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(54) Title: NON-TOXIC ANTIMICROBIAL COMPOSITIONS AND METHODS USING PRO-OXIDATIVE POLYPHENOLS AND ANTIOXIDANTS

(57) Abstract: An antimicrobial, antiviral and antipathogenic composition which combines, in various forms, a redox active polyphenol, an oxidizing agent and a redox-active, transition metal ion. The composition relates to methods for decreasing or eliminating the infectivity, morbidity, and rate of mortality associated with a variety of pathogenic organisms and viruses. The present invention also relates to methods and compositions for treating the HIV virus and cancer caused by pathogenic organisms and for decontaminating areas colonized or otherwise infected by pathogenic organisms and viruses. Moreover, the present invention relates to methods and compositions for decreasing the infectivity of pathogenic organisms in pharmaceuticals, medical devices, personal care products, recreational products and foodstuffs.

NON-TOXIC ANTIMICROBIAL COMPOSITIONS AND METHODS USING PRO-OXIDATIVE POLYPHENOLS AND ANTIOXIDANTS

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FIELD OF THE INVENTION

The present invention relates to compositions and methods for treating cancer and diseases caused by pathogenic organisms and for decreasing the infectivity, morbidity, and rate of mortality associated with a variety of pathogens. The compositions result in said therapeutic benefit through pro-oxidation of polyphenols and antioxidants. Once oxidized, the compositions will become antibacterial, antifungal, antiviral and anticancer agents.

BACKGROUND OF THE INVENTION

Pathogens such as bacteria, fungi and viruses are responsible for a plethora of human and animal ills, as well as contamination of food and biological and environmental samples. The first step in microbial infections of animals is generally attachment or colonization of skin or mucus membranes, followed by subsequent invasion and dissemination of the infectious microbe. The portals of entry of pathogenic bacteria are predominantly the skin and mucus membranes.

Members of the Bacillus genus are also reported to be etiological agents for many human diseases. Bacillus cereus is a common pathogen. It is involved in food borne diseases due to the ability of the spores to survive cooking procedures. It is also associated with local sepsis and wound and systemic infection (See e.g., Drobniewski, Clin. Micro. Rev. 6:324 [1993]). Many bacteria readily develop resistance to antibiotics.

An organism infected with an antibiotic-resistant strain of bacteria faces serious and potentially life-threatening consequences.

Examples of bacteria that develop resistance include Staphylococcus that often cause fatal infections, Pneumococci that cause pneumonia and meningitis; Salmonella and E. coli that cause diarrhea; and Enterococci that cause blood-stream, surgical wound and urinary tract infections (See e.g., Berkelman et. al., J. Infcet. Dis. 170(2):272 [1994]).

Although an invaluable advance, antibiotic and antimicrobial therapy suffers from several problems, particularly when strains of various bacteria appear that are resistant to antibiotics. In addition, disinfectants/biocides (e.g., sodium hypochlorite, formaldehyde and phenols) that are highly effective against Bacillus spores are not well suited for decontamination of the environment, equipment, or patients. This is due to toxicity that leads to tissue necrosis and severe pulmonary injury following inhalation of volatile fumes. The corrosive nature of these compounds also renders them unsuitable for decontamination of sensitive equipment (See e.g., Alasri et al., Can. J. Micro. 39:52 [1993]; Beauchamp et al., Crit. Rev. Tox. 22:143 [1992]; Hess et al., Amer. J. dent. 4:51 [1991]; Lineaweaver et al., Arch. Surg. 120:267 [1985]; Morgan, Tox. Path. 25:291 [1997]; and Russell, Clin. Micro. 3;99 [1990]).

Influenza A virus is a common respirator pathogen that is widely used as a model system to test antiviral agents in vitro (See e.g., Karaivanova and Spiro, Biochem. J. 329:511 [1998]; Mammen et al., J. Med. Chem. 38:4179 [1995]; and Huang et al., FEBS Letters 291:199 [1991]), and in vivo (See e.g., Waghorn and Goa, Drugs 55:721 [1998]; Mendel et al., Antimicrob. Agents Chemother. 42:640 [1998]; and Smith et al., J. med. Chem. 41:787 [1998]). The envelope glycoproteins, hemagglutinin (HA) and neuraminidase (NA), which determine the antigenic specificity of viral subtypes, are able to readily mutate, allowing the virus to evade neutralizing antibodies. Current anti-viral compounds and neuraminidase inhibitors are minimally effective and viral resistance is common.

Plants have an almost limitless ability to synthesize aromatic substances, most of which are phenols or their oxygen-substituted derivatives. In many cases these, substances serve as plant defense mechanisms against predation by microorganisms,

insects and herbivores. Some such as terpenoids, give plants their odors; others, quinines and tannins, are responsible for plant flavor, and some of the same herbs and spices used by humans to season food yield useful medicinal compounds. Antioxidant properties of herbs have uses for anti-inflammatory and cancer prevention therapies, whereas pro-oxidant characteristics have found use for antibacterial, antiviral and cancer treatments.

Pro-oxidants (oxidizers) are molecules that have been oxidized. Such molecules are redox active, which signifies the oxidation of the reduced form of the molecule, resulting in its pro-oxidant state. They can be reduced in the body, thus causing oxidation of nearby molecules and molecular damage. Pro-oxidants can be monitored using protein damage and antibiotic panels. HIV-AIDS, cancer chemotherapy, autoimmune diseases and smoking create increased level of oxidative stress and cellular damage. Antibiotic, antiviral and anticancer products are all redox active compounds, including free radical species initiated during administration. Vitamin C has been shown to be a pro-oxidant under elevated temperature conditions such as fever.

Phenolic compounds are antioxidants (reducers) in that they contain redox active molecules in reduced form. They can be subject to oxidation, the loss of an electron, forming free radicals and ultimately quinones. Thus, during their own oxidation they reduce biological substrates and protect them. Phenolic molecules behave as antioxidants in the reduced form and often pro-oxidants in the oxidized phenolic radical and quinine forms.

Some of the simplest bioactive phytochemicals consist of a single substituted phenolic ring. The major representative classes of phenolics include cinnamic acids, flavones, flavanones, isoflavones, flavan-3-ols, coumarins and chalcones.
Other classes of redox active molecules are: simple phenolic acids, azo dyes, extensively conjugated phenolics, unsaturated fatty acids, and tocopherols & retinols. Additional redox active compounds falling under the above major categories include, but are not limited to, phenolics, such as cinnamic acids (e.g., caffeic acid, caffeoyltartaric acid, caftaric acid, chlorogenic acid, rosmaric acid), flavones (e.g., baicalein), flavanones (e.g., exiguaflavanone B, exiguaflavanone D), isoflavones (e.g., genistin, daidzin, glycetin, genistein, daidzein, glycetein, formononetin, equol), flavan-3-ols (e.g., anthocyanidins,

anthocyanins, catechin, epigallocatechin, epigallocatechin gallate, epicatechin gallate), coumarins (e.g., p-coumaric acid, isocoumarin, aesculetin), chalcones (e.g., butein), and otheres such as simple phenolic acids (e.g., ascorbate, p-hydroxybenzoic acid and other benzoic acid derivatives, gallic acid), azo dyes (e.g., azostilbenes), extensively conjugated phenolics (e.g., anthroaquinones, hypericin and other naphthodianthrones), unsaturated fatty acids (e.g., sorbates), and tocopherols and retinols (e.g., tocopherols, tocotrienols, retinols, beta-carotene).

Cinnamic acid and caffeic acids are common representatives of a wide group of phenylpropane derived compounds which are in the highest oxidation state. The common herbs tarragon and thyme both contain caffeic acid, which is effective against viruses, bacteria and fungi. Catechol and pyrogallol both are hydroxylated phenols, shown to be toxic to microorganisms. Catechol has two OH groups, and pyrogallol has three. The sites and number of hydroxyl groups on the phenol groups are thought to be related to their relative toxicity to microorganisms, with evidence that the number and location of phenolic or hydroxyl groups increased toxicity. Thus, phenols that are more highly oxidized would be expected to exhibit a greater toxicity to microorganisms. The mechanisms thought to be responsible for phenolic toxicity to microorganisms, include enzyme inhibition by the oxidized compounds, possibly through reaction with sulfhydryl groups or through more nonspecific interactions with the proteins.

The sympathetic nervous system neurotransmitters, epinephrine and nor-epinephrine are both catechols and many of the neurotransmitters and homeostatic transmitter hormones are hydroxylated ring structures, including serotonin in the brain. Many of the synthetic molecules were specifically synthesized to compete with or mimic these naturally occurring compounds. The homeostatic actions of such transmitters occurring naturally or affected by administrated drugs may also be influenced by redox state.

Phenolic compounds possessing a C_3 side chain at a lower level of oxidation are classified as essential oils and often cited as antimicrobial. Eugenol is a well-characterized representative found in clove oil. Eugenol is considered bacteriostatic against both fungi and bacteria.

Quinones are aromatic rings with ketone substitutions. They are the oxidation products of phenols. They are ubiquitous in nature and are characteristically highly reactive, oxidizing other molecules to return to their reduced phenolic state. The phenol can then be oxidized again, returning to the quinone state. This repeated oxidation/reduction of a compound is called redox cycling. The switch between diphenol, hydroquinone and diketone or quinine occurs easily through oxidation and reduction reactions. The individual redox potential of the particular quinine-hydroquinone pair is very important in many biological systems and may be related to antibiotic efficacy and selectivity. Vitamin K is a complex napththoquinone. Its antihemorrhagic activity may be related to its ease of oxidation in body tissue. In addition to providing a source of stable free radicals, quinones are known to complex irreversibly with nucleophilic amino acids in proteins, often leading to inactivation of the protein and loss of function.

Flavones are phenolic structures containing one carbonyl group as opposed to the two carbonyls in quinines. The addition of a 3-hydroxyl group yields a flavonol. Flavonoids are also hydroxylated phenolic substances but occur as a C_6-C_3 unit linked to an aromatic ring. Since they are known to be synthesized by plants in response to microbial infection, it should not be surprising that they have been found in vitro to be effective antimicrobial substances against a wide array of microorganisms. Their activity is probably due to their ability to complex with extracellular and soluble proteins and to complex with bacterial cell walls, similar to the mechanism of quinines antimicrobial activity. Flavonoid compounds exhibit inhibitory effects against multiple viruses, particularly in the oxidized form. Delineation of the possible mechanism of action of flavones and flavonoids is hampered by conflicting findings. Flavonoids lacking hydroxyl groups on their β-rings are more active against microorganisms than are those with the –OH groups. This finding supports the idea that their microbial target is the membrane. Lipophilic compounds would be more disruptive of this structure. However, several authors have also found the opposite effect; i.e., the more hydroxylation, the greater the antimicrobial activity. It is safe to say that there is no clear predictability for the degree of hydroxylation and toxicity to microorganisms.

The fragrance of plants is carried in the so called quinta essential, or essential oil fraction. These oils are secondary metabolites that are highly enriched in compounds based on an isoprene. They are called terpenes, their general chemical structure is $C_{30}H_{16}$, and they occur as diterpenes, triterpenes, and tetraterpenes (C_{20}, C_{30} and C_{40}), as well as hemiterpenes (C_5) and sesquiterpenes(C_{15}). When the compounds contain additional elements, usually oxygen, they are termed terpenoids.

Terpenoids are synthesized from acetate units, and as such they share their origins with fatty acids. They differ from fatty acids in that they contain extensive branching and are cyclized. Examples of common terpenoids are methanol, and camphor (monoterpenes) and farnesol ant artemsin (sesquiterpenes). Terpenes or terpenoids are active against bacteria and protozoa. In 1977, it was reported that 60% of essential oil derivatives examined to date were inhibitory to fungi while 30% inhibited bacteria. The mechanism of action of terpenes is not fully understood but is speculated to involve membrane disruption by the lipophilic compounds.

Chili peppers are a food item found nearly ubiquitously in many Mesoamerican cultures. Their use may reflect more than a desire to flavor foods. A flavonoid constituent, capsaicin, has a wide range of biological activities in humans, affecting the nervous, cardiovascular, and digestive systems as well as finding use as an analgesic. The evidence for its antimicrobial activity is mixed. Recently, Cichewicz and Thorpe found that capsaicin might enhance the growth of Candida albicans but that it clearly inhibited various bacteria to differing extents.

Clearly, antipathogenic compositions and methods that decrease the infectivity, morbidity, and mortality associated with pathogenic exposure are needed. Such compositions and methods should preferably not have the undesirable properties of promoting microbial resistance, or of being toxic to the recipient. As a result, a need exists, in a variety of industries, for a product that provides no detectable toxicity or irritation to plant or animal life, while at the same time displaying efficacy for targeted antimicrobial and antipathogenic effects.

SUMMARY OF THE INVENTION

The present invention relates to compositions and methods for treating disease caused by pathogenic organisms and for decreasing the infectivity, morbidity, and rate of mortality associated with a variety of pathogens. The present invention also relates to methods and compositions for decontaminating areas, samples, solutions, and foodstuffs colonized or otherwise infected by pathogens and microorganisms. Certain embodiments of the present compositions are nontoxic and may be safely ingested by humans and other animals. Additionally, certain embodiments of the present invention are chemically stable and non-staining. This invention also encompasses polyphenols and antioxidants, which once oxidized could become antibacterial, antifungal and antiviral/anticancer agents.

As used herein the term "disease" refers to a deviation from the condition regarded as normal or average for members of a species, and which is detrimental to an affected individual under conditions that are not inimical to the majority of individuals of that species (e.g., diarrhea, nausea, fever, pain, and inflammation etc). A disease may be caused or result from contact by microorganisms and/or pathogens.

As used herein the term "microorganism" refers to microscopic organisms and taxonomically related macroscopic organisms within the categories of algae, bacteria, fungi (including lichens), protozoa, viruses, and sub-viral agents. The term microorganism encompasses both those organisms that are in and of themselves pathogenic to another organism (e.g., animals, including humans, and plants) and those organisms that produce agents that are pathogenic to another organism, while the organism itself is not directly pathogenic or infective to the other organism. As used herein the term "pathogen," and grammatical equivalents, refers to an organism, including microorganisms, that causes disease in another organism (e.g., animals and plants) by directly infecting the other organism, or by producing agents that causes disease in another organism (e.g., bacteria that produce pathogenic toxins and the like).

In some embodiments, the present invention provides compositions and methods suitable for treating animals, including humans, exposed to pathogens or the threat of pathogens. In some embodiments, the animal is contacted with effective amounts of the compositions prior to exposure to pathogenic organisms. In other embodiments, the animal is contacted with effective amounts of the compositions after exposure to

pathogenic organisms. Thus, the present invention contemplates both the prevention and treatment of microbiological infections.

As used herein, the term "sample" is used in its broadest sense. In one sense it can refer to animal cells or tissues. In another sense, it is meant to include a specimen or culture obtained from any source, such as biological and environmental samples. Biological samples may be obtained from plants or animals (including humans) and encompass fluids, solids, tissues, and gases. Environmental samples include environmental material such as surface matter, soil, water, and industrial samples. These examples are not to be construed as limiting the sample types applicable to the present invention.

As used herein the term "polyphenol" which is short for polyhydroxy phenol refers to a compound with the characteristic six-carbon aromatic ring which has more than one ("poly") of the –OH groups (also known as hydroxyl groups) attached to it, particularly in ortho and para positions to one another.

In other embodiments, the present invention provides compositions-and methods suitable for decontaminating solutions and surfaces, including organic and inorganic samples that are exposed to pathogens or suspected of containing pathogens. In still other embodiments of the present invention, the compositions are used as additives to prevent the growth of harmful or undesired microorganisms in biological and environmental samples.

As used herein the term "composition" refers to any oil-in-water emulsion, water-in-oil emulsion, suspension, gel, lotion, ointment, powdered formulation, aqueous or non-aqueous solution or other suitable delivery vehicle.

As used herein, the term "surface" is used in its broadest sense. In one sense, the term refers to the outermost boundaries of an organism or inanimate object (e.g., vehicles, buildings, and food processing equipment, etc.) that are capable of being contacted by the compositions of the present invention (e.g., for animals: the skin, hair, and fur, etc., and for plants: the leaves, stems, flowering parts, and fruiting bodies, etc.). In another sense, the term also refers to the inner membranes and surfaces of animals and plants (e.g., for animals: the digestive tract, vascular tissues, and the like, and for plants:

the vascular tissues, etc.) capable of being contacted by compositions by any of a number of transdermal delivery routes (e.g., injection, ingestion, transdermal delivery, inhalation, and the like).

In specific embodiments, the contacting is performed for a time sufficient to kill the pathogenic agent or to inhibit the growth of the agent. In other embodiments, the present invention provides a method of decontaminating an environmental surface harboring harmful or undesired pathogens. In one such embodiment, the pathogenic agent is associated with an environmental surface and the method comprises contacting the environmental surface with an amount of the composition sufficient for decontaminating the surface. While it may be so desired, decontamination need not result in total elimination of the pathogen. In some embodiments, the compositions and methods further comprise dyes, paints, and other marking and identification compounds to as to ensure that a treated surface has been sufficiently treated with the compositions of the present invention.

In certain embodiments, an animal is treated internally with a composition of the present invention. In some preferred embodiments, the contacting is via intradermal, subcutaneous, intramuscular or intraperitoneal injection. In other embodiments, the contacting is via oral, nasal, buccal, rectal, vaginal or topical administration. When the present compositions are administered as pharmaceuticals, it is contemplated that the compositions further comprise pharmaceutically acceptable adjutants, excipients, stabilizers, diluents, and the like. In still further embodiments, the present invention contemplates compositions further comprising additional pharmaceutically acceptable bioactive molecules (e.g., antibodies, antibiotics, means for nucleic acid transfection, vitamins, minerals, co-factors, etc.).

As used herein, the term "topical" refers to application of the compositions of the present invention to the surface of the skin and mucosal cells and tissues (e.g., alveolar, buccal, lingual, masticatory, or nasal mucosa, and other tissues and cells which line hollow organs or body cavities).

As used herein the terms "pharmaceutically acceptable" or "pharmacologically acceptable," as used herein, refer to compositions that do not substantially produce

adverse allergic or immunological reactions when administered to a host (e.g., an animal or a human). Moreover, in certain embodiments, the compositions of the present invention may be formulated for horticultural or agricultural use. Such formulations include dips, sprays, seed dressings, stem injections, sprays, and mists. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, wetting agents (e.g., sodium lauryl sulfate), isotonic and absorption delaying agents, distringants (e.g., potato starch or sodium starch glycolate), and the like. As used herein the term "phenol" refers to an aromatic ring of six carbon atoms with at least one –OH group attached.

The present invention also provides non-toxic, non-irritant compositions comprising a redox active polyphenolic or antioxidant in the presence of atmospheric oxygen and/or an oxidizing agent in the presence of a redox-active transition metal ion (catalyst), wherein said composition is antimicrobial against bacteria, fungi or viruses. In some preferred embodiments, the composition has no detectable toxicity to plants or animals (e.g., to humans). In other preferred embodiments, the composition causes no detectable irritation to plants or animals (e.g., to humans). In some embodiments, the composition further comprises any of the components described below. A redox active polyphenol or antioxidant, including but not limited to Vitamin E, coenzyme Q, uric acid, carotenoids, glutathione, Vitamin A, flavonoids, phenols or polyphenols including those contained in the herbs Aloe, Anise, Barberry, Bayberry, Bitter Melon, Black Elder, Black Pepper, Bloodroot, Blue Cohosh, Burdock, Camphor Tree, Capsicum Pepper, Caraway, Chamomile, Cinnamon, Clove, Coltsfoot, Cypress, Dill, Eucalyptus, Eyebright, Fennel, Feverfew, Ginger, Goldenseal, Horseradish, Lemon Balm, Lentinan, Licorice, Maitake, Marigold, Mistoletoe, Myrrh, Nettles, Oak Bark, Oregano, Pau d'arco, Peppermint, Soap bark, Spruce, Tea Tree Oil, Thistle, White Horehound, Wild Indigo, Wintergreen, Witch Hazel, Wormwood and Woundwart, herbal antioxidants including but not limited to Cat's Claw, Sage, Chaparral, Cranberry, Echinacea, Garlic, Ginkgo, Grape Seed Extract, Green Tea, Plantain, Propolis, Rosemary, St. John's Wort, Tumeric, Uva Ursi, Yarrow and Pine Bark Extract, melatonin and aminoindoles and α-lipoic acid in the presence of atmospheric oxygen, UV light and/or an oxidizing agent including but not limited to a

superoxide radical, hydroxyl radical, ozone, hydrogen peroxide, nitric oxide, nitrogen dioxide, pernitric acid and hypochlorous acid and may also require a redox-active or divalent transition metal ion (catalyst) including but not limited to Ca, Cu, Fe, Zn, or Ag and/or applied electrical potentials, electromagnetic fields, sonic energy and other applied energy fields alone or in combination.

The present invention further provides methods for protecting (e.g., protecting from contamination of a microorganism) or decontaminating an area or product (e.g., decontaminating an area by removing or reducing the number of microorganisms in the area) comprising exposing the area to any of the compositions described herein. The method may be applied to any type of area or composition. For example, in some embodiments, the area comprises a solid surface (e.g., a medical device), a solution, the surface of an organism (e.g., an external or internal portion of a human), or a pharmaceutical or food product.

As used herein, the term "medical devices" includes any material or device that is used on, in, or through a patient's body in the course of medical treatment (e.g., for a disease or injury). Medical devices include, but are not limited to, such items as medical implants, wound care devices, wound dressings, drug delivery devices, and body cavity and personal protection devices. The medical implants include, but are not limited to, urinary catheters, intravascular catheters, dialysis shunts, wound drain tubes, skin sutures, vascular grafts, implantable meshes, intraocular devices, heart valves, and the like. Wound care devices include, but are not limited to, general wound dressings, biologic graft materials, tape closures and dressings, and surgical incise drapes. Drug delivery devices include, but are not limited to, needles, drug delivery skin patches, drug delivery mucosal patches and medical sponges. Body cavity and personal protection devices, include, but are not limited to, tampons, sponges, surgical and examination gloves, and toothbrushes. Birth control devices include, but are not limited to, intrauterine devices (IUDs), diaphragms, and condoms. The present invention also provides methods for modifying any of the compositions described herein, and any existing composition currently used in commerce by adding or removing a component to produce a modified composition. By incorporating the present invention into a composition the amount of

chemical preservatives or other components can be reduced. In some embodiments, the method further comprises the step of testing the modified composition in a biological assay (e.g., an antimicrobial assay to determine the effectiveness of the composition at reducing the amount of microorganisms associated with a treated area or a product). The present invention also contemplates methods of using such modified compositions in commerce.

As used herein the term "solution" refers to an aqueous or non-aqueous mixture.

Another aspect of the invention is directed to a non-toxic method for sanitizing and/or removing algae from water in aquariums, fountains, swimming pools, spas or hot tubs wherein the level of bacteria and/or algae is lowered comprising treating said water with a bactericidal and/or algicidal effective amount of the combination of redox active polyphenolic in the presence of atmospheric oxygen and/or an oxidizing agent in the presence of a redox-active transition metal ion or with applied electrical potentials. Applied electrical potentials can also be used for preservation of drug treatments, analytical standards and manufacturing process intermediates. Many biologically significant compounds are redox active and often subject to oxidation and/or reduction reactions. These compounds can degrade during storage, and some compounds are only stable for a matter of hours in solution, such as vitamin C. These compounds can be protected from oxidation by application of a suitable electrical potential to the solution. This technology could also be used to redox adjust a medicine or formulation immediately prior to administration or at the end of a manufacturing process to produce a desired redox state of a redox-cycling polyphenolic.

As used herein the term “redox state” or “redox potential” means the measure of the tendency of a solution to give up or take up electrons (i.e., to be oxidized or reduced, respectively). The redox potential may also be described as the electron pressure that the electrochemical cell exerts. The redox potential when all components are in their standard states, is called the standard redox potential. The redox potential (eh) is measured electrochemically and expressed in units of electrical potential difference (i.e., volts). As the number of volts increases, there is a higher concentration of oxidant to reductant in solution, and vice versa.

Redox directed drug discovery/synthesis and overcoming antibiotic resistance are two examples where application of this technology can demonstrate significant benefits. Careful placement of electron withdrawing and electron donating substitutions into the polyphenolic compounds, as well as other structural modifications affecting redox potential, can adjust the redox potential of the resulting molecules in predictable ways. Synthetic substitutions to new and existing, antibiotic compounds could be used to carefully manipulate several analogs of a parent compound, each with a slightly different redox potential. Adjustment of the redox potential may yield new clues into efficacy and modes of action for antibiotic/anticancer compounds.

In order to provide compounds in a desired redox state, the redox potential of a given compound can be measured and adjusted and maintained throughout any step including processing, storage and administration. The redox potential, which indicates the level of oxidizing or reducing power of a compound, is fixed and determined by its structure and atoms. However the degree of oxidation of the population of molecules can be adjusted as necessary by adding appropriate amounts of a pH modifying agents, low level transition metal ions, phosphate or carbonate buffers, or applied voltages to correct any variation and maintain the desired redox potential of the compound. It is known in the art, for example, that acidic conditions protect phenolics from oxidation while basic conditions promote oxidation.

DETAILED DESCRIPTION OF THE INVENTION

The principle that governs the embodiment of this invention is hereinafter called the "Active Component System". The "Active Component System" comprises any redox active phenol, polyphenol, antioxidant or combination and/or any oxidizing agent and/or any redox-active transition metal ion which acts as a catalyst or any combination thereof. Redox active phenol, polyphenol or antioxidant including but not limited to Vitamin E, coenzyme Q, uric acid, carotenoids, glutathione, Vitamin A, flavonoids, phenols or polyphenols including but not limited to those contained in the herbs Aloe, Anise, Barberry, Bayberry, Bitter Melon, Black Elder, Black Pepper, Bloodroot, Blue Cohosh, Burdock, Camphor Tree, capsicum pepper, caraway, Chamomile, Cinnamon, Clove,

Coltsfoot, Cypress, Dill, Eucalyptus, Eyebright, Fennel, Feverfew, Ginger, Goldenseal, Horseradish, Lemon Balm, Lentinan, Licorice, Maitake, Marigold, Mistoletoe, Myrrh, Nettles, Oak Bark, Oregano, Pau d'arco, Peppermint, Soap bark, Spruce, Tea Tree Oil, Thistle, White Horehound, Wild Indigo, Wintergreen, Witch Hazel, Wormwood and Woundwart, herbal antioxidants including but not limited to Cat's Claw, Sage, Chaparral, Cranberry, Echinacea, Garlic, Ginkgo, Grape Seed Extract, Green Tea, Plantain, Propolis, Rosemary, St. John's Wort, Tumeric, Uva Ursi, Yarrow and Pine Bark Extract, melatonin and aminoindoles or a-lipoic acid ascorbic acid, ascorbic acid derivative, ascorbic acid salt or ascorbyl palmitate are contemplated for use in the present invention.

The potential "Active Component Systems" that are antibacterial and/or antifungal and/or antiviral and/or anti-cancer are numerous. As used herein the term "active component system" refers to any combination of phenolics, polyphenolics and/or antioxidants and/or any oxidizing agent and/or any redox-active transition metal ion creating a formulation that has polyphenolics et al in oxidized forms (quinones) prepared to oxidize bacteria et al while being reduced themselves. In the presence of transition metal catalysts these reduced phenolic forms can then oxidize again to form the quinone and repeatedly cycle through these forms maintaining free radical concentrations and antibiotic efficacy.

As used herein the term "redox active" means any compound or molecule in the reduced form that can be oxidized to form the pro-oxidant form.

As used herein the term "antioxidant" refers to any compound that is subject to oxidation (loss of an electron) by reacting with free radicals, through metal chelation, and by scavenging singlet oxygen among others.

As used herein, the term "oxidizing agent" refers to any compound that has the ability, through chemical reaction with another, to effectuate the loss of electrons. This can also include applied energy such as light, electrical potential and/or electromagnetic fields that promote oxidation.

As used herein the term "flavonoid" means a group of polyphenolic compounds which includes the anthocyanidins, anthocyanins, aurones, chalcones, flavanols, flavanones, flavones, flavonols, isoflavones or proanthocyanidins.

It is well understood by those experienced in the art that antioxidants function as free radical scavengers to prevent a composition's deterioration by oxygen and/or other reactive compounds. Antioxidants are presently incorporated into compositions in minute quantities (usually below 0.01 % by weight) to prevent the oxidation of plant and animal oils thereby extending a product's shelf life. It is also currently understood that antioxidants by themselves provide no antibacterial, antifungal or antiviral properties. Antioxidants are always used in conjunction with chemical preservatives or other processes, i.e. heat, radiation, to prevent microbiological degradation. Antioxidants and antimicrobial chemical preservatives act independently of each other. Antioxidants do not function indefinitely, but rather are used up and destroyed in the process to form the pro-oxidant form. Antioxidants can also participate in a repeated oxidation/reduction of a compound during free radical reactions, a process called "redox cycling".

As used herein the term "redox cycling" refers to the repeated oxidation/reduction of a compound during free radical reactions. The ability of a redox active compound to be oxidized, reduced again, and oxidized again, etc., allows the compound to create more free radicals than one per compound and be "recycled" at the site. Many redox active compounds are destroyed by oxidation and cannot be recovered or used as a pro-oxidant reactive intermediate. Redox cycling requires extensive conjugation and the associated stability or the resulting free radical. An example would be phenol to quinone to phenol to quinone, with each reaction contributing to the propagation of the overall free radical reaction. Quercetin, a flavonoid with demonstrated antibacterial and antiviral activity, can undergo redox cycling reactions and not be consumed by the oxidations as illustrated in figure 3 below.

Although some phenols and polyphenols in their nonoxidized form have been found to be antibacterial and/or antifungal and/or antiviral, the present invention covers the oxidized or pro-oxidant form of these compounds individually or in combination. In addition, this invention proposes that polyphenols and antioxidants, which once oxidized, have the potential to show antibacterial, antifungal and antiviral/anticancer properties.

The use levels for phenols, polyphenols and antioxidants in pharmaceutical, medical device, personal care, foodstuff and other products is typically less than 0.2

weight %. For many compounds, at concentrations below 0.2 weight % there is minimal or no recognizable antibacterial, antifungal and antiviral activity. However, undissociated forms of some compounds, are only known to be effective in an acidic medium. They are known to be ineffective in a neutral and basic medium. Examples of these include but are not limited to Benzoic acid and Sodium Benzoate, sorbic acid, potassium sorbate, salicylic acid and methyl salicylate, possibly even acetyl salicylate. On the other hand, the oxidized form of benzoic acid and sodium benzoate are antibacterial at a pH 7 and greater, a basic medium and also effective as an antimicrobial in the acidic range. Thus the oxidized version has a broader range, acidic – basic, of antimicrobial activity.

Some existing products contain redox active phenols, polyphenols, or antioxidants or antioxidant systems greater than 0.2% by weight some even as high as 10 to 20 weight %. In all of these products the function of these active components relates to the absorption of potentially damaging free radicals or minimizing the affects of oxygen degradation. None of these products make claim to the antibacterial, antifungal or antiviral properties of the pro-oxidant redox active phenols, polyphenols, or antioxidants present in their formulation. Products that make the claims of antibacterial, antifungal or antiviral properties without documenting the approved active component responsible for being able to make these claims has invoked the principle and content of the present invention.

As used herein the term "antioxidant system" refers to any combination of two or more antioxidants.

The present invention covers the pro-oxidant forms of redox active phenols, polyphenols or antioxidants individually or in combination at use levels between 0.2% and 30% by weight and preferably between 0.5% and 12% or combined with other redox active phenols, polyphenols or antioxidants to form pro- oxidant systems that exhibit antibacterial, antifungal and antiviral activity. Combined redox active phenols, polyphenols or antioxidants at use levels between 0.1 % and 40.0 % by weight preferably between 0.5 % and 15.0 % by weight are contemplated to exhibit antibacterial, antifungal and antiviral properties but will vary depending on the composition and its application.

Concentration of the oxidizing agent should be between 0.02 % and 10.0 % by weight preferably between 0.05 % and 2.0 % by weight. Concentration of the redox active transition metal ion (catalyst) should be between 0.01 % and 5.0 % by weight and preferably between 0.05 % and 1.0 % by weight are contemplated.

The pro-oxidative reaction of the "Active Component System" will occur over time without the presence of the oxidizing agent or transition metal ion in the presence of atmospheric oxygen and UV light, however, to ensure immediate antipathogenic activity in a specific composition it is important for the pro-oxidation antioxidant state to occur quickly within the composition. If the pro-oxidative antioxidant state is slow or delayed because of environmental circumstances, i.e. low temperature or inadequate oxygen, the antibacterial and/or antifungal and/or antiviral benefits may also be delayed. In some embodiments of the present invention specific "Active Antioxidant Systems" can be identified and, once proven to exhibit antibacterial and/or antifungal and/or antiviral properties, can be isolated, concentrated and made available commercially specifically for the purposes of antibacterial and/or antifungal and/or antiviral activity.

Carbonyl-hydroxyl Interaction

One common feature of antibiotics is the carbonyl-hydroxyl interaction and the resulting configuration. When multiple aromatic rings are fused side by side, the bottom edge can be visualized as a flattened M shape. If there is a phenolic hydroxyl OH group on the bottom of one ring, then a quinine group on the bottom of the adjacent ring, one carbon removed (the bridging carbon) there is again special stability and metal cation chelation with resulting pro-oxidant free radicals. Hypericin, flavonones , flavones, and isoflavones exhibit this configuration.

Ortho-diphenolics

Aromatic compounds with phenolic OH groups in adjacent (ortho) positions exhibit enhanced stability due to resonance stabilization and intramolecular hydrogen transfer. For these reasons this feature is an automatic indication of antioxidant activity. Additionally they can be redox cycled with a reactive radical intermediate. This is one of

the primary features of antibiotic compounds. These compounds are very efficient transition metal chelators as shown below with quercetin and ascorbate. Chelation of metal cations renders them catalytically inactive, and the new complex is the redox cycling entity. Para diphenolics, with one OH group opposite the other on the ring, is also resonance stabilized, but not additionally by intramolecular hydrogen transfer.

Use of Oxidated Form of Minoxidil for Treatment of Alopecia

Another aspect of the present invention is to enhance the properties of minoxidil sulphate as a therapeutic agent to stimulate the rate of hair growth. Minoxidil is a known vasodilator. Following reports of the use of minoxidil and related compounds to stimulate hair growth, and as a treatment of male pattern alopecia, other vasodilators including "viprostol" and "diazoxide" are reported as being evaluated by others to stimulate hair growth. See U.S. Pat. Nos. 4,431,833 and 4,311,707, as well as European Patent 027,665 (published 04/29/81). Vasodilators as a general class of therapeutic agents have, so far as applicants are aware, never proven effective to grow hair on the scalp as a result of topical application thereof to bald areas. This invention relates to a method of enhancing the properties of minoxidil sulphate such that the manner in which hair growth is stimulated is improved relative to that form of minoxidil currently available.

For purposes of the present invention, we need only consider two types of hair, namely "terminal hairs" and "vellus hairs". Terminal hairs are coarse, pigmented, long hairs in which the bulb of the hair follicle is seated deep in the dermis. Vellus hairs, on the other hand, are fine, thin, non-pigmented short hairs in which the hair bulb is located superficially in the dermis. As alopecia progresses, a transition takes place in the area of approaching baldness wherein the hairs themselves are changing from the terminal to the vellus type.

Redox Directed Drug Discovery

When an isolated natural product is identified as a potential drug, synthetic analogs are created. Naturally occurring compounds are difficult to protect, synthesized analogs can be patented. Most drug discovery techniques focus on shape or symmetry, with various analogs evaluated. Redox potential could be used as a parameter for design of synthetic analogs. It would also be logical to slightly modify the redox potential of existing medications to extend patents and overcome resistant strains of bacteria etc. These ideas are based on the observation that there is selectivity based on molecule evident in antibiotic/antiviral/anticancer efficacy. This effect is considered to be redox related and best targeted with redox directed drug discovery.

The present invention comprises compositions and methods for decreasing the infectivity, morbidity, and rate of mortality associated with a variety of microbial and pathogenic organisms. The present invention also relates to methods and compositions for decontaminating areas colonized or otherwise infected by pathogenic organisms. Moreover, the present invention relates to methods and compositions for decreasing the infectivity of pathogenic organisms in foodstuffs. In preferred embodiments, decreased pathogenic organism infectivity, morbidity, and mortality are accomplished by contacting the pathogenic organism in a composition containing at least one active component or an "Active Component System". In some preferred embodiments, the compositions of the present invention are non-toxic, non-irritant, and non-corrosive, while possessing potency against a broad spectrum of microorganisms, including bacteria, fungi and viruses. Certain illustrative embodiments of the present invention are described below. The present invention is not limited to these specific embodiments. The description is provided in the following sections: I) Exemplary Compositions; II) Exemplary Formulation Techniques; III) Properties and Activities; IV) Exemplary Uses; and V) Experimental Examples.

I. Exemplary Compositions

In preferred embodiments, the emulsions of the present invention comprise (A) an

aqueous phase; (B) an oil phase; and at least one additional compound. In some embodiments of the present invention, these additional compounds are admixed into either the aqueous or oil phases of the composition. Certain exemplary embodiments of the various compounds contemplated for use in the compositions of the present invention are presented below.

Additional functional classes of ingredients suitable for use in the compositions of the present invention include but are not limited to: absorbants, abrasives, anti-acne agents, anti-caking agents, antifoaming agents, antimicrobial agents, antioxidants, binders, biological additives, buffering agents, bulking agents, chelating agents, chemical additives, colorants, cosmetic astringents, cosmetic biocides, denaturants, drug astringents, external analgesics, film formers, fragrance components, humectants, opacifying agents, pH adjusters, plasticers, preservatives, propellants, reducing agents, skin bleaching agents, skin-conditioning agents (emollient, humectants, miscellaneous, and occlusive), skin protectants, solvents, foam boosters, hydrotropes, solubilizing agents, suspending agents (nonsurfactant), sunscreen agents, ultraviolet light absorbers, and viscosity increasing agents (aqueous and nonaqueous). Examples of other functional classes of materials useful herein that are well known to one of ordinary skill in the art include emulsifiers, sequestrants, skin sensates, and the like. Nonlimiting examples of these additional components cited in the CTFA Cosmetic Ingredient Handbook, as well as other materials useful herein, include the following: vitamins; oil or sebum control agents such as clays silicones and drug actives; sunscreening agents; other silicone material such as dimethiconol, dimethicone copolyol, and amodimethicone, and the like; anti-oxidants; anti-microbial agents; preservatives; emulsifiers; polyethylene glycols and polypropylene glycols; polymers for aiding the film-forming properties and substantivity of the compositions (such as a copolymer of eicosene and vinyl pyrrolidone, an example of which is available from GAF Chemical Corporation as Ganex.RTM. V-220); preservatives for maintaining the antimicrobial integrity of the compositions; anti-acne medicaments (e.g., resorcinol, sulfur, salicylic acid, erythromycin, zinc, and the like); skin bleaching (or lightening) agents including but not limited to hydroquinone, kojic acid; chelators and sequestrants; thickening agents such as carbomers (homopolymers of

acrylic acid crosslinked with an allyl ether of pentaerythritol or an ally ether of sucrose), crosslinked and noncrosslinked nonionic and cationic polyacrylamides and mineral oil, proteins and peptides; enzymes; ceramides; aesthetic components such as fragrances, pigments, colorings, essential oils, skin senates, astringents, skin soothing agents, skin healing agents and the like, (nonlimiting examples of these aesthetic components include clove oil, menthol, camphor, eucalyptus oil, eugenol, menthyl lactate, witch hazel distillate, bisabolol, dipotassium glycyrrhizinate and the like); and skin conditioning agents such as urea and glycerol, and also the propoxylated glycerols described in U.S. Pat. No. 4,976,953, or Orr et al., issued Dec. 11, 1990.

A. Aqueous Phase

In certain preferred embodiments, the emulsion comprises about 20 % to 90 % by weight, preferably 60% to 85% by weight aqueous phase, based on the total weight of the emulsion, although higher and lower amounts are contemplated. In preferred embodiments, the aqueous phase comprises water at a pH of about 4 to 10, preferably about 6 to 8. The water is preferably de-ionized (hereinafter "DiH.sub.2O") or distilled. In some embodiments the aqueous phase comprises phosphate buffered saline (PBS). In those embodiments of the present invention intended for consumption by, or contact to, a host, the aqueous phase, and any additional compounds provided in the aqueous phase, may further be sterile and pyrogen free.

As used herein the term "emulsion," as used herein, includes classic oil-in-water or water-in-oil dispersions or droplets.

B. Oil Phase and Solvents

In certain preferred embodiments, the oil phase (e.g., carrier oil) of the emulsion of the present invention comprises 5 % - 90% by weight of oil, emulsifiers and other oil soluble ingredients based on the total weight of the emulsion, although higher and lower amounts are contemplated. Suitable oils include, but are not limited to, soybean oil, avocado oil, flaxseed oil, apricot kernal oil, grape seed oil, coconut oil, cottonseed oil, squalene oil, olive oil, canola oil, corn oil, rapeseed oil, safflower oil, sunflower oil, pine oil (e.g., 15%), Olestra oil, fish oils, flavor oils, water insoluble vitamins and mixtures thereof. In particularly preferred embodiments, soybean oil is used. Additional

contemplated oils include mineral oils, and butter. In preferred embodiments of the present invention, the oil phase is preferably distributed throughout the aqueous phase as droplets having a mean particle size in the range from about 1-2 microns, more preferably from 0.2 to 0.8, and most preferably about 0.8 microns. In other embodiments, the aqueous phase can be distributed in the oil phase.

II. Exemplary Formulation Techniques

In section A), set forth below, the present invention describes exemplary techniques for making generic formulations of the disclosed compositions.

A. Formulation Techniques

The pathogen inactivating oil-in-water emulsions of the present invention can be formed using classic emulsion forming techniques. In brief, the oil phase is mixed with the aqueous phase under relatively high shear forces (e.g., using high hydraulic and mechanical forces) to obtain an oil-in-water emulsion containing oil droplets, which are approximately 0.5 to 5 microns, preferably 1-2 microns, in diameter. The emulsion is formed by blending the oil phase with an aqueous phase on a volume-to-volume basis ranging from about 1:9 to 5:1, preferably about 5:1 to 3:1, most preferably 4:1, oil phase to aqueous phase. The oil and aqueous phases can be blended using any apparatus capable of producing shear forces sufficient to form an emulsion such as French Presses or high shear mixers (e.g., FDA approved high shear mixers are available, for example, from Admix, Inc., Manchester, N.H.). Methods of producing such emulsions are described in U.S. Pat. Nos. 5,103,497 and 4,895,452. In preferred embodiments, the compositions used in the methods of the present invention comprise droplets of an oily discontinuous phase dispersed in an aqueous continuous phase, such as water. In preferred embodiments, the compositions of the present invention are stable, and do not decompose even after long storage periods (e.g., one or more years). Certain compositions of the present invention are non-toxic and safe when swallowed, inhaled, or contacted to the skin of a host. This is in contrast to many chemical microbicides, which are known irritants. Additionally, in some embodiments, the compositions are also non-toxic to plants.

As used herein, the terms "contacted" and "exposed," refers to bringing one or more of the compositions of the present invention into contact with a pathogen or a sample to be protected against pathogens such that the compositions of the present invention may inactivate the microorganism or pathogenic agents, if present. The present invention contemplates that the disclosed compositions are contacted to the pathogens or microbial agents in sufficient volumes and/or concentrations to inactivate the pathogens or microbial agents.

As used herein the terms "host" or "subject," as used herein, refer to organisms to be treated by the compositions of the present invention. Such organisms include organisms that are exposed to, or suspected of being exposed to, one or more pathogens. Such organisms also include organisms to be treated so as to prevent undesired exposure to pathogens. Organisms include, but are not limited to animals (e.g., humans, domesticated animal species, wild animals) and plants.

The compositions of the present invention can be produced in large quantities and are stable for many months at a broad range of temperatures. Some compositions in the preferred embodiments can be diluted and sprayed to decontaminate surfaces. These properties provide a flexibility that is useful for a broad range of antimicrobial applications. Additionally, these properties make the compositions of the present invention particularly well suited to decontamination applications.

B. Additional Formulations

The specific formulations described above are simply examples to illustrate the variety of compositions that find use in the present invention. The present invention contemplates that many variations of the above formulation, as well as many additional existing emulsion formulations of many different companies, will find use in the methods of the present invention.

The candidate composition should have efficacy for its intended use. For example, an anti-bacterial composition should kill or disable bacteria to a detectable level. As shown herein, certain compositions of the present invention may have efficacy against specific microorganisms, but not against others. Using the methods described herein, one is capable of determining the suitability of a particular candidate composition

against the desired microorganism. Generally, this involves exposing the microorganism to the composition for one or more time periods in a side-by-side experiment with the appropriate control samples (e.g., a negative control such as water) and determining if, and to what degree, the composition kills or disables the microorganism.

Dry mixtures can also be formulated to allow the mixing and reaction of the active component system internally to achieve a desired oxidative condition. Alternatively, powdered or dry formulations containing the active component system can also be oxidized during processing, formulated for oxidation in a tea brewing process or formulated to become active after being ingested within the stomach. For example, compounds of the invention which contain the active component system can be coated and taken internally to provide pro-oxidative antibacterial, antiviral, antifungal and anti-cancer benefits.

No prior existing reports on inventions identical to the one outlined here were found to our knowledge. .

One of the other inventions describes adding chelators or Fe (III) complexes directly to the medium, and using Fe in the context of antitumor activity (Clinical Cancer Research (9), 402-414, 2003). This is different from present invention, which employs transition metal ion in combination with a redox active polyphenol for antimicrobial activity.

Also, the present invention uses combinations of pro-oxidant forms of redox active phenols, polyphenols or antioxidants individually or in combination with other redox active phenols, polyphenols or antioxidants to form pro- oxidant systems that exhibit antibacterial, antifungal and antiviral activity. The oxidizing agent and redox active transition metal ion are included to ensure immediate antipathogenic activity in a specific composition (i.e., pro-oxidation antioxidant state to occur quickly within the composition).

Thus it differs from other literature with similar inventions, in terms of components included in the formulation. (U.S. Patent No. 6,475,526, U.S. Patent No. 5,840,278 and US Patent No. 6,558,710).

III. Properties and Activities

The specific compositions of the present invention possess a range of beneficial activities and properties. A number of the exemplary beneficial properties and activities are set forth below: A) Microbicidal and Microbistatic Activity; B) Viricidal and Viralstatic Activity; C) Fungicidal and Fungistatic Activity and D) Anticancer Activity

A. Microbicidal and Microbistatic Activity

The methods of the present invention can be used to rapidly inactivate bacteria. In certain embodiments, the compositions are particularly effective at inactivating Gram positive and Gram negative bacteria. In preferred embodiments, the inactivation of bacteria occurs after about five to ten minutes. Thus, bacteria may be contacted with a composition according to the present invention and will be inactivated in a rapid and efficient manner. It is expected that the period of time between the contacting and inactivation may be as little as 5-10 minutes or less where the bacteria are directly exposed to the composition. However, it is understood that when the compositions of the present invention are employed in a therapeutic context and applied systemically, the inactivation may occur over a longer period of time including, but not limited to, 5, 10, 15, 20, 25, 30, 60 minutes post application. Further, in additional embodiments it may be that the inactivation may take two, three, four, five or six hours to occur.

As used herein, the term "inactivating," and grammatical equivalents, means having the ability to kill, eliminate or reduce the capacity of a pathogen to infect and/or cause a pathological responses in a host.

B. Viricidal and Viralstatic Activity

In additional embodiments, it was demonstrated that the compositions of the present invention have anti-viral properties.

C. Fungicidal and Fungistatic Activity

Yet another property of the compositions of the present invention is that they possess antifungal activity. While external fungus infections can be relatively minor, systemic fungal infections can give rise to serious medical consequences. There is an

increasing incidence of fungal infections in humans, attributable in part to an increasing number of patients having impaired immune systems. Fungal disease, particularly when systemic, can be life threatening to patients having an impaired immune system.

One of skill in the art will be able to take the formulations of the present invention and place them into appropriate formulations for the treatment of fungal disease. The compositions of the present invention find use in combating infections such as athletes' foot, candidosis and other acute or systemic fungal infections.

It is believed the present inventions also represents viable, non-toxic alternatives to the problems with existing aquarium, swimming pool and spa/hot tub bactericides, algicides and fungicides. Water in swimming pools, spas and hot tubs is constantly recirculated and fresh water is normally added only to maintain the desired volume. Although this water is usually filtered continuously to keep it free of suspended matter, it frequently contains bacteria and algae. Treatment with one or more sanitizers and/or algicides to control the bacteria count and limit algae growth is necessary. These sanitizers are all pro-oxidant formulations including oxidizers and often catalysts such as transition metals.

Numerous chemical compounds have been reported for use in swimming pools, spas, and hot tubs. These chemicals include various quaternary ammonium salts, copper salts, and oxidants such as chlorine sources or peroxy compounds such as hydrogen peroxide and potassium monopersulfate (OXONE). The use of combinations of such compounds is also known.

At the present time, the main disinfectant used in swimming pools, spas and hot tubs is chlorine. It is an effective bactericide, but suffers from two main disadvantages. One, it may cause eye irritation. Two, it has to be added at frequent intervals to maintain an effective concentration for killing bacteria.

Ozone has also been used as a disinfectant for swimming pools, spas and hot tubs. But, it also requires frequent or continuous dosing to maintain an effective concentration for killing bacteria. Also, if people come into contact with water containing high concentrations of ozone, such as where the ozone is injected into the water, they may experience unpleasant headaches and the like.

Quaternary ammonium compounds have also been reported as being useful in swimming pools, spas, and hot tubs as bacteristats, bactericides, or algaecides. Those used as bacteristats and bactericides have required relatively high levels (e.g. over 100 ppm by weight) to be effective or have required prolonged contact-times. However, at such high concentration levels, quaternary ammonium salts in general have the potential of producing objectionable, aesthetically unpleasing turbid swimming pool water having a high total organic carbon (TOC) content. Furthermore, such high concentrations of quaternary ammonium salts may increase the likelihood of skin irritation of people using those bathing facilities.

Quaternary ammonium salts have also been used in swimming pools, spas and hot tubs as algaecides. For example, known commercial algaecide products include SUN.RTM. Algae Prevention (an alkyl dimethyl benzyl ammonium chloride) and HTH.RTM. Non-Foaming Algaecide Concentrate [poly[oxyethylene-(dimethyliminio)ethylene(dimethyliminio) ethylene dichloride]]. Such algaecides are used in relatively low concentrations (under 10 ppm by weight). At such concentrations, these known quaternary ammonium algaecides do not act as effective bactericides.

In practice, harmful bacteria must be killed rapidly if they are present in a swimming pool, spa or hot tub. Indeed, the standard test method for disinfectants in swimming pools [American Organization of Analytical Chemists (A.O.A.C.) test method 4.047 entitled "Disinfectants (Water) for Swimming Pools"] requires that a swimming pool bactericide kills high levels of bacteria in only 30 seconds of contact. With quaternary ammonium salts, this rapid bactericidal activity must be accomplished at low concentrations, e.g., 60 ppm or less, to avoid the potential of producing objectional, unpleasing turbid swimming pool water having a high total organic carbon (TOC) content as well as increasing the likelihood of skin irritation of people using these bathing facilities.

It is believed that the present invention also represents viable non-toxic alternatives to the above-noted problems with existing aquarium, swimming pool, spa and hot tub bactericides and algicides.

D. Anticancer Activity

Polyphenols and antioxidants, which once oxidized, are capable of imparting anticancer properties. The compositions of the present invention can thus be potentially used as cancer therapeutics.

IV. Exemplary Uses

Set forth below are a number of exemplary uses for the compositions disclosed herein: A) Pharmaceuticals and Therapeutics; B) Decontamination and Sterilization; and C) Food Preparation, as well as a description of methods and systems for the D) Modification, Preparation, and Delivery of the compositions of the present invention.

A. Pharmaceuticals and Therapeutics

The present invention contemplates formulations that may be employed in pharmaceutical and therapeutic compositions and applications suitable for combating and/or treating microbial infections including those induced as a part of bioterrorism. Such compositions may be employed to reduce infection, kill microbes, inhibit microbial growth or otherwise abrogate the deleterious effects of microbial infection. In addition, these formulations have potential applications in cancer therapy.

For in vivo applications, the compositions can be administered in any effective pharmaceutically acceptable form to warm blooded animals, including human and animal subjects. Generally, this entails preparing compositions that are essentially free of pyrogens, as well as other impurities that could be harmful to humans or animals.

Particular examples of pharmaceutically acceptable forms include but are not limited to oral, nasal, buccal, rectal, vaginal, topical or nasal spray or in any other form effective to deliver active compositions of the present invention to a site of microorganism infection. In preferred embodiments, the route of administration is designed to obtain direct contact of the compositions with the infecting microorganisms. In other embodiments, administration may be by orthotopic, intradermal, subcutaneous, intramuscular or intraperitoneal injection. The compositions may also be administered to subjects parenterally or intraperitonealy. Such compositions would normally be administered as pharmaceutically acceptable compositions. Except insofar as any conventional pharmaceutically acceptable media or agent is incompatible with the

emulsions of the present invention, the use of known pharmaceutically acceptable media and agents in these particular embodiments is contemplated. In additional embodiments, supplementary active ingredients also can be incorporated into the compositions.

For topical applications, the pharmaceutically acceptable carrier may take the form of a liquid, cream, foam, lotion, or gel, and may additionally comprise organic solvents, emulsifiers, gelling agents, moisturizers, stabilizers, surfactants, wetting agents, preservatives, time release agents, and minor amounts of humectants, sequestering agents, dyes, perfumes, and other components commonly employed in pharmaceutical compositions for topical administration. These formulations would work well with an electromedical device such as TENS and be amenable to iontophoretic delivery to skin via electrochemical patch, where they could control redox state of molecules at the site. Potential applications of this could include wound and cancer treatment.

Tablet and dosage forms of the compositions in which the emulsions are formulated for oral or topical administration include liquid capsules, and suppositories. In solid dosage forms for oral administration, the compositions may be admixed with one or more substantially inert diluent (e.g., sucrose, lactose, or starch, and the like) and may additionally comprise lubricating agents, buffering agents, enteric coatings, and other components well known to those skilled in the art.

B. Decontamination and Sterilization

In another embodiment of the invention, the compositions of the invention may be specifically designed for in vitro applications, such as disinfecting or sterilization of medical instruments and devices, contact lenses and the like, particularly when the devices or lenses are intended to be used in contact with a patient or wearer. For example, the compositions may be used to cleanse and decontaminate medical and surgical instruments and supplies prior to contacting a subject. Additionally, the compositions may be used to post-operatively, or after any invasive procedure, to help minimize the occurrence of post operative infections. In especially preferred embodiments, the compositions are administered to subjects with compromised or ineffective immunological defenses (e.g., the elderly and the very young, burn and trauma victims, and those infected with HIV and the like). For applications of this type, the compositions

may be conveniently provided in the form of a liquid, foam, paste or gel and may be provided with emulsifiers, surfactants, buffering agents, wetting agents, preservatives, metal ions, antibiotics and other components commonly found in compositions of this type.

In other embodiments, the compositions may be impregnated into absorptive materials, such as sutures, bandages, and gauze, or coated onto the surface of solid phase materials, such as surgical staples, zippers and catheters to deliver the compositions to a site for the prevention of microbial infection. Other delivery systems of this type will be readily apparent to those skilled in the art.

In yet another embodiment, the compositions can be used in the personal health care industry in deodorants, soaps, acne/dermatophyte treatment agents, treatments for halitosis, treatments for vaginal yeast infections, and the like. The compositions can also be used to treat other internal and external microbial infections (e.g., influenza, H. simplex, etc.). In these applications, the emulsions can be formulated with therapeutic carriers as described above.

In certain embodiments, the antimicrobial compositions and methods of the present invention also include a variety of combination therapies. For example, often single antimicrobial agents are much less effective at inhibiting microbes than are several agents employed in conjunction with each other. This approach is often advantageous in avoiding the problems encountered as a result of multi-drug resistance. This is particularly prevalent in bacteria that have drug transporters that mediate the efflux of drugs from the organism. The present invention further contemplates the use of the present methods and compositions in such combination therapies.

There are an enormous amount of antimicrobial agents currently available for use in treating bacterial, fungal and viral infections. For a comprehensive treatise on the general classes of such drugs and their mechanisms of action, the skilled artisan is referred to Goodman & Gilman's "The Pharmacological Basis of Therapeutics" Eds. Hardman et al., 9th Edition, Pub. McGraw Hill, chapters 43 through 50, 1996. Generally, these agents include agents that inhibit cell wall synthesis (e.g., penicillins, cephalosporins, cycloserine, vancomycin, bacitracin); and the imidazole antifungal agents

(e.g., miconazole, ketoconazole and clotrimazole); agents that act directly to disrupt the cell membrane of the microorganism (e.g., detergents such as polmyxin and colistimethate and the antifungals nystatin and amphotericin B); agents that affect the ribosomal subunits to inhibit protein synthesis (e.g., chloramphenicol, the tetracyclines, erythromycin and clindamycin); agents that alter protein synthesis and lead to cell death (e.g., aminoglycosides); agents that affect nucleic acid metabolism (e.g., the rifamycins and the quinolones); the antimetabolites (e.g., trimethoprim and sulfonamides); and the nucleic acid analogues such as zidovudine, gangcyclovir, vidarabine, and acyclovir which act to inhibit viral enzymes essential for DNA synthesis. Various combinations of antimicrobials may be employed.

The formulations relating to the present invention can not only display antimicrobial activity like antibiotics, but also have additional, potential anticancer properties.

Antibiotics are almost always redox active phenolics that are administered as "salts". For many acids salts are formed by addition of a base. However, in case of redox active phenolics, deprotonation is the first step in the oxidation process and there is an immediate color change, from clear to yellow, following conditions necessary to make a "salt" of a redox active phenolic. The yellow color is indicative of the quinone formation.

The person responsible for administration will, in any event, determine the appropriate dose for the individual subject. Moreover, for human administration, preparations should meet sterility, pyrogenicity, general safety and purity standards as required by the FDA Office of Biologics standards.

Certain embodiments of the present invention specifically contemplate the use of the present compositions in disinfectants and detergents to decontaminate soil, machinery, vehicles and other equipment, and waterways that may have been subject to an undesired pathogen. Such decontamination procedures may involve simple application of the formulation in the form of a liquid spray or may require a more rigorous regimen. Also, the present emulsions can be used to treat crops for various plant viruses (in place of or for use with conventional antibiotics). Compositions may also be used to

decontaminate farm animals, animal pens, surrounding surfaces, and animal carcasses to eliminate, for example, nonenveloped virus of hoof and mouth disease.

In addition to their use in decontamination of land and equipment, the formulations also find use in household detergents for general disinfectant purposes. An interesting and likely application of the formulations presented in this invention could thus also be in countering microbial contamination as a consequence of bioterrorism. Moreover, some embodiments of the present invention can be used to prevent contamination of food with bacteria or fungi (e.g., non-toxic compositions). This can be done either in the food preparation process, or by addition to the food as an additive, disinfectant, or preservative.

Accordingly, the foregoing Active Component Systems can be admixed with one or more aqueous carrier liquids. The choice of aqueous carrier is not critical. However, it should be safe and it should be chemically compatible with the inventive compositions. In some embodiments, the aqueous carrier liquid comprises solvents commonly used in hard surface cleaning compositions. Such solvents should be compatible with the inventive compositions and should be chemically stable at the pH of the composition.

In preferred embodiments, the aqueous carrier is water or a miscible mixture of alcohol and water. The alcohol can be used to adjust the viscosity of the compositions. In some embodiments, the alcohols are preferably C2-C4 alcohols. In particularly preferred embodiments, ethanol is employed. For example, in one preferred embodiment, the aqueous carrier liquid is water or a water-ethanol mixture containing from about 0 to about 50% ethanol. The present invention also embodies non-liquid compositions. These non-liquid compositions can be in granular, powder or gel forms, preferably in granular forms.

In still other embodiments, the compositions may be used by health care workers, or any persons contacting persons or areas with microbial infections, for their personal health-safety and decontamination needs. In addition, the inventive emulsions can be formulated into sprays for hospital and household uses such as cleaning and disinfecting medical devices and patient rooms, household appliances, kitchen and bath surfaces, etc. In similar embodiments, the compositions may be used by sanitation and environmental

services workers, food processing and agricultural workers and laboratory personnel when these individuals are likely to contact infectious biological agents. Additionally, the compositions may be used by travelers and persons contacting areas likely to harbor infectious and pathological agents.

C. Food Preparation

The present invention also contemplates that certain compositions described herein may be employed in the food processing and preparation industries in preventing and treating food contaminated with food born bacteria, fungi and toxins. Thus, such compositions may be employed to reduce or inhibit microbial growth or otherwise abrogate the deleterious effects of microbial contamination of food. For these applications, the compositions are applied in food industry acceptable forms such as additives, preservatives or seasonings.

The phrase "acceptable in the food industry" refers to compositions that do not substantially produce adverse, or allergic reactions when taken orally by humans or animals. As used herein, "acceptable in food industry media" includes any and all solvents, dispersion substances, any and all spices and herbs and their extracts. Except insofar as any conventional additives, preservatives and seasonings are incompatible with the emulsions of the present invention, their use in preventing or treating food born microbes and their toxic products is contemplated. Supplementary active ingredients may also be incorporated into the compositions. For such applications, acceptable carriers may take the form of liquids, creams, foams, gels and may additionally comprise solvents, emulsifiers, gelling agents, moisturizers, stabilizers, wetting agents, preservatives, sequestering agents, dyes, perfumes and other components commonly employed in food processing industry.

In another embodiment of the present invention, the compositions may be specifically designed for applications such as disinfecting or sterilization food industry devices, equipment, and areas where food is processed, packaged and stored. For applications of this type, the compositions may be conveniently provided in the form of a liquid or foam, and may be provided with emulsifiers, surfactants, buffering agents, wetting agents, preservatives, and other components commonly found in compositions of

this type. In some embodiments, the compositions are applied to produce or agricultural products prior to or during transportation of those goods. Compositions of the invention may be impregnated into absorptive materials commonly used in packaging material for the prevention of food contamination during transport and storage (e.g., cardboard or paper packaging). Other delivery systems of this type will be readily apparent to those skilled in the art.

Actual amounts of the compositions and enhancing agents in the compositions of the invention may be varied so as to obtain appropriate Active Component System concentrations to effectively prevent or inhibit food contamination caused by food born microbes and their toxic products. Accordingly, the selected concentrations will depend on the nature of the food product, packaging, storage procedure and other factors. It should be understood that a range between 0.2% and 5.0% of the Active Component System is specifically contemplated to be encompassed within the metes and bounds of the present invention.

In particular embodiments, compositions can be used as disinfectants and detergents to decontaminate and prevent microbial infection of food, soil and water, machinery and other equipment, and animals.

The inventive compositions can be used by the food industry to prevent contamination. For example, inclusion of the composition within the food product itself would be effective in killing bacteria that may have been accidentally contaminated meat or poultry. This could also allow the industry to use a potentially broader spectrum of food products and reduce costs.

Certain embodiments of the present invention can also be used in the beverage industry. For example, the inventive emulsions could be included in juice products to prevent growth of certain fungi, which cause contamination and lead to production of mycotoxins, which are dangerous to consumers.

The inventive emulsions can be used to essentially remove infectious agents on machinery and other equipment. For example, the emulsions can be used to eliminate contaminations in meat processing plants, particularly of organisms such as Listeria

monocytogenes and Salmonellae microorganisms, by cleaning slaughterhouses or food packaging facilities on a continual basis with the composition.

The person responsible for administration will, in any event, determine the appropriate dose for individual application. Moreover, said above application should meet general safety and purity standards as required by the FDA office.

D. Modification, Preparation, and Delivery

The present invention further provides a variety of methods and systems for the modification of the compositions of the present invention, the incorporation of these compositions into other products, packaging and delivery of the compositions of the present invention, and methods for reducing the costs associated with the use or handling of materials or samples that might be contaminated with microorganisms. The following description is intended to simply provide some examples of the modification, preparation, and delivery of the compositions of the present invention. Those skilled in the art will appreciate variations of such methods.

In some embodiments, the present invention provides methods for improving or altering the composition described herein. Such methods include, for example, taking a composition described herein and changing one or more components of the composition. Such changes include, but are not limited to, adding or removing one or more components. The altered composition can then be tested to determine if it has desired or useful properties. In some embodiments of the present invention, compositions of the present invention, or those derived from the compositions of the present invention are diluted. The diluted samples can then be tested to determine if they maintain the desired functionality.

In some embodiments of the present invention, the compositions of the present invention are added to another product to add or improve anti-microbial capabilities of the product or to test a suspected or provide a perceived improved anti-microbial capability to the product (i.e., it is contemplated that the addition of a composition of the present invention into a product is within the scope of the present invention regardless of whether it has a detectable, or any, antimicrobial capabilities). For example, in some

embodiments, the compositions of the present invention are added to cleaning or disinfectant materials (e.g., household cleaning agents). In other embodiments, the compositions are added to medical or first aid materials. For example, the compositions may be added to (or used directly as) sterilization agents and wound care products. In still other embodiments, the compositions are added to food products. For example, the compositions can be added to beverages to prevent the growth of unwanted organisms in the beverage.

The composition of the present invention, whether alone, or in conjunction with other materials can be provided in many different types of containers and delivery systems. For example, in some embodiments of the present invention, the compositions are provided in a cream or other solid or semi-solid form. During the development of the present invention, it was determined that the emulsions of the present invention may be incorporated into hydrogel formulations while maintaining antimicrobial capabilities. The use of the emulsions in hydrogel provides a number of useful features. For example, hydrogels can be prepared in semi-solid structures of desired sizes and shapes. This allows, for example, the insertion of the hydrogel materials into tubes or other passageways to create antimicrobial filters (i.e., materials passed through the hydrogel are decontaminated by the compositions of the present invention).

The compositions can be delivered (e.g., to user or customers) in any suitable container. Container can be used that provide one or more single use or multi-use dosages of the composition for the desired application. In some embodiments of the present invention, the compositions are provided in a suspension or liquid form. Such compositions can be delivered in any suitable container including spray bottles (e.g., pressurized spray bottles). For industrial or other large-scale uses, large volumes (e.g., tens to thousands of liters) of composition may be provided in a single container configured appropriately to allow distribution or use of the composition.

In some preferred embodiments of the present invention, compositions of the present invention are used in conjunction with an existing business practice to reduce the costs associated with or improve the safety of the operation of the business practice. For example, the use of the compositions of the present invention can reduce costs associated

with the use or handling of materials or samples that might be contaminated with microorganisms. In some embodiments, the compositions of the present invention are used to improve safety or reduce the costs associated with the medical industries. For example, the compositions find use as cheap and efficient sterilization agents for use on medical materials (e.g., surface that come in contact with animals, people, or biological samples) or with patients (e.g., internally or externally). The compositions also find use as cheap and efficient sterilization agents for food processing and handling and industrial applications. In some such embodiments, the present invention provides non-toxic compositions. For example, compositions are provided herein that include ingredients that are currently approved by the appropriate regulatory agencies (e.g., FDA, USDA, etc.) for use in medical, agriculture, and food applications. Furthermore, methods are provided herein for the generation of additional compositions with the desired functionality that can be composed entirely of non-toxic and approved substances. As such, the compositions of the present invention can be used in applications without incurring having to undergo the time consuming and expensive process of gaining regulatory approval. Indeed, the compositions can be less toxic than the sum of their individual components.

E. Additional Examples

The compositions of the present invention may be used alone, or in conjunction with other materials and products to perform specific desired functions. For example, the compositions may be added to or formulated with health care products, personal care products, hygiene products, and household products to prevent contamination of the products and/or to add or improve anti-microbial properties of the products.

Oral dosage forms such as pills, tablets and cough drops can also be used to deliver the active component system internally to promote the minimization and/or destruction of the many harmful pathogenic microorganism that invade the body. Compounds of the invention which contain the active component system can be coated and taken internally to provide pro-oxidative antibacterial, antiviral, antifungal and anti-cancer benefits.

V. Experimental Examples

The following examples serve to illustrate certain preferred embodiments and aspects of the present invention and are not to be construed as limiting the scope thereof. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many variations thereof are possible without departing from the spirit and scope of the invention.

In the experimental disclosure, which follows, the following abbreviations apply: mu. (micron); M (Molar); g (grams); mg (milligrams); L (liters); mL (milliliters); cm (centimeters); mm (millimeters); and degree. C. (degrees Centigrade).

EXAMPLES

EXAMPLE 1

Methods of Formulating Emulsions

An oil-in-water emulsion is prepared by combining the following ingredients below.

The emulsion is produced as follows: In a suitable vessel Phase A (oil phase) is made by blending oil phase ingredients and then heating while mixing the resulting mixture at 85-90 degree C until all the ingredients are solubilized and homogenous. The Phase B (water phase) ingredients listed below are heated while stirring to about 70 degrees C. The Phase C ingredients (Active Component System) are mixed in a separate vessel at room temperature. The Phase D ingredients are mixed in a separate vessel at room temperature. Using a Silverson high sheer mixer Phase A is added to Phase B and mixed for 1-30 minutes, preferably for 10 minutes. The Active Component System is the added and mixed for 1-30 minutes preferably about 10 minutes. Below 45 degrees C, Phase D is added to the mixture and mixed for 10 minutes.

Ingredient	**Weight Percent**
PHASE A	
Soybean Oil	8.0
Ritacol 1000	5.0
DEA Cetyl Phosphate	0.4
Dimethicone	0.1
Cetyl Alcohol	2.5
Ascorbyl Palmitate	0.01
PHASE B	
Water	QS 100
Glycerin	5.0
Sodium PCA	2.0
Aloe Vera Gel	1.0
Guar Tripropyltrimonium Chloride	0.3

PHASE C	
Ascorbic Acid	1.0
Ferrous Chloride	0.1
PHASE D	
Fragrance	0.5
Vitamin E	0.01

Microbial Challenge Testing:

The BP (British Pharmacopoeia) and USP (United States Pharmacopoeia) only call for a single-inoculation challenge test. We used Dow Chemical Company's challenge testing, which is more stringent using a 4-cycle bacterial challenge test and a 3-cycle fungi challenge test.

A formulation with a relatively high count of the challenge species after 7 days may be considered inadequately preserved. A predictive judgment can be made after 14 days, with a final judgment at 28 days. Many formulations, however, would appear inadequately preserved if intended to exhibit similar fungicidal and bactericidal activity after 7 days, owing to the non-attainability of a 10^2 reduction of fungi in 7 days.

Bacterial Testing Method

The Test Bacteria Pool included *Enterobacter gergoviae, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Pseudomonas putida, Staphylococcus aureus, Burkholderia cepacia, Streptococcus gordonii and Staphylococcus epidermis.* The formulation / emulsion sample was inoculated by adding 0.125 ml of the bacteria test pool mixture and was mixed well with a sterile tongue depressor. The sample was inoculated at each inoculation time period and incubated at 30 degrees C. The inoculation schedule was as follows: day 0, day 2, day 7 and day 14. Plating was performed at each of the following times: day 0 (immediately after inoculation), day 1, day 2 (before inoculation), day3, day 8, day 13, day 15, day 20, and day 27. Test samples were streaked onto tryptic soy agar plates using a sterile cotton-tipped applicator. Plates were incubated for 48 to 96 hours at 30 degrees C.

Bacterial Survival Is Rated Using The Following Criteria:

Plating Results	Score	Approximate Population Represented
No detectable survival	0	<100 CFU/mL
1 – 10 colonies	1	100 – 1,000 CFU/mL
11 – 20 colonies	2	1,100 – 2,000 CFU/mL
21 – 50 colonies	3	2,100 – 5,000 CFU/mL
51 – 100 colonies	4	5,100 – 10,000 CFU/mL
>100 colonies	5	>10,000 CFU/mL

Ratings of 2 or greater in all but day 0 streak are considered failing. This is because it would mean that the formulation was not effective as an antimicrobial agent. Since the level of organisms in inoculated samples is approximately 2.5 x 10^6 CFU per gram or mL of test sample, no detectable survival (<100 CFU/mL), represents a 1 x 10^4 (or 4 log) kill of the population.

If the test trends are consistent with minimal growth recorded over the entire 28 days, the challenge test is considered to have scored a positive result.

Fungi Test Method

Aspergillus niger (An)- mold and *Saccharomyces cerevisiae* (Sc)- yeast are maintained on Sabaroud Dextrose Agar (SDA) slants at 4 degrees C. The slants are taken out from the 4 degree C chamber to warm up to room temperature. The Sc culture is harvested by adding 9.9 mL of sterile 0.85% NaCl solution to the Sc slant. The surface of the slant is rubbed gently with a sterile cotton swab to free the cells. The resulting suspension is then diluted 1:10 in 9 mL of sterile 0.85% saline.

The An culture is harvested by dipping a sterile wood applicator stick into a bottle of Triton X-1 surfactant, then adding a drop of the surfactant to the inside of the tube above the slant and adding 9.9mL of sterile 0.85% saline solution to the slant. With a sterile

cotton swab, the surface of the slant is rubbed gently to free the cells. The resulting suspension is then diluted 1 to 10 in 9mL of sterile 0.85% saline solution.

Sterility streaks of each sample to be tested are done on TSA(tryptic soy agar) plates and SDA(Sabaroud Dextrose Agar) plates with sterile cotton swabs. The plates are incubated at 30 degrees C for 48 hours. This is the 0 cycle. The plates are read using a colony counter and rated for microbial growth according to the following rating scale.

Mold and Yeast Three Cycle Rating Scale and Approximate Number of Organisms Per mL:

Plating Results	Score	CFU/mL Sample
No detectable survival	0	$<10^2$ CFU/mL
1 – 10 colonies	1	$1 \times 10^2 - 1 \times 10^3$
11 – 20 colonies	2	$1.1 \times 10^3 - 2 \times 10^3$
21 – 50 colonies	3	$2.1 \times 10^3 - 5 \times 10^3$
51 – 100 colonies	4	$5.1 \times 10^3 - 1 \times 10^4$
TNTC(too numerous to count)	5	$> 1 \times 10^4$ CFU/mL

The fungi results are not scored as a ratio (0/1) of yeast/mold but just their method of showing the fungi challenge test scores for both yeast and mold in the same table.

EXAMPLE 1 Four-Cycle Bacterial Challenge Test Results

4CCT	Day 0	Day 1	Day 2	Day 3	Day 6	Day 8	Day 13	Day 15	Day 20	Day 27
Example 1* (Control)	5	5	5	5	5	5	5	5	5	5
Example 1	5	0	0	0	0	0	0	0	0	0

Example 1 (Control) delete Phase C (Active Component System) from Example 1 Formula above.

Thus no detectable survival of the bacteria was seen using the Active Component System of Example 1 (a score of 0 beyond day 1). In contrast, the control set lacking this system showed no inhibition of bacterial proliferation (a score of 5 until day 27; the end-point of experimental determinations).

EXAMPLE 1 Three Cycle Fungal Challenge Test Results

3CCT	Day0	Day2	Day4	Day7/9	Day 11	Day 14/16	Day 18
Example 1* (Control)	1/1**	1/3	0/0	0/5	1/5	0/5	0/5
Example 1	1/1	0/0	0/0	0/0	0/0	0/0	0/0

** A fraction (An rating/Sc rating) is used to record the growth ratings. The mold (An) rating is the numerator and the yeast (Sc) rating is the denominator.

No detectable survival of the 2 types of fungi was seen using the Active Component System of Example 1 (a score of 0 beyond day 1). In contrast, the control set lacking this system showed little inhibition of *Saccharomyces cerevisiae* growth (a score of 5 until day 18; the end-point of experimental determinations).

EXAMPLE 2

Methods of Formulating an Aqueous Gel

An aqueous gel is prepared by combining the following ingredients below.

The aqueous gel is produced as follows: in a suitable vessel Phase A (water phase) ingredients listed below are heated while stirring to about 50 degrees C. The Phase B ingredients are mixed in a separate vessel at room temperature. The Phase C (Active Component System) ingredients are mixed in a separate vessel at room temperature. Using a Silverson high sheer mixer Phase B is added to Phase A and mixed for 1-30 minutes, preferably for 10 minutes. The Phase C ingredients are then added and mixed for 1-30 minutes preferably about 10 minutes.

Ingredient	Weight Percent
PHASE A	
Almond Meal Extract	26.3
Aqueous Botanical Extract Blend	61.4
Glycerin	4.0
Sodium PCA	2.0
Aloe Vera Gel	1.0
PHASE B	
Guar Tripropyltrimonium Chloride	1.0
Potassium Aluminum Silicate	0.5
Zinc Oxide	0.5
PHASE C	
Ascorbic Acid	3.0
Ferrous Chloride	0.3

EXAMPLE 2 Four Cycle Bacterial Challenge Test Results

4CCT	Day 0	Day 1	Day 2	Day 3	Day 6	Day 8	Day 13	Day 15	Day 20	Day 27
Example 2* (Control)	5	5	5	5	5	5	5	5	5	5
Example 2	5	5	4	0	0	0	0	0	0	0

*Example 2 (Control) delete Phase C (Active Component System) from Example 2 Formula above.

Thus no detectable survival of the bacteria was seen using the Active Component System of Example 1 (a score of 0 beyond day 3). In contrast, the control set lacking this system showed no inhibition of bacterial proliferation (a score of 5 until day 27; the end-point of experimental determinations).

EXAMPLE 2 Three Cycle Fungal Challenge Test Results

3CCT	Day0	Day2	Day4	Day7/9	Day11	Day 14/16	Day 18
Example 2* (Control)	1/1**	1/1	0/0	0/1	0/5	0/5	0/5
Example 2	1/1	0/0	0/0	0/0	0/0	0/0	0/0

** A fraction (An rating/Sc rating) is used to record the growth ratings. The mold (An) rating is the numerator and the yeast (Sc) rating is the denominator.

No detectable survival of the 2 types of fungi was seen using the Active Component System of Example 1 (a score of 0 beyond day 1). In contrast, the control set lacking this system showed little inhibition of *Saccharomyces cerevisiae* growth (a score of 5 until day 18; the end-point of experimental determinations).

EXAMPLE 3

Methods of Formulating an Aqueous Solution

An aqueous solution is prepared by combining the following ingredients below.

The aqueous solution is produced as follows: in a suitable vessel Phase A (water phase) ingredients listed below are heated while stirring to about 50 degrees C. The Phase B (Active Component System) ingredients are mixed in a separate vessel at room temperature. Using a Silverson high sheer mixer Phase B is added to Phase A and mixed for 1-30 minutes, preferably for 10 minutes.

Ingredient	Weight Percent
PHASE A	
Almond Meal Extract	97.8
PHASE B	
Ascorbic Acid	2.0
Ferrous Chloride	0.2

EXAMPLE 3 Four-Cycle Bacterial Challenge Test Results

4CCT	Day0	Day1	Day 2	Day 3	Day 6	Day 8	Day 13	Day 15	Day 20	Day 27
Example 3* (Control)	5	1	0	0	0	5	5	5	5	5
Example 3	5	5	4	0	0	0	0	0	0	0

*Example 3 (Control) delete Phase B(Active Component System) from Example 3 Formula above.

Thus no detectable survival of the bacteria was seen using the Active Component System of Example 1 (a score of 0 beyond day 3). In contrast, the control set lacking this system showed no inhibition of bacterial proliferation (a score of 5 until day 27; the end-point of experimental determinations).

Scores for days 2, 3 and 6 are off here as compared with the rest of the values for the control set.

EXAMPLE 3 Three Cycle Fungal Challenge Test Results

3CCT	Day 0	Day 2	Day 4	Day 7/9	Day 11	Day 14/16	Day 18
Example 3	0/0**	0/5	0/5	0/5	0/1	0/0	0/0

** A fraction (An rating/Sc rating) is used to record the growth ratings. The mold (An) rating is the numerator and the yeast (Sc) rating is the denominator.

No detectable significant survival of the 2 types of fungi was seen using the Active Component System as in Example 1.

EXAMPLE 4

Methods of Formulating an Aqueous Gel

An aqueous gel is prepared by combining the following ingredients below.

The aqueous gel is produced as follows: in a suitable vessel Phase A (water phase) ingredients listed below are heated while stirring to about 50 degrees C. The Phase B ingredients are mixed in a separate vessel at room temperature. The Phase C

(Active Component System) ingredients are mixed in a separate vessel at room temperature. Using a Silverson high sheer mixer Phase B is added to Phase A and mixed for 1-30 minutes, preferably for 10 minutes. The Phase C ingredients are then added and mixed for 1-30 minutes preferably about 10 minutes.

Ingredient	**Weight Percent**
PHASE A	
Almond Meal Extract	21.1
Aqueous Botanical Extract Blend	52.4
Honey	20.0
PHASE B	
Guar Tripropyltrimonium Chloride	1.0
Potassium Aluminum Silicate	0.5
Zinc Oxide	0.5
PHASE C (Active Component System)	
Capsicum	0.5
Ferrous Chloride	0.2

EXAMPLE 4 Four Cycle Bacterial Challenge Test Results

4CCT	Day 0	Day 1	Day 2	Day 3	Day 6	Day 8	Day 13	Day 15	Day 20	Day 27
Example 4* (Control)	5	5	5	5	5	5	5	5	5	5
Example 4	5	1	5	1	0	0	0	0	0	0

*Example 4 (Control) delete Phase C (Active Component System) from Example 4 Formula above.

Thus no detectable survival of the bacteria was seen using the Active Component System of Example 1 (a score of 0 beyond day 6). In contrast, the control set lacking this

system showed no inhibition of bacterial proliferation (a score of 5 until day 27; the end-point of experimental determinations).

The score for day 1 is off, as compared with the rest of the values for the Example 4, which has the Active Component System.

EXAMPLE 4 Three Cycle Fungal Challenge Test Results

3CCT	Day 0	Day 2	Day 4	Day 7/9	Day 11	Day 14/16	Day 18
Example 4* (Control)	1/1**	1/1	0/0	0/0	0/0	1/1	0/0
Example 4	1/1	1/1	0/0	0/0	0/0	1/1	0/0

** A fraction (An rating/Sc rating) is used to record the growth ratings. The mold (An) rating is the numerator and the yeast (Sc) rating is the denominator.

EXAMPLE 5 Oxidized Form of Minoxidil Improves Efficacy

The current trend in the medical profession has been to prevent the oxidation of compounds, as it was believed that the oxidation of compounds resulted in an unstable state. The oxidized compounds turned a yellow color (the quinines) and were thought to exhibit a loss of efficacy for a given compound's intended use as a result. As shown in this Example, this is not the case at all, as the pro-oxidized form of minoxidil is much more effective when compared to the original formulation of minoxidil.

Minoxidil only claims effectiveness on the top of the head and takes four to six months for a person, using it twice daily, to begin to notice a difference. One individual has used the original formulation of minoxidil for two and half years. During that time, very little hair growth was observed. When the same individual used the pro-oxidant form of minoxidil, which was a yellow-orange color, in the same areas for two and half months, there was substantial hair growth observed. This is attributed to the oxidized form of minoxidil exhibiting much more efficacy, thus rebutting the presumption in the field that oxidized compounds are somehow less effective.

PREPARATION OF THE RDX HAIR GROWTH COMPLEX

Minoxidil formulation currently available to the public:

TABLE 1

Compound	Supplier	Ingredient	Weight%
Minoxidil Hair Growth	Kirkland	Minoxidil active	5.0%
		Ethyl alcohol	30%.
		Propylene Glycol	55%
		Water	10%

RDX Minoxidil Hair Growth Complex Preparation:

STEP 1: The Kirkland Minoxidil Hair Growth product above is weighed and placed in a beaker on a stirring plate.

TABLE 2

Compound	Supplier	Ingredient	Weight%
Minoxidil Active Zinc Complex	RDX Tech.	Zinc Acetate	0.5%
		Hydrogen Peroxide (3%)	5.0%

STEP 2: At room temperature the Kirkland 5% minoxidil is mixed with 0.5% (w/w%) zinc acetate for 30 minutes. The zinc acetate dissolves after mixing for 15 minutes. The solution turns a medium yellow color.

STEP 3: 5% of the 3% hydrogen peroxide is added to the mixture in STEP 2. The solution turns a dark yellow color. Allow to mix for 30 minutes. The pH is about 6.8. After about 2 hours of continued mixing the solution turns a light orange color. The solution is transparent and somewhat stable in the acidic pH.

A thin film of the RDX Hair Growth Complex prepared above is applied to the scalp twice daily, once in the morning and once in the evening. Case study observations of the frontal hair line seem to reveal that repeated use of the RDX Hair Growth Complex stimulates the rate of growth of terminal hair by converting vellus hair to terminal hair. The growth occurs initially at the existing hair line and with continued use the hair line becomes thicker and fuller and extends downward reversing a receeding hair line.

All publications and patents mentioned in the above specification are herein incorporated by reference. Various modifications and variations of the described method

and system of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in relevant fields are intended to be within the scope of the following claims.

We claim:

1. A composition in a physical form selected from the group consisting of an oil-in-water emulsion, water-in-oil emulsion, ointment, aqueous gel, aqueous solution, or powder or other comprising an oxidizing formulation, the formulation comprising:

(a) an effective amount of at least one compound from the redox active polyphenol class of compounds, the compound(s) selected from the group consisting of Vitamin E, coenzyme Q, uric acid, carotenoids, glutathione, Vitamin A, flavonoids, Aloe, Anise, Barberry, Bayberry, Bitter Melon, Black Elder, Black Pepper, Bloodroot, Blue Cohosh, Burdock, Camphor Tree, Capsicum Pepper, Caraway, Chamomile, Cinnamon, Clove, Coltsfoot, Cypress, Dill, Eucalyptus, Eyebright, Fennel, Feverfew, Ginger, Goldenseal, Horseradish, Lemon Balm, Lentinan, Licorice, Maitake, Marigold, Mistoletoe, Myrrh, Nettles, Oak Bark, Oregano, Pau d'arco, Peppermint, Soap bark, Spruce, Tea Tree Oil, Thistle, White Horehound, Wild Indigo, Wintergreen, Witch Hazel, Wormwood and Woundwart, Cat's Claw, Sage, Chaparral, Cranberry, Echinacea, Garlic, Ginkgo, Grape Seed Extract, Green Tea, Plantain, Propolis, Rosemary, St. John's Wort, Tumeric, Uva Ursi, Yarrow and Pine Bark Extract and combinations thereof;

(b) an effective amount of at least one agent classified as an oxidizing agent, the agent(s) selected from the group consisting of superoxide radicals, hydroxyl radicals, ozone, hydrogen peroxide, nitric oxide, nitrogen dioxide, pernitric acid and hypochlorous acid and combinations thereof;

(c) an effective amount of at least one metal ion classified as a divalent transition metal ion, the ion(s) selected from the group consisting of Ca, Cu, Fe, Zn, or Ag and combinations thereof; and

wherein the total composition has no detectable toxicity to plants or animals.

2. The composition of claim 1, whereby the redox active polyphenols oxidized by a method selected from the group consisting of

(a) subjecting the composition to atmospheric oxygen;

(b) subjecting the composition to ultraviolet light; and

(c) subjecting the composition to an oxidizing agent

3. The composition of claim 1, wherein said composition is antimicrobial against at least once class of microbes selected from the group consisting of bacteria, virus, fungi, and algae.

4. The composition of claim 1, whereby said composition includes anti-cancer properties.

5. The composition of claim 1, whereby said composition cause no detectable irritation to animals.

6. A method for decontaminating water comprising treating said water with an effective amount of a composition selected from the group consisting of an oil-in-water emulsion, water-in-oil emulsion, ointment, aqueous gel, or aqueous solution, powder or other comprising an oxidizing formulation, the formulation comprising:

(a) an effective amount of at least one compound from the redox active polyphenol class of compounds, the compound(s) selected from the group consisting of Vitamin E, coenzyme Q, uric acid, carotenoids, glutathione, Vitamin A, flavonoids, Aloe, Anise, Barberry, Bayberry, Bitter Melon, Black Elder, Black Pepper, Bloodroot, Blue Cohosh, Burdock, Camphor Tree, Capsicum Pepper, Caraway, Chamomile, Cinnamon, Clove, Coltsfoot, Cypress, Dill, Eucalyptus, Eyebright, Fennel, Feverfew, Ginger, Goldenseal, Horseradish, Lemon Balm, Lentinan, Licorice, Maitake, Marigold, Mistoletoe, Myrrh, Nettles, Oak Bark, Oregano, Pau d'arco, Peppermint, Soap bark, Spruce, Tea Tree Oil, Thistle, White Horehound, Wild Indigo, Wintergreen, Witch Hazel, Wormwood and Woundwart, Cat's Claw, Sage, Chaparral, Cranberry, Echinacea, Garlic, Ginkgo, Grape Seed Extract, Green Tea, Plantain, Propolis, Rosemary, St. John's Wort, Tumeric, Uva Ursi, Yarrow and Pine Bark Extract and combinations thereof;

(b) an effective amount of at least one agent classified as an oxidizing agent, the agent(s) selected from the group consisting of superoxide radicals, hydroxyl radicals,

ozone, hydrogen peroxide, nitric oxide, nitrogen dioxide, pernitric acid and hypochlorous acid and combinations thereof;

(c) an effective amount of at least one metal ion classified as a divalent transition metal ion, the ion(s) selected from the group consisting of Ca, Cu, Fe, Zn, or Ag and combinations thereof.

7. The method of claim 6, wherein said composition has no detectable toxicity to plants or animals.

8. A method of preparing the topical or oral anti-pathogenic product of claim 1, wherein the ingredient or ingredients have a desired therapeutic effect when administered:

(a) mixing the components;

(b) inducing oxidation during formulation or by using electrical potential; and

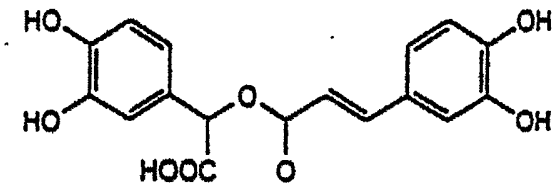
(c) controlling and maintaining the desired redox state of the finished product during packaging or storage.

9. A method of preparation of minoxidil sulphate consisting of forming a composition of minoxidil sulphate and a compound containing a metal ion, wherein the the metal ion is selected from the group consisting of Ca, Cu, Fe, Zn, or Ag and combinations thereof.

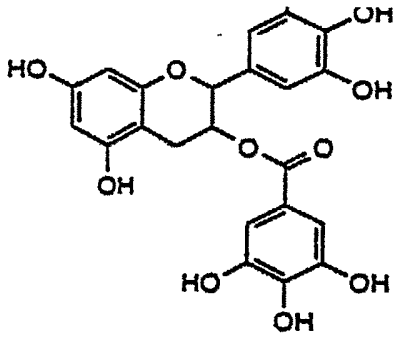
10. The method of claim 9, wherein the minoxidil sulphate contains between 1% and 10% active minoxidil.

11. The method of claim 9, wherein the zinc acetate comprises between .1% and 5% by weight of the mixture.

12. The method of claim 9, wherein the compound is zinc acetate.

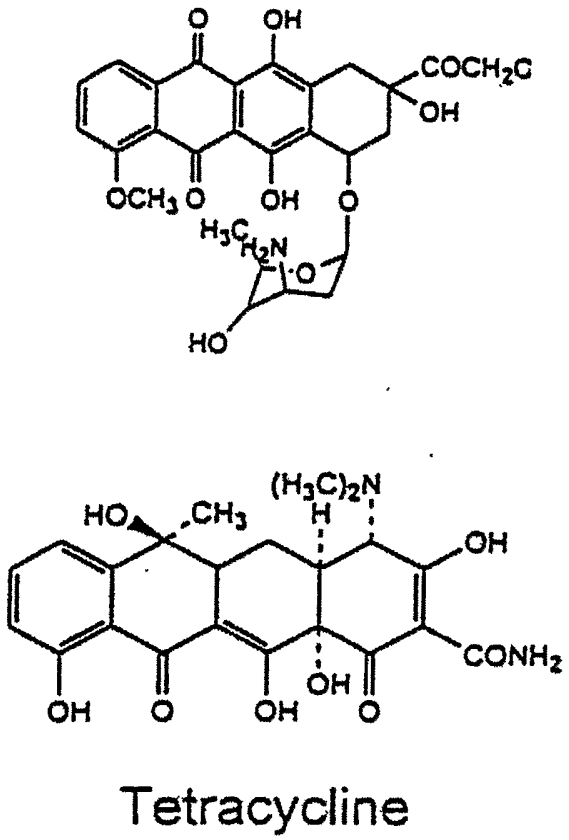


Rosmarinic Acid



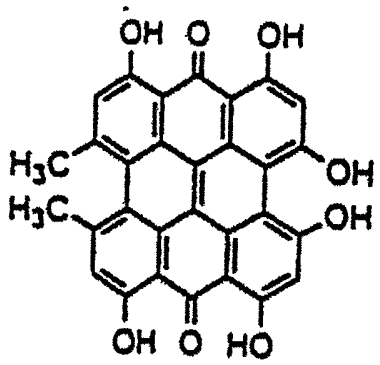
Epigallocatechin gallate

Figure 1. Antioxidants – Rosemarinic Acid and Epigallocatechin Gallate

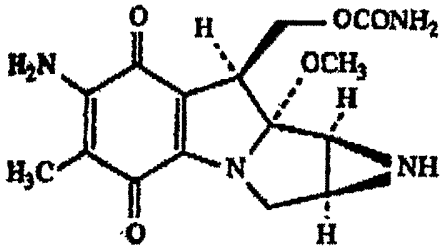


Tetracycline

Figure 2. Antibiotics – Adriamycin and Tetracycline



Hypericin



mitomycin C

Figure 3. Anticancer compounds Hypericin and mitomycin C.

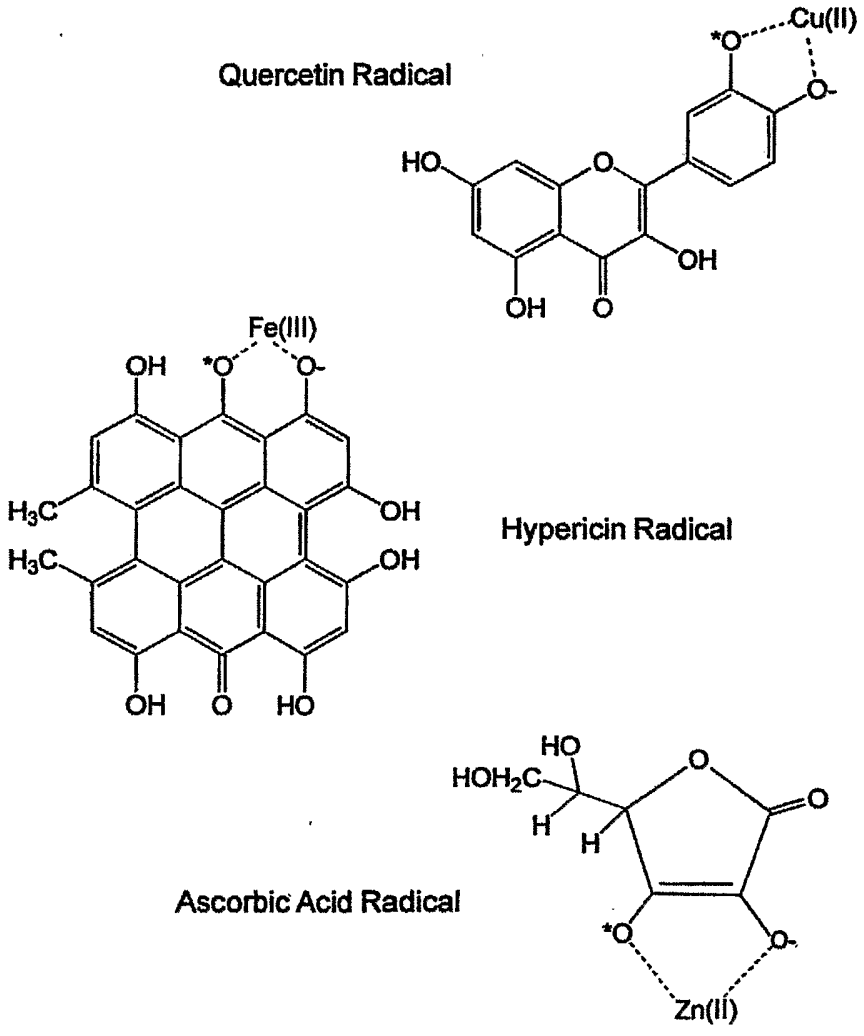


Figure 4. Phenolic Anion Salt Radicals

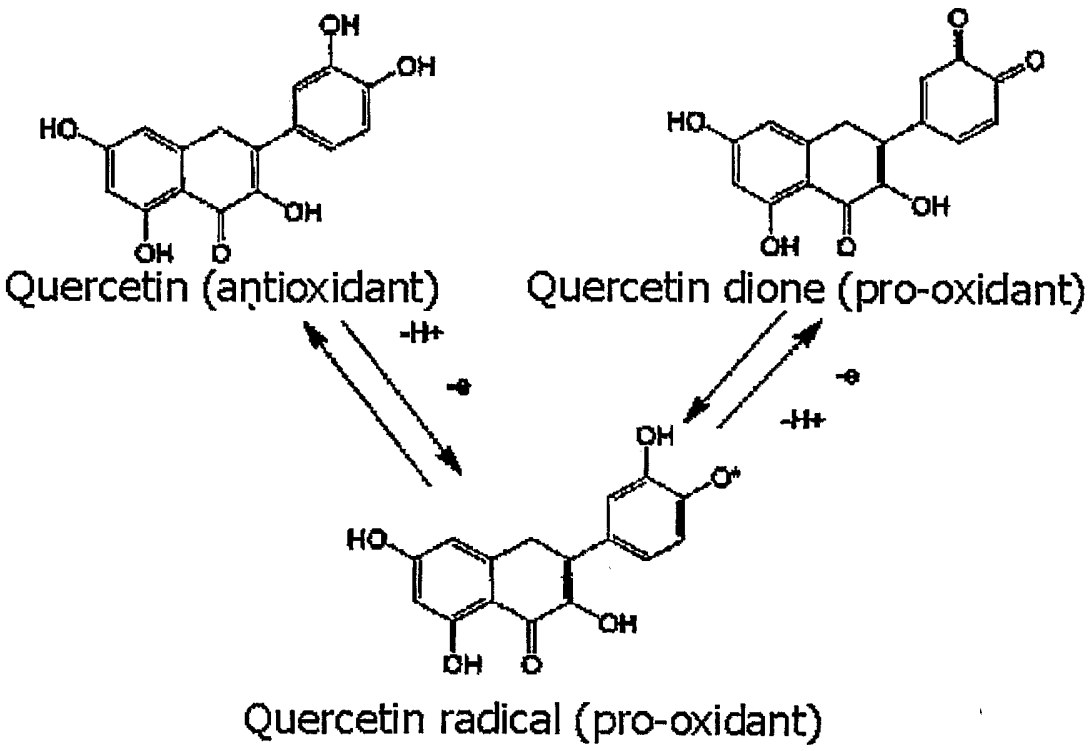


Figure 5. **Redox Cycling of Quercetin**