FUNCTIONAL FOOD COMPOSITIONS AND METHODS

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to compositions including bioactive components carried within solid lipid particles dispersed in a food based carrier and to methods of producing such compositions.

Nutraceutical, a term combining the words "nutrition" and "pharmaceutical", is a food or food product that provides health and medical benefits, including the prevention and treatment of diseases. Neutraceuticals include, among other categories, functional foods and medical foods [see Chen et al. Trends in Food Science & Technology 17 (2006) 272–283; and Lemes and McClements Trends in Food Science & Technology 20 (2009)].

Functional foods are consumed close to their natural state and include components or ingredients that provide a specific medical or physiological benefit beyond (or in addition to) the nutritional effects of the food. Garlic, which includes sulfur compounds, and fish, which include omega-3 fatty acids, are examples of functional foods. Functional foods can be enriched or fortified to restore or supplement the nutrient content or physiological effect of food.

Medical foods are formulated to be consumed or administered internally under the supervision of a physician and are intended for dietary management of a disease or condition for which there are specific nutritional requirements.

Incorporation of bioactive components such as vitamins, probiotics, bioactive peptides, and antioxidants into food based carriers provide a simple way to develop novel functional foods that may have physiological benefits or reduce the risks of diseases. However, functional and medical foods are oftentimes limited in as far as their bioactive agents loading capacity (i.e, the concentration of the bioactive agent in the food base carrier), especially in cases where the active agent can not be readily solubilized or emulsified in the food base carrier.

Bioactive food components are biomolecules that are present in foods such as fruits and vegetables and which exhibit the capacity to modulate one or more metabolic processes, and thus can be used in the treatment of disease and promotion of better health.

Bioactive food components can be ingested as part of the source food or they can be ingested in purified form. In many cases it is unclear whether such components are ingested at effective dosages required for health benefits due to their limited bioavailability, however.

Methods of enhancing the bioavailability of bioactive food components are well known in the art and include formulations which are designed to increase the gastrointestinal (GI) absorption of the bioactive food components and/or limit their breakdown in the GI tract or body (see, Davis, DDT, Volume 10, Number 4, Feb. 2005).

Although such formulations can be used to increase bioavailability of bioactive food components, food derived biomolecules are oftentimes difficult to ingest due to offensive odors or smells and do not provide the nutritional value associated with the food from which the bioactive food components are derived.

Thus, there remains a need for composition that includes a nutritional base and bioactive components devoid of the above limitations.

The present invention successfully addresses the shortcomings of the presently known configurations by providing food-based physiologically-functional compositions that are capable of oral delivery of physiologically effective amounts of a bioactive agent.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

SUMMARY OF THE INVENTION

It is one object of the present invention to provide a method of producing a functional food, comprising:

melting a lipid solvent in the presence of a lipophilic bioactive agent;

heating the melted lipid solvent and bioactive agent to a temperature of at least 65 °C;

adding a food base carrier to said melted lipid solvent and bioactive agent; and,

emulsifying said melted lipid solvent, said bioactive agent, and said food base carrier until an emulsion is formed, said emulsion comprising lipid particles comprising said bioactive agent.

It is another object of the present invention to provide the method as defined above, wherein said step of heating the melted lipid solvent and bioactive agent to a temperature of at least 65 °C comprises a step of heating the melted lipid solvent and bioactive agent to a temperature of between 70 °C and 90 °C.

It is another object of the present invention to provide the method as defined above, wherein said step of emulsifying is at least partially effected simultaneously with a step of cooling.

It is another object of the present invention to provide the method as defined above, wherein said step of cooling further comprises a step of cooling to about 45 °C.

It is another object of the present invention to provide the method as defined above, wherein said step of cooling further comprises a step of cooling to a temperature at least 20 °C below the emulsification temperature.

It is another object of the present invention to provide the method as defined above, further comprising heating an emulsifier to a temperature of at least 90 °C in the presence of said bioactive agent prior to said step of melting said lipid solvent in the presence of said bioactive agent.

It is another object of the present invention to provide the method as defined above, wherein said emulsifier is chosen from the group consisting of PEG esters and sucrose esters.

It is another object of the present invention to provide the method as defined above, wherein said emulsifier is a PEG ester chosen from PEG6000 esters, PEG100 stearate, and PEG40 stearate.

It is another object of the present invention to provide the method as defined above, further comprising a step of heating at least part of said food base carrier prior to said step of adding said food base carrier to said melted lipid solvent and bioactive agent.

It is another object of the present invention to provide the method as defined above, wherein said step of heating at least part of said food base carrier comprises heating a first part of said food base carrier to a first predetermined temperature and heating a second part of said food base carrier to a second predetermined temperature lower than said first predetermined temperature.

It is another object of the present invention to provide the method as defined above, wherein said first predetermined temperature is at least 60 °C and said second predetermined temperature is not above 50 °C.

It is another object of the present invention to provide the method as defined above, wherein said step of adding a food base carrier further comprises adding said first part of said food base carrier, and further comprising a step of adding said second part of said food base carrier during said step of emulsifying, said step of adding said second part taking place only when the temperature of the other components being emulsified is below 60 °C.

It is another object of the present invention to provide the method as defined above, further comprising:

heating a portion of said food base carrier in the presence of potassium sorbate until a solution forms;

cooling said solution to room temperature; and,

adding said solution to said melted lipid phase and bioactive agent.

It is another object of the present invention to provide the method as defined above, wherein said food base carrier is a semisolid at room temperature.

It is another object of the present invention to provide the method as defined above, wherein said food base carrier is a liquid at room temperature.

It is another object of the present invention to provide the method as defined above, wherein said bioactive agent comprises a bioactive food component.

It is another object of the present invention to provide the method as defined above, wherein said step of melting a lipid solvent in the presence of a lipophilic bioactive agent comprises melting a lipid solvent in the presence of a bioactive agent is chosen from the group consisting of curcumin, diindolylmethane, quercetin, diadezin, silymarin, genistein, essential fatty acids, and phytosterols.

It is another object of the present invention to provide the method as defined above, wherein said food base carrier is chosen from the group consisting of saccharide syrups and polysaccharide syrups.

It is another object of the present invention to provide the method as defined above, wherein said syrup is chosen from the group consisting of honey, date syrup, and maple syrup.

It is another object of the present invention to provide the method as defined above, further comprising a step of allowing at least part of said lipid to solidify into particles within said food base carrier.

It is another object of the present invention to provide the method as defined above, further comprising a step of dispersing homogeneously said particles within said food base carrier.

It is another object of the present invention to provide the method as defined above, wherein said step of allowing at least part of said lipid to solidify into particles within said food base carrier further comprises allowing at least part of said lipid to solidify into microspheres within said food base carrier.

It is another object of the present invention to provide the method as defined above, wherein said step of allowing at least part of said lipid to solidify into microspheres within said food base carrier further comprises a step of allowing at least part of said lipid to solidify into microspheres of diameter between 0.5 μm and 5 μm within said food base carrier.

It is another object of the present invention to provide the method as defined above, wherein said step of allowing said lipid to solidify into particles within said food base carrier further comprises a step of allowing said lipid to solidify into particles within said food base carrier chosen from the group consisting of solid particles and semisolid particles.

It is another object of the present invention to provide the method as defined above, wherein at least 70% of said bioactive agent is associated with said particles.

It is another object of the present invention to provide the method as defined above, wherein at least 80% of said bioactive agent is associated with said particles.

It is another object of the present invention to provide the method as defined above, wherein between 90% and 95% of said bioactive agent is associated with said particles.

It is another object of the present invention to provide the method as defined above, further comprising a step of obtaining at least one lipid solvent chosen from the group consisting of hydrogenated castor oil; stearin; palm oil; high-omega-3 sage oil; pomegranate oil; avocado oil; olive oil; and any combination thereof.

It is another object of the present invention to provide the method as defined above, further comprising a step of mixing a bioactive agent with said food base carrier.

It is another object of the present invention to provide the method as defined above, wherein said step of mixing a bioactive agent with said food base carrier further comprises a step of mixing a bioactive agent chosen from the group consisting of vitamins and minerals with said food base carrier.

It is another object of the present invention to provide the method as defined above, wherein said step of mixing a bioactive agent with said food base carrier further comprises a step of mixing a hydrophilic bioactive agent with said food base carrier.

It is another object of the present invention to provide the method as defined above, wherein said step of mixing a hydrophilic bioactive agent with said food base carrier further comprises a step of mixing a hydrophilic bioactive agent chosen from the group consisting of cobalamin, folate, and ferrous gluconate to said food base carrier with said food base carrier.

It is another object of the present invention to provide a functional food comprising a lipophilic bioactive agent, a lipid, and a food base carrier, wherein said lipid is at least partially dispersed as particles within said food base carrier and said at least part of lipophilic bioactive agent is contained within said particles.

It is another object of the present invention to provide the functional food as defined above, wherein said particles constitute between 5% and 40% (w/w) of the food.

It is another object of the present invention to provide the functional food as defined above, wherein said lipophilic bioactive agent is a bioactive food component.

It is another object of the present invention to provide the functional food as defined above, wherein said lipophilic bioactive agent comprises at least one component chosen from the group consisting of curcumin, diindolylmethane, quercetin, diadezin, silymarin, genistein, essential fatty acids, and phytosterols.

It is another object of the present invention to provide the functional food as defined above, wherein said lipid is chosen from the group consisting of hydrogenated castor oil; stearin; palm oil; high-omega-3 sage oil; pomegranate oil; avocado oil; olive oil; and any combination thereof.

It is another object of the present invention to provide the functional food as defined above, wherein said food base carrier is a liquid at room temperature.

It is another object of the present invention to provide the functional food as defined above, wherein said food base carrier is a semisolid at room temperature.

It is another object of the present invention to provide the functional food as defined above, wherein said food base carrier is chosen from the group consisting of saccharide syrups and polysaccharide syrups.

It is another object of the present invention to provide the functional food as defined above, wherein said syrup is chosen from the group consisting of honey, date syrup, and maple syrup.

It is another object of the present invention to provide the functional food as defined above, wherein said particles are homogeneously dispersed within said food base carrier.

It is another object of the present invention to provide the functional food as defined above, wherein said particles comprise microspheres.

It is another object of the present invention to provide the functional food as defined above, wherein said microspheres have diameters between 0.5 μm and 5 μm.

It is another object of the present invention to provide the functional food as defined above, wherein said particles are chosen from the group consisting of solid particles and semisolid particles.

It is another object of the present invention to provide the functional food as defined above, wherein at least 70% of said bioactive agent is associated with said particles.

It is another object of the present invention to provide the functional food as defined above, wherein at least 80% of said bioactive agent is associated with said particles.

It is another object of the present invention to provide the functional food as defined above, wherein between 90% and 95% of said bioactive agent is associated with said particles.

It is another object of the present invention to provide the functional food as defined above, further comprising an emulsifier.

It is another object of the present invention to provide the functional food as defined above, wherein said emulsifier is chosen from the group consisting of PEG esters and sucrose esters.

It is another object of the present invention to provide the functional food as defined above, wherein said emulsifier is a PEG ester chosen from the group consisting of PEG6000 esters, PEG100 stearate, and PEG40 stearate.

It is another object of the present invention to provide the functional food as defined above, wherein said food base carrier is mixed with at least one additional bioactive agent.

It is another object of the present invention to provide the functional food as defined above, wherein said at least one additional bioactive agent is chosen from the group consisting of vitamins and minerals.

It is another object of the present invention to provide the functional food as defined above, wherein said at least one additional bioactive agent is a hydrophilic bioactive agent.

It is another object of the present invention to provide the functional food as defined above, wherein said hydrophilic bioactive agent is chosen from the group consisting of cobalamin, folate, and ferrous gluconate.

It is another object of the present invention to provide a method of providing at least one bioactive agent to a subject in need comprising administering a functional food comprising at least one lipophilic bioactive agent associated with lipid particles dispersed within a food base carrier.

It is another object of the present invention to provide the method as defined above, wherein said step of administering a functional food further comprises a step of administering a functional food characterized by at least one of the following:

said lipophilic bioactive agent is chosen from the group consisting of curcumin, diindolylmethane, quercetin, diadezin, silymarin, genistein, essential fatty acids, and phytosterols; and,

said food base carrier is chosen from the group consisting of saccharide and polysaccharide syrups.

It is another object of the present invention to provide the method as defined above, wherein said step of administering a functional food further comprises a step of administering a functional food comprising an emulsifier.

It is another object of the present invention to provide the method as defined above, wherein said step of administering a functional food comprising an emulsifier further comprises administering a functional food comprising an emulsifier chosen from the group consisting of PEG esters and sucrose esters.

It is another object of the present invention to provide the method as defined above, wherein said step of administering a functional food further comprises a step of administering a

functional food comprising at least one additional bioactive agent, said at least one additional bioactive agent mixed with said food base carrier.

It is another object of the present invention to provide the method as defined above, wherein said step of administering a functional food comprising at least one additional bioactive agent mixed with said food base carrier further comprises a step of administering at least one hydrophilic bioactive agent mixed with said food base carrier.

It is another object of the present invention to provide a method of producing functional food comprising:

a. melting a lipid solvent including a bioactive agent at a temperature of at least 65°C; and,

b. emulsifying the product of step (a) with a semi-solid food base carrier until the formation of an emulsion comprising solid lipid particles; said solid lipid particles comprising said bioactive agent.

It is another object of the present invention to provide a method of producing functional food comprising:

a. melting a lipid solvent including a bioactive agent at a temperature of at least 65°C; and,

b. emulsifying (a) with a liquid food base carrier until the formation of an emulsion comprising solid lipid particles; said solid lipid particles comprising said bioactive agent.

It is another object of the present invention to provide the method as defined above, wherein said bioactive agent is a bioactive food component.

It is another object of the present invention to provide the method as defined above, wherein said bioactive food component is curcumin.

It is another object of the present invention to provide the method as defined above, wherein said bioactive food component is DIM.

It is another object of the present invention to provide the method as defined above, wherein said food base carrier is honey.

It is another object of the present invention to provide the method as defined above, wherein said lipid solvent includes at least one selected from a group consisting of hydrogenated

castor oil, stearin, palm oil, Alina™ oil, High-omega-3 sage oil, pomegranate oil, avocado oil, olive oil, and any combination thereof.

It is another object of the present invention to provide the method as defined above, wherein said lipid solvent further includes an emulsifier.

It is another object of the present invention to provide the method as defined above, wherein said emulsifier includes a PEG ester or a sucrose ester.

It is another object of the present invention to provide the method as defined above, wherein said temperature is 70-90°C.

It is another object of the present invention to provide the method as defined above, wherein said food base is heated to at least 65°C prior to step (b).

It is another object of the present invention to provide the method as defined above, wherein a diameter of said solid lipid particles is in a range of 0.5 to 5 microns.

It is another object of the present invention to provide the method as defined above, wherein step (b) is effected while gradually cooling a mixture of said lipid solvent including said bioactive agent and said food base to a temperature of about 45°C.

It is another object of the present invention to provide a composition of matter comprising a food-based carrier comprising solid lipid particles homogenously dispersed therein and at least one bioactive agent, wherein at least 80% of said at least one bioactive agent is associated with said solid lipid particles.

It is another object of the present invention to provide the composition of matter as defined above, wherein said bioactive agent is a bioactive food component.

It is another object of the present invention to provide the composition of matter as defined above, wherein said bioactive food component is curcumin.

It is another object of the present invention to provide the composition of matter as defined above, wherein said bioactive food component is Diindolylmethane (DIM).

It is another object of the present invention to provide the composition of matter as defined above, wherein said food base carrier is honey.

It is another object of the present invention to provide the composition of matter as defined above, wherein said solid lipid particles includes at least one selected from a group consisting

of hydrogenated castor oil, stearin or palm oil, Alina™ oil, High-omega-3 sage oil, pomegranate oil, avocado oil, olive oil, and any combination thereof.

It is another object of the present invention to provide the composition of matter as defined above, further comprising an emulsifier.

It is another object of the present invention to provide the composition of matter as defined above, wherein said emulsifier is PEG.

It is another object of the present invention to provide the composition of matter as defined above, wherein a diameter of said solid lipid particles is in a range of 0.5 to 5 microns.

It is another object of the present invention to provide a method of providing a biaoactive agent to a subject in need comprising administering a food-based carrier including solid lipid particles homogenously dispersed therein and at least one bioactive agent, wherein at least 80% of said at least one bioactive agent is associated with said solid lipid particles.

It is another object of the present invention to provide the method as defined above, wherein administering is via an oral route.

It is another object of the present invention to provide a composition of matter comprising a honey carrier including solid lipid particles homogenously dispersed therein and curcumin and/or DIM entrapped within said solid lipid particles.

It is another object of the present invention to provide the functional food as defined above, wherein said functional food is stable to storage at 32 °C for three months.

It is another object of the present invention to provide the composition of matter as defined above, wherein said composition of matter is stable to storage at 32 °C for three months.

It is a further object of this invention to disclose a method for increasing the concentration of a lipophilic bioactive agent within the body of a patient, comprising: incorporating said lipophilic bioactive agent into a functional food as defined in any of the above; and, administering a predetermined quantity of said functional food to a patient in need.

It is a further object of this invention to disclose a method for increasing the concentration of a lipophilic bioactive agent within the body of a patient, comprising: administering to a patient in need a predetermined quantity of a functional food as defined in any of the above comprising said lipophilic bioactive agent.

It is a further object of this invention to disclose such a method for increasing the concentration of a lipophilic bioactive agent within the body of a patient as defined in either of the above, wherein said lipophilic bioactive agent is a bioactive food component.

It is a further object of this invention to disclose such a method for increasing the concentration of a lipophilic bioactive agent within the body of a patient as defined in any of the above, wherein said lipophilic bioactive agent comprises at least one component chosen from the group consisting of curcumin, diindolylmethane, quercetin, diadezin, silymarin, genistein, essential fatty acids, and phytosterols.

It is a further object of this invention to disclose such a method for increasing the concentration of a lipophilic bioactive agent within the body of a patient as defined in any of the above, wherein said lipid solvent is chosen from the group consisting of hydrogenated castor oil; stearin; palm oil; high-omega-3 sage oil; pomegranate oil; avocado oil; olive oil; and any combination thereof.

It is a further object of this invention to disclose such a method for increasing the concentration of a lipophilic bioactive agent within the body of a patient as defined in any of the above, further comprising a step of raising the concentration of said lipophilic bioactive agent in the blood of said patient in need.

It is a further object of this invention to disclose such a method for increasing the concentration of a lipophilic bioactive agent within the body of a patient as defined in any of the above, further comprising a step of raising the concentration of said lipophilic bioactive agent in the liver of said patient in need.

It is a further object of this invention to disclose such a method for increasing the concentration of a lipophilic bioactive agent within the body of a patient as defined in any of the above, further comprising a step of raising the concentration of said lipophilic bioactive agent in the gastrointestinal mucosa of said patient in need.

It is a further object of this invention to disclose a method for treating a condition ameliorated by a lipophilic bioactive agent comprising: incorporating said lipophilic bioactive agent into a functional food as defined in any of the above and administering a predetermined quantity of said functional food to a patient suffering from said condition.

It is a further object of this invention to disclose a method for treating a condition ameliorated by a lipophilic bioactive agent, comprising administering to a patient in need a predetermined

quantity of a functional food as defined in any of the above comprising said lipophilic bioactive agent.

It is a further object of this invention to disclose such a method for treating a condition ameliorated by a lipophilic bioactive agent as defined in either of the above, wherein said lipophilic bioactive agent is a bioactive food component.

It is a further object of this invention to disclose such a method for treating a condition ameliorated by a lipophilic bioactive agent as defined in any of the above, wherein said lipophilic bioactive agent comprises at least one component chosen from the group consisting of curcumin, diindolylmethane, quercetin, diadezin, silymarin, genistein, essential fatty acids, and phytosterols.

It is a further object of this invention to disclose such a method for treating a condition ameliorated by a lipophilic bioactive agent as defined in any of the above, wherein said lipid solvent is chosen from the group consisting of hydrogenated castor oil; stearin; palm oil; high-omega-3 sage oil; pomegranate oil; avocado oil; olive oil; and any combination thereof.

It is a further object of this invention to disclose such a method for treating a condition ameliorated by a lipophilic bioactive agent as defined in any of the above, wherein said condition is chosen from the group consisting of immune diseases, heart disease, respiratory diseases, inflammation, cancer, leukemia, lymphoma, gastrointestinal cancers, genitourinary cancers, breast cancer, ovarian cancer, head and neck squamous cell carcinoma, lung cancer, melanoma, neurological cancers, gastrointestinal conditions, gastric ulcers, colitis, bowel disease, crohn's disease, colorectal cancer, fatty liver disease and Non-Alcoholic Steatohepatitis (NASH), edema, arthritis, pancreatitis, ocular conditions, inflammatory diseases and any combination thereof.

It is a further object of this invention to disclose such a method for treating a condition ameliorated by a lipophilic bioactive agent as defined in any of the above, wherein said condition is chosen from the group consisting of respiratory papillomatosis, prostatitis, cataracts, allergies, bronchitis, asthma, celiac disease, non-celiac gluten sensitivity, and irritable bowel syndrome.

It is a further object of this invention to disclose a method for providing adjunct therapy to a patient suffering from cancer, comprising incorporating said lipophilic bioactive agent into a functional food by the method as defined in any of the above and administering a

predetermined quantity of said functional food to said patient in conjuction with another anticancer therapy.

It is a further object of this invention to disclose a method for providing adjunct therapy to a patient suffering from cancer, comprising administering to said patient a predetermined quantity of a functional food as defined in any of the above comprising said lipophilic bioactive agent in conjunction with another anticancer therapy.

It is a further object of this invention to disclose a method for providing therapy in term of Parma, i.e. botanical drug to a patient suffering from solid cancers, leukemia, lymphoma, gastrointestinal cancers, genitourinary cancers, breast cancer, ovarian cancer, head and neck squamous cell carcinoma, lung cancer, melanoma, neurological cancers, and sarcoma, also gastrointestinal conditions such as: gastric ulcers, colitis, bowel disease, crohn's disease, colorectal cancer, fatty liver disease and Non-Alcoholic Steatohepatitis (NASH), edema, arthritis, pancreatitis, ocular conditions, inflammatory diseases, comprising incorporating said lipophilic bioactive agent into a pharmaceutical drug by the method as defined in any of the above.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of the preferred embodiments of the present invention only, and are presented in the cause of providing what is believed to be the most useful and readily understood description of the principles and conceptual aspects of the invention. In this regard, no attempt is made to show structural details of the invention in more detail than is necessary for a fundamental understanding of the invention, the description taken with the drawings making apparent to those skilled in the art how the several forms of the invention may be embodied in practice.

In the drawings:

FIG. 1 illustrates the chemical structure of curcumin and its metabolites.

FIG. 2 is a flow chart outlining a method of producing a solid lipid fine dispersion of curcumin (and/or DIM) in honey.

FIG. 3 is a microscope image of curcumin powder particles (crystals) in honey with particle sizes of 5 - 100 μm.

FIG. 4 presents microscope images of curcumin solid lipid particles (SLPs) in honey with a mean particle size of <5 μm; the curcumin SLPs dispersed in water; and curcumin powder dispersed in water.

FIGs. 5a-5c presents graphs of curcumin levels in rats following administration of 400 mg/kg unformulated curcumin or curcumin that had been formulated according to one embodiment of the present invention.

Fig. 6a illustrates the delta in the plasma curcumin concentration while using the SLP and Meriva as a function of time (15 minutes, 30 minutes, 60 minutes and 120 minutes).

FIG. 6b illustrates the delta in the mucosa curcumin concentration while using the SLP and Meriva as a function of time (15 minutes, 30 minutes, 60 minutes and 120 minutes).

DETAILED DESCRIPTION OF THE INVENTION

The following description is provided, alongside all chapters of the present invention, so as to enable any person skilled in the art to make use of the invention and sets forth the best modes contemplated by the inventor of carrying out this invention. Various modifications, however, is adapted to remain apparent to those skilled in the art, since the generic principles of the present invention have been defined specifically to provides a unique functional food and a method of producing the same.

Furthermore, the present invention provides a composition which can be used to treat disorders and promote well being. Specifically, the present invention can be used to treat subjects suffering from e.g., immune disorders cancer, solid cancers, leukemia, lymphoma, gastrointestinal cancers, genitourinary cancers, breast cancer, ovarian cancer, head and neck squamous cell carcinoma, lung cancer, melanoma, neurological cancers, and sarcoma, also gastrointestinal conditions such as: gastric ulcers, colitis, bowel disease, crohn's disease, colorectal cancer, fatty liver disease and Non-Alcoholic Steatohepatitis (NASH), edema, arthritis, pancreatitis, ocular conditions, inflammatory diseases, comprising incorporating said lipophilic bioactive agent into a pharmaceutical drug or any combination thereof as will be described hereinafer.

It is within the scope of the present invention to disclose a method for providing therapy in term of Parma, i.e. botanical drug to a patient suffering from solid cancers, gastrointestinal

conditions such as: gastric ulcers, colitis, bowel disease, crohn's disease, colorectal cancer, edema, arthritis, pancreatitis, ocular conditions, inflammatory diseases, comprising incorporating said lipophilic bioactive agent into a pharmaceutical drug by the method as will be disclosed hereinafter.

The principles and operation of the present invention may be better understood with reference to the drawings and accompanying descriptions.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not limited in its application to the details set forth in the following description or exemplified by the examples. The invention is capable of other embodiments or of being practiced or carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein is for the purpose of description and should not be regarded as limiting.

While reducing the present invention to practice, the present inventors have devised a novel approach for formulating a composition which includes a food based carrier mixed with solid lipid particles loaded with a bioactive agent. The present composition facilitates delivery of the bioactive agent to the GI tract while providing a nutrient base and eliminating or reducing offensive odors or tastes associated with the bioactive agent.

Thus, according to one aspect of the present invention there is provided a composition which can be used to treat a condition or disorder or promote or maintain well being in a subject such as a human. As is described hereinbelow, the present composition can be used alone or as a supplement to other treatment approaches.

It is a further object of this invention to disclose a method for providing therapy in term of Parma, i.e. botanical drug to a patient suffering from solid cancers, gastrointestinal conditions such as: gastric ulcers, colitis, bowel disease, crohn's disease, colorectal cancer, edema, arthritis, pancreatitis, ocular conditions, inflammatory diseases, comprising incorporating said lipophilic bioactive agent into a pharmaceutical drug by the method as defined in any of the above.

The present composition includes a food-based carrier mixed with solid lipid particles loaded with at least one bioactive agent.

As used herein, the phrase **"food-based carrier"** refers to any liquid or semi-solid composition which is defined as food or is derived from food. Examples of food-based

carriers include saccharide or polysaccharide syrups such as honey, date syrup and maple syrup. Preferred are food based carriers that naturally include a high nutrient content as well as beneficial elements such as minerals.

As used herein, the term **"particles"** when used with reference to solid lipids refers to nano or micro particles.

As used herein, the phrase **"bioactive agent"** refers to a substantially purified substance that exerts a local or systemic biological (e.g. physiological) effect. A bioactive component can include one or more bioactive agents. A bioactive component can be derived from an extract of a vegetable or fruit or other natural sources.

As used herein, with reference to quantities, the term **"about"** refers to ± 10 % of the nominal quantity.

As is further described below and in the Examples section which follows, the present inventors have devised a novel approach for producing the present composition. Such an approach enables formation of the solid lipid particles (SLPs) loaded with the bioactive agent within the food based carrier, thus eliminating the need first to manufacture the bioactive agent-loaded SLPs and then to mix them with the carrier. It will be appreciated that such an approach substantially reduces the time and effort, as well as costs needed for production. In addition, such an approach obviates the need to use harmful organic solvents such as ethanol, hexanol, ethyl acetate, acetone, ketones or ethyl methyl ketone (see US Pat. 6,086,915).

As is described in detail in the Examples section which follows, the present composition is produced by co-melting lipophilic bioactive agents and lipids (that are solid at room temperature), heating to a temperature of between 65 and 90 °C and emulsifying the melt in honey (or similar food based carrier) while cooling (in preferred embodiments, to 45 °C) thereby allowing the lipids to solidify into solid or semisolid microspheres within the honey.

The present composition is characterized by several unique features. The solid lipid particles are homogenously dispersed within the food-based carrier and constitute 5-40% (w/w) of the composition with. At least 70% (in preferred embodiments, at least 80%; in the most preferred embodiments, at least 90-95%) of the bioactive agent or agents are associated with the solid lipid particles.

This enables as much as 30% loading of a carrier such as honey with a bioactive agent thereby enabling delivery of large amounts of the bioactive agent using the present composition.

In addition, the use of solid lipid particles for entrapping the bioactive agent masks offensive odors or tastes associated therewith as well as protecting the bioactive agent from GI tract degradation.

Furthermore, the solid lipid particles within the functional food disclosed herein are small and uniform in size and thus facilitate dissolution and delivery of the active ingredient entrapped therein as well as maintaining the smooth texture of the food carrier. For example, in the case of curcumin, SLP packaging of this active agent reduced the particle size (in water) severalfold (see Figure 4a-c).

In addition, since release of the bioactive agent from SLPs depends upon enzymatic degradation of the lipid, a more controlled and targeted release of the bioactive agent is enabled.

Finally, since SLP-carried bioactive agents are dispersed in the stomach as very fine micronized particles (See Figure 4b), dissolution and solubility of a bioactive agent is substantially enhanced by the present formulation.

As is mentioned above, several types of food based carriers are suitable for use with the present composition; carriers such as honey (in raw or mostly raw forms), date syrup and maple syrup are presently preferred due to their nutrient and mineral/element content.

Honey

The end result of the work of the bee community is honey. It contains about 41% fructose. This makes it the sweetest sugar known to mankind. It also contains about 35% glucose, about 17% water, about 2% sucrose, and small amounts of minerals and amino acids.

Honey also contains nearly all of the trace elements that the human body needs. The health benefits of honey depend on its quality which is a function of the pollen collected by honey bees. The quality of honey is also dictated by processing which can remove many of the phytonutrients found in raw honey.

Raw honey contains small amounts of the same resins found in propolis which is a complex mixture of resins and other substances that honeybees use to seal the hive and make it safe from bacteria and other micro-organisms. The resins found in propolis only represent a small part of the phytonutrients found in propolis and honey, other phytonutrients found both in honey and propolis have been shown to possess cancer-preventing and anti-tumor properties. These substances include caffeic acid methyl caffeate, phenylethyl caffeate, and phenylethyl dimethylcaffeate. Researchers have discovered that these substances prevent colon cancer in animals by shutting down the activity of two intracellular enzymes, phosphatidylinositol-specific phospholipase C and lipoxygenase. When raw honey is extensively processed and heated, the benefits of these phytonutrients are largely eliminated.

Date Syrup

Dates (Phoenix dactylifera L.) are an important crop in the desert regions of Middle Eastern countries.

Date fruit is a highly nutritious food product. It is rich in calories and in minerals such as iron and potassium and contains modest amounts of folate, and a small amount of vitamins A and B. Dates are considered beneficial for treatment of anemia, constipation and fatigue.

Date syrup has a consistency similar to that of honey while being darker in appearance and having a unique flavor. Date syrup contains about 88% sugars, mainly glucose and fructose, and is a good source of essential elements such as calcium, phosphorus, potassium and magnesium. Date syrup is low in sodium, and as such it is a suitable food for low sodium diets.

Several bioactive agents can be used with the present composition including for example, curcumin, Silymarin, DIM, Genistein, Quercetin and Diadezin. Combinations of bioactive agents, e.g. curcumin + diindolylmethane (DIM) or essential fatty acids (EPA and EHA) and phytosterols such as beta sitosterol, stigmasterol, campesterol, and brassicasterol can also be used with the present invention.

The bioactive agent or agents are preferably associated with the solid lipid particles (e.g. entrapped therein) as described herein, although in some cases, the composition can also include additional bioactive agents (e.g. vitamins or minerals) that are directly mixed with the food based carrier.

Since solid lipid particles are designed for entrapping hydrophobic (water insoluble) compounds, hydrophilic bioactive agents would not be suitable for SLP entrapment and as such are preferably added directly to the carrier of the present composition.

Thus, bioactive agents such as curcumin and DIM as well as quercetin and diadezin which are hydrophobic and thus poorly miscible in a food-based carrier are preferably entrapped in the solid lipid particles of the present composition, while other bioactive agents such as cobalamin, folate and iron (as ferrous gluconate) are preferably mixed directly into the food-based carrier of the present composition.

Curcumin

Curcumin a plant polyphenol is an edible component of the plant Curcumina longa, a key ingredient of Indian curry. Curcumin has been shown to be non-toxic, to have antioxidant activity, to inhibit the proliferation of cancer cells, and to inhibit inflammation. Curcumin inhibits the production of pro-inflammatory cytokines, such as TNFa, Interferon gamma, and IL-6 secreted by activated macrophages and T cells during an inflammatory response. The mechanism of action of curcumin involves, among other things, the inhibition of important intracellular signaling pathways that participate in cancer cells and in the inflammatory response mediated by NFkappaB, COX, lipooxygenase (LOX), and inducible nitric oxide synthase (iNOS). Curcumin is capable of reducing aberrant up-regulation of COX and/or iNOS in early stages of carcinogenesis and to also inhibit key intracellular elements involved in cancer cell proliferation. Significant preventive and/or curative effects by curcumin have been observed in experimental animal models of a number of diseases, including cancer. Because of its lack of apparent toxicity, curcumin has been recently added (August, 2009) to FDA's GRAS (Generally Regarded As Safe) list. The recommended maximum safe daily dose was set at up to 1.75 grams, per human, per day.

Ingested curcumin exhibits low plasma and tissue levels of mostly due to poor absorption, rapid metabolism (see Figure 1), and rapid systemic elimination (Anand et al. Molecular Pharmaceutics Vol. 4, No. 6; 2007). Numerous approaches have been undertaken to improve the bioavailability of curcumin. These approaches include use of adjuvants such as piperine that interfere with glucuronidation; use of liposomal or particulate delivery approaches; use of curcumin phospholipid complexes; and use of curcumin structural analogues (e.g., EF-24).

Figures 4a-c illustrate SLP-curcumin particles mixed in a honey-based carrier (Figure 4a), dispersed in water (Figure 4b) and curcumin crystals resultant from mixing curcumin powder with water (Figure 4c).

Diindolylmethane (DIM)

DIM is a bioactive agent derived from Brassica vegetables such as cabbage, cauliflower, Brussels sprouts and broccoli. Results of several studies indicate that DIM exhibits promising cancer-protective activities, especially against mammary neoplasia (breast cancer). Oral intubation of DIM in a single dose before carcinogen treatment reduced the incidence and multiplicity of dimethylbenzanthracene-induced mammary tumors in rats by 70 to 80% (Wattenberg et al., Cancer Res., 38, (1978) 1410–1413). Also, repeated oral administrations of DIM during the promotion stage of dimethylbenzanthracene-induced mammary tumorogenesis inhibited tumor growth in rodents by as much as 95% (Chen et al., Carcinogenesis 19 (1998), pp. 1631–1639).

DIM is also widely used as adjunct therapy for recurrent respiratory papillomatosis (Auborn et al., Antivir. Ther. 7 (2002) 1-9.), caused by certain types of human papillomaviruses (HPVs).

DIM's anti-tumor activity is possibly through modulation of the immune response. Studies have shown that exposure to DIM could influence major immune responses, including natural killer cell activity, antibody production, and T-cell-mediated immunity. Importantly, DIM upregulates the expression of both interferon (IFN)-γ and IFN-γ receptor, and potentiates the effects of IFN-γ-induced expression of MHC I antigens in human breast cancer cells, making them susceptible to effector T cells.

IFN-γ is a central regulator of immune and inflammatory responses that contributes to the inhibition of primary and transplanted tumor development, as well as anti viral response. Thus, if DIM has generalized immune stimulatory properties, these capacities might indeed contribute to its anti-carcinogenic effects. In mice, DIM was shown to induce splenocyte (B and T cell) proliferation, reactive oxygen species (ROS) generation, cytokine production and resistance to viral infection (Xue et al., J. Nutr. Biochem. 19, (2008), 336-344). The addition of DIM to cultured cells enhanced both splenocyte proliferation and ROS production by peritoneal macrophages. Since cytokines are major mediators of host defense they regulate communication between antigen-presenting cells, lymphocytes and other host cells during an

immune response. The cytokine repertoire present at a tissue site determines the type of host response directed against a tumor or an infection. Indeed, cytokines promoting the development of T-cell mediated immunity can induce or enhance the anti-tumor and anti-microbial immunity. Importantly, the hematopoietic growth factor, G-CSF is a cytokine that induces the bone marrow to generate more leukocytes, which are essential for fighting infection and cancer. Collectively, these data strongly suggest that DIM has potent immunomodulating activities that are consistent with the anti-tumor, anti-viral and anti-bacterial activities of this dietary Indole.

Quercetin

Quercetin is a plant-derived flavonoid that may have anti-inflammatory and antioxidant properties. Quercetin may have positive effects in combating or helping to prevent cancer, prostatitis, heart disease, cataracts, allergies/inflammations, and respiratory diseases such as bronchitis and asthma. An 8-year study found that the presence of the three flavonols kaempferol, quercetin, and myricetin in a person's normal diet was associated with a reduced risk of pancreatic cancer. Quercetin has demonstrated significant anti-inflammatory activity by inhibiting both manufacture and release of histamine and other allergic/inflammatory mediators. In addition, it exerts potent antioxidant activity and vitamin C-sparing action. In mice, an oral quercetin dose of 12.5 to 25 mg/kg increased gene expression of mitochondrial biomarkers and improved exercise endurance. An in vitro study showed that the combination of quercetin and resveratrol inhibited production of fat cells.

Genistein/Diadezin

Genistein and diadzein are isoflavones found in a number of plants including lupin, fava beans, soybeans, kudzu, and psoralea. Besides functioning as antioxidants and anthelmintics, many isoflavones have been shown to interact with animal and human estrogen receptors, causing effects in the body similar to those caused by the hormone estrogen.

Genistein and other isoflavones have been found to have antiangiogenic effects (blocking formation of new blood vessels), and may block the uncontrolled cell growth associated with cancer, most likely by inhibiting the activity of substances in the body that regulate cell division and cell survival. Studies have also found genistein to be useful in combating

leukemia and that it can be used in combination with certain other leukemia combating drugs to improve their efficacy.

Silymarin

Silymarin (SM) is a lipophilic extract of milk thistle and is composed of several isomer flavonolignans. In vitro and animal research suggest that silibinin (major active component of silymarin) has hepatoprotective (antihepatotoxic) properties and anti-cancer effects in human prostate adenocarcinoma cells, estrogen-dependent and -independent human breast carcinoma cells, human ectocervical carcinoma cells, human colon cancer cells, and both small and nonsmall human lung carcinoma cells; see, for example, http://en.wikipedia.org/wiki/Silibinin#cite_note-0.

Cobalamin (Vitamin B_{12})

Cobalamin contributes to the formation of red blood cells and bone marrow, the metabolism of carbohydrates, fats and proteins, nerve and cardiovascular functions and plays a role in DNA synthesis. Deficiency of this vitamin may cause anemia, exhaustion, irritation, depression, shortness of breath, difficulty walking, memory loss, mood swings, disorientation, dementia and constipation. Cobalamin doses greater than 3 milligrams daily may cause eye conditions. Cobalamin deficiency occurs primarily in people with malabsorption and myelodysplastic syndrome. The remaining cases of nutrient-deficiency anemia are usually associated with cobalamin, most frequently related to food-cobalamin malabsorption, and/or Folate deficiency. Cobalamin deficiency occurs frequently among patients with malabsorption, but it is often unrecognized or not investigated because the clinical manifestations are subtle.

Folate

Folate plays an important role in the metabolism of nucleic acids and amino acids. Consequentially, it is essential for cell growth and development and normal functionality of the nervous system. Folate deficiency in the elderly is characterized by anemia which is accompanied by symptoms such as, shortness of breath, fatigue and weakness. Folate deficiency may also cause a sore tongue, depression, nerve damage and infant neural tube defects, heart defects and limb malformations. Folate doses larger than 400 micrograms daily may cause anemia and may mask symptoms of a cobalamin deficiency.

Iron

Iron is an essential part of many biological molecules such as hemoglobin. The human body absorbs iron from animal sources faster than iron from plant sources. Iron deficiency is a common condition and can lead to disorders such as anemia. The recommended daily dose of iron for humans is about 10 milligrams; a normal diet typically provides that amount but patients with malabsorption or frequent diarrhea require supplementation.

As is mentioned above, the present composition can be used to treat disorders or promote good health.

Thus, according to another aspect of the present invention there is provided a method of treating a subject having a disorder which would benefit from the physiological effects of the curcumin and/or DIM provided by the present composition and the nutritional effects of the food based carrier of the composition.

One example of such a disorder is cancer. In cancer treatment, the food based carrier is honey in its minimally processed form, since it contains natural anti-cancer chemicals and provides nutrition and the physiologically active ingredients are DIM and optionally curcumin (both in SLPs).

Such a composition is especially suitable for use as adjunct cancer therapy. The effect of chemotherapy is not specific to cancer cells and as such, it leads to severe side effects, such as immunosuppression and myelosuppression. DIM would reduce chemotherapy-induced granulocytopenia, and stimulate immune responses in chemotherapy-treated cancer patients that are immunocompromised. In addition, since honey, DIM and curcumin have anti-viral and anti-bacterial properties, consumption of the present composition by chemotherapy-treated cancer patients, can help reduce the incidence of viral and bacterial infections associated with chemotherapy.

Cancer patients can be treated with three daily doses of the present composition, with each dose including 1 gram of honey, about 200 mg of DIM and about 400 mg of curcumin.

The present invention can also be used to treat disorders associated with aging and immunosenescence.

The immune system undergoes characteristic and multifaceted changes with aging. These changes occur in all type of leukocytes, including, neutrophils, T-cells, B-cells,

monocyte/macrophages, dendritic cells and natural killer cells. Accordingly, aging affects both innate and adaptive immune functions. Collectively, this process is called "immunosenescence" and it refers to the natural gradual deterioration of the immune system with advancing age. It involves both the host's capacity to respond to infections and the development of long-term immune memory, especially by vaccination. This age-associated immune deficiency is ubiquitous and found in both long- and short-lived species as a function of their age relative to life expectancy rather than chronological time. It is considered a major contributory factor to the increased frequency of morbidity and mortality among the elderly. Immunosenescence is not a random deteriorative phenomenon, rather it appears to inversely repeat an evolutionary pattern and most of the parameters affected by immunosenescence appear to be under genetic control. Immunosenescence can also be sometimes envisaged as the result of the continuous challenge of the unavoidable exposure to a variety of antigens such as viruses and bacteria. Immunosenescence is a multifactorial condition leading to many pathologically significant health problems in the aged population. Age-dependent biological changes such as depletion of hematopoietic stem cells, decline in the total number of phagocytes and NK cells and a decline in humoral immunity contribute to the onset of immunosenescence.

Thus aging is associated with a decline in both the production of new naive lymphocytes and the functional competence of memory cell populations. This has been implicated in the increasing frequency and severity of diseases such as cancer, chronic inflammatory disorders and autoimmunity. A problem of infections in the elderly is that they frequently present with non-specific signs and symptoms. Ultimately, this provides problems in diagnosis and subsequently, treatment.

Anemia is highly prevalent in the elderly population, including those individuals who are in long term care facilities and geriatric wards. Importantly, even mild anemia is associated with adverse health outcomes. Therefore, anemia is of a great healthcare concern. The most frequent etiologies of anemia in the elderly are anemia of chronic disease/inflammation; iron, folate and vitamin B_{12} (cobalamin).

A composition including honey, DIM and vitamins can be used to treat viral and bacterial infections as well as anemia in populations such as the elderly, the malnourished and the like. The honey and DIM would provide antibacterial and antiviral functions while DIM would

increase hematopoietic cytokine production. Key vitamins such as cobalamin and folate will enhance blood production.

Treatment can include five daily doses of a composition including 1 g of honey, 200 mg of DIM, 50 μg of cobalamin, 20 μg of folate and 3 mg of iron.

The present invention can also be used to treat disorders such as Celiac Disease (CD), Non-Celiac Gluten Sensitivity (NCGS) and Irritable Bowel Syndrome (IBS).

Celiac disease is an immunologically-mediated enteropathy, triggered in genetically susceptible subjects, many of whom carry the HLA-DQ (haplotypes 2 or 8). The intake of certain proteins, primarily gluten from wheat, and similar proteins from barley and rye induce the disease. Up to 1% of the entire population suffers from CD. People with CD also have one or more additional food allergies, which may include milk protein, corn and soy. Symptoms include chronic diarrhea, abdominal pain, cramping, weight loss or growth inhibition, musculoskeletal pain, neurological involvement and fatigue.

There is evidence suggesting that upon exposure to gluten an immune reaction is triggered towards gluten-derived peptides generated by the enzyme transglutaminase. In turn, these gluten-derived peptides stimulate immune cross-reaction against self components of the small bowel. This classical autoimmune response gives rise to an inflammatory reaction in the intestines. CD causes small-bowel mucosal villous atrophy with crypt hyperplasia. Importantly, the disease significantly increases the risk of adenocarcinoma of the small intestines and lymphoma of the small bowel.

The inflammatory process, mediated predominantly by T cells, leads to disruption of the structure and function of the small bowel's mucosal lining and causes malabsorption; it impairs the body's ability to absorb nutrients, minerals such as calcium and iron, and fat-soluble vitamins. In fact, CD can be considered as an archetypal malabsorption syndrome, and is a frequent cause of anemia. In many cases anemia has been reported as the only initial manifestation, or the most frequent extra-intestinal symptom of CD. Folate (vitamin B9) and cobalamin (vitamin B12) deficiencies are known complications of CD. Another common nutritional anemia associated with CD is iron deficiency. Iron deficiency anemia was reported in up to 46% of patients with subclinical CD. Some CD patients also develop osteoporosis and bone fractures due to the malabsorption of vitamin D and hypocalcaemia.

Gluten intolerance is a broad term which includes various degrees of gluten sensitivity. It is estimated that about 15% of all people are gluten sensitive, but only about 1% have CD as determined by testing positive in the currently available immunoassays and biopsies. Although antibody serology is an important tool in the confirmation of CD, it does not always correlate with the typical mucosal appearance of CD, namely, the villus atrophy of the small intestine. Some patients with positive CD serology have normal intestinal mucosa without full blown symptoms of CD. However, they are at increased risk of future CD development.

The majority of people with gluten sensitivity do not have CD. Rather, they have a condition called Non Celiac Gluten Sensitivity (NCGS). People with NCGS exhibit gastrointestinal symptoms including, diarrhea, bloatdeness, cramping, etc. Also associated with NCGS are headache, fatigue, infertility, miscarriage and malabsorption. It is believed that, like in CD, the immune response of people with NCGS is triggered by gluten, but it does not lead to the destruction and remodeling of the intestines. A recent publication suggests that, even in the absence of fully developed CD, gluten can induce symptoms similar to irritable bowel syndrome (IBS). That study presented the hypothesis that gluten sensitivity and post-infectious IBS provide two triggers that can explain at least part of the spectrum that constitutes IBS.

IBS affects between 5-20% of the population of the western world. The wide range may be linked to the fact that the symptoms of non-specific dyspepsia are sometimes confused with those of IBS. Importantly, IBS is the second leading cause of work absenteeism. Women are four times more likely to suffer from IBS than men. Symptoms of IBS include irregular bowel function, bloating, abdominal pain, cramping, diarrhea, and constipation. Stress and other psychological factors are known to exacerbate the intensity and frequency of the syndrome.

The main characteristic of IBS is irregular defecation, and IBS is divided into two types based on the irregularity observed: IBS-D (diarrhea) and IBS-C (constipation). It is estimated that about 50% of all IBS patients use alternative medicine because of the lack of effectiveness of currently prescribed medications.

Recent scientific data indicate that inflammation plays an important role in the pathophysiology of IBS. IBS patients have a significantly elevated level of the pro-inflammatory cytokine IL-6 in their circulation, as well as a very high level of the

cyclooxygenase (COX) cycle metabolite prostaglandin E2, which is known to be produced by inflammatory stimuli. Evidence also indicates that the inflammatory response is the result of immune activation. The current scientific working hypothesis for the syndrome is that there is a link between the central nerve system and immune activation of unknown etiology which interacts and leads to gastrointestinal inflammation.

At present, the only effective treatment of CD, and NCGS is a life-long gluten free diet. No medication exists that will prevent the damage or prevent the immune/inflammatory system from attacking the gut when gluten is present. With the exception of CD patients who became refractory to gluten-free diet, strict adherence to the gluten-free diet allows the intestines to heal, leading to resolution of all symptoms in most cases. Also, depending on how soon the gluten-free diet has begun, the increased risk of osteoporosis and the development of intestinal cancer are reduced. In many countries, gluten-free products are available by physician's prescription and are reimbursed by health insurance plans. The diet, however, can be cumbersome; failure to comply with the diet causes the severe relapse of symptoms. Gluten-free products are usually more expensive and harder to find than common gluten-containing foods. The total market of gluten-free products in the USA is about $2 billion a year.

The common pathophysiological manifestation of CD, NCGS and IBS is intestinal inflammation. Thus, a composition including a food based carrier and curcumin in solid lipid particles can be used to treat such disorders. Curcumin inhibits stimulus-dependent activation of immune cells and the production of pro-immune/inflammatory cytokines without causing the severe side-effects frequently associated with the use of anti-inflammatories that inhibit the COX and LOX cycles.

It should be noted that curcumin has a chemopreventive effect against the development of cancer. Therefore, its consumption via honey, on a regular basis, may reduce the high risk of adenocarcinoma and lymphoma development in the intestines of people with CD, as well other patients' populations suffering from intestinal malfunction.

Treatment can include three daily doses of a composition that includes 1 gram of the honey and about 400 mg of curcumin (in SLPs).

The present compositions can be presented in a dispenser device, such as a squeeze bottle or foil sachet or encapsulated in ingestible capsule (e.g. gel capsule) which may be packaged in foil blisters. The dispenser device or pack may include one or more dosage units of the

present composition. The dispenser device or capsule pack may be accompanied by instructions for consumption. The dispenser device or pack may also be accompanied by a notice in a form prescribed by a governmental agency regulating the manufacture, use, or sale of neutraceuticals, which notice is reflective of approval by the agency of the form of the compositions for human or veterinary administration. Such notice, for example, may include labeling approved by the U.S. Food and Drug Administration.

Additional objects, advantages, and novel features of the present invention will become apparent to one ordinarily skilled in the art upon examination of the following examples, which are not intended to be limiting. Additionally, each of the various embodiments and aspects of the present invention as delineated hereinabove and as claimed in the claims section below finds experimental support in the following examples.

EXAMPLES

Reference is now made to the following examples, which together with the above descriptions, illustrate the invention in a non limiting fashion.

Solid Lipid Micronized Dispersions of Curcumin in Honey

A solid lipid dispersion is a delivery system in which the bioactive agent is solubilized or dissolved in hot melted lipids that do solidify at room temperature. The hot melt is emulsified with an aqueous medium and cooled to room temperature to solidify as particles which include the bioactive agent within their core.

The present study tested whether curcumin, a polyphenolic compound derived from dietary spice turmeric, can be emulsified within a honey-based carrier using Solid Lipid Dispersion technology.

In order to optimize the solid lipid emulsion and enhance its curcumin-carrying capability, the present inventors conducted several pre-formulation studies which included the following:

(i) testing solubility of curcumin in various oils;

(ii) design of solid lipid formulation matrixes for curcumin in honey;

(iii) testing formulations properties including consistency and organoleptic, taste and odor properties; and

(iv) testing the formulation in a pilot process for physical and chemical stability.

A general list of components used in the present study is provided in Table 1 below.

Table 1: materials

Material Name	Synonym
Cocoglycerids	Novata A
Glyceryl Monostearate GMS V PH	Cutina GMS V PH
Mono/Diglycerids of caprylic acid	Capmul MCM C8
Peg-40 stearate	Mirj 52s
Polyethylene glycol 100 stearate	Myrj 59P
Polyethylene glycol 400	PEG 400
Polysorbate 80	Montanox 80 G P/Twe
Polyethylene Glycol 6000	PEG 6000
Sucrose Fatty Acid 1811	Surfope 1811
Sucrose Fatty Ester	Surfope 1815
Hydrogenated castor oil	Cutina HR PH
MCT oil	Capric/Caprilic Triglycerides
Honey	
3,3- Diindolylmethane	DIM
Curcumin C3 complex	Curcumin

EXAMPLE 1

Curcumin Solubility

Curcumin is insoluble in water and therefore its solubility was tested in various solvents. Curcumin solubility was measured by vigorously mixing 400 mg of curcumin in 2 g of a test solvent and heating the sample to 90 °C. Samples were cooled to room temperature and inspected visually and solubility recorded. Table 2 below provides the results of the solubility study. Curcumin showed very limited or poor solubility in the oils tested, but was soluble in Polyethylene glycol (PEG).

Table 2: Curcumin solubility

Curcumin solubility Solvent	0.4g Curcumin in 2gr Solvent Solubility
Capmul MCM C8	partly soluble, recrystallizes at low temp
Propylene Glycol Monocaprylate Capryol 90 HLB6	not soluble
MCT oil	not soluble
Glycerin	not soluble
PEG 400	soluble
Honey room temperature	not soluble
Honey 50C	not soluble
crushed sesame seeds – 0.4g curcumin in 7g	not soluble, dispersive
olive oil	not soluble
glycerin mono oleate	not soluble
Span 60	not soluble
Triomal (Omega3 and 6)a	not soluble
crushed sesame seeds and honey	not soluble, dispersive, colors tong yellow

In order to further test curcumin solubility, a solubility matrix was constructed (Table 3). The solubility of curcumin in various lipid mixtures was tested and the mixture was then homogenized in honey.

Table 3: Curcumin solubility matrix

	CUR1	CUR2	CUR3	CUR4	CUR5	CUR6	CUR7	CUR8
	W/W	W/W	W/W	W/W	W/W	W/W	W/W	W/W
Curcumin	33.33	33.33	33.33	33.33	33.33	33.33	33.33	33.33
Hydrogenated Castor oil	33.33					33.33		
Caprylic/Capric triglycerids		33.33	33.33				33.33	
Cocoglycerids				33.33	33.33			33.33
PEG 100 stearate	33.33	33.33		33.33				
Sucrose Ester 1815			33.33		33.33			
Polysorbate 80						33.33	33.33	33.33
Total	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
Mix temp	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
Solubility	partly	no	no	partly	no	partly	partly	partly
Crystals	Yes in SLN	yes	yes	yes	yes	yes	yes	yes
State	solid	two phases	semi solid	solid	solid	solid	two phases	semi solid

Using the solubility matrix of Table 3, the present inventors discovered that curcumin solubility or partial solubility correlates with the presence of PEG and that PEG therefore contributes to curcumin solubility. Microscopic inspection of curcumin in hydrogenated castor oil (Cutina HR) with PEG 100 stearate produced curcumin as solid lipids. This combination was then selected as the initial lipid phase of the curcumin-honey formulation.

EXAMPLE 2

Development of a Solid Lipid Curcumin in Honey Formulation

'Hot melt emulsification' procedures were developed and tested with respect to production of very fine micronized SLP well dispersed in honey. Procedures were optimized to maximize entrapment of curcumin in the SLPs and minimize crystallization or precipitation of free curcumin in honey. In addition, parameters related to taste, smell and texture of the honey carrier were also monitored. The general production process is outlined in Figure 2.

Procedure A: The lipid phase (curcumin in hydrogenated castor oil with PEG 100 stearate) was heated to 90 °C and the honey was heated to 70 °C. The heated lipid and honey phases were mixed and homogenized using Heidolph DIAX 900 homogenizer at speed 3 until the temperature dropped to at least 20 °C below the emulsification temperature and the formulation appeared semi solid.

Procedure B: Same as procedure A, but a portion of the honey is not heated above 50 °C in order to preserve unique honey properties that are destroyed above 55C. The lipid phase was heated to 90 °C; half the honey was heated to 70 °C and the rest to 40 °C - 50 °C . The lipid and the hot honey (70 °C) phases were mixed and homogenized with Heidolph homogenizer DIAX 900 at speed 3 until the temperature dropped below 60 °C. The rest of the honey was then heated to 50 °C and added while vigorously mixing and/or homogenizing to the Lipid-honey mix until the formulation reached homogeneity.

The formulations produced by the present study were visually inspected for homogeneity, observed under a microscope, tested for smell taste and texture, and for physical and chemical stability.

Table 5 summarizes the results of three curcumin in honey formulations, CUR13, 14 and 15.

Table 5: Hydrogenated Castor oil-PEG 100 Stearate Formulations

	CUR13		CUR14		CUR15
	W/W%		W/W		W/W
Curcumin	11.11		5.50		0.00
Hydroginated Castor oil	11.11		5.50		11.11
PEG 100 stearate	11.11		5.50		11.11
Hot Honey (70C)	66.67		33.33		75.00
Cold Honey (40-50C)	0.00		50.00		0.00
Total	100.00		99.83		97.22
Production:					
Production process	A		B		A
Solubility in oil phase	yes		yes		yes
Lipid phase temp (process B)	100C		90		90
Tests ZT:					
Crystals	Few and small		Few and small		Few amorphous
State	semi solid		semi solid		semi solid
Smell	Honey		Honey		Honey
Mixing with water	good		good		good
Taste	Honey		Honey		Honey

CUR13 and CUR15 were produced using procedure A, while CUR14 was produced using procedure B. Hydrogenated castor oil was the lipid base and PEG100 stearate was used as an emulsifier. CUR15 was a control formulation used for examining the effect of lipid phase concentration and the production procedure on particle size. This formulation was microscopically compared to CUR13 and CUR14.

Following these tests, the present inventors concluded that PEG100 stearate is a good stabilizer and curcumin solvent, but that the mixture solidifies at a relatively high temperature (above 70 °C), making it difficult to carry out the preparation procedure and thus encouraging the present inventors to seek alternative stabilizing emulsifiers.

Table 6: lecithin Formulation

Lecitin	5.698005698
Sucrose Ester 1811	
Glyceryl Monostearate	5.698005698
Hot Honey (70C)	38.46153846
Cold Honey (40-50C)	38.46153846
Total	100
Production:	
Production process	B
Solubility in oil phase	no
Lipid phase temp (process B)	110

PEG 100 Stearate was replaced with PEG 40 Stearate which has a lower melting point (CUR17, Table 7). This formulation was produced using procedure A and exhibited satisfactory results. Processing was easier due to lower temperature solidification and the resulting formulation was characterized by good stability and solubility. It had a typical honey smell. The observation of a small number of curcumin crystals indicates that the curcumin was not completely solubilized. The amount of solubilization was not quantified, but it is estimated that the fraction of curcumin that remained unsolubilized was between 1 to 10%.

Table 7: PEG 40 Stearate Formulation

	CUR17
Ingredients	**%W/W**
Curcumin	7.14
Hydroginated Custor oil	7.14
PEG 40 stearate	7.14
Hot Honey (70C)	78.57
Cold Honey (40-50C)	0.00
Total	100.00
Production:	
Production process	A
Solubility in oil phase	partly
)Homogenization temperture (process A	80
Tests ZT:	
Crystals	few
State	semi solid
Smell	honey
Mixing with water	poor

In the formulation of Table 8, the concentration of PEG 40 stearate was reduced and PEG 6000 was added to the lipid phase. The formulation was produced using procedure A. The result was a honey smelling formulation with very few detectable crystals and good water miscibility of the product and homogeneous dispersion of the SLP in water following honey dissolution. Particles are typically 0.5 – 5 μm in diameter, indicating that they are capable of being dispersed efficiently in gastric fluid.

Table 8: PEG 6000 Formulation

	CUR18
Ingredients	**%W/W**
Curcumin	7.14
Hydroginated Custor oil	7.14
Polyethylene Glycol 6000	4.29
PEG 40 stearate	2.86
Hot Honey (70C)	78.57
Cold Honey (40-50C)	0.00
Total	100.00
Production:	
Production process	A
Solubility in oil phase	partly
)Homogenization temperture (process A	80
Tests ZT:	
Crystals	few
State	semi solid
Smell	honey
Mixing with water	very good

In the formulations of Table 9, a sucrose ester component was tested as the sole stabilizing emulsifier for curcumin using procedure A. The resulting formulation included fine micronized solid lipid particles exhibiting poor water miscibility, probably due to a lack of hydrophilic components such as the PEG moiety of the PEG stearate component.

Table 9: Sucrose Ester Formulation

	CUR19
Ingredients	**%W/W**
Curcumin	7.14
Hydroginated Custor oil	7.14
Polyethylene Glycol 6000	4.29
Sucrose Ester 1811	2.86
Hot Honey (70C)	78.57
Cold Honey (40-50C)	0.00
Total	100.00
Production:	
Production process	A
Solubility in oil phase	partly
)Homogenization temperture (process A	80
Tests ZT:	
Crystals	few
State	semi solid
Smell	honey
Mixing with water	none

CUR 20 and CUR21 (Table 10) were produced using procedure A. CUR20 contained sucrose ester with PEG40 stearate, while that of CUR21 contained sucrose ester with Tween 80 as stabilizing surfactants. Both were well miscible in water; in the CUR21 formulation the typical smell of honey was lost.

Table 10: Sucrose Ester and PEG 40 Stearate or Tween 80 Formulations

	CUR20		CUR21
Ingredients	**%W/W**		**%W/W**
Curcumin	7.14		7.14
Hydrogenated Castor oil	7.14		7.14
Polyethylene Glycol 6000	4.29		4.29
PEG 40 stearate	1.00		0.00
Tween 80	0.00		1.00
Sucrose Ester 1811	1.00		1.00
Hot Honey (70C)	78.57		78.57
Cold Honey (40-50C)	0.00		0.00
Total	99.14		100.14
Production:			
Production process	A		A
Solubility in oil phase	partly		partly
Homogenization temperture (process A)	80		80
Tests ZT:			
Crystals	few		few
State	semi solid		semi solid
Smell	honey		less then honey
Mixing with water	good		good
particle size	0-6micron		0-6micron

CUR22 was produced using procedure A while CUR 22(2) was produced using procedure B (Table 11). The lipid phase was identical for both formulations, and included 0.5% sucrose ester and 1.0% PEG40 stearate. Both were miscible in water, and both exhibited a typical honey smell and a curcumin aftertaste.

Table 11: Optimization of Sucrose Ester concentration and production procedure

	CUR22		CUR22(2)
Ingredients	**%W/W**		**%W/W**
Curcumin	7.14		7.14
Hydroginated Custor oil	7.14		7.14
Polyethylene Glycol 6000	4.29		4.29
PEG 40 stearate	1.00		1.00
Sucrose Ester 1811	0.50		0.50
Hot Honey (70C)	78.57		39.20
Cold Honey (40-50C)	0.00		39.20
Total	98.64		98.47
Production:			
Production process	A		B
Solubility in oil phase	partly		partly
Homogenization temperature (process A)	80		80
Tests ZT:			
Crystals	almost none		Few
State	semi solid		semi solid

CUR23 (Table 12) was produced using procedure A or B. The lipid phase was identical to the CUR22 formulation but 4% curcumin was used. The result was a smooth semisolid formulation with typical honey smell and no aftertaste.

Table 12: 4% Curcumin Formulation

	CUR23
Ingredients	**%W/W**
Curcumin	4.00
Hydrogenated Castor oil	7.14
Polyethylene Glycol 6000	4.29
PEG 40 stearate	1.00
Sucrose Ester 1811	0.50
Hot Honey (70C)	78.57
Cold Honey (40-50C)	0.00
Total	95.50
Production:	
Production process	A
Solubility in oil phase	partly
Homogenization temperture (process A)	70
Tests ZT:	
Crystals	very little
State	semi solid

CUR24 (Table 13) was produced with food grade stearin as the lipid solvent. CUR25 (Table 13) was produced with food grade palm oil as the lipid solvent. Both formulations were produced using procedure A and resulted in a formulation having a smooth texture, a honey

smell and no aftertaste. The microscopic observations showed solid lipid spherical particles loaded with curcumin and very few free curcumin crystals. The diameter of the solid lipid spheres was between 0.5 and 5.0 μm.

Table 13: Stearin of Palm oil (as lipid solvent) formulations

	CUR24		CUR25
Ingredients	**W/W**		**W/W**
Curcumin	4.00		4.00
Stearin	7.00		0.00
Palm oil	0.00		7.00
Polyethylene Glycol 6000	4.00		4.00
PEG 40 stearate	1.00		1.00
Sucrose Ester 1811	0.50		0.50
Hot Honey (70C)	83.50		83.50
Cold Honey (40-50C)	0.00		0.00
Total	100.00		100.00
Production:			
Production process	A		A
Solubility in oil phase	partly		partly
)Homogenization temperture (process A	70C		70C
Tests ZT:			
Crystals	few		few
State	semi solid		semi solid
Smell	honey		honey

CUR26 is the same formulation as CUR24 but without PEG6000; CUR27 is the same formulation as CUR25 but without PEG6000 (Table 14). The purpose of these formulations was to determine whether PEG6000 was necessary as the curcumin solvent. Both formulations were produced using procedure A and in both lipid phases no curcumin solubility was observed. Microscopic observation of these formulations showed spherical lipid particles with no curcumin entrapment and curcumin crystals of various size and unusual shapes. These formulations did not exhibit a homogeneous texture. Both formulations were characterized by a honey smell and a good taste.

Table 14: Formulations without PEG 6000

	CUR26		CUR27
Ingredients	**W/W**		**W/W**
Curcumin	4.00		4.00
Stearin	7.00		0.00
Palm oil	0.00		7.00
Polyethylene Glycol 6000	0.00		0.00
PEG 40 stearate	1.00		1.00
Sucrose Ester 1811	0.50		0.50
Hot Honey (70C)	87.50		87.50
Cold Honey (40-50C)	0.00		0.00
Total	100.00		100.00
Production:			
Production process	A		A
Solubility in oil phase	no		no
)Homogenization temperture (process A	70C		70C
Temp at the end of production	55C		55C
Prod Homogeneity	yes		yes
Tests ZT:			
Crystals	yes		yes
State	semi solid		semi solid
Smell			

In addition to the above specific examples, the present approach can also be used to generate DIM, Genistein, Diadzin or Quercetin SLP in honey formulations. Table 15 below provides a list of ingredients that can be used in such formulations.

Table 15

Formulation	DIM1	DIM2	DIM3	DIM4	GEN/DI	QUE
Ingredients	%W/W	%W/W	%W/W	%W/W	%W/W	%W/W
Diindolylmethane	2	2	3	3	--	--
Genistein or Diadezin	--	--	--	--	1	--
Quercetin	--	--	--	--	--	1
Stearin	10	8	10	8	12	12
Sucrose ester HLB 6	2	2	2	2	2	2
Tween 80	1	0.5	1	0.5	0.5	0.5
PEG 6000	--	8	--	8	--	--
Honey	To 100	To 100	To 100	To 100	To 100	To 100

EXAMPLE 3

CUR64 (Table 16 below) was produced with Alina™ oil (omega-3 rich sage oil).

CUR64 (Table 16 below) was produced using procedure A and resulted in a formulation having a smooth texture, a semisolid product with no smell, a honey sweet taste, and no aftertaste.

Table 16: production with Alina™ oil (sage omega3 rich oil)

Ingredients		CUR64 - production with Alina™ oil
		W/W
Curcumin	Curcumin	4
Alina oil		5
Polyethylene Glycol 6000	PEG 6000	6
Sucrose Ester HLB 15	Sisterna SP70	1
Polysorbate 80	Tween 80	0.5
Polyglyceryl-3-Dioleate	Plurol Oleique 497	1
Cold Honey		51
Date syrup hot	Tamar Kineret	31.5
SUM		100
Tests ZT:		
Crystals		mostly small, some 25micron
Emulsification		mostly sub-micron, with few particles up to 6micron
State		semi solid
Smell		good
Mixing with water		good
taste		sweet
texture		smooth

EXAMPLE 4

CUR65, CUR66 and CUR67 (Table 17) were produced with pomegranate oil (CUR65), with avocado oil (CUR66) and with olive oil (CUR67).

CUR65, CUR66 and CUR67 (Table 17) were produced using procedure A and resulted in a smooth semisolid product having a smooth texture, no smell, a sweet taste, and no aftertaste.

In all three formulations (CUR65, CUR66 and CUR67) microscopic observation revealed a few 10-25 μm curcumin crystals and lipid particles up to 3 μm in diameter.

Table 17: production with Pomegranate oil (CUR65), with Avocado oil (CUR66) and with Olive oil (CUR67)

	production with pomegranate oil	production with avocado oil	production with olive oil
	CUR65	CUR66	CUR67
	%W/W	%W/W	%W/W

Curcumin	4	4	4
Pomegranate seed oil	5	--	--
Avocado oil	--	5	--
Olive oil	--	--	5
Polyethylene Glycol 6000	6	6	6
Sucrose Ester HLB 15	1	1	1
Polysorbate 80	0.5	0.5	0.5
Polyglyceryl-3-Dioleate	1	1	1
Cold Honey	51	51	51
Date syrup hot	31.5	31.5	31.5
SUM	100	100	100
Tests ZT:			
Crystals	some 10-25micron	some 10-25micron	some 10-25micron
Emulsification	mostly sub-1micron, some 3micron	submicron to 3micron	submicron to 2micron
State	semi solid	semi solid	semi solid
Smell	Typical pomegranate oil	good	good
Mixing with water	good	good	good
taste	sweet with typical smell	sweet	sweet
texture	smooth	smooth	smooth

EXAMPLE 5

The ingredients of CUR66-1, CUR66-2 and CUR66-3 ingredients are given in Table 18.

CUR66-1 was produced as follows (production of 1 kg):

a. Curcumin was melted with PEG6000 to 90 °C ;
b. Lipid phase was added to the PEG-curcumin solution and heated with stirring to 80 °C ;
c. 90% of the date syrup was heated to 75 °C; since 10% was used to solubilize the microbial preservative potassium sorbate
d. 10% of the date syrup was heated to 70 °C with potassium sorbate, solubilised and cooled to room temperature;
e. The mixture was homogenized with "Silverson L4RT emulsor screens";
f. The lipid phase was homogenized at 5000 rpm and date syrup was added slowly with homogenization for 3 min;
g. The homogenization speed was reduced to 4000 rpm for 4 min with cooling in a water bath;
h. Honey and potassium sorbate were added at room temperature;

i. The mixture was mixed manually.

CUR66-2 was produced as follows (production of 1.5 kg):

a. Curcumin was melted with PEG6000 and lipid phase to 95 °C;
b. Date syrup was heated to 75 °C;
c. 10% of the date syrup was heated to 70 °C with potassium sorbate, solubilised, and cooled to room temperature;
d. The date syrup was added to lipid phase and mixed with a spatula;
e. The mixture was homogenized with Silverson L4RT emulsor screens;
f. The lipid phase and date syrup were homogenized at 6000 rpm for 1 min;
g. The lipid phase and date syrup were further homogenized at 5000 rpm for 3 min;
h. The homogenization speed was reduced to 4000 rpm for 4 min with cooling in a water bath to 56 °C;
i. Room temperature honey and potassium sorbate were added;
j. The mixture was mixed manually.

CUR66-3 was produced as follows (production of 1.5 kg):

a. Curcumin was melted with PEG6000 and lipid phase to 90 °C;
b. Date syrup was heated to 70 °C ;
c. 10% of the date syrup was heated to 70 °C with potassium sorbate, solubilised and cooled to room temperature;
d. The lipid phase was homogenized at 6000 rpm for about 20 s;
e. Date syrup was added slowly with homogenization for 3 min;
f. The lipid phase and date syrup were homogenized at 5000 rpm for 3 min;
g. The homogenization speed was reduced to 4000 rpm for 4 min with cooling in a water bath;
h. Honey and potassium sorbate were added at room temperature;
i. The mixture was mixed manually.

All three formulations produced a smooth, semisolid product with a sweet taste.

In all three formulations microscopic observation revealed a few 10-25 μm curcumin crystals and lipid particles up to 3 μm.

All the formulations were subjected to an accelerated stability test consisting of storage at a temperature of 32 °C or 40 °C for three months and monitoring of physical stability by visual inspection and of curcumin chemical stability by HPLC assay at zero time and after three months' storage. All formulations found stable at 32 °C and some showed slight creaming at 40 °C. Curcumin was found to be stable with no detectable chemical degradation.

Table 18: production with Pomegranate oil (CUR65), with Avocado oil (CUR66) and with Olive oil (CUR67)

Rational	production Pilot	production Pilot	production Pilot
	CUR66-1	CUR66-2	CUR66-3
	%W/W	%W/W	%W/W
Curcumin	4	4	4
Avocado oil	5	5	5
Polyethylene Glycol 6000	6	6	6
Sucrose Ester HLB 15	1	1	1
Polysorbate 80	0.6	0.5	0.5
Polyglyceryl-3-Dioleate	1	1	1
Potassium sorbate	0.05	0.05	0.05
Cold Honey	51	51	51
hot date syrup	31.35	31.45	31.45
SUM	100	100	100
Production:	Curcumin was melted with PEG6000 to 90C. Lipid phase added to melted curcumin	Curcumin was melted with PEG6000 and lipid phase to 95C	Curcumin was melted with PEG6000 and lipid phase to 90C
Tests ZT:			
Crystals	some 10-25micron	some 10-25micron	some 10-25micron
Emulsification	submicron to 3micron	submicron to 3micron, very few 6micron	submicron to 3micron, very few 6micron
State	semi solid	semi solid	semi solid
Smell	good	good	good
Mixing with water	good	good	good
taste	sweet	sweet	sweet
texture	smooth	smooth	smooth

Curcumin HPLC assay Zero time

1: The quantitative results of Curcumine:

no.	Sample name	Tami name	HPLC/UV files.D	% Curcumine (w/w)
1	[A] Room temperature 66(1) 17/3 production	LL1975 2011-10996-2	LL1974/15,31	3.8
2	[B] Room temperature 66(2) 17/3 production	LL1976 2011-10996-3	LL1974/16,32	4.2
3	[C] Room temperature 66(3) 17/3 production	LL1977 2011-10996-4	LL1974/17,33	4.0

Curcumin HPLC assay after three months storage at 40°C

1: The quantitative results of Curcumine:

no.	Sample name	Tami name	HPLC/UV files.D	% Curcumine (w/w)
1	CUR 66(1)	LL2128 2011-11892-1	LL2128/13-18	4.4
2	66(2) 17/3	LL2129 2011-11892-2	LL2128/20-25	4.2
3	66(3) 17/3	LL2130 2011-11892-3	LL2128/27-32	4.3

EXAMPLE 6

Curcumin is known to possess poor systemic availability, in his natural form, i.e. mixed in drinks or food, therefore an *in vivo* model was used to determine the extent to which the formulations of the present invention increase its oral bioavailability.

In the tests, male Wistar rats received 400 mg/kg of either unformulated curcumin or curcumin formulated in the solid lipid particles (SLP) formulation, according to the present invention, by oral gavage. Rats were killed at 15, 30, 60 and 120 min post administration. Plasma, intestinal mucosa and liver were analyzed for the presence of curcumin using HPLC with UV detection.

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Curcumin was identified in plasma, intestinal mucosa and liver of rats which had received the solid lipid particles (SLP) formulated curcumin. The curcumin plasma level peak after administration of the SLP formulated curcumin was tenfold higher than the equivalent values seen after unformulated curcumin. Similarly, liver levels of curcumin were higher after administration of SLP formulated curcumin as compared to unformulated curcumin. In contrast, curcumin concentrations in the gastrointestinal mucosa after ingestion of the SLP formulated curcumin were somewhat lower than those observed after administration of unformulated curcumin.

The results indicate that SLP formulated curcumin significantly increases systemic absorption of curcumin than the unformulated form. This formulation presents a great solution for compounds that posse's high medicinal benefit with poor systemic availability. This study emphasis the contribution of this specific formulation as a delivery formulation, in comparison to another product named "*Mariva*®".

The formulation of *Mariva*® is basically Curcumin (CAS 458-37-7) and curcumin phospholipid complex. The preparation of Meriva® was performed byusing EpiKuron™ 130 P, a de-oiled, powdered soybean lecithin enriched with 30% phosphatidylcholine. Meriva contained 16.89% curcuminoids, of which 93.82% was curcumin, the ratio of curcumin to Epikuron™ 130 P was 1:4.

"*Meriva*®" is been marketed by a company whom conducted the same protocol of clinical study in purpose to published a new formulation for curcumin, whose added value is to increase the curcumin absorption through the mucosa tissue into the blood stream (See Timothy H. Marczylo et al., Cancer Chemother Pharmacol, 2007, 60:171–177).

When the two studies are being compared the results from the present invention clinical study with the SLP formulation showed higher curcumin concentration that was absorbed into the plasma and liver than the results of those of the "*Meriva*®". Furthermore the incline in the curcumin absorption that presented in the present invention is moderated and continuing to rise up to 60 min after oral administration while the "*Meriva*®" published results present a steep incline that stopped already 15 min after administration. This comparison emphasis the innovatively and the benefits of the SLP formulation, as provided by the present invention, that enable a continuing ongoing absorption which increase moderately up to 60 min after oral administration, therefore provides stability to the active compound. The stability quality enable long active period for the compound in the tissues.

To emphasis the improvement absorption of the SLP formulation versus the Meriva® product we added two tables that present the delta of the curcumin concentration in each time point.

Reference is now made to FIG. 5a, which shows plasma curcumin levels in rats that had received 400 mg/kg curcumin by oral gavage as a function of time following the administration of the curcumin. The solid line shows results for rats that received SLP formulated curcumin, while the broken line shows results for results that received unformulated curcumin (represented as C3).

Reference is now made to FIG. 5b, which shows liver curcumin levels in rats that had received 400 mg/kg curcumin by oral gavage as a function of time following the administration of the curcumin. The solid line shows results for rats that received SLP formulated curcumin, while the broken line shows results for results that received unformulated curcumin (represented as C3).

Reference is now made to FIG. 5c, which shows curcumin levels in the gastrointestinal mucosa of rats that had received 400 mg/kg curcumin by oral gavage as a function of time following the administration of the curcumin. The solid line shows results for rats that received SLP formulated curcumin, while the broken line shows results for results that received from unformulated curcumin (i.e., the control, represented as C3).

Reference is now made to FIG. 6a, which illustrates the delta in the plasma curcumin concentration while using the SLP and Meriva as a function of time (15 minutes, 30 minutes, 60 minutes and 120 minutes).

The SLP concentration was calculated was as follows: SLP formulation concentration minus C3 (i.e., the control) curcumin concentration.

The Meriva concentration was calculated was as follows: Meriva formulation concentration minus C3 (i.e., the control) curcumin concentration.

The delta was calculated for each time point. The units of the numbers are ng/ml.

The minus mark appears where the C3 curcumin concentration is higher than the SLP/ Meriva curcumin concentration.

Reference is now made to FIG. 6b, which illustrates the delta in the mucosa curcumin concentration while using the SLP and Meriva as a function of time (15 minutes, 30 minutes, 60 minutes and 120 minutes).

The SLP concentration was calculated was as follows: SLP formulation concentration minus C3 (i.e., the control) curcumin concentration.

The Meriva concentration was calculated was as follows: Meriva formulation concentration minus C3 (i.e., the control) curcumin concentration.

The delta was calculated for each time point. The units of the numbers are mg/g. The minus mark appears where the C3 curcumin concentration is higher than the SLP/ Meriva curcumin concentration.

Conclusions

Hot melt procedures for emulsification of curcumin-filled solid lipid particles in honey were developed and tested. Solid lipid particles produced by hot melt emulsification were the method of choice for curcumin incorporation in honey. The present inventors have shown that curcumin is soluble in mixtures of ethylene oxide polymers and lipids. The present inventors have also shown that free curcumin forms curcumin crystals in honey and water.

Testing of several product parameters has shown that curcumin solubility is pivotal to product quality and that use of hydrogenated castor oil, stearin, and palm oil as lipid solvent components is preferred since it results in a curcumin-in-honey formulation that does not have an aftertaste, exhibits smooth texture, has a honey smell and includes substantially all of the curcumin in the lipid microparticles suspended in the honey base.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the scope of the appended claims, with the proper scope determined only by the broadest interpretation of the claims.

All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention.

CLAIMS

We claim:

1. A method of producing a functional food, comprising:

   melting a lipid solvent in the presence of a lipophilic bioactive agent;

   heating the melted lipid solvent and bioactive agent to a temperature of at least 65 °C;

   adding a food base carrier to said melted lipid solvent and bioactive agent; and,

   emulsifying said melted lipid solvent, said bioactive agent, and said food base carrier until an emulsion is formed, said emulsion comprising lipid particles comprising said bioactive agent.

2. The method according to claim **1**, wherein said step of heating the melted lipid solvent and bioactive agent to a temperature of at least 65 °C comprises a step of heating the melted lipid solvent and bioactive agent to a temperature of between 70 °C and 90 °C.

3. The method according to claim **1**, wherein said step of emulsifying is at least partially affected simultaneously with a step of cooling.

4. The method according to claim **3**, wherein said step of cooling further comprises a step of cooling to about 45 °C.

5. The method according to claim **3**, wherein said step of cooling further comprises a step of cooling to a temperature at least 20 °C below the emulsification temperature.

6. The method according to claim **1**, further comprising heating an emulsifier to a temperature of at least 90 °C in the presence of said bioactive agent prior to said step of melting said lipid solvent in the presence of said bioactive agent.

7. The method according to claim **6**, wherein said emulsifier is chosen from the group consisting of PEG esters and sucrose esters.

8. The method according to claim **7**, wherein said emulsifier is a PEG ester chosen from PEG6000 esters, PEG100 stearate, and PEG40 stearate.

9. The method according to either one of claims **1** or **3**, further comprising a step of heating at least part of said food base carrier prior to said step of adding said food base carrier to said melted lipid solvent and bioactive agent.

10. The method according to claim **9**, wherein said step of heating at least part of said food base carrier comprises heating a first part of said food base carrier to a first predetermined

temperature and heating a second part of said food base carrier to a second predetermined temperature lower than said first predetermined temperature.

11. The method according to claim **10**, wherein said first predetermined temperature is at least 60 °C and said second predetermined temperature is not above 50 °C.

12. The method according to claim **10**, wherein said step of adding a food base carrier further comprises adding said first part of said food base carrier, and further comprising a step of adding said second part of said food base carrier during said step of emulsifying, said step of adding said second part taking place only when the temperature of the other components being emulsified is below 60 °C.

13. The method according to claim **1**, further comprising:

heating a portion of said food base carrier in the presence of potassium sorbate until a solution forms;

cooling said solution to room temperature; and,

adding said solution to said melted lipid phase and bioactive agent.

14. The method according to claim **1**, wherein said food base carrier is a semisolid at room temperature.

15. The method according to claim **1**, wherein said food base carrier is a liquid at room temperature.

16. The method according to claim **1**, wherein said bioactive agent comprises a bioactive food component.

17. The method according to claim **1**, wherein said step of melting a lipid solvent in the presence of a lipophilic bioactive agent comprises melting a lipid solvent in the presence of a bioactive agent is chosen from the group consisting of curcumin, diindolylmethane, quercetin, diadezin, silymarin, genistein, essential fatty acids, and phytosterols.

18. The method according to claim **1**, wherein said food base carrier is chosen from the group consisting of saccharide syrups and polysaccharide syrups.

19. The method according to claim **18**, wherein said syrup is chosen from the group consisting of honey, date syrup, and maple syrup.

20. The method according to claim **1**, further comprising a step of allowing at least part of said lipid to solidify into particles within said food base carrier.

21. The method according to claim **20**, further comprising a step of dispersing homogeneously said particles within said food base carrier.

22. The method according to claim **21**, wherein said step of allowing at least part of said lipid to solidify into particles within said food base carrier further comprises allowing at least part of said lipid to solidify into microspheres within said food base carrier.

23. The method according to claim **22**, wherein said step of allowing at least part of said lipid to solidify into microspheres within said food base carrier further comprises a step of allowing at least part of said lipid to solidify into microspheres of diameter between 0.5 μm and 5 μm within said food base carrier.

24. The method according to claim **20**, wherein said step of allowing said lipid to solidify into particles within said food base carrier further comprises a step of allowing said lipid to solidify into particles within said food base carrier chosen from the group consisting of solid particles and semisolid particles.

25. The method according to claim **20**, wherein at least 70% of said bioactive agent is associated with said particles.

26. The method according to claim **25**, wherein at least 80% of said bioactive agent is associated with said particles.

27. The method according to claim **26**, wherein between 90% and 95% of said bioactive agent is associated with said particles.

28. The method according to claim **1**, further comprising a step of obtaining at least one lipid solvent chosen from the group consisting of hydrogenated castor oil; stearin; palm oil; high-omega-3 sage oil; pomegranate oil; avocado oil; olive oil; and any combination thereof.

29. The method according to claim **1**, further comprising a step of mixing a bioactive agent with said food base carrier.

30. The method according to claim **29**, wherein said step of mixing a bioactive agent with said food base carrier further comprises a step of mixing a bioactive agent chosen from the group consisting of vitamins and minerals with said food base carrier.

31. The method according to claim **29**, wherein said step of mixing a bioactive agent with said food base carrier further comprises a step of mixing a hydrophilic bioactive agent with said food base carrier.

32. The method according to claim **31**, wherein said step of mixing a hydrophilic bioactive agent with said food base carrier further comprises a step of mixing a hydrophilic bioactive agent chosen from the group consisting of cobalamin, folate, and ferrous gluconate to said food base carrier with said food base carrier.

33. A functional food comprising a lipophilic bioactive agent, a lipid, and a food base carrier, wherein said lipid is at least partially dispersed as particles within said food base carrier and said at least part of lipophilic bioactive agent is contained within said particles.

34. The functional food according to claim **33**, wherein said particles constitute between 5% and 40% (w/w) of the food.

35. The functional food according to claim **33**, wherein said lipophilic bioactive agent is a bioactive food component.

36. The functional food according to claim **33**, wherein said lipophilic bioactive agent comprises at least one component chosen from the group consisting of curcumin, diindolylmethane, quercetin, diadezin, silymarin, genistein, essential fatty acids, and phytosterols.

37. The functional food according to claim **33**, wherein said lipid is chosen from the group consisting of hydrogenated castor oil; stearin; palm oil; high-omega-3 sage oil; pomegranate oil; avocado oil; olive oil; and any combination thereof.

38. The functional food according to claim **33**, wherein said food base carrier is a liquid at room temperature.

39. The functional food according to claim **33**, wherein said food base carrier is a semisolid at room temperature.

40. The functional food according to claim **33**, wherein said food base carrier is chosen from the group consisting of saccharide syrups and polysaccharide syrups.

41. The functional food according to claim **40**, wherein said syrup is chosen from the group consisting of honey, date syrup, and maple syrup.

42. The functional food according to claim **33**, wherein said particles are homogeneously dispersed within said food base carrier.

43. The functional food according to claim **33**, wherein said particles comprise microspheres.

44. The functional food according to claim **43**, wherein said microspheres have diameters between 0.5 μm and 5 μm.

45. The functional food according to claim **33**, wherein said particles are chosen from the group consisting of solid particles and semisolid particles.

46. The functional food according to claim **33**, wherein at least 70% of said bioactive agent is associated with said particles.

47. The functional food according to claim **46**, wherein at least 80% of said bioactive agent is associated with said particles.

48. The functional food according to claim **47**, wherein between 90% and 95% of said bioactive agent is associated with said particles.

49. The functional food according to claim **33**, further comprising an emulsifier.

50. The functional food according to claim **49**, wherein said emulsifier is chosen from the group consisting of PEG esters and sucrose esters.

51. The functional food according to claim **50**, wherein said emulsifier is a PEG ester chosen from the group consisting of PEG6000 esters, PEG100 stearate, and PEG40 stearate.

52. The functional food according to claim **33**, wherein said food base carrier is mixed with at least one additional bioactive agent.

53. The functional food according to claim **52**, wherein said at least one additional bioactive agent is chosen from the group consisting of vitamins and minerals.

54. The functional food according to claim **52**, wherein said at least one additional bioactive agent is a hydrophilic bioactive agent.

55. The functional food according to claim **54**, wherein said hydrophilic bioactive agent is chosen from the group consisting of cobalamin, folate, and ferrous gluconate.

56. A method of providing at least one bioactive agent to a subject in need comprising administering a functional food comprising at least one lipophilic bioactive agent associated with lipid particles dispersed within a food base carrier.

57. The method according to claim **56**, wherein said step of administering a functional food further comprises a step of administering a functional food characterized by at least one of the following:

said lipophilic bioactive agent is chosen from the group consisting of curcumin, diindolylmethane, quercetin, diadezin, silymarin, genistein, essential fatty acids, and phytosterols; and,

said food base carrier is chosen from the group consisting of saccharide and polysaccharide syrups.

58. The method according to claim **56**, wherein said step of administering a functional food further comprises a step of administering a functional food comprising an emulsifier.

59. The method according to claim **58**, wherein said step of administering a functional food comprising an emulsifier further comprises administering a functional food comprising an emulsifier chosen from the group consisting of PEG esters and sucrose esters.

60. The method according to claim **56**, wherein said step of administering a functional food further comprises a step of administering a functional food comprising at least one additional bioactive agent, said at least one additional bioactive agent mixed with said food base carrier.

61. The method according to claim **60**, wherein said step of administering a functional food comprising at least one additional bioactive agent mixed with said food base carrier further comprises a step of administering at least one hydrophilic bioactive agent mixed with said food base carrier.

62. A method of producing functional food comprising:

a. melting a lipid solvent including a bioactive agent at a temperature of at least 65°C; and,

b. emulsifying the product of step (a) with a semi-solid food base carrier until the formation of an emulsion comprising solid lipid particles; said solid lipid particles comprising said bioactive agent.

63. A method of producing functional food comprising:

a. melting a lipid solvent including a bioactive agent at a temperature of at least 65°C; and,

b. emulsifying (a) with a liquid food base carrier until the formation of an emulsion comprising solid lipid particles; said solid lipid particles comprising said bioactive agent.

64. The method of either one of claims **62** or **63**, wherein said bioactive agent is a bioactive food component.

65. The method of claim **64**, wherein said bioactive food component is curcumin.

66. The method of claim **64**, wherein said bioactive food component is DIM.

67. The method of either one of claims **62** or **63**, wherein said food base carrier is honey.

68. The method of either one of claims **62** or **63**, wherein said lipid solvent includes at least one selected from the group consisting of hydrogenated castor oil, stearin, palm oil, high-omega-3 sage oil, pomegranate oil, avocado oil, olive oil, and any combination thereof.

69. The method of either one of claims **62** or **63**, wherein said lipid solvent further includes an emulsifier.

70. The method of claim **69**, wherein said emulsifier includes an ester chosen from the group consisting of PEG esters and sucrose esters.

71. The method of either one of claims **62** or **63**, wherein said temperature is 70-90°C.

72. The method of either one of claims **62** or **63**, wherein said food base is heated to at least 65°C prior to step (b).

73. The method of either one of claims **62** or **63**, wherein a diameter of said solid lipid particles is in a range of 0.5 to 5 microns.

74. The method of either one of claims **62** or **63**, wherein step (b) is effected while gradually cooling a mixture of said lipid solvent including said bioactive agent and said food base to a temperature of about 45°C.

75. A composition of matter comprising a food-based carrier comprising solid lipid particles homogenously dispersed therein and at least one bioactive agent, wherein at least 80% of said at least one bioactive agent is associated with said solid lipid particles.

76. The composition of matter of claim **75**, wherein said bioactive agent is a bioactive food component.

77. The composition of matter of claim **76**, wherein said bioactive food component is curcumin.

78. The composition of matter of claim **76**, wherein said bioactive food component is Diindolylmethane (DIM).

79. The composition of matter of any one of claims **75** – **78**, wherein said food base carrier is honey.

80. The composition of matter of claim **75**, wherein said solid lipid particles includes at least one selected from a group consisting of hydrogenated castor oil, stearin, palm oil, Alina™ oil, high-omega-3 sage oil, pomegranate oil, avocado oil, olive oil, and any combination thereof.

81. The composition of matter of claim **75**, further comprising an emulsifier.

82. The composition of matter of claim **81**, wherein said emulsifier is PEG.

83. The composition of matter of claim **75**, wherein the diameter of said solid lipid particles is in a range of 0.5 to 5 microns.

84. A method of providing a biaoactive agent to a subject in need comprising administering a food-based carrier including solid lipid particles homogenously dispersed therein and at least one bioactive agent, wherein at least 80% of said at least one bioactive agent is associated with said solid lipid particles.

85. The method of claim 84, wherein administering is via an oral route.

86. A composition of matter comprising a honey carrier including solid lipid particles homogenously dispersed therein and curcumin and/or DIM entrapped within said solid lipid particles.

87. The functional food of claim **33**, wherein said functional food is stable to storage at 32 °C for three months.

88. The composition of matter of claim **75**, wherein said composition of matter is stable to storage at 32 °C for three months.

89. A method for increasing the concentration of a lipophilic bioactive agent within the body of a patient, comprising:

incorporating said lipophilic bioactive agent into a functional food by the method of claim **1**; and,

administering a predetermined quantity of said functional food to a patient in need.

90. The method of claim **89**, wherein said lipophilic bioactive agent is a bioactive food component.

91. The method of claim **89**, wherein said lipophilic bioactive agent comprises at least one component chosen from the group consisting of curcumin, diindolylmethane, quercetin, diadezin, silymarin, genistein, essential fatty acids, and phytosterols.

92. The method of claim **89** wherein said lipid solvent is chosen from the group consisting of hydrogenated castor oil; stearin; palm oil; high-omega-3 sage oil; pomegranate oil; avocado oil; olive oil; and any combination thereof.

93. The method of claim **89**, further comprising a step of raising the concentration of said lipophilic bioactive agent in the blood of said patient in need.

94. The method of claim **89**, further comprising a step of raising the concentration of said lipophilic bioactive agent in the liver of said patient in need.

95. The method of claim **89**, further comprising a step of raising the concentration of said lipophilic bioactive agent in the gastrointestinal mucosa of said patient in need.

96. A method for increasing the concentration of a lipophilic bioactive agent within the body of a patient, comprising:

administering to a patient in need a predetermined quantity of a functional food of claim **33** comprising said lipophilic bioactive agent.

97. The method of claim **96**, wherein said lipophilic bioactive agent is a bioactive food component.

98. The method of claim **96**, wherein said lipophilic bioactive agent comprises at least one component chosen from the group consisting of curcumin, diindolylmethane, quercetin, diadezin, silymarin, genistein, essential fatty acids, and phytosterols.

99. The method of claim **96**, wherein said lipid is chosen from the group consisting of hydrogenated castor oil; stearin; palm oil; high-omega-3 sage oil; pomegranate oil; avocado oil; olive oil; and any combination thereof.

100. The method of claim **96**, further comprising a step of raising the concentration of said lipophilic bioactive agent in the blood of said patient in need.

101. The method of claim **96**, further comprising a step of raising the concentration of said lipophilic bioactive agent in the liver of said patient in need.

102. The method of claim **96**, further comprising a step of raising the concentration of said lipophilic bioactive agent in the gastrointestinal mucosa of said patient in need.

103. A method for treating a condition ameliorated by a lipophilic bioactive agent comprising:

incorporating said lipophilic bioactive agent into a functional food by the method of claim **1**; and,

administering a predetermined quantity of said functional food to a patient suffering from said condition.

104. The method of claim **103**, wherein said lipophilic bioactive agent is a bioactive food component.

105. The method of claim **103**, wherein said lipophilic bioactive agent comprises at least one component chosen from the group consisting of curcumin, diindolylmethane, quercetin, diadezin, silymarin, genistein, essential fatty acids, and phytosterols.

106. The method of claim **103**, wherein said lipid solvent is chosen from the group consisting of hydrogenated castor oil; stearin; palm oil; high-omega-3 sage oil; pomegranate oil; avocado oil; olive oil; and any combination thereof.

107. The method of claim **103**, wherein said condition is chosen from the group consisting of immune diseases, heart disease, respiratory diseases, inflammation, cancer, leukemia, lymphoma, gastrointestinal cancers, genitourinary cancers, breast cancer, ovarian cancer, head and neck squamous cell carcinoma, lung cancer, melanoma, neurological cancers, gastrointestinal conditions, gastric ulcers, colitis, bowel disease, crohn's disease, colorectal cancer, fatty liver disease and Non-Alcoholic Steatohepatitis (NASH), edema, arthritis, pancreatitis, ocular conditions, inflammatory diseases and any combination thereof.

108. The method of claim **103**, wherein said condition is chosen from the group consisting of respiratory papillomatosis, prostatitis, cataracts, allergies, bronchitis, asthma, celiac disease, non-celiac gluten sensitivity, and irritable bowel syndrome.

109. A method for treating a condition ameliorated by a lipophilic bioactive agent, comprising:

administering to a patient in need a predetermined quantity of a functional food of claim **33** comprising said lipophilic bioactive agent.

110. The method of claim **109**, wherein said lipophilic bioactive agent is a bioactive food component.

111. The method of claim **109**, wherein said lipophilic bioactive agent comprises at least one component chosen from the group consisting of curcumin, diindolylmethane, quercetin, diadezin, silymarin, genistein, essential fatty acids, and phytosterols.

112. The method of claim **109**, wherein said lipid solvent is chosen from the group consisting of hydrogenated castor oil; stearin; palm oil; high-omega-3 sage oil; pomegranate oil; avocado oil; olive oil; and any combination thereof.

113. The method of claim **109**, wherein said condition is chosen from the group consisting of immune diseases, heart disease, respiratory diseases, inflammation, cancer, leukemia, lymphoma, gastrointestinal cancers, genitourinary cancers, breast cancer, ovarian cancer, head and neck squamous cell carcinoma, lung cancer, melanoma, neurological cancers, gastrointestinal conditions, gastric ulcers, colitis, bowel disease, crohn's disease, colorectal cancer, fatty liver disease and Non-Alcoholic Steatohepatitis (NASH), edema, arthritis, pancreatitis, ocular conditions, inflammatory diseases and any combination thereof.

114. The method of claim **109**, wherein said condition is chosen from the group consisting of respiratory papillomatosis, prostatitis, cataracts, allergies, bronchitis, asthma, celiac disease, non-celiac gluten sensitivity, and irritable bowel syndrome.

115. A method for providing adjunct therapy to a patient suffering from cancer, comprising:

incorporating said lipophilic bioactive agent into a functional food by the method of claim **1**; and,

administering a predetermined quantity of said functional food to said patient in conjuction with another anticancer therapy.

116. A method for providing adjunct therapy to a patient suffering from cancer, comprising:

administering to said patient a predetermined quantity of a functional food of claim **33** comprising said lipophilic bioactive agent in conjunction with another anticancer therapy.