<head> <meta content="text/html; charset=windows-1252" http-equiv="Content-Type"> <title>Bruce Halstead -- Antiviral compounds</title>

rexresearch.com

Bruce HALSTEAD
Cancer Therapy

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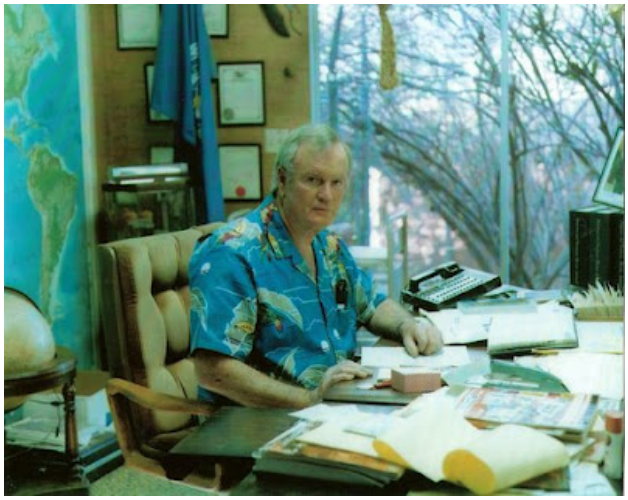
http://brucehalstead.blogspot.com/2007/09/bruce-w-halstead-and-world-life.html



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http://www.apfn.org/thewinds/1997/09/bruce_halstead.html

FDA AND STATE AUTHORITIES WAR AGAINST NATURAL REMEDIES

A decade's-long dispute between a highly respected physician/scientist and the State of California ended with the elderly doctor, Bruce Halstead, on criminal probation and stripped of his license to practice medicine.

In light of this and other recent actions taken by state governmental authorities in cooperation with such U. S. institutions as the Food and Drug Administration (FDA) and the FTC (Federal Trade Commission), the government appears to be engaged in a concerted war against a domain of the healing arts known as alternative medicine. This war, ostensibly for the protection of American citizens from unscrupulous "quacks," has apparently moved into a new phase. The FDA's pursuit of medical "public enemies" is no longer restricted primarily to non-MD practitioners not trained at established medical schools--those the general public largely considers the unorthodox fringe of the medical world. These federal agencies are now engaging the force of the government's legal machinery in the prosecution of physicians practicing "conventional medicine"--those who have dared to recognize and even incorporate into their practices the efficacy of holistic natural remedies.

Dr. Halstead is a graduate of Loma Linda University, a medical school which, to those in the field of the human physiological sciences, ranks as one of the more prestigious schools of medicine and scientific research in the world.

The 77-year-old physician is currently on probation under the State of California, Los Angeles County, for his activities involving the prescribing of alternative medication, specifically for his cancer patients. Dr. Halstead has been suspended from any form of medical practice. "In fact," he told The WINDS, "I can't even talk to a patient about nutrition."

When his home and clinic in San Bernardino County were raided by the Los Angeles District Attorney, "I challenged their legal jurisdiction," Halstead informed The WINDS, "since I had never lived or worked in Los Angeles County, but that did not matter. I was a legal novice and had not yet learned that jurisdiction and venue were merely legal fantasies which have no meaning in actual fact for the alternative health physician." (Nor, apparently, does the constitutional doctrine of habeas corpus).

Dr. Halstead was charged with twenty-eight counts of conspiracy, grand theft and violations of the Health and Safety Code, along with twenty felony and misdemeanor counts.

"The prosecutor wanted me to go to prison for eight years," he told The WINDS, "but the court ultimately reduced the sentence to 32 months. I was offered, on at least ten different occasions, the 'opportunity' of plea bargaining for a crime which I did not commit," Halstead explained. "My reply was 'not until hell freezes over.'"

The assault upon alternative medicine "is not just against me," he said. "They're after everybody and everything" connected with the field.

THE QUALIFICATIONS

Dr. Halstead, acclaimed as a genius even among his peers, has authored hundreds of books and research publications. Among them are benchmark works such as Poisonous and Venomous Marine Animals of the World which the U.S. Navy considers of such importance as to fund a project to put the entire three-volume tome on CD-ROM.

The WINDS obtained a copy of Dr. Halstead's Curriculum Vitae, the academician's equivalent of a resume´. The following qualifications belong to a man whom the government deems dangerous to his patients, incompetent to practice medicine and academically inadequate to determine what is harmful or beneficial to human physiology:

* Eleven years teaching on the medical faculty of Loma Linda University.
* Specializes in global preventive medicine, tropical diseases and biotoxicology.
* Assistant Director on the School of Tropical and Preventive Medicine, Loma Linda University, Loma Linda, California.
* Assisted in developing a global preventive military medical program at the U.S. Naval Medical School, Bethesda, Maryland.
* Lectured on biotoxicology at the School of Aerospace Medicine, U.S. Air Force, San Antonio, Texas.
* Conducted Arctic expeditions for the U.S. Army, Navy, Air Force and National Institutes of Health, studying poisonous and venomous marine animals, and potential drugs from the sea.
* Contributor to Dorland's Medical Dictionary and the Encyclopedia Britannica, 15th Ed.
* Engaged in marine scientific research with the Jacques Cousteau Society, traveling extensively with the Cousteaus for eighteen years.

Additionally, Dr. Halstead has been deeply involved in the study of the use of oriental herbal therapy on immune deficiency disorders.

If the foregoing portrayal of a physician/scientist depicts a man who is unqualified to recommend treatment to his patients, to whom would the government have its citizens resort?--to those whose abysmal record of success appears to condemn far more patients to death than life. With the aforementioned credentials ascribed to him, one could ask how any law enforcement agency, tasked with the medical oversight and welfare of its citizens, could be so zealous as to prosecute one such as Dr. Halstead and class him with the "snake oil" peddlers they sometimes encounter.

In 1959 Dr. Halstead founded the World Life Research Institute in Grand Terrace, California. It was his work with this organization that, years later, ran him afoul of the Food and Drug Administration when he attempted to incorporate his massive knowledge and experience into the treatment of cancer.

THE MOTIVE SURFACES

Perhaps something else Dr. Halstead revealed to The WINDS has played a part in the FDA's zeal to relegate him to the medical "scrap heap". "We have been monitoring the illicit regulatory activities of the FDA and the cancer establishment, " Halstead claims, "and are in constant contact with a network of organizations and attorneys dealing with their illegal health activities in this country which are steadily driving up our national health costs."

Is it not interesting how money keeps introducing itself into the mix? Halstead concurs making the ominous assertion that, "Cancer is the sacred cow of the medical industry. More people make money by treating cancer than there are victims dying from the disease."

After a 25-year effort into medical/biological research, "I was shocked," Dr. Halstead exclaimed, "to find upon my Rip Van Winkle return to clinical medicine that dangerous toxic drugs, all FDA approved, had proliferated to a frightening extent--over 1.54 billion prescriptions written in the U.S. per year.

"I found," Halstead continues, "that many of these drugs destroy your immune system and are carcinogenic. New and awesome medical technologies were also being spawned, mind-blowing in both their diagnostic capability and staggering costs to the consumer.

"However, in evaluating this new drug and health technology, I did not find a commensurate improvement in either morbidity or mortality statistics in chronic degenerative afflictions such as cardiovascular disease and cancer. Costs had increased, but not the overall health index. We had dropped to about 23[rd] position among the nations of the world in health care."

This data, presented by an eminent physician/scientist, raises the logical question as to whether this may be a reasonable explanation as to why the strike by New York doctors several years ago resulted in a decline in the city's overall death rate. "At this point in time," Halstead concludes, "I have the profound conviction that America is on a disaster course in health care both economically and therapeutically....A dangerous therapeutic mind set exists in this country that it is better to die in an orthodox fashion than to survive in an unorthodox manner."

THE RAID

In reference to his implication that the government would rather allow an individual to die than to condone the application of "unorthodox" treatment, Dr. Halstead relates the following event he presented in his court trial:

"During my final oral argument I recounted the incident when defendant Alfred Dix and his wife had their home raided by the Los Angeles District Attorney. Mr. Dix had been using and selling the herbal drink." [The doctor is here speaking of a specific compound of Japanese herbs (ADS) from which a tea is made that many clinical trials, according to Halstead, have proven very effective in the treatment of cancer].

"Mrs. Dix had been diagnosed as having terminal abdominal cancer. She had had surgery, nine different types of chemotherapy, and over ninety different treatments of radiation, all of which had failed. Her doctors told her that she had only 30 to 45 days to live. She was bedridden, had given up hope, and was preparing to die. She and her husband had even contacted a mortician to make funeral arrangements.

"Mr. Dix then came in contact with ADS [the herbal compound]. After taking ADS for about ten days, Mrs. Dix began to feel better, started doing housework, shopping, traveling, and started entertaining again. I met Mr. and Mrs. Dix one day in the lobby of a hotel in Pasadena. She was walking, mentally alert, happy and laughing, and stated emphatically that she was feeling great. No aches or pains - thanks to ADS.

"At the time of the raid at the Dix home, the D.A. confiscated all of her ADS. Her husband begged and tearfully pleaded with the D.A. to release enough of the ADS for his wife's use. The D.A. refused to release any of the tea to her.

"The next time I saw Mrs. Dix was in the courtroom. She looked pale, in a weakened condition, unable to walk, crestfallen and anguished. A few days later she died - a broken woman, a victim of the land of the free and the home of the brave.

"What has happened to our national ideal of life, liberty and pursuit of happiness? Why has the prosecution denied Mrs. Dix the right to retain a cup of harmless adaptogenic tea which she purchased for her own cancerous condition? What has happened to her civil liberties?

"I could not think of a single tyrannical country in which this scenario could have taken place."

Perhaps, one might reason, Dr. Bruce Halstead's case and claims are somewhat of an isolated example of government intervention into the medical lives of Americans.

BURZYNSKI TOUCHES SACRED COW

Case-in-point #2: Stanislaw Burzynski, MD, PhD., who, in 1970, fled the repressive Communist regime of his native Poland and came to the "land of the free and the home of the brave" where he soon became a researcher at Baylor College of Medicine in Houston.

"During the next several years," as reported by radio commentator and columnist Paul Weyrich, "he authored and co-authored sixteen papers, mostly on cancer research. He became a member in good standing of both the AMA and the American Association for Cancer Research. It was during this period that he developed a non-toxic, experimental therapy which resulted in a synthetically-produced protein sequence which reprogrammed and reverted the activity of cancer cells.

"Over the past eighteen years," Weyrich continued in his commentary entitled, "Time to Review the FDA", "2500 people have been treated by Dr. Burzynski. Not a single one of them became ill from the treatment. But more importantly, every single patient showed anti-tumor activity and most of these patients are in a state of complete remission. That should be enough to earn Dr. Burzynski a place alongside such famous medical pioneers as Jonas Salk. But, unfortunately for Dr. Burzynski, for the second time in his life, he has encountered the oppressive hand of the all-powerful state. Thinking that he had come to America to escape the repressions of communism, the good doctor has been, for the past twelve years, fighting the Food and Drug Administration."

Dr. Burzynski has been another of those scientists to have touched the medical "sacred cow" of cancer research and been unfortunate enough, it seems, to have discovered an effective treatment for the disease.

Another logical question arises from the confusingly inconsistent application of "human rights" by this nation's government. The WINDS has been discussing the fate of two highly respected physician/scientists, well established in not only the medical community but in the halls of scientific research. Their "crimes" were sharing with fellow human beings--those who happened to also be patients, suffering with maladies that are, for the most part, still a mystery to conventional medical science-- remedies for which there have been ample empirical and reproducible scientific evidence of effectiveness. Why were these men's actions deemed criminal by federal authorities? According to standard "government think", it is largely because the medical community does not, or will not, recognize the validity of most natural remedies. They are not sufficiently profit-intensive thereby, robbing the large, multi-national pharmaceutical companies of immense profits. Many very effective medications can be found growing as "weeds" in the forest, urban fields or even in one's own back yard where there is no law (yet) against harvesting and using them.

A support organization established in Burzynski's name has erected a web site, the contents of which appears to be a carefully recorded chronology of events describing the interaction between Dr. Burzynski and the Food and Drug Administration. That chronology includes quoted statements by FDA officials that render a chilling perspective on that powerful organization's support of large industrial pharmaceutical companies and the federal government's attitude of consigning the individual to relative insignificance.

Former FDA Bureau of Drugs Director, Richard Crout, is quoted as stating that any organization, other than large research establishments who desire the Administration's approval to conduct clinical trials, should be subject to "harsh regulations....Sometimes we say it is proper to hinder research."

For those who question that power and money are the controlling influences in the drug industry, Dr. Crout is also quoted as saying, "I never have and never will approve a drug to an individual, but only to a large pharmaceutical firm with unlimited resources."
alternative medicine in stocks

NOW IT BECOMES KNOWN

Occasionally, there appears a light within the federal juggernaut emanating from one that seems to understand this nation's tenth amendment to the constitution. One such light resides in a statement from FDA official, William Nychis who is quoted by Burzynski as informing Herbert Koch, MD, of the Harris County Medical Society that, "a physician who manufactures and uses a drug within his own practice of medicine...is not subject to [FDA regulations] since the practice of medicine is properly regulated by state or local authorities."

Apparently the FDA was not enlightened by Nychis' statement. In a response to a U.S. District Court Judge's tacit approval of Dr. Burzynski's use of his anti-cancer drug within Texas state boundaries, the FDA allegedly issued the statement that if the federal judge does not comply with its demands, the "...government would then be obliged to pursue other less efficient remedies, such as actions for seizure

and condemnation of the drugs or criminal prosecution of individuals...."

This they did when Dr. Stanislaw Burzynski, MD, PhD, was subjected to four Grand Jury investigations in which one U.S. Assistant Attorney was disciplined for prosecutorial misconduct and "FDA Commissioner David Kessler face[d] harsh questioning by Congressman Joe Barton's Investigations Subcommittee about FDA's abuse of Grand Juries, and about how he can justify four Grand Juries with no indictment."

A fifth Grand Jury attempt by the government to indict Burzynski, however, was successful on the grounds that he "released his out-of-state patients to return home with a supply of antineoplastons [the drug at issue]. The charges are based upon 'interstate commerce of a new drug.'"

FDA GOES FOR THE THROAT

In an article published in Reason Magazine, former FDA Chief Counsel, Peter Barton Hutt, makes a startling claim: "If you beat the FDA in court," Hutt asserts, "you have an angry FDA that is willing to slit your throat. When the FDA loses a case, it has a mind like an elephant. It's just something you've got to understand about the FDA. Once the agency makes a collective decision, trying to make it let go is almost impossible. These are FDA crusades -- in a real sense they are vendettas."

On May 27, as reported by the Houston Chronicle, Dr. Burzynski "who once faced 75 federal charges stemming from the interstate shipment of his experimental cancer treatment drug was acquitted...of the lone remaining count. "The verdict ended, without a single conviction, a 14-year effort by federal authorities to make a criminal case against the Polish-born physician."

The Chronicle went on to report that,

"Patients and their families who packed the courtroom in a show of support wept and shouted when the verdict was read after about three hours of jury deliberation.

"Burzynski, too, was elated.

"It's the end of 14 years of war. It's the beginning of the end of the war on cancer," he said.

"He predicted that the verdict would put his class of experimental drugs, known as antineoplastons, on the fast track for approval by the U.S. Food and Drug Administration.

"Burzynski now treats about 300 patients from all over the country, most of whom have brain cancer and non-Hodgkin's lymphoma under an FDA program for investigational new drugs."

"I found the government's behavior offensive," one of the jurors, a Houston attorney, is quoted as saying. "A lot of people felt it was. This was a Big Brother issue." (ibid.)

Among the growing list of those who are finding the "government's behavior offensive are a few examples related to The WINDS by the publisher of The Echo, a Washington State-based watchdog publication that keeps track of such abuses.

* Glen Warner, MD, helped draft a Washington state law prohibiting any medical oversight authority from suspending or revoking the license of a physician for practicing and prescribing alternative or holistic medicine. In a continuing illustration that the government respects no laws limiting its own authority, shortly after the aforementioned law went into effect, state medical authorities revoked Dr. Warner's medical license for his involvement in alternative medicine.

* Dr. Jonathan Wright, Kent, Wa. Federal authorities seized over $100,000 worth of vitamins. He was raided for use of injectable B-12. The Justice Department reviewed the case and threw it out.

WHAT IS REALLY HAPPENING?

Why this growing intervention from federal authorities in instances where the public's safety and well-being are clearly not an issue; instances where conventional medicine has demonstrated an impotence in dealing with the maladies being addressed? A series of rhetorical questions could be posed whose answers would seem ridiculously obvious.

Does money have anything to do with the government's handling of the aforementioned instances? Does the fact that an inordinate number of FDA officials, according to congressional inquiries, accept executive positions with large pharmaceutical companies upon retirement play any role in creating an atmosphere where such super-lucrative business ventures, as cancer research, will be endlessly perpetuated? Recall Dr. Bruce Halstead's statement, "Cancer is the sacred cow of the medical industry. More people make money by treating cancer than there are victims dying from the disease."

If, as national death statistics indicate, 500,000 people per year die of the disease, the "cancer economy" of this nation is staggering in both the number of individuals employed and the quantity of capital outlay for research and pharmaceuticals. Could there be another even more insidious agenda behind this obstruction by the government of potentially massive lifesaving research?

According to the document that is the expression of the spirit guiding the New World Order since its inception, the answer is clear, "The upper class, which enjoyed by law the labor of the workers, was interested in seeing that the workers were well fed, healthy and strong. We are interested in just the opposite--in the diminishment, the killing out of the nations. Our power is in the chronic...physical and mental weakness of the worker. What that results in is his being made the slave of our will, and he will not find in the authorities of his own society either the strength or energy to oppose us... for an excited patient [one that is under stress] loses all power of judgment and easily yields to suggestion,"-- even the suggestion, it would seem, to die rather than reject the fallacious authority of those invoking his servitude

to mindless administrative regulations.

If one were to describe, without including the details of the situation, the forgoing scenario of a government refusing to allow a person control over their own body, the narrative would most likely be mistaken for an anti-abortion or "pro-life" argument. The concept of "pro-choice" is, after all, a term applicable only when it applies to the destruction of children while still residing in their mother's body. The idea that the abstraction might apply to one attempting to save his or her own life or that of a loved one, is anathema to the collective consciousness of "the land of the free and the home of the brave."

Written 9/15/97

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http://www.ncahf.org/nl/1997/5-6.html

BRUCE HALSTEAD IMPRISONED AFTER 12-YEAR DELAY

In 1985, Bruce W. Halstead was convicted of 24 counts of cancer fraud. After losing an appeal, he was stripped of his medical license and sentenced to 32 months in prison. But federal officials never handed down the order for him to start serving his sentence. Twelve years passed, during which Halstead even landed an important Department of Defense contract to develop a computerized bank of toxin research data to provide doctors with instant access to such information (Halstead is a respected marine toxicologist). But last summer Halstead was recognized by an Orange County prosecutor when he testified in court as an expert witness. A call to the Los Angeles County district attorney's office brought the SNAFU to light. (SNAFU is military jargon for "Situation Normal, All Fouled Up!") After several months of legal maneuvering, Halstead was taken into custody in February. His age (77) and medical condition bought him some leniency. His sentence was shortened with a release date of May 12.

[Los Angeles Times, April 12, 1997, B1&6]

Comment: Although Halstead no longer is allowed to practice medicine, he still promotes questionable health products, including to cancer patients. NCAHF has been told that he appeared at a cancer support group where he bashed standard care. He also sells a dietary supplement, Age Defense Tonic, which he imports from China to his company Bio-Defense Nutritions of Grand Terrace, California. The list of ingredients reveals that it is a concoction of herbs, vitamins, and other substances not likely to have any real effect on aging, but since the passage of the 1994 Dietary Supplements Health & Education Act, almost anything goes. Halstead also has a legal defense fund to which his disciples may contribute and publishes a newsletter that expounds his views. None of these activities are illegal.

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http://www.quackwatch.org/search/webglimpse.cgi?ARCHID_1=1&query=halstead&rankby=DEFAULT&errors=0&age=&maxfiles=50&maxlines=30&maxchars=10000&cache=yes

OTA Report: Regulation of Practitionerss, 13/1/2006

Bruce Halstead, a practitioner of unconventional cancer treatments, has been convicted of multiple criminal charges. In 1986, after three years of investigation by the California Board of Medical Quality Assurance and the resolution of several complex international and interstate legal issues, Halstead's medical license was permanently revoked and he was convicted of several criminal charges. Halstead used an unconventional treatment called Agua del Sol (ADS) to treat patients with cancer and other chronic diseases. ADS has been described as a homeopathic herbal treatment consisting of mulberry, hydrangea, and poppy, that is reportedly incubated in outdoor tanks containing water and bacteria. The ADS administered to Halstead's cancer patients had been manufactured in Costa Rica, shipped through Japan, and then purchased through a distributor in the United States (371).

The charges brought against Halstead under California's Penal Code and Health and Safety Code originally included:

Unassisted by an attorney for much of the litigation, Halstead relied on the testimony of his patients, family, friends, ministers, and colleagues. A special "Hearing Report," submitted on his behalf by the National Center for Institutions and Alternatives, urged that only a probationary sanction be issued. Halstead, who denied wrongdoing, asked to be allowed to continue practicing medicine under terms of probation, or community service, or both.

However, at the sentencing hearing, the probation officer assigned to the case testified that the current charges against Halstead were not isolated incidents. Halstead had been called before the Board of Medical Quality Assurance in the past, his license had been suspended at least once, and he had previously been placed on probation. This history, combined with the probation officer's finding that Halstead "shows little or no remorse for his...crimes," led to the conclusion that unless his license was revoked, Halstead would continue to prescribe unconventional treatments. In addition, the probation officer noted that Halstead "used his position of trust, as a physician" to sell unconventional treatments to terminally and chronically ill patients. He recommended that Halstead "be removed from the community for as long a period of time as is legally possible" (371). The court found Halstead guilty of 20 felonies and several misdemeanors. In addition to the permanent revocation of his medical license, he was sentenced to 4 years in prison and fined $10,000 (372).

Be Wary of the National Health Federation (1993), 16/12/2008

Bruce Halstead, M.D., was convicted in 1985 of twenty-four counts of cancer fraud and grand theft for selling an herbal tea called ADS to ten patients with cancer and other serious diseases for $125 to $150 per quart.

Although he maintained that ADS was a "nutritional supplement," analysis showed it to be 99.4 percent water and a brownish sludge composed mainly of coliform bacteria (the same bacteria found in human feces). Halstead, who operated the Halstead Preventive

Medicine Clinic in Colton, California, has been a leading promoter of laetrile, chelation therapy, and many other questionable practices.

Following the trial, which lasted for five months, Los Angeles County Deputy District Attorney Hyatt Seligman called Halstead "a crook selling swamp water." He was fined $10,000 and sentenced to four years in prison, but remains free during the appeals process. According to an article published by Michael Evers, Halstead maintained during his trial that he was the target of a "Medical Gestapo" out to destroy health practitioners who deviate from orthodox cancer therapies such as surgery, radiation and chemotherapy. In 1992, his license to practice medicine in California was revoked. He is still vice-president of the Committee for Freedom of Choice in Medicine.

OTA Report: References, 13/1/2006
371. Halstead, B., "The Halstead Cancer Battle: A Legal Epilogue," Townsend Letter for Doctors 38:157, 188-190, June 1986.

372. Halstead, B., "The Lynching of a Doctor: Halstead Receives a Draconian Sentence," Townsend Letter for Doctors 38:157, June 1986.

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http://articles.latimes.com/1985-10-06/local/me-5858_1_cancer-fraud
October 06, 1985

Jury Convicts Colton Doctor of Cancer Fraud, Grand Theft

PAUL FELDMAN
Times Staff Writer

A Colton physician who sold cancer victims ADS--a substance consisting of 99.4% water with the remainder a brownish sludge made up primarily of coliform bacteria--has been convicted of 24 counts of cancer fraud and grand theft.

Dr. Bruce Halstead, 65, who sold the murky potion for $125 to $150 a liter, faces up to eight years in prison when he is sentenced Oct. 31 by Los Angeles Superior Court Judge Marvin D. Rowen.

http://www.quackwatch.org/search/webglimpse.cgi?ARCHID_1=1&query=halstead&rankby=DEFAULT&errors=0&age=&maxfiles=50&maxlines=30&maxchars=10000&cache=yes

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372. Halstead, B., "The Lynching of a Doctor: Halstead Receives a Draconian Sentence," Townsend Letter for Doctors 38:157, June 1986.

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http://articles.latimes.com/1986-06-28/news/mn-25555_1_medical-license
June 28, 1986

Doctor in Cancer Potion Fraud Receives 4-Year Term

TERRY PRISTIN | Times Staff Writer

Dr. Bruce Halstead, a physician convicted of selling cancer patients a substance that was 99.4% water, lost his chance for leniency Friday when a judge decided that he had not made a "vigorous" effort to sell his clinic and was continuing to portray himself as a victim of a medical conspiracy.

"The court is unhappy with the response it has gotten to its openly voiced concerns about Dr. Halstead's conduct," said Pasadena Superior Court Judge Marvin D. Rowen in ordering the physician to serve a four-year prison term.

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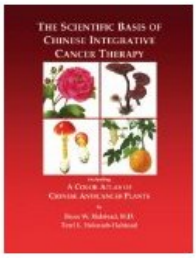
http://www.randomhouse.com/book/74067/the-scientific-basis-of-chinese-integrative-cancer-therapy-by-bruce-halstead-and-terry-halstead

The Scientific Basis of Chinese Integrative Cancer Therapy



Including a Color Atlas of Chinese Anticancer Plants

Written by Bruce HalsteadAuthor Alerts: Random House will alert you to new works by Bruce Halstead and Terry HalsteadAuthor Alerts: Random House will alert you to new works by Terry Halstead

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http://www.amazon.com/Scientific-Chinese-Integrative-Cancer-Therapy/dp/1556435851

The Scientific Basis Of Chinese Integrative Cancer Therapy

This useful text features an extensive discussion of the history, development, and science of Chinese medicine, and a summary of the authors fact-finding research trip to countries and hospitals that use Chinese herbs in the treatment of cancer. Central to the book is a substantial section of 103 colored botanical plates, constituting an atlas of the most important...

$85-

Contents

* Machine derived contents note: Table of Contents
* Dedication
* Acknowledgements
* Foreward by Daniel Clark, M.D. & Frank Cousineau
* Introduction
* The Bad News-Current Cancer Statistics
* The Good News About Cancer
* Preface
* About this Book
* Table of Contents
* Section I: The Remarkable Tien Hsien Herbal Products

* Chapter 9: The Chinese Rationale of Integrative Cancer Prevention and Therapy
* Yin and Yang
* Relative Balance - Cellular Homeostasis
* Seasonal Energy Balance of the Yin and Yang
* Application of Yin and Yang to Herbology
* Herb Tonics
* Yin and Yang Domains within the Body
* Five Elements and the System of Numbers
* Chinese Approach to the Use of Healing Herbs
* Concept of Adaptogenic Medicine
* Classification and Properties of Chinese Herbs
* The Four Essences (Energies)
* Five Flavors
* Formulating Healing Herbs
* Seven Effects of Herbs
* The Four Directions of Herbs
* The Relationship Between Foods, Drugs, and Poisons
* Chinese Herbal Formulations
* Dosage Forms of Traditional Chinese Drugs
* Herbs and their Therapeutic Actions on Channels
* Energy - Si Qi
* Actions on Channels
* General Concepts of Chinese Health Care
* Chapter 10: The Preparation of Plant Extracts
* Preparation of Plant Extracts
* Traditional Processing Methods
* Pesticidal Contamination
* New Technologies Applied in Herbal Concentrating
* Non-Toxic Comprehensive Extraction Process
* Full Spectrum Standardized Herbal Extracts
* Section Iii: A Color Atlas Of Anticancer Plants
* Chapter 11: A Color Atlas of Chinese Anticancer Plants
* Literature Cited
* Appendix: About the Authors
* Bruce W. Halstead, M.D.
* Terri Lee Holcomb-Halstead
* Index.

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http://www.tienhsien.com/products.htm

Tien Hsien Liquid

Bruce Halstead, M.D. (Institute Director, World Life Research (USA) "*... Number 1, there is no magic connected with your (Tien Hsien) product. It's a very very good product. It has a sound, solid, scientific basis to it. I have thoroughly investigated that. I can show you the scientific literature."*

As the parallel worlds of traditional and modern medicine merge, people everywhere are discovering the true value of alternative healing methods. Tien Hsien Liquid No. 1 is composed of rare selected herbs and is produced under the strictest guidelines ensuring a product that is pure and free of contaminants. Tien Hsien Liquid has been in used for over 10 years by over one million people from all over the world and has had tremendous success. Although Tien Hsien Liquid No. 1 was originally formulated for the purpose of treating cancer, it is not being marketed in the United States as a cure or prevention for the disease.

There have been many instances, however, where cancer patients who were suffering from the side effects of chemotherapy or radiation treatments, reported that their symptoms have lessened, and in some cases, even totally subsided as a result of using Tien Hsien Liquid No. 1.

Tien Hsien Liquid No. 1 has very powerful and unique anti-oxidant qualities that scavenge for health damaging free radicals within our system. It is non-toxic and formulated to increase the anti-cancer functions of the body's own immune system. Stimulating and strengthening the immune system will serve to better inhibit tumor growth.

After taking 4 to 6 courses of Tien Hsien Liquid # 1, the growth of cancerous cells in the human body should be under control. They may even cease to multiply completely as time goes by.

Extending the life expectancy of cancer patients and eliminating the threat of them leaving their loved ones too early is what we strive to accomplish along with easing the unbearable side effects of Western Cancer therapies.

Tien Hsien Liquid Composition

Name / Proportion / Effect

Radix Ginseng 12.5%
Great tonic, reinstating circulation and innervation, alimenting, respiratory, salivant and sedative.

Radix Astragali 15%
Functioning, astringent, diuretic, detox, and sore healing

Cordyceps 24%
A tonic for lung, kidney, hemostatic and expectorant.

Ganoderma 17%
Regulating, defensing, tonic and anti-aging

Rhizoma Dioscoreae 11%
Alimenting, salivant, lung and kidney tonic and sperm keeping.

Herba Scutellariae Barbatae 2%
Clears heat and toxin, activates blood circulation and removes blood-stasis, promotes diuresis.

Margarita 4%
Calming liver and catabolism, sedating and sight helping.

Fructus Lycii 9%
A tonic for liver and kidney, reproduction and sight.

Fructus Ligustri Lucidi 0.5%
A tonic for liver, kidney and sight and hair darkening.

Radix Glcyrrhizae 5%
Alimenting, functioning, defervescent, detox, expectorant, antitussive, and formula harmonizing.

Other ingredients
Water, Honey, Sorbic Acid

Functions of Tien Hsien Liquid

Block Cancer Cells

The contents of Tien Hsien Liquid block the growth and multiplication of cancer cells; block the multiplication of cancer cells at a certain stage and thereby killing them; stop cancer cells breathing at the metabolism; damage cancer cells and let them dissolve.

Adjust Metabolism

To improve one's immunity against cancer cells; suppress the multiplication of cancer cells by adjusting one's own metabolism (not allowing what cancer cells requires to multiply).

Improve Immunity

To suppress cancer cell multiplication and to produce immunity; control easy-to-increase environment; promote cancerous cell killing activities.

(Raw Medicines that improves immunity): Radix Rehmanniae, Fungi, Radix Acanthopanacis Senticosi, Radix Astragali, Ginseng, Poria Polysaccharide, Ginsen Soapgenein, Radix Astragali Polysaccharide, Radix Trichosanthis.

Micro-Elemental Effect

To improve the physiological aspect of the body through micro-elemental activities, to promote genetic activities and to kill cancer cells.

To suppress cancer cells' entrance into our genes; suppress the growth and spread of tumor.

The above statements have not been evaluated by the FDA. This product is not intended to diagnose, cure or prevent any disease.

Dr. Wang Zhen Guo (Tien Hsien inventor) in his garden plantation.

Images :

A section of the Chang Bai Shan was named "Dr. Bruce Halstead Herbal Mountain Garden".
One section in the Tien Hsien plantation.
Dr. Wang describes a plant in Chang Bai Shan mountains (China).

To better understand the manner in which Tien Hsien Liquid works, an independent study by the Taipei FRC Biology Study Center was conducted. The study encompassed fifteen experimental topics and verification processes where Tien Hsien Liquid was identified as subject FRC001 for the purpose of maintaining a completely unbiased and objective analysis of the product. The testing was concluded after two years where four primary directives were addressed. The following is a summary of those results:

Experiments on the Removal of Free Radicals

Tien Hsien Liquid is able to effectively remove different free radicals in the body.
Tien Hsien Liquid can remove super oxide free radical with a clearance capacity of 300,000 units of SOD activity per cc.
Tien Hsien Liquid can remove free radical generated by white blood cells, which Vitamin E fails to effectuate.
Tien Hsien Liquid can remove hydroxyl free radical, which Vitamin E fails to effectuate.
Tien Hsien Liquid has the capacity to remove lipid peroxides more effectively than Vitamin E.

Toxicology Experiments

In clinical studies, Tien Hsien Liquid was able to pass very stringent testing which included:

Acute Toxicity Test
Micro-Nuclear Bone Marrow Cell test
Sperm Distortion Tests
Ames Test
Immunization Function Tests
Test conducted on laboratory mice concluded that Tien Hsien Liquid:
May increase the phagocytosis of macrophage.
May greatly strengthen lymphatic conversion for the spleen.
Raises the serum homolysis reaction and anti-host reaction indicative of significant benefits toward immunization.

Inhibitory Effect on Tumors

It has been demonstrated that Tien Hsien Liquid's inhibitory effects were not inferior to that of 5-Fu (chemical) when evaluated on laboratory mice affected with sarcoma and hepatocarcinoma - and further, exhibited a quantum reaction, i.e. the larger the dose, the better the inhibitory effect - which was greatly superior when compared to the reference group consisting of glossy ganoderma and green algaes.

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http://video.tianxian.com/index.htm
http://video.tianxian.com/thailand/1-wang.htm

Dr. Wang Zhen Guo (China)

From the Heart of Chang Bai Mountain

Duration : 17:03 minutes
Language : Chinese (Mandarin) with English Translation

Summary :

The story of the Tian Xian liquid stems from the mountains of Chang Bai in North Eastern China. During those times when people neither had the means nor the resources to cure their Cancer, they would boil a traditional Chinese herb which grows in the heart of Chang Bai Mountain. It is this herb that has been found to help cure Cancer. Over the years, a number of medical experts from both the United States and China have studied this Chinese herb and have contributed to the birth of the Tian Xian Liquid—a remedy that now offers hope to myriads of Cancer patients.

'Xue Piao Wu Cheng." Snow falls silently from the heavens and covers the earth. This seems insignificant. But when the time comes for this snow to melt, it nurtures the earth and gives birth to new life. This traditional Chinese saying summarizes the efforts of those medical experts who studied and developed the raw herb from the Chang Bai Mountain – an old herb that can give new life. Some of these medical forerunners who have contributed to the development of Tian Xian liquid are Dr. Wang Zhen Guo and Dr. Bruce Halstead. They, and many others, have opened the way for more studies to be made to vouch for the effectiveness of the Tian Xian liquid.

Antiviral methods and compositions
US2006264510

FIELD OF THE INVENTION

[0001] The field of the invention is antiviral compositions.

BACKGROUND OF THE INVENTION

[0002] Viral infections are relatively common infectious diseases, and various methods of treating a viral infection available to a practitioner. In one method of treating a viral infection, the immune response of an immune system is stimulated. For example, in some instances the Th1 response of the patient can be increased relative to the Th2 response. An increase in the Th1 response is thought to be beneficial because many viral infections are associated with a shift in the cytokine profile toward a Th2 response, and a bias towards a Th1 response is known to be facilitated by several approaches.

[0003] In one approach, cytokines are administered to modulate the Th1/Th2 balance towards a Th1-type response. For example, Knight et al. postulate that treatment with IL-12 (Interleukine-12), a cytokine that promotes the development of Th1 cells, may be used as a treatment for AIDS since IL-12 administration has been shown to be effective at restoring cell-mediated immunity in mice infected with mouse AIDS virus or with RLV [Knight, S. C. and Patterson, S., Annu. Rev. Immunol. 1994. 15: 593-615]. In another example, Gracie, J. A. et al., demonstrated that administration of IL-18 to mice exhibited pleiotropic activities critical to the development of Th1 responses. [Gracie et al. J Clin Invest 1999 Nov 15; 104(10):1393-1401]. Although the administration of cytokines typically results in relatively specific increases in desired Th1 cytokines, prolonged administration of cytokines may be problematic for various reasons. For example, the production of recombinant cytokines is relatively expensive, and isolation of non-recombinant cytokines from natural sources is generally difficult due to the very low concentration of cytokines in natural sources. Moreover, depending on the nature of the cytokine, cytokines may not be well tolerated in patients.

[0004] In another approach, immunomodulatory substances other than cytokines may be employed to increase the Th1 response. For example, Sprietsma J. E. suggests that zinc ions (Zn^{2+}) and nitric oxide (NO), together with glutathione (GSH) and its oxidized form, GSSG, may help to regulate an immune response to antigens [Sprietsma J. E; Med Hypotheses 1999 July; 53(1):6-16]. The author reports in more detail that deficiencies of Zn^{2+}, NO and/or GSH shift the Th1/Th2 balance towards Th2, and that replenishment with Zn^{2+}, NO and/or GSH may shift the Th1/Th2 balance towards Th1. Administration of Zn^{2+} or GSH/GSSG is especially advantageous, since these substances are non-toxic at even elevated concentrations, and inexpensive to produce. Furthermore, Zn^{2+} and GSH/GSSG preparations may be orally administered, and therefore significantly reduce the risk of allergic reactions, especially when the preparations are not ultrapure. However, the administration of Zn^{2+} and/or GSH/GSSG seems to be beneficial only to restore a Th1/Th2 balance from a Th2 dominated state, whereas it is unclear if administration of Zn^{2+} and/or GSH/GSSG may increase a Th1 response from a normal Th1/Th2 balance.

[0005] In another method of treating a viral infection, the virus is directly targeted with an appropriate anti-viral drug. For example, patients infected with the HIV virus often receive a cocktail of drugs to block virus propagation, and various classes for direct anti-viral treatment are known in the art. Some direct anti-viral drugs block the reverse transcriptase of a retrovirus. Reverse transcriptase (RT) inhibitors are typically nucleoside analogs such as AZT, 3TC, or ddI. Alternatively, non-nucleoside RT inhibitors, including quercetin may be employed. In vitro, RT inhibitors are typically potent anti-viral drugs. However, in vivo, and especially during a period of relatively fast viral replication, the generation of RT inhibitor resistant virus mutants is problematic. Moreover, many RT inhibitors also exhibit undesirable activity on DNA replication in the host organism and significant cytotoxicity at elevated concentrations, thereby limiting the concentration that may be administered without severe side effects.

[0006] Among other direct anti-viral drugs are the protease inhibitors, which block or interfere with virus protein processing. Protease inhibitors are typically highly specific towards the viruses' proteolytic enzymes, however, due to their mostly hydrophobic nature, administration at desirable concentrations often becomes problematic. Another problem is that development of cross-resistance and severe side effects frequently occur. In order to reduce the development of multidrug resistant virus strains, mixtures of RT inhibitors and protease inhibitors may be prescribed. Although such mixtures are presently employed relatively successfully, the relatively high occurrence of adverse side effects and the potential of generating multidrug resistant virus strains persist.

[0007] To circumvent at least some of the problems associated with side effects and relatively high costs of antiviral drugs, Bennett et al. describe in U.S. Pat. No. 5,602,180 the use of EDTA complexes in a suppository. The use of chelating agents, including EDTA, has been found to promote disintegration of retroviruses [Wunderlich, V. and Sydow, G. Arch. Virol. 1982, 73:171-183]. Bennett's suppositories contain disodium EDTA and controlled-release agents, which release the disodium EDTA over a period of about three to four hours after rectal placement of the suppository. However, Bennett's suppositories are limited to disodium EDTA that exhibits relatively moderate selectivity between Mg^{2+} and Ca^{2+}.

[0008] Although various antiviral compositions and antiviral treatments are known in the art, all or almost all of them have one or more disadvantages. Therefore, there is a need to provide improved methods and compositions for treatment of viral infections.

SUMMARY OF THE INVENTION

[0009] The present invention is directed to an antiviral composition having a supply of chelating agent that chelates an alkaline earth metal ion, wherein the chelating agent is formulated in a rectal deposition formulation, and wherein the supply of chelating agent has an immediate bioavailability. When rectally administered to a subject in an effective dose in vivo, contemplated agents promote disintegration of a virus.

[0010] In one aspect of the inventive subject matter, generally preferred chelating agents are various chelators other than ethylenediamine-N,N,N',N'-tetraacetic acid (EDTA), chelate Ca^{2+} and/or Mg^{2+}, and include at least three carboxylic acid groups. While particularly preferred chelating agents include at least three acetic acid groups, especially contemplated chelating agents are 1,2-Bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid (BAPTA), Ethylenebis(oxyethylenenitrilo)tetraacetic acid (EGTA), 1,2-bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid tetrakis(acetoxymethyl ester) (BAPTA-AM), diethylenetriamine-pentaacetic acid (DTPA), trimethylaminetricarboxylic acid (NTA), trans-1,2-diaminocyclohexane-tetraacetic acid (CDTA), poly(aspartic acid), and poly(glutamic acid).

[0011] In another aspect of the inventive subject matter, contemplated viruses include a retrovirus, and especially contemplated retroviruses include the HIV virus. Preferred rectal deposition formulations are a liquid or a solid, and where the rectal deposition formulation is a solid and administered to the colon of a subject, substantially of the supply of chelating agent is present in the colon in a readily absorbable form in less than 2 hours, preferably less than 1 hour, and more preferably less than 30 minutes. With respect to the effective dose in a rectal administration, it is contemplated that the chelating agent is employed in an amount of 500 mg, and more preferably 1500 mg.

[0012] In yet another aspect of the inventive subject matter, chelating agents other than EDTA may also be employed for purposes other than antiviral treatment, including heavy metal detoxification, and reduction of atherosclerotic plaques, wherein the chelating agent may be orally or parenterally administered.

[0013] Various objects, features, aspects and advantages of the present invention will become more apparent from the following detailed description of preferred embodiments of the invention.

DETAILED DESCRIPTION

[0014] As used herein, the term "chelating agent" refers to a molecule that binds a metal ion and/or an alkaline earth metal ion via a non-covalent bond, most commonly a coordinate bond, with a KD of less than 10<-3 > mol<-1> , wherein the chelating agent may be in acid form, base form or a salt form. For example, EGTA in protonated or sodium salt form is considered a free chelating agent, because EGTA binds Mg<2+> and Ca<2+> with a KD of less than 10<-3 > mol<-1> .

[0015] As also used herein, the term "immediate bioavailability" means that a composition or molecule is present in an active form in a formulation such that a substantial portion of a dose of the composition or molecule exhibits some systemic chelating effect within minutes, preferably within less than 15 min, more preferably within less than 10 min, and most preferably within less than 5 min. For example, a molecule that is dissolved in a carrier solution is regarded to have immediate bioavailability.

[0016] It is known that retroviruses can be disintegrated by chelating agents, especially by agents that chelate Mg<2+> and/or Ca<2+> , and that chelating agents may further reduce infectivity of certain viruses [Wunderlich, V. and Sydow, G. Arch. Virol. 1982, 73:171-183]. Thus, it is contemplated that an antiviral composition generally has a supply of a chelating agent that chelates an alkaline earth metal ion, and it is particularly contemplated that the chelating agent in the antiviral composition is formulated in a rectal deposition formulation, wherein the supply of chelating agent has an immediate bioavailability.

[0017] It should be appreciated that many chelating agents are known in the art, and that all of the known chelating agents are contemplated for use herein. It is generally preferred that contemplated chelating agents include at least three carboxylic acid groups, all of which are preferably acetic acid groups. Although not excluded, it is further contemplated that appropriate chelating agents are chelating agents other than EDTA. The choice of the particular chelating agent is predominantly determined by the desired physicochemical properties and tolerability of the chelating agent. For example, where a relatively high solubility (e.g., 1M) is desired, EGTA, CDTA or NTA may advantageously be employed. Where a more pronounced selectivity of chelation towards Ca<2+> is desirable, BAPTA may be utilized, and BAPTA-AM may be particularly suitable where sequestration of Ca<2+> within a cell is desired. Alternatively, contemplated chelating agents may include DTPA, NTA, and polymeric forms of aspartic acid, glutamic acid, and any reasonable combination thereof.

[0018] With respect to viruses that can be disintegrated and/or reduced in infectivity, virus particles that require Ca<2+> and/or Mg<2+> for structural integrity of their envelope are generally contemplated and include DNA and RNA viruses. Particularly contemplated RNA viruses are retroviruses in general, and HIV in particular. Further especially contemplated viruses include the hepatitis C and hepatitis D virus. Contemplated DNA viruses include polyomaviruses, HBV, etc. However, many more viruses are also contemplated, and a collection of appropriate viruses are listed in Fields Virology, Third Edition (Lippincot Williams & Wilkins), pages 40-41, 52, and 1767-1847, and Arch. Virol. 1982, 73:171-183, both of which are incorporated by reference herein.

[0019] It is still further contemplated that chelating agents are preferably formulated in a rectal deposition formulation, which may be in solid or liquid form. Where the formulation is in a solid form, it is further contemplated that appropriate forms include dissolvable carriers such as wages, fatty acids and oils with melting points of about 30[deg.]-35[deg.] C. Especially preferred formulations are formulations known in the art that are employed in the fabrication of rectal suppositories, so long as such formulations allow an immediate bioavailability. Thus, where a supply of chelating agent is administered into the colon of a subject in a solid form, it is particularly contemplated that substantially all of the supply of chelating agent is present in the colon in a readily absorbable form in less than 2 hours, more preferably less than 1 hour, and most preferably less 30 minutes after the administration of the formulation. Availability of the chelating agent or a portion of the chelating agent in less that 2 hrs, less than 1 hr or less than 30 min may be achieved by a variety of time release formulations, and contemplated time release formulations may include formulations with a melting point of less than 37[deg.] C., enzymatically degradable carriers, dissolving or swellable carriers, etc. Thus, it is contemplated that an entire dose of chelating agent may be available (or released from the time release formulation) in less than 2 hours, preferably less than 1 hour, and even more preferably in less than 30 min. A particular advantage of such time release formulations is that relatively high dosages may be administered that might otherwise pose a potential risk if administered without a time release formulation. However, it should be appreciated that administrations without time release may safely be administered by employing smaller dosages at multiple administrations.

[0020] Where the formulation is in a liquid form, it is contemplated that appropriate liquid forms may include buffered and unbuffered solutions, solutions with relatively high viscosity such as gels, creams, foams and ointments, which may or may not have a decreased viscosity at elevated temperatures. Liquid forms are particularly advantageous, since the delivery of the chelating agent is almost instantaneous. Where the solutions are buffered, it is contemplated that the buffers have an alkaline pH, and a preferred pH range is a range between 8.0 and 10.0.

[0021] Alternatively, the chelating agent may also be administered in various alternative routes, and it is especially contemplated that where the chelating agent is an agent other than EDTA that appropriate routes include oral and parenteral administration. For example, CDTA may be orally administered in form of an acid resistant caplet or capsule. However, oral administration need not be limited to a

caplet or capsule, and alternative oral administrations include syrups, powders, tablets, etc. In another example, EGTA may be parenterally administered by intravenous injection. It is contemplated, however, that alternative parenteral administrations may also include inhalation, transdermal delivery, injections into sites other than a vein, etc.

[0022] In a particularly contemplated aspect of the inventive subject matter, it is preferred that the administration of the chelating agent is accompanied by (preferably oral) administration of a nutritional supplement. Preferred nutritional supplements include supplements that help replenish calcium levels and particularly preferred supplements include aragonite calcium carbonate from fossil coral minerals. Other contemplated supplements that include herbal products (e.g., adaptogenic formulations with no apparent cytotoxicity) are contemplated to assist in inhibition of viral replication (e.g., by inhibiting the production of reverse transcriptase). It is further contemplated that such supplements may also help boost the immune system and potentially improve overall vitality and stamina. It is further contemplated that such adaptogenic supplements are considered to have tumor preventive and radio-protective properties, and may help increase the functioning of the immune system by increasing the T-cell population. Exemplary compositions for contemplated nutritional supplements are shown in Tables 1 and 2.

TABLE 1

Ingredient	Amount (mg/tablet)
Arcticum lappa	40 mg (10:1 concentrate)
Viola yedoensis	40 mg (10:1 concentrate)
Andrographis paniculata	40 mg (10:1 concentrate)
Lonicera erythrorhizon	40 mg (10:1 concentrate)
Epimedium saggittatum	40 mg (10:1 concentrate)

[0023]

TABLE 2

Ingredient	Amount (mg/tablet)
Arcticum lappa	10 mg (10:1 concentrate)
Viola yedoensis	10 mg (10:1 concentrate)
Andrographis paniculata	10 mg (10:1 concentrate)
Lonicera erythrorhizon	10 mg (10:1 concentrate)
Altemanthera philoeroides	10 mg (10:1 concentrate)

It should be appreciated, however, that various additional ingredients may be added to the supplement depicted in Table 1 and 2 to either enhance or modulate the activity of the herbal components.

[0024] With respect to the amount of chelating agent it is contemplated, that the chelating agent is administered to a subject in vivo in a dose effective to promote disintegration of a virus in the subject. The actual dose of the chelating agent may thereby vary among individual subject and may further be determined by the particular virus that is to be disintegrated. Therefore, an effective dose may comprises rectal administration of the chelating agent between about 5 mg-2500 mg, and generally contemplated doses include rectal administration of 500 mg or 1500 mg of the chelating agent. However, where even higher dosages of the chelating agent are required, or where it is preferred to maintain relatively high dosages over an extended period of time, multiple dosages are also contemplated.

[0025] It should further be appreciated that appropriate formulations may further comprise active and/or inactive ingredients. For example, active ingredients may include compositions to stimulate the immune system, an immunomodulating composition, a coral mineral product, compositions to facilitate uptake of the chelating agent into the blood stream, or direct antiviral compounds such as nucleoside analogs, etc. The term "immunomodulating composition" as used herein refers to a composition that enhances at least one of a humoral and cellular response towards a challenge. For example, an immunomodulating composition may increase an antibody titer against a challenge, or an activity of cytotoxic T-lymphocytes. Inactive ingredients may include fillers, coloring agents, thixotropic compositions, and foam building agents.

[0026] In an exemplary use, a person diagnosed with an HIV infection receives twice daily an enema of 20 ml of a 50 mg/ml solution of EGTA in 10 mM sodium phosphate buffer pH8.4 for at least 30 consecutive days. It should be recognized, however, that the exemplary use need not be limited to the specified amounts and times, but treatment schedules may vary considerably. For example, where the person already receives an antiviral medication (e.g., protease inhibitor cocktail, RT-inhibitor, etc.), lower dosages or less frequent administrations are contemplated, while in cases where the person does not receive another antiviral treatment, higher dosages and more frequent administrations are contemplated. It is also contemplated that the antiviral composition may be employed in a preventative fashion, i.e., the antiviral composition may be employed in a person that is not infected with a virus.

[0027] It is still further contemplated that the compositions according to the inventive subject matter may have advantageous properties and uses in therapeutic applications other than antiviral activity, especially where the chelating agent is a substance other than EDTA, and particularly contemplated uses include heavy metal detoxification in animal and human, and reduction of atherosclerotic plaque.

[0028] With respect to heavy metal detoxification in animal and human, it is known in the art that upon oral administration or injection EDTA complexes various metals and heavy metals other than Ca<2+> , and oral administration or injection of EDTA has therefore found widespread use in detoxifycation of some heavy metal poisonings. Various alternative oral or injectable chelation agents for heavy metals have also been described [e.g., Llobet, J. M. et al. Arch. Environ. Contam. Toxicol. 1990, 19(2): 185-9; Treatment of acute lead intoxication. A quantitative comparison of a number of chelating agents. Llobet, J. M. et al. Arch. Toxicol. 1988, 61(4):321-3; Antidotes for zinc intoxication in mice] and include oral and injectable forms of penicillamine, 2,3-dimercaptosuccinic acid, and 2,3-dimercapto-1-propanesulfonate. However, it is not known to the inventors that chelators other than EDTA have been used for detoxification of heavy metals in animal and human via rectal administration. Rectal administration is particularly advantageous for various reasons. For example, suppositories can be self-administered by almost all patients. Furthermore, rectal administration inflicts only relatively low discomfort to the patient. Moreover, rectal administration bypasses the stomach, a highly acidic environment that may lead to at least partial destruction of some of the chelating agents.

[0029] Therefore, it is contemplated that rectal administration of chelating agents may also be employed in a method to reduce a heavy metal concentration in a subject, wherein in one step a chelating agent is provided that chelates a metal ion, wherein the chelating agent is formulated in a rectal deposition formulation and wherein the supply of chelating agent has an immediate bioavailability. Alternatively, the rectal deposition formulation may further comprise a time release agent to release the chelating agent in a period of between 0-30 min, 30-60 min, 60-120 min, 120-180 min, or longer. In another step, the chelating agent is rectally administered to the subject in a concentration effective to reduce the heavy metal ion concentration.

[0030] It is generally contemplated that the heavy metal may be in elemental or ionic form, and particularly contemplated heavy metals include mercury, Zn<2+> , Cu<+> , Cd<2+> , and Co<2+> . However, various alternative metals and their ionic forms are also contemplated, including nickel, arsenic, selenium, iron, mercury, chromium, antimony, beryllium, thallium, silver, scandium, titanium, vanadium, chromium, manganese, etc. While it is generally contemplated that all known chelating agents may be suitable for reduction of heavy metals in a subject, it is particularly preferred that the chelating agent comprises a plurality of carboxylic acid groups and it is even more preferred that the chelating agent is EDTA, EGTA, CDTA, or DTPA. With respect to the rectal deposition formulation the same considerations as already described above apply.

[0031] An exemplary method of reducing a heavy metal concentration in a subject may therefore comprise a single rectal administration of 20 ml of a 10 mg/ml buffered aqueous solution of CDTA three times daily over a period of about 15-20 days. It should be recognized, however, that depending on the particular heavy metal, the site of accumulation, and the concentration of the heavy metal in the subject many treatment schedules other than a single rectal administration of 20 ml of a 10 mg/ml buffered aqueous solution of CDTA three times daily over a period of about 15-20 days are also appropriate.

[0032] For example, where treatment is prophylactic or necessitated by relatively low concentrations of a heavy metal, total daily dosages of less than 600 mg are contemplated, including total daily dosages of 200-600 mg, 50-200 mg, and less that 50 mg. Likewise, where acute and/or severe heavy metal intoxications are to be treated by a method according to the inventive subject matter, higher total daily dosages of more than 600 mg are contemplated, including total daily dosages of 600-1500 mg, 1500-2500 mg, and more than 2500 mg. With respect to the formulation it should be appreciated that numerous alternative formulations are also appropriate, and contemplated alternative formulations include the formulations already described above. Similarly, it should be appreciated that various alternative administration periods other than a period of about 15-20 days are also appropriate, including single administrations in cases where treatment is prophylactic, or administration over a period of less than 15 days, where the heavy metal concentration is relatively low. On the other hand, where the heavy metal is predominantly is tissues that bind the heavy metal relatively firmly (e.g. lipophilic tissue) administrations of 2-6 weeks and longer are contemplated.

[0033] With respect atherosclerotic plaques it is contemplated that rectal administration of chelating agents may also be employed in a method to reduce a atherosclerotic plaques in a subject, wherein in one step a chelating agent is provided that chelates an alkaline earth metal ion, wherein the chelating agent is formulated in a rectal deposition formulation and wherein the supply of chelating agent has an immediate bioavailability. In another step, the chelating agent is rectally administered to the subject in a concentration effective to reduce the atherosclerotic plaque in a subject. As used herein, the term "reducing the atherosclerotic plaque" refers to a gross reduction in size and/or volume of one or more atherosclerotic plaques, which may also include complete disappearance of the atherosclerotic plaque or plaques.

[0034] In an exemplary method of reducing atherosclerotic plaque, a person diagnosed with atherosclerotic plaques receives once daily an enema of 10 ml of a 50 mg/ml solution of EGTA in 10 mM sodium phosphate buffer pH8.4 for a period of about 12 weeks. However, it should be appreciated that the exemplary method need not be limited to the specified amounts and times, and formulation and treatment schedules may vary considerably. For example, where the person already underwent a vasodilation procedure, lower dosages or less frequent administrations are contemplated, while in cases where the person did not receive previous treatment to reduce the atherosclerotic plaques, higher dosages and more frequent administrations are contemplated.

[0035] Likewise, the chelating agent need not be limited to EGTA, but may be various alternative chelating agents including EDTA, CDTA, and DTPA, wherein the choice of the chelating agent will predominantly depend on the desired specificity of the chelator and the tolerability at a particular concentration. Furthermore, the formulation of the chelating agent need not be restricted to 10 ml of a 50 mg/ml solution of EGTA in 10 mM sodium phosphate buffer pH8.4. For example, alternative formulations may be employed to achieve a larger distribution, faster absorbption, etc., and appropriate formulations include those already described above.

[0036] Thus, specific embodiments and applications of antiviral compositions have been disclosed. It should be apparent, however, to those skilled in the art that many more modifications besides those already described are possible without departing from the inventive concepts herein. For example, the route of administration need not necessarily be restricted to a rectal administration of the chelating agent, but may also include vaginal administration. The inventive subject matter, therefore, is not to be restricted except in the spirit of the appended claims. Moreover, in interpreting both the specification and the claims, all terms should be interpreted in the broadest possible manner consistent with the context. In particular, the terms "comprises" and "comprising" should be interpreted as referring to elements, components, or steps in a non-exclusive manner, indicating that the referenced elements, components, or steps may be present, or utilized, or combined with other elements, components, or steps that are not expressly referenced.

Composition having reverse transcriptase inhibitor activity
US2003083226

[0001] This application claims the benefit of U.S. provisional application No. 60/294,480 filed May 30, 2001, incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The field of the invention is antiviral compositions.

BACKGROUND OF THE INVENTION

[0003] Treatment of viral infections is frequently limited by the availability, tolerability, and cost of known and approved pharmacological agents. Moreover, even if one or more antiviral agents are relatively well tolerated (physically as well as financially), resistance to such agents tends to develop rather quickly. Therefore, there is a continuing need for novel antiviral compositions that are well tolerated and relatively inexpensive.

DETAILED DESCRIPTION

[0004] The inventors recognized that various plant extracts exhibit significant antiviral activity and that reverse transcriptase inhibitors (RTI) may be isolated for such plant extracts. Moreover, the inventors contemplate that such RTIs can be characterized and/or synthesized de novo.

[0005] Particularly contemplated plants include Abies webbiana, Acacia spec., Acacia Arabia, Agrimonia eupatoria, Ajuga decumbens, Allium cepa, Allium sativum, Aloe vera, Altemanthera philoxeroides or sessiles, Ammi maius, Andographis paniculata, Apium graveolens, Apium leptophyllum, Arachis hypogaea, Arctium lappa, Amebia euhcroma, Asparagus racemosus, Astragalus spinosus, Astragalus lentingosis swainsonine, Buchenavia capita, Bryonia cretica ssp. Dioica, Bryonia angustifolia, Camellia theifera, Camellia sinensis, Cedrela toona, Chrysanthemum morifolium, Coffea arabica, Coptis chinesis, Coptis teetoides, Coptis japonica, Coraria nepalensis, Coriandrum sativum, Curcuma longa, Datura metel syn alba, Daucus carota, Echinacea angustiflora and purpurea, Echinacea simulata, Echinacea pallida, Epimedium grandiflorum, Epimedium sagittatum, Epimedium sinense, Epilobium angustifolium, Erigeron Canadensis, Eugenia or Syzigium claviflorum, Fagara xanthox, Foeniculum vulgarel, Gardenia coronaria, Gaultheria trichophylla, Glycine max, Glycyrrhiza labra, Gossypium herbaceum, Heracleum sphondylium, Hypericum perforatum, Hypericum japonicum, Hyssopus officinalis, Jasminum officinale, Lithospermum erythrorhizon, Lonicera japonica, Luffa luffa, Lycopus europaeus, Magnolia officinalis, Mallotus repandus, Mallotus philippinesis, Matricaria chamomil, Matricaria recutitia, Melissa parviflora, Melissa officinalis, Momordica balsamina, Momordica charantia, Narcissus tazetta, Narcissus pseudonarcissus, Oenthera rosea, Paeonia spec., Papaver somniferum, Perilla frutescens, Phyllanthus niruri, Pinus koraicenis, Pinus parviflora, Piper nirgum, Plumeria rubra, Polyantha suberosa, Prunella vulgaris, Prunus bakariensis, Prunus amygdalus, Psoralea corylifolia, Randia dunatorum, Raphanus sativus, Rheum palmatum, Rhus coriaria, Rhus chinesis, Ricinus communis, Rosmarinus officinalis, Salvia miltiorhiza and officinalis, Sambucus ebulus, Saussurea lappa, Scilla griffithii, Scutellaria baicalensis baiealein, Sedum sediforme, Senecio scandens, Senecio aereus, Skimmia laureola, Solarium niporum, Swertia franchetiana, Terminalia chebula, Terminalia catappa, Terminalia alata, Thula occidentalis, Trapalaponica spec., Trichosanthes dioica, Trichosanthes kirilowii, Urtica dioica, Viola yeodensis, Woodfordia fruticosa, Woodwardia spec., and Zanoxylum nitidum. However, in alternative aspects many plants other than the above-listed plants are also contemplated. In fact, all plants are contemplated that exhibit antiviral activity.

[0006] With respect to the identification of an RTI in contemplated plants, it should be appreciated that numerous assays are known in the art, and can readily be adapted to a screening process in which a fractions of a plant extract are screened for RTI activity. For example, U.S. Pat. No. 6,130,036 to Loeb et al. describes a high throughput assay system in which positive selective pressure is employed to select and/or identify an RTI. Once a fraction has been identified as having RTI activity, it is contemplated that further separation of the components in that fraction will eventually lead to an isolated (single or complex) compound.

[0007] It is still further contemplated that such isolated compounds may then be characterized using various forms of mass spectroscopy (e.g., ESMS, FAB-MS, GC-MS, etc.), UV-, IR-, and VIS-spectroscopy, atom absorption spectroscopy, various forms of NMR (<1>H-NMR, <13>C-NMR, NOE-NMR, etc.), or other analytical method. While not limiting to the inventive subject matter, it is preferred that such characterization methods will lead to a chemical structure of the RTI, which may be employed to synthesize the RTI de novo, or to modify the structure to arrive at an RTI with improved or altered physico-chemical properties.

[0008] Particularly contemplated modifications of isolated and characterized RTIs include increased specificity towards the viral polymerase over non-specific interactions with non-reverse transcriptase molecules in a cell or biological system, higher affinity of the modified RTI towards the reverse transcriptase, reduced toxicity, increased solubility, etc.

[0009] Consequently, it is contemplated that pharmacological composition comprises a synthetic reverse transcriptase inhibitor having a structure of a molecule that is present in a plant extract demonstrated to have an antiviral effect, wherein the molecule produces at least in part of the antiviral effect.

[0010] Thus, specific embodiments and applications of compositions having reverse transcriptase inhibitor activity have been disclosed. It should be apparent, however, to those skilled in the art that many more modifications besides those already described are possible without departing from the inventive concepts herein. The inventive subject matter, therefore, is not to be restricted except in the spirit of the appended contemplated claims. Moreover, in interpreting both the specification and the contemplated claims, all terms should be interpreted in the broadest possible manner consistent with the context. In particular, the terms "comprises" and "comprising" should be

interpreted as referring to elements, components, or steps in a non-exclusive manner, indicating that the referenced elements, components, or steps may be present, or utilized, or combined with other elements, components, or steps that are not expressly referenced.

Treatment of virus using chelator and antiviral agent
US2002182227

[0001] This application claims the benefit of U.S. provisional application No. 60/294,481 filed May 30, 2001, incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The field of the invention is antiviral compositions.

BACKGROUND OF THE INVENTION

[0003] Viral infections are unfortunately an almost unavoidable challenge to the health of most human and other mammals, and while many viral infections are successfully cleared by the immune system of the infected individual before substantial damage arises, some viral infections lead to severe damage or even death. There are many known antiviral drugs, however, all or almost all of them suffer from one or more disadvantages, most notably adverse side-effects, built-up of viral resistance, complicated administration schedules, and often high cost. Therefore, there is a need for simple and effective antiviral compositions that are well tolerated, simple to administer, and relatively inexpensive.

DETAILED DESCRIPTION

[0004] The inventors discovered that treatment of a viral infection can be significantly improved by coadministration of an antiviral agent with a chelator. More specifically, the inventors contemplate that particularly suitable chelators deplete the viral environment sufficiently to promote disintegration of the viral envelope.

[0005] Consequently, the inventors contemplate a pharmacological composition that includes an antiviral agent and a chelator in a quantity sufficient to reduce a serum concentration of a bivalent metal in an amount of at least 25%.

[0006] Suitable antiviral agents particularly include direct antiviral agents and indirect antiviral agents. As used herein, the term "direct antiviral drug" refers to an agent that directly interferes with one or more viral components. For example, virus protein specific antibodies, reverse transcriptase inhibitors or protease inhibitors are considered direct antiviral agents, because such compounds directly bind and to and/or reduce the activity of their respective viral target structures. As also used herein, the term "indirect antiviral drug" refers to a compound that indirectly interferes with a replication or propagation of a virus, and particularly include immunomodulatory agents (e.g., cytokines, various nucleoside analogs, and/or Zn<2>+). However, it should be appreciated that chelators are explicitly excluded from the definitions of direct and indirect antiviral compounds.

[0007] Especially preferred antiviral compounds include plant extracts and/or one or more isolated compounds (isolated from the plant or synthesized de novo) that are present in a plant extract demonstrated to have an antiviral effect. Particularly suitable plants for contemplated extracts and isolated compounds include Abies webbiana; Acacia spec. Acacia Arabia; Agrimonia eupatoria; Ajuga decumbens; Allium cepa; Allium sativum; Aloe vera; Altemanthera philoxeroides or sessiles; Ammi maius; Andographis paniculata; Apium graveolens; Apium leptophyllum; Arachis hypogaea; Arctium lappa; Amebia euhcroma; Asparagus racemosus; Astragalus spinosus; Astragalus lentingosis swainsonine; Buchenavia capita; Bryonia cretica ssp. Dioica; Bryonia angustifolia; Camellia theifera; Camellia sinensis; Cedrela toona; Chrysanthemum morifolium; Coffea arabica; Coptis chinesis; Coptis teetoides; Coptis japonica; Coraria nepalensis; Coriandrum sativum; Curcuma longa; Datura metel syn alba; Daucus carota; Echinacea angustiflora and purpurea; Echinacea simulata; Echinacea pallida; Epimedium grandiflorum; Epimedium sagittatum; Epimedium sinense; Epilobium angustifolium; Erigeron Canadensis; Eugenia or Syzigium claviflorum; Fagara xanthox; Foeniculum vulgarel; Gardenia coronaria; Gaultheria trichophylla; Glycine max; Glycyrrhiza labra; Gossypium herbaceum; Heracleum sphondylium; Hypericum perforatum; Hypericum japonicum; Hyssopus officinalis; Jasminum officinale; Lithospermum erythrorhizon; Lonicera japonica; Luffa luffa; Lycopus europaeus; Magnolia officinalis; Mallotus repandus; Mallotus philippinesis; Matricaria chamomil; Matricaria recutitia; Melissa parviflora; Melissa officinalis; Momordica balsamina; Momordica charantia; Narcissus tazetta; Narcissus pseudonarcissus; Oenthera rosea; Paeonia spec.; Papaver somniferum; Perilla frutescens; Phyllanthus niruri; Pinus koraicenis; Pinus parviflora; Piper nirgum; Plumeria rubra; Polyantha suberosa; Prunella vulgaris; Prunus bakariensis; Prunus amygdalus; Psoralea corylifolia; Randia dunatorum; Raphanus sativus; Rheum palmatum; Rhus coriaria; Rhus chinesis; Ricinus communis; Rosmarinus officinalis; Salvia miltiorhiza and officinalis; Sambucus ebulus; Saussurea lappa; Scilla griffithii; Scutellaria baicalensis baiealein; Sedum sediforme; Senecio scandens; Senecio aereus; Skimmia laureola; Solarium niporum; Swertia franchetiana; Terminalia chebula; Terminalia catappa; Terminalia alata; Thula occidentalis; Trapalaponica spec.; Trichosanthes dioica; Trichosanthes kirilowii; Urtica dioica; Viola yeodensis; Woodfordia fruticosa; Woodwardia spec. Zanoxylum nitidum;

[0008] With respect to the chelator it is generally contemplated that all chelating agents are suitable for use in conjunction with the teachings presented herein so long as such chelators (a) reduce serum concentration of a bivalent metal (e.g., Ca<2+> and Mg<2+>) in an amount of at least 25%, and (b) are at least partially effective to promote viral disintegration at an administered dosage. Particularly contemplated bivalent metals include Ca<2+> and Mg<2+>. Particularly preferred chelators include 1,2-Bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid, Ethylenebis(oxyethylenenitrilo)tetraacetic acid, 1,2-bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid tetrakis(acetoxymethyl ester), trans1,2-diaminocyclohexane-tetraacetic acid, and diethyllenetriamine-pentaacetic acid, trimethylaminetricarboxylic acid, poly(aspartic acid), and poly(glutamic acid), ethylenediamine-N,N,N',N'-tetraacetic acid, and EGTA.

[0009] It is further contemplated that suitable compositions will reduce the viral serum titer of a virus in an amount of at least 10% (e.g.,

as determined by RT-PCR), and especially contemplated viruses include retroviruses (e.g., HIV, HCV), dsDNA and ssDNA viruses.

[0010] With respect to the administration of contemplated compositions, it should be recognized that various protocols are suitable, and especially contemplated protocols include substantially simultaneous administration of the chelator (e.g., coadministration in a single tablet), or administration of the chelator (or antiviral agent) while there is a measurable concentration of the antiviral agent (or chelator) in the patient. For example, it is contemplated that suitable antiviral agents may be orally administered, while the chelator is parenterally administered (e.g., via injection or mucosal presentation).

[0011] Consequently, the dosage and formulation of contemplated antiviral agents and chelators may vary substantially, however, it is preferred that the antiviral agent is administered in approved and/or known dosages and formulations. Similarly, it is preferred that dosages and formulations of appropriate chelators are identical or similar to those known in the art.

[0012] Thus, specific embodiments and applications of antiviral treatments using a chelator and an antiviral agent have been disclosed. It should be apparent, however, to those skilled in the art that many more modifications besides those already described are possible without departing from the inventive concepts herein. The inventive subject matter, therefore, is not to be restricted except in the spirit of the appended contemplated claims. Moreover, in interpreting both the specification and the contemplated claims, all terms should be interpreted in the broadest possible manner consistent with the context. In particular, the terms "comprises" and "comprising" should be interpreted as referring to elements, components, or steps in a non-exclusive manner, indicating that the referenced elements, components, or steps may be present, or utilized, or combined with other elements, components, or steps that are not expressly referenced.

Time release chelators
US2002182217

[0001] This application claims the benefit of U.S. provisional application No. 60/294,478 filed May 30, 2001, incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The field of the invention is antiviral compositions.

BACKGROUND OF THE INVENTION

[0003] Numerous antiviral drugs are known in the art, however, all or almost all of them suffer from one or more disadvantages. Particularly problematic in the administration is of such drugs is their relatively low solubility and/or comparably short serum half-life time. Consequently, many patients need to follow a strict regimen to maintain effective serum concentration of such drugs, frequently resulting in repeated disruptions of an otherwise productive lifestyle. Therefore, there is a need for improved antiviral compositions that are well tolerated, simple to administer, and maintain a relatively long serum half-life.

DETAILED DESCRIPTION

[0004] The inventors contemplate that treatment of a viral infection can be significantly improved by administration of a chelator in a time-release formulation. Furthermore, the inventors contemplate that the chelator is co-administered in a time-release formulation with a second or further agent with antiviral effect (which may be administered following a conventional protocol or in a second time release formulation). Contemplated viruses include retroviruses (e.g., HIV, HCV), ssDNA and dsDNA.

[0005] Consequently, the inventors contemplate a pharmacological composition that includes an a chelator in a time release formulation in a concentration such that a single administration of the chelator reduces the serum concentration of a bivalent metal in an amount of at least 20% for a period of at least 8 hours, more preferably at least 30% for a period of at least 10 hours, and most preferably at least 40% for a period of at least 12 hours.

[0006] With respect to the chelator it is generally contemplated that all chelating agents are suitable for use in conjunction with the teachings presented herein so long as such chelators (a) reduce serum concentration of a bivalent metal (e.g., Ca<2+> and Mg<2+>) in an amount of at least 25%, and (b) are at least partially effective to promote viral disintegration at an administered dosage. Particularly contemplated bivalent metals include Ca<2+> and Mg<2+>. Particularly preferred chelators include 1,2-Bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid, Ethylenebis(oxyethylenenitrilo)tetraacetic acid, 1,2-bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid tetrakis(acetoxymethyl ester), trans-1,2-diaminocyclohexane-tetraacetic acid, and diethyllenetriamine-pentaacetic acid, tri-methylaminetricarboxylic acid, poly(aspartic acid), and poly(glutamic acid), ethylenediamine-N,N,N',N'-tetraacetic acid, and EGTA.

[0007] There are numerous methods of preparing a time release formulation known in the art, all of which are contemplated suitable for use in conjunction with the teachings herein. However, particularly contemplated time release formulations include ion exchange resins, encapsulations with acid or base resistant coatings, compacting the formulation to control solvation, slow-melting carriers, enzyme-degradable carriers, etc.

[0008] Depending on the amount chelator in contemplated compositions, it is contemplated that the viral titer in the serum of a patient infected with the virus will decrease at least 10% for at least 4 hours, more preferably at least 25% for at least 6 hours, and most preferably at least 40% for at least 8 hours after administration of a single dose of contemplated compounds.

[0009] It should further be appreciated that contemplated compositions may further comprise direct antiviral agents and/or indirect antiviral agents. As used herein, the term "direct antiviral agent" refers to an agent that directly interferes with one or more viral components. For example, virus protein specific antibodies, reverse transcriptase inhibitors or protease inhibitors are considered direct

antiviral agents, because such compounds directly bind and to and/or reduce the activity of their respective viral target structures. As also used herein, the term "indirect antiviral agent" refers to a compound that indirectly interferes with a replication or propagation of a virus, and particularly include immunomodulatory agents (e.g., cytokines, various nucleoside analogs, and/or Zn<2+>). However, it should be appreciated that chelators are explicitly excluded from the definitions of direct and indirect antiviral compounds.

[0010] With respect to the administration of contemplated compositions, it should be recognized that various protocols are suitable, and especially contemplated protocols include oral and parenteral administration (e.g., via a tablet, syrup, injection, suppository, topical administration transcutaneous administration, etc.). Consequently, the dosage and formulation of contemplated compositions may vary substantially. However, it is generally preferred that a single dosage is within the range of about 10 mg to about 3000 mg.

[0011] Thus, specific embodiments and applications of chelators in time release format have been disclosed. It should be apparent, however, to those skilled in the art that many more modifications besides those already described are possible without departing from the inventive concepts herein. The inventive subject matter, therefore, is not to be restricted except in the spirit of the appended contemplated claims. Moreover, in interpreting both the specification and the contemplated claims, all terms should be interpreted in the broadest possible manner consistent with the context. In particular, the terms "comprises" and "comprising" should be interpreted as referring to elements, components, or steps in a non-exclusive manner, indicating that the referenced elements, components, or steps may be present, or utilized, or combined with other elements, components, or steps that are not expressly referenced.

Methods of treatment of HIV-associated conditions
US2002182272

[0001] This application claims the benefit of U.S. provisional application No. 60/294,479 filed May 30, 2001, incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The field of the invention is treatment of HIV-associated conditions.

BACKGROUND OF THE INVENTION

[0003] Most patients infected with the HIV virus will develop AIDS, reflecting a breakdown in their immune system's capability to ward off foreign and "self"-generated antigens. For example, Kaposi sarcoma, and numerous bacterial and yeast infections are relatively common diseases associated with AIDS. Typically, these secondary diseases are treated with drugs that specifically target the etiologic agent (e.g., sarcoma cell, bacterium, or virus) of those diseases, thereby often increasing an already long list of undesired side effects brought on by attempts to control the propagation of the HIV virus.

DETAILED DESCRIPTION

[0004] The inventors contemplate that treatment of HIV related conditions can be significantly improved by administration of a composition that comprises at least one of a chelator and an antiviral agent, wherein the antiviral agent comprises a plant extract, or a synthetic or isolated compound from a plant that is demonstrated to have an antiviral effect.

[0005] The term "HIV related condition" as used herein refers to intrinsic and extrinsic challenges to an immune system that may develop into an apparent (i.e., detectable by diagnotic tools) disease while the patient has a detectable HIV serum virus titer. Particularly contemplated conditions include bacterial infections (e.g., pneumocystis carnii, tuberculosis, salmonellosis, mycobacterium avium complex, etc.), viral infections (e.g., cytomegalovirus, herpes simplex, hepatitis, varicella zoster, Epstein-barr, etc.), fungal infections (e.g., candidiasis, cryptococcal meningitis, histoplasmosis, etc.), parasite infections (e.g., toxoplasmosis, cryptosporidiosis, etc.), and Kaposi sarcoma.

[0006] Suitable compositions are described in copending provisional patent applications with the title "Treatment of Virus Using Chelator and Antiviral Agent" by Bruce Halstead et al., filed on or about May 30, 2001, "Time Release Chelators" by Bruce Halstead et al., filed on or about May 30, 2001, and "Time Release reverse transcriptase inhibitors" by Bruce Halstead et al., filed on or about May 30, 2001, all of which are incorporated by reference herein.

[0007] In a preferred aspect of the inventive subject matter, a method of treating a patient comprises one step in which a patient infected with HIV is diagnosed with an HIV related condition. In a further step, a composition is administered to the patient that comprises at least one of a chelator and an antiviral agent, wherein the antiviral agent comprises a plant extract or a synthetic or isolated compound from a plant that is demonstrated to have an antiviral effect. It should be recognized that all patients infected with an HIV virus may be treated using contemplated methods, however, patients with a CD4<+> count of less than 200 are particularly contemplated. Consequently, especially preferred patients include patients with developing or fully developed AIDS, wherein such patients may or may not receive pharmacological treatment.

[0008] With respect to the administration of contemplated compounds, it should be appreciated that a particular dosage and regimen will typically depend on the particular HIV-related condition. It is generally contemplated that the dosage, route and formulation is substantially identical or similar to those described in the copending provisional applications. However, where appropriate, alternative dosages, routes, and formulations may be employed, and in fact all dosages formulations and routes are contemplated that result in a positive response of the patient to the administration.

[0009] Thus, specific embodiments and applications of treatment of HIV-related conditions have been disclosed. It should be apparent, however, to those skilled in the art that many more modifications besides those already described are possible without departing from the

inventive concepts herein. The inventive subject matter, therefore, is not to be restricted except in the spirit of the appended contemplated claims. Moreover, in interpreting both the specification and the contemplated claims, all terms should be interpreted in the broadest possible manner consistent with the context. In particular, the terms "comprises" and "comprising" should be interpreted as referring to elements, components, or steps in a non-exclusive manner, indicating that the referenced elements, components, or steps may be present, or utilized, or combined with other elements, components, or steps that are not expressly referenced

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Time release reverse transcriptase inhibitors
US2002187957

[0001] This application claims the benefit of U.S. provisional application No. 60/294477 filed May 30, 2001, incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The field of the invention is antiviral compositions.

BACKGROUND OF THE INVENTION

[0003] Numerous antiviral drugs are known in the art, however, all or almost all of them suffer from one or more disadvantages. Particularly problematic in the administration is of such drugs is their relatively low solubility and/or comparably short serum half-life time. Consequently, many patients need to follow a strict regimen to maintain effective serum concentration of such drugs, frequently resulting in repeated disruptions of an otherwise productive lifestyle. Therefore, there is a need for improved antiviral compositions that are well tolerated, simple to administer, and maintain a relatively long serum half-life.

DETAILED DESCRIPTION

[0004] The inventors contemplate that treatment of a viral infection can be significantly improved by administration of an antiviral agent in a time-release formulation. More specifically, the inventors contemplate that a reverse transcriptase inhibitor in a time-release formulation is administered to a patient suffering from a viral infection. Particularly contemplated viruses include retroviruses (e.g., HIV, HCV), ssDNA and dsDNA.

[0005] In an especially preferred aspect, the reverse transcriptase inhibitor (RTI) is an extract from a plant that is known to have an antiviral effect, or an isolated or synthetically prepared compound that can be found in a plant known to have an antiviral effect. Especially contemplated plants include Abies webbiana; Acacia spec. Acacia Arabia; Agrimonia eupatoria; Ajuga decumbens; Allium cepa; Allium sativum; Aloe vera; Altemanthera philoxeroides or sessiles; Ammi maius; Andographis paniculata; Apium graveolens; Apium leptophyllum; Arachis hypogaea; Arctium lappa; Amebia euhcroma; Asparagus racemosus; Astragalus spinosus; Astragalus lentingosis swainsonine; Buchenavia capita; Bryonia cretica ssp. Dioica; Bryonia angustifolia; Camellia theifera; Camellia sinensis; Cedrela toona; Chrysanthemum morifolium; Coffea arabica; Coptis chinesis; Coptis teetoides; Coptis japonica; Coraria nepalensis; Coriandrum sativum; Curcuma longa; Datura metel syn alba; Daucus carota; Echinacea angustiflora and purpurea; Echinacea simulata; Echinacea pallida; Epimedium grandiflorum; Epimedium sagittatum; Epimedium sinense; Epilobium angustifolium; Erigeron Canadensis; Eugenia or Syzigium claviflorum; Fagara xanthox; Foeniculum vulgarel; Gardenia coronaria; Gaultheria trichophylla; Glycine max; Glycyrrhiza labra; Gossypium herbaceum; Heracleum sphondylium; Hypericum perforatum; Hypericum japonicum; Hyssopus officinalis; Jasminum officinale; Lithospermum erythrorhizon; Lonicerajaponica; Luffa luffa; Lycopus europaeus; Magnolia officinalis; Mallotus repandus; Mallotus philippinesis; Matricaria chamomil; Matricaria recutitia; Melissa parviflora; Melissa officinalis; Momordica balsamina; Momordica charantia; Narcissus tazetta; Narcissus pseudonarcissus; Oenthera rosea; Paeonia spec.; Papaver somniferum; Perilla frutescens; Phyllanthus niruri; Pinus koraicenis; Pinus parviflora; Piper nirgum; Plumeria rubra; Polyantha suberosa; Prunella vulgaris; Prunus bakariensis; Prunus amygdalus; Psoralea corylifolia; Randia dunatorum; Raphanus sativus; Rheum palmatum; Rhus coriaria; Rhus chinesis; Ricinus communis; Rosmarinus officinalis; Salvia miltiorhiza and officinalis; Sambucus ebulus; Saussurea lappa; Scilla griffithii; Scutellaria baicalensis baiealein; Sedum sediforme; Senecio scandens; Senecio aereus; Skimmia laureola; Solarium niporum; Swertia franchetiana; Terminalia chebula; Terminalia catappa; Terminalia alata; Thula occidentalis; Trapalaponica spec.; Trichosanthes dioica; Trichosanthes kirilowii; Urtica dioica; Viola yeodensis; Woodfordia fruticosa; Woodwardia spec. Zanoxylum nitidum.

[0006] Alternatively it should be appreciated that RTIs other than plant extracts are also appropriate, and such agents particularly include known and commercially available RTIs as indicated in

TABLE 1

Drug	Generic Name	Brand Name	Analogue
3TC	lamivudine	Epivir/3TC	cytidine
ABC	abacavir	Ziagen	guanosine
AZT	zidovudine	Retrovir	thymidine
ddC	zalcitabine	HIVID	cytidine
ddI	didanosine	Videx	adenosine

d4T stavudine Zerit thymidine

F-ddA lodenosine adenosine

FTC emtricitabine Coviracil cytidine

PMEA adefovir dipivoxil Preveon adenosine

PMPA tenofovir disoproxil adenosine

[0007] In further especially preferred aspects, contemplated antiviral agents may include a chelating agent that chelates a bivalent metal ion, preferably Mg<2+ >and/or Ca<2+>. Especially preferred chelating agents include EDTA, EGTA, 1,2-Bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid, Ethylenebis(oxyethylenenitrilo)tetraacetic acid, 1,2-bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid tetrakis(acetoxymethyl ester), trans-1,2-diaminocyclohexane-tetraacetic acid, and diethyllenetriamine-pentaacetic acid, trimethylaminetricarboxylic acid, poly(aspartic acid), and poly(glutamic acid).

[0008] There are numerous known methods of preparing a time-release formulation, and all of the known methods are contemplated suitable for use in conjunction with the teachings herein. Particularly contemplated time release formulations include ion exchange resins, encapsulations with acid or base resistant coatings, compacting the formulation to control solvation, slow-melting carriers, enzyme-degradable carriers, etc.

[0009] With respect to the dosage of contemplated compositions, it is contemplated that the RTI is present in a single dose in a concentration such that the viral titer is reduced at least 20% over a period of at least 6 hours, more at least 30% over a period of at least 8 hours, and most preferably at least 45% over a period of at least 12 hours. Furthermore, it is contemplated that where contemplated compositions further comprise a chelating agent, the chelating agent is present in a single dose in a concentration such that the serum Mg<2+ >and/or Ca<2+ >concentration is reduced at least 20% over a period of at least 6 hours, more preferably at least 35% over a period of at least 12 hours, and most preferably at least 45% over a period of at least 12 hours.

[0010] With respect to the administration of contemplated compositions, it should be recognized that various protocols are suitable, and especially contemplated protocols include oral, topical, and parenteral administration. Consequently, the formulation of contemplated compositions may vary substantially, however, it is preferred that the RTI is administered in approved and/or known formulations.

[0011] Thus, specific embodiments and applications of time release RTIs have been disclosed. It should be apparent, however, to those skilled in the art that many more modifications besides those already described are possible without departing from the inventive concepts herein. The inventive subject matter, therefore, is not to be restricted except in the spirit of the appended contemplated claims. Moreover, in interpreting both the specification and the contemplated claims, all terms should be interpreted in the broadest possible manner consistent with the context. In particular, the terms "comprises" and "comprising" should be interpreted as referring to elements, components, or steps in a non-exclusive manner, indicating that the referenced elements, components, or steps may be present, or utilized, or combined with other elements, components, or steps that are not expressly referenced.

Methods for testing oxidative stress
US6541267

[0002] This is a continuation-in-part of allowed U.S. application Ser. No. 09/253,223, filed Feb. 19, 1999, now U.S. Pat. No. 6,165,797 which is incorporated by reference herein.

FIELD OF THE INVENTION

[0003] The field of the invention is detection and quantification of oxidative stress in a subject.

BACKGROUND

[0004] It is by now common knowledge that stress in mammalian subjects develops directly or indirectly into a display of oxygenated species, which tends to change the usually reduced state of the body to a hyperoxygenated state. This hyperoxygenated state includes generation and reaction of hydroxides, peroxides and free radical species, which are thought to be implicated in physiological imbalance and actual physical damage. Physical damage can produce pathological states, which for example, may lead to atherosclerotic plaques. Such plaques often result in the deposition of lipids and may further lead to blockage of arteries that can cause a cessation of blood flow to the heart with a resulting heart attack. This is one of many human disease states that are thought to be caused by free radical attack from the hyperoxygenated state caused by stress. Despite the relatively large body of information linking oxidative stress to various diseases and/or disease states, there is still an appreciable need for suitable markers and test systems to determine the level of oxidative stress in a simple and inexpensive manner.

[0005] Malondialdehyde is a component of normal urine, and its presence can be determined using relatively expensive and typically stationary equipment such as spectrophotometers, fluorometers, high performance liquid chromatographs and gas chromatograph mass spectrometers. Such equipment typically enables an operator to determine not only the quantity of a particular aldehyde, but also to determine the chemical nature of a particular molecule with an aldehyde function. Unfortunately, the operator of such equipment needs to be highly trained, and the weight and size of the equipment is generally prohibitive for point-of-care tests.

[0006] Alternatively, a broad spectrum of chemically distinct aldehydes may be detected by mixing a drop of sample solution (which may contain the aldehyde) with 2 ml of 72 percent sulfuric acid in a test tube (disclosed at page 395 in "Qualitative Analysis by Spot Tests",

Third Edition, authored by F. Feigl and published by Elsevier Publishing Company, Inc.). A small amount of solid chromatropic acid (1,8-dihydroxynapthlanene-3,6-disulfate) is added to the mixture, and the test tube is heated in a 60[deg.] C. water bath for about ten minutes. If an aldehyde is present, a bright violet color appears in the test solution. While the test is relatively non-specific for a particular aldehyde, the sensitivity of the test is reportedly about 3 ppm. However, the reaction mixture typically requires vigorous heating for at least 10 minutes to provide an at least semi-quantitative and reliable test result.

[0007] In yet another method generally applicable to aldehydes, described at pages 339-340 of the Feigl publication, a drop of aqueous (or alcoholic) solution suspected of containing an aldehyde is treated on a spot plate with a drop of sulfurous acid and a drop of fuchsin/sulfuric acid and allowed to react on the plate. A red to blue color appears within about two to thirty minutes, according to the amount of aldehyde present in the test solution being tested. Such test is reportedly sensitive to about one microgram of formaldehyde in the drop of solution being tested. Although the fuchsin/sulfuric acid reaction can advantageously be performed at room temperature, the test results tend to vary depending on the time allowed for the reaction.

[0008] Although various quantitative and qualitative tests for aldehydes are known in the art, all or almost all of them suffer from one or more disadvantage. Moreover, despite the existence of known tests, it has never been appreciated that such tests can be applied to malondialdehyde in urine to detect oxidative stress. Thus, there is still a need to provide methods and apparatus for detecting oxidative stress in subjects.

SUMMARY OF THE INVENTION

[0009] It has been discovered that the oxidative stress state of a person can be measured from the release into the urine of an aldehyde, and particularly malondialdehyde, and that an aldehyde-reactive chromogen based calorimetric test can measure the released aldehyde in a rapid, easily performed test.

[0010] In particular, a method of determining oxidative stress in a subject has one step in which presence of an aldehyde in a biological fluid of a subject is correlated with an oxidative stress in the subject. In another step, a test reagent comprising a pH regulator, a reducing agent, and an aldehyde-reactive chromogen is provided, and the test reagent is combined with the biological fluid to produce an aldehyde-modified chromogen. In yet another step, a color of the aldehyde-modified chromogen is correlated with the oxidative stress.

[0011] In one aspect of the inventive subject matter, any biological fluid is considered suitable for use with the test, and especially preferred fluids include saliva, serum, plasma, and spinal fluid, most preferably urine. It is further contemplated that such fluids are derived from a mammalian system (e.g., human, live stock, pet, or cell culture).

[0012] In a further aspect of the inventive subject matter, the aldehyde comprises a dialdehyde, and especially contemplated dialdehydes include malondialdehyde. Particularly preferred pH regulators comprise a buffer or an acid, such as phosphoric acid and/or glacial acetic acid, and reducing agents typically have a sulfur (e.g., sodium metabisulfide) and/or phosphorous atom (e.g., TCEP). Further preferred aldehyde-reactive chromogens (e.g., fuchsin) include a reactive group that selectively reacts with an aldehyde and thereby shift their absorption maximum towards higher or lower wavelength in a concentration dependent manner.

DETAILED DESCRIPTION

[0013] A test kit for determination of oxidative stress in a subject generally comprises a test reagent with a pH regulator, a reducing agent, and an aldehyde-reactive chromogen, wherein the aldehyde-reactive chromogen in the test reagent reacts with an aldehyde from a biological fluid to form an aldehyde-modified chromogen, and wherein the aldehyde-modified chromogen has a color intensity that correlates with the oxidative stress in the subject.

[0014] Consequently, a method of determining oxidative stress in a subject has a step in which the presence of an aldehyde in a biological fluid of a subject is correlated with an oxidative stress in the subject. In another step, a test reagent comprising a pH regulator, a reducing agent, and an aldehyde-reactive chromogen is provided, and the test reagent is combined with the biological fluid to produce an aldehyde-modified chromogen. In a yet further step, a color of the aldehyde-modified chromogen is correlated with the oxidative stress.

[0015] In a particularly preferred aspect of the inventive subject matter, a testing solution or reagent for testing for the presence of aldehyde in an aqueous solution comprises a solution of acetic acid, preferably about 20% acetic acid, and two additional ingredients designated herein as "Ingredient A" and "Ingredient B". Ingredient A consists essentially of sodium metabisulfite, phosphoric acid, and deionized water. The preferred proportions of the elements of ingredient A are about 18-22 grams sodium metabisulfite, 9-11 ml of concentrated phosphoric acid, and about 450-550 ml deionized water. Most preferably, the proportions are 20 grams sodium metabisulfite, 10 ml phosphoric acid, and about 500 ml deionized water. Ingredient B consists essentially of a mixture of basic fuchsin (certified grade) and Ingredient A in the preferred proportions of about 0.45-0.55 grams basic fuchsin in about 90-110 ml of Ingredient A. Most preferably, the proportions are about 0.50 grams of basic fuchsin in about 100 ml of Ingredient A.

[0016] The components of the reagent are mixed in the proportion of about 90 to 110 parts of 20% acetic acid, 13.5-16.5 parts Ingredient A, and about 4.5-5.5 parts Ingredient B. An alternative method of making the reagent is as follows. First, dissolve 4 grams of sodium metabisulfite in 80 ml of deionized water. Then, add 2 ml of concentrated phosphoric acid, and dilute the mixture with a quantity of deionized water sufficient to make 100 ml of dilute mixture. Then add 0.5 gram of basic fuchsin, and about 10 grams of bone charcoal to decolorize the mixture. Remove the charcoal by centrifuging and filtering the mixture. Then, to 100 ml of the decolorized solution, add 100 ml of 20%-40% glacial acetic acid, and finally, add 100 ml of deionized water. The active components are present in the reagent made this way in about the same proportion as in the method previously described.

[0017] The testing solution described above is preferably stored in individual, sealed test-size ampoules or vials of conventional medical solution type. When packaged in such a manner and stored in a cool, dry place, the sealed bottles or vials have an expected shelf storage life of at least 12 months. Assurance of active testing solution may be achieved, as described below, by positive aldehyde test procedures.

[0018] A test for the presence of malondialdehyde in an aqueous solution is then made by mixing about 1 ml of test solution (containing

traces of aldehyde) into about 0.2-0.6 ml of testing solution formulated as above. If the mixture of the test sample and testing solution remains colorless after a waiting period of about 2-5 minutes, the test is negative and the test sample therefore contains less than about 2 ppm aldehyde. Any color change of the mixture indicates presence of aldehyde in the test solution in a concentration greater than about 2 ppm. A positive malondialdehyde test is preferably by quality control techniques made before testing the test samples to assure that the testing solution is properly formulated or that, for example, the reagent bottles have not been replaced with other bottles containing non-testing solutions.

[0019] The positive malondialdehyde test is preferably performed by injecting 1 ml of available "Positive Aldehyde Test Solution (Standard)" into a bottle containing about 0.2-0.6 ml of the test solution. In approximately 2-5 minutes, the solution in the bottle should develop a pinkish-purple color provided the bottle contains properly formulated aldehyde testing solution. Otherwise, the bottle of "testing solution" from which the test bottle was selected should be discarded. The above-described positive test for aldehyde is sensitive to 10 ppm or more of aldehyde. For a 5 ppm, a positive test for aldehyde, 0.5 ml of deionized water is used. A color less intense than that of the 10 ppm aldehyde test is obtained for the 5 ppm aldehyde test.

[0020] Basic fuchsin is a purple powder which reacts with aldehydes in the skin, urine or blood plasma. With low or no aldehydes present, there is no color development. With moderate or high levels of aldehydes, color gradations are roughly dependent on the level of aldehydes present. The amino group of the fuchsin couples with the aldehyde to produce the pink to purple color approximately dependent on the amount of aldehyde present in the blood or urine. A 40% glacial acetic acid solution gives maximum color development for the fuchsin reaction. Sodium metabisulfite ties up free oxygen so that only the aldehydes react with the fuchsin group. Basic fuchsin changes color in an acidic solution, relative to the amount of aldehyde present in the urine samples. The color developed depends on the pH, which is controlled by the amount of acid present. Metabisulfite is used to stop the interference of oxygen from air. Establishing a nitrogen blanket over the reagent mixture gives greater shelf life of the reagent to stop any oxygen reaction with the reagent. The phosphoric acid stabilizes the pH in a rough adjustment and the acetic acid gives the fine acid pH stabilization.

[0021] In alternative aspects of the inventive subject matter, it should be appreciated that the order, composition, and relative molar ratios of the reagents may vary substantially, and numerous modifications are contemplated so long as the test reagent comprises a pH regulator, a reducing agent (which may even be optional), and an aldehyde-reactive chromogen.

[0022] For example, the pH regulator need not necessarily be limited to phosphoric acid and glacial acetic acid, and alternative pH regulators may include a buffer, an organic, an inorganic acid, or any reasonable combination thereof. For example, depending on the desired pH or pH range, suitable pH regulators may include a glycin-HCL buffer, a citrate buffer, a phosphate buffer, an acetate buffer, etc., and appropriate acids may include nitric acid, sulfuric acid, hydrochloric acid, and so forth. Still further, it should be appreciated that where the reaction between the aldehyde and the aldehyde-reactive chromogen is base-facilitated or base-catalyzed, organic or inorganic bases may be employed, and contemplated bases include sodium hydroxide, potassium hydroxide, deprotonated weak organic acids, and any reasonable combination thereof.

[0023] With respect to the reducing agent, it is contemplated that many alternative reducing agents are also appropriate, and alternative reducing agents include agents with a sulfur and/or phosphorous atom. For example, where cost effectiveness is especially desirable mercaptoethanol, dithioerythrol (DTE) or dithiothreitol (DTT) may be utilized. On the other hand, where the objectionable odor of sulfur-based reagents is to be circumvented, phosphorous based reducing agents such as tris(2-carboxyethyl)phosphine (TCEP) may be employed. While the use of a reducing agent is generally preferred, it is also contemplated that no reducing agent may be necessary at all, especially where the remaining reagents/fluids have been purged (e.g., with argon) and/or have been kept under nitrogen or other oxygen free atmosphere.

[0024] In yet further contemplated aspects, the aldehyde-reactive chromogen need not be limited to fuchsin, and various alternative aldehyde-reactive chromogens are contemplated. It is generally contemplated that suitable aldehyde-reactive chromogens comprise an aromatic system which may further be conjugated with at least another double- or triple bond containing system, and it is especially preferred that such aldehyde-reactive chromogens will have an absortion maximum of between about 240 nm to approximately 900 nm. With respect to the molar extinction coefficient, it is generally preferred that the molar extinction coefficient if the aldehyde-modified chromogen is between 100-100000, more preferably between 1000 and 50000, and most preferably between 10000 and 35000. It is further contemplated that suitable aldehyde-reactive chromogens have at least one reactive group that specifically reacts with an aldehyde, and particularly contemplated reactive groups include nucleophilic groups such as -NH, -NH2, -SH, -OH, etc. Suitable aldehyde-reactive chromogens are contemplated to have an absorption maximum and a reactive group that selectively reacts with the aldehyde, wherein the absorption maximum exhibits a hyperchromatic or hypochromatic shift when the reactive group reacts with the aldehyde. Alternatively, the maximum may be unaffected by the reaction of the reactive group, and it is then contemplated that the aldehyde-modified chromogen has (or looses) an additional maximum when compared to the aldehyde-reactive chromogen.

[0025] It is generally contemplated that the concentration of aldehyde-modified chromogen can be visually (i.e., in an non-automated manner) determined, for example, by employing a reference chart which may be part of a test kit. Contemplated reference charts may thereby include a relative or arbitrary readout, or a semi-quantitative or quantitative readout. Alternatively, it is contemplated that the determination of the aldehyde may include an at least partially automated routine, and particularly contemplated routines may include a spectrophotometer (single or multiple wave length).

[0026] With respect to molar proportions of alternative components, it should be appreciated that a particular composition will typically dictate particular molar proportions of the components, however, only such molar proportions are contemplated that will result in an observable and/or quantifiable change in light absorption (typically UV/VIS) when the aldehyde-reactive chromogen reacts with the aldehyde. While it is generally contemplated that the change in absorption has a substantially linear dependence on the concentration of the aldehyde-modified chromogen (i.e., follows the Lambert-Beer law), non-linear dependence is also contemplated. For example, where the aldehyde generates a catalytic intermediate species, logarithmic or pseudo-logarithmic dependence may occur.

[0027] It is generally contemplated that malondialdehyde (MDA) and other related aldehydes are released from the breakdown of long chain polyunsaturated fatty acids by free radical attack. Interestingly, high levels of MDA and related aldehydes are found in a variety of diseases and disease states other than oxidative stress. Therefore, it should be especially appreciated that the methods and compositions

according to the inventive subject matter may also be useful in detecting and/or confirming abnormal metabolism states, including coronary artery disease, type-1 and type-2 diabetes, and Parkinson disease.

[0028] Thus, specific embodiments and applications of tests for oxidative stress have been disclosed. It should be apparent, however, to those skilled in the art that many more modifications besides those already described are possible without departing from the inventive concepts herein. The inventive subject matter, therefore, is not to be restricted except in the spirit of the appended claims. Moreover, in interpreting both the specification and the claims, all terms should be interpreted in the broadest possible manner consistent with the context. In particular, the terms "comprises" and "comprising" should be interpreted as referring to elements, components, or steps in a non-exclusive manner, indicating that the referenced elements, components, or steps may be present, or utilized, or combined with other elements, components, or steps that are not expressly referenced.

ANTIVIRAL METHODS AND COMPOSITIONS
WO0189545

Field of The Invention

The field of the invention is antiviral compositions.

Background of The Invention

Viral infections are relatively common infectious diseases, and various methods of treating a viral infection available to a practitioner. In one method of treating a viral infection, the immune response of an immune system is stimulated. For example, in some instances the Thl response of the patient can be increased relative to the Th2 response. An increase in the Thl response is thought to be beneficial because many viral infections are associated with a shift in the cytokine profile toward a Th2 response, and a bias towards a Thl response is known to be facilitated by several approaches.

In one approach, cytokines are administered to modulate the Thl/Th2 balance towards a Thl-type response. For example, Knight et al. postulate that treatment with
IL-12 (Interleukine-12), a cytokine that promotes the development of Thl cells, may be used as a treatment for AIDS since IL 12 administration has been shown to be effective at restoring cell-mediated immunity in mice infected with mouse AIDS virus or with RLV [Knight, S. C. and Patterson, S., Annu. Rev. Immunol. 1994.15: 593-615].

In another example, Gracie, J. A. et al., demonstrated that administration of IL-18 to mice exhibited pleiotropic activities critical to the development of Thl responses. [Gracie et al. J Clin Invest 1999 Nov 15; 104 (10): 1393-1401]. Although the administration of cytokines typically results in relatively specific increases in desired Thl cytokines, prolonged administration of cytokines may be problematic for various reasons. For example, the production of recombinant cytokines is relatively expensive, and isolation of non-recombinant cytokines from natural sources is generally difficult due to the very low concentration of cytokines in natural sources. Moreover, depending on the nature of the cytokine, cytokines may not be well tolerated in patients.

In another approach, immunomodulatory substances other than cytokines may be employed to increase the Thl response. For example, Sprietsma J. E. suggests that zinc ions (un2) and nitric oxide (NO), together with glutathione (GSH) and its oxidized form, GSSG, may help to regulate an immune response to antigens [Sprietsma J. E; Med Hypotheses 1999 Ju1 ; 53 (1) : 6-16]. The author reports in more detail that deficiencies of
Zn2+, NO and/or GSH shift the Thl/Th2 balance towards Th2, and that replenishment with Zn2+, NO and/or GSH may shift the Thl/Th2 balance towards Thl. Administration of Zn2+ or GSH/GSSG is especially advantageous, since these substances are non-toxic at even elevated concentrations, and inexpensive to produce. Furthermore, Zn2+ and GSH/GSSG preparations may be orally administered, and therefore significantly reduce the risk of allergic reactions, especially when the preparations are not ultrapure. However, the administration of Zn2+ and/or GSH/GSSG seems to be beneficial only to restore a Thl/Th2 balance from a Th2 dominated state, whereas it is unclear if administration of Zn2+ and/or GSH/GSSG may increase a Thl response from a normal
Thl/Th2 balance.

In another method of treating a viral infection, the virus is directly targeted with an appropriate anti-viral drug. For example, patients infected with the HIV virus often receive a cocktail of drugs to block virus propagation, and various classes for direct anti-viral treatment are known in the art. Some direct anti-viral drugs block the reverse transcriptase of a retrovirus. Reverse transcriptase (RT) inhibitors are typically nucleoside analogs such as AZT, 3TC, or ddI. Alternatively, non-nucleoside RT inhibitors, including quercetin may be employed. In vitro, RT inhibitors are typically potent antiviral drugs. However, in vivo, and especially during a period of relatively fast viral replication, the generation of RT inhibitor resistant virus mutants is problematic. Moreover, many RT inhibitors also exhibit undesirable activity on DNA replication in the host organism and significant cytotoxicity at elevated concentrations, thereby limiting the concentration that may be administered without severe side effects.

Among other direct anti-viral drugs are the protease inhibitors, which block or interfere with virus protein processing. Protease inhibitors are typically highly specific towards the viruses'proteolytic enzymes, however, due to their mostly hydrophobic nature, administration at desirable concentrations often becomes problematic. Another problem is that development of cross-resistance and severe side effects frequently occur. In order to reduce the development of multidrug resistant virus strains, mixtures of RT inhibitors and protease inhibitors may be prescribed. Although such mixtures are presently employed relatively successfully, the relatively high occurrence of adverse side effects and the potential of generating multidrug resistant virus strains persist.

To circumvent at least some of the problems associated with side effects and relatively high costs of antiviral drugs, Bennett et al. describe in U. S. Pat. No.

5,602,180 the use of EDTA complexes in a suppository. The use of chelating agents, including EDTA, has been found to promote disintegration of retroviruses [Wunderlich, V. and Sydow, G. Arch. Virol. 1982,73: 171-183]. Bennett's suppositories contain disodium EDTA and controlled-release agents, which release the disodium EDTA over a period of about three to four hours after rectal placement of the suppository. However, Bennett's suppositories are limited to disodium EDTA that exhibits relatively moderate selectivity between Mg2+ and Ca2+.

Although various antiviral compositions and antiviral treatments are known in the art, all or almost all of them have one or more disadvantages. Therefore, there is a need to provide improved methods and compositions for treatment of viral infections.

Summary of the Invention

The present invention is directed to an antiviral composition having a supply of chelating agent that chelates an alkaline earth metal ion, wherein the chelating agent is formulated in a rectal deposition formulation, and wherein the supply of chelating agent has an immediate bioavailability. When rectally administered to a subject in an effective dose in vivo, contemplated agents promote disintegration of a virus.

In one aspect of the inventive subject matter, generally preferred chelating agents are various chelators other than ethylenediamine-N, N, N', N'-tetraacetic acid (EDTA), chelate Ca2+ and/or Mg2+, and include at least three carboxylic acid groups.

While particularly preferred chelating agents include at least three acetic acid groups, especially contemplated chelating agents are 1, 2-Bis (2-aminophenoxy) ethane
N, N, N', N'-tetraacetic acid (BAPTA), Ethylenebis (oxyethylenenitrilo) tetraacetic acid (EGTA), 1, 2-bis (2-aminophenoxy) ethane-N, N, N', N'-tetraacetic acid tetrakis (acetoxymethyl ester) (BAPTA-AM), diethylenetriamine-pentaacetic acid (DTPA), trimethylaminetricarboxylic acid (NTA), trans-1, 2-diaminocyclohexanetetraacetic acid (CDTA), poly (aspartic acid), and poly (glutamic acid).

In another aspect of the inventive subject matter, contemplated viruses include a retrovirus, and especially contemplated retroviruses include the HIV virus. Preferred rectal deposition formulations are a liquid or a solid, and where the rectal deposition formulation is a solid and administered to the colon of a subject, substantially of the supply of chelating agent is present in the colon in a readily absorbable form in less than 2 hours, preferably less than 1 hour, and more preferably less than 30 minutes.

With respect to the effective dose in a rectal administration, it is contemplated that the chelating agent is employed in an amount of 500mg, and more preferably 1500mg.

In yet another aspect of the inventive subject matter, chelating agents other than EDTA may also be employed for purposes other than antiviral treatment, including heavy metal detoxification, and reduction of atherosclerotic plaques, wherein the chelating agent may be orally or parenterally administered.

Various objects, features, aspects and advantages of the present invention will become more apparent from the following detailed description of preferred embodiments of the invention.

Detailed Description

As used herein, the term"chelating agent"refers to a molecule that binds a metal ion and/or an alkaline earth metal ion via a non-covalent bond, most commonly a coordinate bond, with a KD of less than 10-3 mol'1, wherein the chelating agent may be in acid form, base form or a salt form. For example, EGTA in protonated or sodium salt form is considered a free chelating agent, because EGTA binds Mg2+ and Ca2+ with a KD of less than 10-3 mol-1.

As also used herein, the term"immediate bioavailability"means that a composition or molecule is present in an active form in a formulation such that a substantial portion of a dose of the composition or molecule exhibits some systemic chelating effect within minutes, preferably within less than 15min, more preferably within less than 10 min, and most preferably within less than 5min. For example, a molecule that is dissolved in a carrier solution is regarded to have immediate bioavailability.

It is known that retroviruses can be disintegrated by chelating agents, especially by agents that chelate Mg2+ and/or Ca2+, and that chelating agents may further reduce infectivity of certain viruses [Wunderlich, V. and Sydow, G. Arch. Virol. 1982, 73: 171183]. Thus, it is contemplated that an antiviral composition generally has a supply of a chelating agent that chelates an alkaline earth metal ion, and it is particularly contemplated that the chelating agent in the antiviral composition is formulated in a rectal deposition formulation, wherein the supply of chelating agent has an immediate bioavailability.

It should be appreciated that many chelating agents are known in the art, and that all of the known chelating agents are contemplated for use herein. It is generally preferred that contemplated chelating agents include at least three carboxylic acid groups, all of which are preferably acetic acid groups. Although not excluded, it is further contemplated that appropriate chelating agents are chelating agents other than EDTA. The choice of the particular chelating agent is predominantly determined by the desired physicochemical properties and tolerability of the chelating agent. For example, where a relatively high solubility (e. g., 1M) is desired, EGTA, CDTA or NTA may advantageously be employed. Where a more pronounced selectivity of chelation towards Ca2+ is desirable, BAPTA may be utilized, and BAPTA-AM may be particularly suitable where sequestration of Ca2+ within a cell is desired. Alternatively, contemplated chelating agents may include DTPA, NTA, and polymeric forms of aspartic acid, glutamic acid, and any reasonable combination thereof.

With respect to viruses that can be disintegrated and/or reduced in infectivity, virus particles that require Ca2+ and/or Mg2+ for structural integrity of their envelope are generally contemplated and include DNA and RNA viruses. Particularly contemplated RNA viruses are retroviruses in general, and HIV in particular. Further especially contemplated viruses include the hepatitis C and hepatitis D virus. Contemplated DNA viruses include polyomaviruses, HBV, etc. However, many more viruses are also contemplated, and a collection of appropriate viruses are listed in Fields Virology, Third Edition (Lippincot Williams & Wilkins), pages 40-41,52, and 1767-1847, and Arch. Virol. 1982,73: 171-183, both of which are incorporated by reference herein.

It is still further contemplated that chelating agents are preferably formulated in a rectal deposition formulation, which may be in solid or liquid form. Where the formu- lation is in a solid form, it is further contemplated that appropriate forms include dissolvable carriers such as waxes, fatty acids and oils with melting points of about 30 - 35 C. Especially preferred formulations are formulations known in the art that are employed in the fabrication of rectal suppositories, so long as such formulations allow an immediate bioavailability. Thus, where a supply of chelating agent is administered into the colon of a subject in a solid form, it is particularly contemplated that substantially all of the supply of chelating agent is present in the colon in a readily absorbable form in less than 2 hours, more preferably less than 1 hour, and most preferably less 30 minutes after the administration of the formulation. Availability of the chelating agent or a portion of the chelating agent in less that 2hrs, less than lhr or less than 30min may be achieved by a variety of time release formulations, and contemplated time release formulations may include formulations with a melting point of less than 37 C, enzymatically degradable carriers, dissolving or swellable carriers, etc. Thus, it is contemplated that an entire dose of chelating agent may be available (or released from the time release formulation) in less than 2 hours, preferably less than lhour, and even more pref- erably in less than 30min. A particular advantage of such time release formulations is that relatively high dosages may be administered that might otherwise pose a potential risk if administered without a time release formulation. However, it should be appreciated that administrations without time release may safely be administered by employing smaller dosages at multiple administrations.

Where the formulation is in a liquid form, it is contemplated that appropriate liquid forms may include buffered and unbuffered solutions, solutions with relatively high viscosity such as gels, creams, foams and ointments, which may or may not have a decreased viscosity at elevated temperatures. Liquid forms are particularly advantageous, since the delivery of the chelating agent is almost instantaneous. Where the solutions are buffered, it is contemplated that the buffers have an alkaline pH, and a preferred pH range is a range between 8.0 and 10.0.

Alternatively, the chelating agent may also be administered in various alternative routes, and it is especially contemplated that where the chelating agent is an agent other than EDTA that appropriate routes include oral and parenteral administration. For example, CDTA may be orally administered in form of an acid resistant caplet or capsule. However, oral administration need not be limited to a caplet or capsule, and alternative oral administrations include syrups, powders, tablets, etc. In another example, EGTA may be parenterally administered by intravenous injection. It is contemplated, however, that alternative parenteral administrations may also include inhalation, transdermal delivery, injections into sites other than a vein, etc.

In a particularly contemplated aspect of the inventive subject matter, it is preferred that the administration of the chelating agent is accompanied by (preferably oral) administration of a nutritional supplement. Preferred nutritional supplements include supplements that help replenish calcium levels and particularly preferred supplements include aragonite calcium carbonate from fossil coral minerals. Other contemplated supplements that include herbal products (e. g., adaptogenic formulations with no apparent cytotoxicity) are contemplated to assist in inhibition of viral replication (e. g., by inhibiting the production of reverse transcriptase). It is further contemplated that such supplements may also help boost the immune system and potentially improve overall vitality and stamina. It is further contemplated that such adaptogenic supplements are considered to have tumor preventive and radio-protective properties, and may help increase the functioning of the immune system by increasing the T-cell population. Exemplary compositions for contemplated nutritional supplements are shown in Tables 1 and 2.

Ingredient Amount (m/tablet)
Arcticum lappa 40mg (10: 1 concentrate)
Viola yedoensis 40mg (10: 1 concentrate)
Andrographis paniculata 40mg (10: 1 concentrate)
Lonicera erythrorhizon 40mg (10: 1 concentrate)
Epimedium med um aEt~um
Table 1 Ingredient Amount (mg/tablet)
Arcticum lappa 1 Omg (10: 1 concentrate) Viola yedoensis 1 Omg (10: 1 concentrate)
Andrographis paniculata 1 Omg (10: 1 concentrate)
Lonicera erythrorhizon 1 Omg (10: 1 concentrate) Altemanthera philoeroides 1 Omg (10 : 1 concentrate)
Table 2

It should be appreciated, however, that various additional ingredients may be added to the supplement depicted in Table 1 and 2 to either enhance or modulate the activity of the herbal components.

With respect to the amount of chelating agent it is contemplated, that the chelating agent is administered to a subject in vivo in a dose effective to promote disintegration of a virus in the subject. The actual dose of the chelating agent may thereby vary among individual subject and may further be determined by the particular virus that is to be disintegrated. Therefore, an effective dose may comprises rectal administration of the chelating agent between about 5mg-2500mg, and generally contemplated doses include rectal administration of 500mg or 1500mg of the chelating agent. However, where even higher dosages of the chelating agent are required, or where it is preferred to maintain relatively high dosages over an extended period of time, multiple dosages are also contemplated.

It should further be appreciated that appropriate formulations may further comprise active and/or inactive ingredients. For example, active ingredients may include compositions to stimulate the immune system, an immunomodulating composition, a coral mineral product, compositions to facilitate uptake of the chelating agent into the blood stream, or direct antiviral compounds such as nucleoside analogs, etc. The term "immunomodulating composition"as used herein refers to a composition that enhances at least one of a humoral and cellular response towards a challenge. For example, an immunomodulating composition may increase an antibody titer against a challenge, or an activity of cytotoxic T-lymphocytes. Inactive ingredients may include fillers, coloring agents, thixotropic compositions, and foam building agents.

In an exemplary use, a person diagnosed with an HIV infection receives twice daily an enema of 20ml of a 50mg/ml solution of EGTA in 10mM sodium phosphate buffer pH8.4 for at least 30 consecutive days. It should be recognized, however, that the exemplary use need not be limited to the specified amounts and times, but treatment schedules may vary considerably. For example, where the person already receives an antiviral medication (e. g., protease inhibitor cocktail, RT-inhibitor, etc.), lower dosages or less frequent administrations are

contemplated, while in cases where the person does not receive another antiviral treatment, higher dosages and more frequent administrations are contemplated. It is also contemplated that the antiviral composition may be employed in a preventative fashion, i. e., the antiviral composition may be employed in a person that is not infected with a virus.

It is still further contemplated that the compositions according to the inventive subject matter may have advantageous properties and uses in therapeutic applications other than antiviral activity, especially where the chelating agent is a substance other than EDTA, and particularly contemplated uses include heavy metal detoxification in animal and human, and reduction of atherosclerotic plaque.

With respect to heavy metal detoxification in animal and human, it is known in the art that upon oral administration or injection EDTA complexes various metals and heavy metals other than Ca2+, and oral administration or injection of EDTA has therefore found widespread use in detoxifycation of some heavy metal poisonings. Various alternative oral or injectable chelation agents for heavy metals have also been described [e. g., Llobet, J. M. et al. Arch. Environ Contam. Toxicol. 1990,19 (2): 185-9; Treatment of acute lead intoxication. A quantitative comparison of a number of chelating agents.

Llobet, J. M. et al. Arch. Toxicol. 1988,61 (4): 321-3; Antidotes for zinc intoxication in mice] and include oral and injectable forms of penicillamine, 2,3-dimercaptosuccinic acid, and 2,3-dimercapto-1-propanesulfonate. However, it is not known to the inventors that chelators other than EDTA have been used for detoxification of heavy metals in animal and human via rectal administration. Rectal administration is particularly advantageous for various reasons. For example, suppositories can be self-administered by al most all patients. Furthermore, rectal administration inflicts only relatively low discomfort to the patient. Moreover, rectal administration bypasses the stomach, a highly acidic environment that may lead to at least partial destruction of some of the chelating agents.

Therefore, it is contemplated that rectal administration of chelating agents may also be employed in a method to reduce a heavy metal concentration in a subject, wherein in one step a chelating agent is provided that chelates a metal ion, wherein the chelating agent is formulated in a rectal deposition formulation and wherein the supply of chelating agent has an immediate bioavailability. Alternatively, the rectal deposition formulation may further comprise a time release agent to release the chelating agent in a period of between 0-30min, 30-60min, 60-120min, 120-180min, or longer. In another step, the chelating agent is rectally administered to the subject in a concentration effective to reduce the heavy metal ion concentration.

It is generally contemplated that the heavy metal may be in elemental or ionic form, and particularly contemplated heavy metals include mercury, Zn2+, Cu+, Cd2+, and Co2+. However, various alternative metals and their ionic forms are also contemplated, including nickel, arsenic, selenium, iron, mercury, chromium, antimony, beryllium, thallium, silver, scandium, titanium, vanadium, chromium, manganese, etc. While it is generally contemplated that all known chelating agents may be suitable for reduction of heavy metals in a subject, it is particularly preferred that the chelating agent comprises a plurality of carboxylic acid groups and it is even more preferred that the chelating agent is EDTA, EGTA, CDTA, or DTPA. With respect to the rectal deposition formulation the same considerations as already described above apply.

An exemplary method of reducing a heavy metal concentration in a subject may therefore comprise a single rectal administration of 20ml of a l Omg/ml buffered aqueous solution of CDTA three times daily over a period of about 15-20 days. It should be recognized, however, that depending on the particular heavy metal, the site of accumulation, and the concentration of the heavy metal in the subject many treatment schedules other than a single rectal administration of 20ml of a l Omg/ml buffered aqueous solu- tion of CDTA three times daily over a period of about 15-20 days are also appropriate.

For example, where treatment is prophylactic or necessitated by relatively low concentrations of a heavy metal, total daily dosages of less than 600mg are contemplated, including total daily dosages of 200-600mg, 50-200mg, and less that 50mg.

Likewise, where acute and/or severe heavy metal intoxications are to be treated by a method according to the inventive subject matter, higher total daily dosages of more than 600mg are contemplated, including total daily dosages of 600-1500mg, 15002500mg, and more than 2500mg. With respect to the formulation it should be appreciated that numerous alternative formulations are also appropriate, and contemplated alternative formulations include the formulations already described above. Similarly, it should be appreciated that various alternative administration periods other than a period of about 15-20 days are also appropriate, including single administrations in cases where treatment is prophylactic, or administration over a period of less than 15 days, where the heavy metal concentration is relatively low. On the other hand, where the heavy metal is predominantly is tissues that bind the heavy metal relatively firmly (e. g. lipophilic tissue) administrations of 2-6 weeks and longer are contemplated.

With respect atherosclerotic plaques it is contemplated that rectal administration of chelating agents may also be employed in a method to reduce a atherosclerotic plaques in a subject, wherein in one step a chelating agent is provided that chelates an alkaline earth metal ion, wherein the chelating agent is formulated in a rectal deposition formulation and wherein the supply of chelating agent has an immediate bioavailability.

In another step, the chelating agent is rectally administered to the subject in a concentration effective to reduce the atherosclerotic plaque in a subject. As used herein, the term "reducing the atherosclerotic plaque"refers to a gross reduction in size and/or volume of one or more atherosclerotic plaques, which may also include complete disappearance of the atherosclerotic plaque or plaques.

In an exemplary method of reducing atherosclerotic plaque, a person diagnosed with atherosclerotic plaques receives once daily an enema of 10ml of a 50mg/ml solution of EGTA in 1 OmM sodium phosphate buffer pH8.4 for a period of about 12 weeks.

However, it should be appreciated that the exemplary method need not be limited to the specified amounts and times, and formulation and treatment schedules may vary considerably. For example, where the person already underwent a vasodilation procedure, lower dosages or less frequent administrations are contemplated, while in cases where the person did not receive previous treatment to reduce the atherosclerotic plaques, higher dosages and more frequent administrations are contemplated.

Likewise, the chelating agent need not be limited to EGTA, but may be various alternative chelating agents including EDTA, CDTA, and DTPA, wherein the choice of the chelating agent will predominantly depend on the desired specificity of the chelator and the tolerability

at a particular concentration. Furthermore, the formulation of the chelating agent need not be restricted to 1 Oml of a 50mg/ml solution of EGTA in 1 OmM sodium phosphate buffer pH8.4. For example, alternative formulations may be employed to achieve a larger distribution, faster absorbption, etc., and appropriate formulations include those already described above.

Thus, specific embodiments and applications of antiviral compositions have been disclosed. It should be apparent, however, to those skilled in the art that many more modifications besides those already described are possible without departing from the inventive concepts herein. For example, the route of administration need not necessarily be restricted to a rectal administration of the chelating agent, but may also include vaginal administration. The inventive subject matter, therefore, is not to be restricted except in the spirit of the appended claims. Moreover, in interpreting both the specification and the claims, all terms should be interpreted in the broadest possible manner consistent with the context. In particular, the terms"comprises"and"comprising"should be interpreted as referring to elements, components, or steps in a non-exclusive manner, indicating that the referenced elements, components, or steps may be present, or utilized, or combined with other elements, components, or steps that are not expressly referenced.
