30
20
10
0
-10
0
10
20
30
40
50
60
90
120
TIME(MINUTES)

Fig. 1B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/24606

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 31/355, 31/60
US CL : 514/458, 165
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/458, 165

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN: COMPOUNDS AND METHODS OF USE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	Chemical abstracts, volume 124, number 5, issued 25 July 1996, TOMEO et al, "Antioxidant effects of tocotrienols in patients with hyperlipidemia and carotid stenosis", page 1094, cloumn 2, abstract number 54478j, Lipids, 30(12), pages 1479-83, see entire abstract	1-3, 6-7 ---------- 1-54
Y	Chemical abstracts, voulme 3, issued 17 January 1994, SINZINGER et al, "The use of aspirin in grafts, coronary angioplasty", page 2, abstract number 22921z, "Aspirin and Other Salicylates", Vane et al Ed., Chapman & Hall, London, 1992, pages 417-46, see entire abstract.	1-54

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
07 JANUARY 1999

Date of mailing of the international search report
01 FEB 1999

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
RUSSELL TRAVERS
Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/24606

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US, 5,591,772 A (LANE ET AL) 07 January 1997, see entire document.	1-3, 6-7 --------- 1-54