COMPOSITIONS COMPRISING NON-ACIDIC BOSWELLIA OIL FRACTION AS A BIO-ENHANCER FOR ENHANCING THE BIOAVAILABILITY OF BIOLOGICAL AGENTS

Field of the Invention:

The invention provides non-acidic Boswellia low polar gum resin extract fraction (BLPRE), Boswellia volatile oil fraction (BVOIL) or Boswellia oil fraction (BOIL) comprising BLPRE and BVOIL for increasing the bioavailability of biological agents.

The present invention provides composition(s) comprising at least one component selected from Boswellia oil (BOIL), Boswellia volatile oil (BVOIL) and Boswellia low polar gum resin extract (BLPRE) in combination with a biological agent for increasing the bioavailability of biological agents.

Objective of the invention:

There are numerous pharmaceutical, herbal ingredient(s) and biologically active molecules that are effective in vitro against a disease condition or disorder. However, several of them are not effective or not bioavailable in vivo (warm blooded animals). It is thus important to explore, identify and invent safe and effective agents that help to increase the bioavailability of the ingredient(s). In the present invention, the inventors have screened a number of extracts, fractions, phytochemical(s) and compound(s) originating from plants, animals and microorganisms.

Back ground of the invention:

The gum resin of Boswellia has been very widely used since ancient times. For example, the gum resin of *Boswellia serrata* (Burseraceae) has long been in use for the treatment of rheumatoid arthritis and gout by the practitioners of Ayurvedic medicines inthe Indian system of medicine. Various extracts of the gum resin have shown potent anti-inflammatory and anti-atherogenic activity in laboratory animals [Cuaz-Pérolin et al.,*ArteriosclerThrombVascBiol*Feb 2008]. The extract of Boswellia was found to be a potent anti-arthritic agent [Kimmatkar et al; *Phytomedicine*. 2003, 10(1): 3-7]. *Boswellia* gum resin and its extracts also demonstrated significant therapeutic improvements

inhuman clinical trials thus confirming the *in vivo* anti-inflammatory effects. [E Ernest, BMJ2008; 337: a2813].

The origin of the anti-inflammatory action of *Boswellia* gum resin and its extracts has been attributed to a group of triterpene acids called Boswellic acids that were isolated from the gum resin of *Boswellia serrata*. Boswellic acids exert anti-inflammatory actions by inhibiting 5-lipoxygenase (5-LOX). 5-LOX is a key enzyme for the biosynthesis of leukotrienes from arachidonic acid. Leukotrienes are considered to be involved in the initiation and propagation of a variety of inflammatory diseases. In addition to their 5-lipoxygenase inhibition, Boswellic acids inhibit human leukocyte elastase (HLE), an enzyme of different pro-inflammatory pathway [Safayahi, H., et. al., J. Pharmacol. Exp.Ther., 1997: 281; p 460-463]. 3-O-Acetyl-11-keto-β-Boswellicacid (AKBA) is biologically the most active component among its congeners, with an IC_{50} of 1.5 μM for the inhibition of 5-LOX [Sailer, E. R., et. al., British J. Pharmacol., 1996: 117; p 615-618].

The U.S. patents US5716928 and US5665386 relate to a method for increasing bioavailability of an orally administered hydrophobic pharmaceutical compound, which comprises orally administering the pharmaceutical compound to a mammal in need of treatment with the compound concurrently with an essential oil or essential oil component in an amount sufficient to provide bioavailability of the compound in the presence of the essential oil or essential oil component greater than bioavailability of the compound in the absence of the essential oil or essential oil component, wherein the essential oil or essential oil component has an activity of at least 10% inhibition at a concentration 0.01wt.or less in an assay that measures reduced conversion of cyclosporine to hydroxylated products using an assay system containing 250 'mu'g rat liver microsomes, 1 'mu'Mcyclosporine and 1 mM reduced nicotinamide adenine dinucleotide phosphate (NADPH)in 1 ml of 0.1 M sodium phosphate buffer, pH 7.4.

PCT publication WO 02/15916, constituting its priority from German patent DE-A 10041 217, disclose dihydro Boswellia acids, physiologically acceptable salts thereof and hydrogenated extracts from *Boswellia*. Said publications suggest the use of these compounds for the prophylactic and/or therapeutic treatment of undesired physical and

psychic conditions, in particular of somatic, psychosomatic and psychic diseases, such as inflammatory processes caused by increased leukotriene formation, leukocyte elastase or plasmin activity.

There is however no prior art, to the best of inventors knowledge, relating to the use of non-acidic Boswellia low polar gum resin extract fraction (BLPRE), Boswellia volatile oil fraction (BVOIL) or Boswellia oil fraction (BOIL) comprising BLPRE and BVOIL for increasing the bioavailability of biological agents in warm blooded animals.

Approximately 30 percent of older Americans do not get the dietary requirements of all the essential nutrients. The hazards of food-drug interactions in depleting essential nutrients are well recognized. It is unavoidable that old age calls for increased use of medications. For example, use of certain antibiotics decreases absorption of calcium and iron, while EDTA chelation therapy decreases absorption of zinc, iron, copper, and magnesium.

In addition, many foods which increase the risk of cancer and cardiovascular disease have to be eliminated from the diet, which further depletes the sources of essential nutrients.For example, excellent sources of vitamin B and vitamin D, such as red meat, liver, egg yolk, cheese and dairy products, are often limited because of their high cholesterol content.

Limited menu also causes a depletion of essential amino acids, such as tryptophan, which is important precursor of neurotransmitters, and may play a role in the prevention of brain deterioration with aging. The availability of essential nutrients is further compromised by poor gastrointestinal absorption.

The traditional way to offset insufficient nutrient supplementation, insufficient gastrointestinal absorption and insufficient metabolic utilization of essential nutrients is to administer large doses of compensating materials, such as vitamin and mineral supplements.

Hence, there exists a great need for the development of a compound/composition which helps in increasing the availability of biological agent(s) through one or more mechanism(s) comprising increasing the bioavailability, increasing the serum concentration, improving gastrointestinal absorption, improving systemic utilization, improving cross over through certain biological barriers such as respiratory lining, urinary lining, blood brain barrier and skin in warm blooded animals.

Summary of the invention:

In an important aspect the invention provides Boswellia oil(BOIL) for increasing the bioavailability of biological agents.

In another important aspect the invention provides Boswellia volatile oil fraction (BVOIL) for increasing the bioavailability of biological agents.

In another important aspect the invention provides Boswellia low polar gum resin extract fraction (BLPRE) for increasing the bioavailability of biological agents.

In another aspect the invention provides compositions comprising at least one component selected from Boswellia oil (BOIL), Boswellia volatile oil (BVOIL) and Boswellia low polar gum resin extract (BLPRE) obtained from Boswellia gum resin in combination with a biological agent, for increasing the bioavailability of biological agent in warm blooded animals in need thereof.

In another aspect the invention provides Boswellia derived bioenhancing agents for increasing the bioavailability of one or more biological ingredients or functional ingredients.

In another aspect the invention provides Boswellia derived bioenhancing agents for increasing the bioavailability of one or more pharmaceutical drugs/synthetic drugs.

In another aspect the invention provides Boswellia derived bioenhancing agents for increasing the bioavailability of one or more Boswellia derived components.

In another aspect the invention provides Boswellia derived bioenhancing agents for increasing the bioavailability of one or more Curcuma derived components.

Description of figures:

Figure I: Figure shows structural formulae 1 - 9 representing prominent compounds of *Boswellia serrata* low polar gum resin extract (BsLPRE).

Figures II represents a plot of serum concentration of AKBA after oral administration of the composition LI13108F containing *Boswelliaserrata*low polar gum resin extract (BsLPRE) and Boswellia serrata extract selectively enriched to 30% 3-O_acetyl-11-keto-β-boswellic acid (AKBA) and composition LI13119F containing *Boswellia serrata* volatile oil fraction (BsVOIL) and Boswellia serrata extract selectively enriched to 30% 3-O_acetyl-11-keto-β-boswellic acid (AKBA) to albino rats at doses equivalent to 30 mg/kg of AKBA.

Figure III represents a plot of serum concentration of Bisdemethylcurcumin (LI01008) after oral administration of composition (LI13124F1) containing Bisdemethylcurcumin and Boswellia serrata low polar gum resin extract (BsLPRE) in 2:1 ratio at concentration of 450 mg/kg or Bisdemethylcurcumin (LI01008) alone at 300 mg/kg body weight.

Detailed description of the invention:

1. 'Boswellia oil' or 'non-acidic Boswellia extract' or 'BOIL' used herein refers to non-acidic Boswellia gum resin extract containing non-acidic Boswellia low polar gum resin extract fraction (BLPRE) and Boswellia volatile oil fraction (BVOIL) obtained from gum resin of any of the Boswellia species.
2. '*Boswellia serrata* oil' or 'non-acidic *Boswellia serrata* extract' or 'BsOIL' used herein refers to non-acidic *Boswellia serrata* gum resin extract containing non-acidic *Boswellia serrata* low polar gum resin extract fraction (BsLPRE) and *Boswellia serrata* volatile oil fraction (BsVOIL) obtained from gum resin of the *Boswellia serrata* species.
3. '*Boswellia carterii* oil' or 'non-acidic *Boswellia carterii* extract' or 'BcOIL' used herein refers to non-acidic *Boswellia carteri i*gum resin extract containing non-acidic *Boswellia carterii* low polar gum resin extract fraction (BcLPRE) and *Boswellia carterii* volatile oil fraction (BcVOIL) obtained from gum resin of the *Boswellia carterii* species.
4. 'Boswellia low polar gum resin extract fraction' or 'Boswellia low polar gum resin extract' or 'BLPRE' used herein refers to non-acidic Boswellia gum resin extract oil fraction comprising sesquiterpenes, diterpenes, triterpenes and other oily phytochemicals obtained after removing the volatile components from Boswellia oil obtained from gum resin of any of the Boswellia species by any of the processes described.
5. '*Boswellia serrata* low polar gum resin extract fraction' or '*Boswellia serrata* low polar gum resin extract' or 'BsLPRE' used herein refers to non-acidic *Boswellia serrata*

gum resin extract oil fraction comprising sesquiterpenes, diterpenes, triterpenes and other oily phytochemicals obtained after removing the volatile components from Boswellia oil obtained from gum resin of *Boswellia serrata* species by any of the processes described.

6. '*Boswellia carterii* low polar gum resin extract fraction' or '*Boswellia carterii* low polar gum resin extract' or 'BcLPRE' used herein refers to non-acidic *Boswellia carterii* gum resin extract oil fraction comprising sesquiterpenes, diterpenes, triterpenes and other oily phytochemicals obtained after removing the volatile components from *Boswellia carterii* oil obtained from gum resin of *Boswellia carterii* species by any of the processes described.

7. 'Boswellia volatile oil fraction' or 'Boswellia volatile oil' or 'volatile oil' or 'volatile fraction' or 'BVOIL' used herein refers to the volatile fraction/extract comprising monoterpenes, sesquiterpenes, volatile oils and other oily phytochemicals obtained from gum resin of any of the Boswellia species by anyof the processes described.

8. '*Boswellia serrata* volatile oil fraction' or '*Boswellia serrata* volatile oil' or 'serrata volatile oil' or 'serrata volatile fraction' or 'BsVOIL' used herein refers to the volatile fraction/extract comprising monoterpenes, sesquiterpenes, volatile oils and other oily phytochemicals obtained from gum resin of the *Boswellia serrata* species by any of the processes described.

9. '*Boswellia carterii* volatile oil fraction' or '*Boswellia carterii* volatile oil' or 'carterii volatile oil' or 'carterii volatile fraction' or 'BcVOIL' used herein refers to the volatile fraction/extract comprising monoterpenes, sesquiterpenes, volatile oils and other oily phytochemicals obtained from gum resin of the *Boswellia carterii* species by any of the processes described.

10. 'Gum' or 'Gum resin' or 'resin' used herein refers to an exudate of Boswellia plant species.

11. 'Phytochemical' refers to a pure or semi-pure compound or compounds isolated from plants.

12. 'Bioenhancer(s)' refers to agents that enhance the availability of biological agent(s) through one or more mechanism(s) in warm blooded animals comprising increasing the bioavailability, enhancing the serum concentration, improving gastrointestinal absorption, improving systemic utilization, improving cross over through certain biological barriers such as respiratory lining, urinary lining, blood brain barrier and skin.

13. 'Bioenhancing composition(s)' refer to compositions comprising Boswellia derived oil fraction as Bioenhancer in combination with one or more biological agent(s).

14. 'Biological agent(s)' refer to one or more agents selected from biologically active ingredient(s), functional ingredient(s), anti-oxidant(s), vitamin(s), mineral(s),amino acid(s), and oil(s) their mixtures obtained from plant(s)/animal(s)/ microorganism(s)/ synthesis and semi synthesis.

15. 'BSE 85%' used herein refers to *Boswellia serrata* extract standardized to 85% Boswellic acids.

16. 'BCE 85%' used herein refers to *Boswellia carterii* extract standardized to 85% Boswellic acids.

17. 'CLE 95%' refers to Curcuma longa extract standardized to 95% Curcuminoids.

18. 'CAE 20%' refers to Curcuma aromatica extract standardized to 20% Curcuminoids.

19. 'Biologically active ingredient(s)' refers to any pharmaceutically or nutraceutically or dietetically acceptable active ingredient(s); compound(s), extract(s), fraction(s), phytochemical(s), synthetic drug(s) or their salts or mixtures thereof derived from plants or animals or microorganisms or chemical synthesis or semi-synthesis.

20. 'functional ingredient(s)' refers to any herbal ingredients, dietary supplements, antioxidants, vitamins, minerals, amino acids, fatty acids, essential oils, fish oils, enzymes, glucosamine, Chondroitin and probiotics or their salts or mixtures thereof derived from plants or animals or microorganisms or chemical synthesis or semi-synthesis.

The gum resin of Boswellia has been very widely used since ancient times. The gum resin of various species of Boswellia such as *Boswellia serrata, Boswellia carterii* or *Boswellia papyrifera* is a complex mixture comprising Boswellia oil fraction (BOIL) containing essential oil/Boswellia volatile oil fraction (BVOIL) and non-acidic Boswellia low polar gum resin extract fraction (BLPRE); boswellic acids, sugars and polysaccharide fraction. The *Boswellia serrata/Boswelli acarterii/Boswellia papyrifera* extracts widely available in the international markets are acidic fractions separated from the gum resin which are standardized to contain 65% or 85% total Boswellic acids by titrimetric method of analysis. During the execution of commercial process for regular Boswellia extracts derived from *Boswellia serrata/ Boswellia carterii/ Boswellia papyrifera* (85% total Boswellic acids), the acidic fraction, which contains predominantly triterpene acids

including Boswellic acids is separated from the rest of gum resin components. The sugars and other polymeric materials get separated out into the aqueous phase during the enrichment process for total Boswellic acids. The remaining water immiscible low polar compounds are separated as Boswellia oil fraction/extract. These low polar compounds are either absent or present at very low concentration in both, commercial Boswellia extracts standardized to boswellic acids and Boswellia extracts selectively enriched in 3-O-acetyl-11-keto-β-Boswellic acid (AKBA).

Process for obtaining non-acidic Boswellia oil (BOIL) fraction:

A representative process for obtaining Boswellia oil comprises:

a) procuring the gum resin of one or more of the plant(s) selected from but not limited to *Boswellia serrata* or *Boswellia carterii* or *Boswellia papyrifera* or mixtures thereof,

b) extraction of the gum resin with a water immiscible organic solvent,

c) filtering the extract carefully to remove the insoluble resin material,

d) washing the organic solvent extract repeatedly with an aqueous alkali solution such as aqueous potassium hydroxide,

e) washing the organic layer with water and brine and,

f) evaporating the organic layer under vacuum and high temperature to obtain the oily residue (BOIL).

Processes for obtaining Boswellia volatile oil (BVOIL) fraction:

The process for obtaining Boswellia volatile oil (BVOIL) is through steam distillation or using high vacuum from Boswellia gum resin.

A representative process for obtaining Boswellia volatile oil comprises:

a) procuring the gum resin of Boswellia and

b) separating the Volatile oil component by either steam distillation or distillation under high vacuum, low temperature from the said gum resin to obtain BVOIL.

In an alternative process,

a) BOIL is prepared according to the process described above,

b) BOIL is then subjected to steam distillation or vacuum distillation to collect Boswellia volatile oil (BVOIL).

Processes for obtaining Boswellia low polar gum resin extract (BLPRE) fraction:

A representative procedure for obtaining Boswellia low polar gum resin extract (BLPRE) comprises:

a) extraction of the gum resin of Boswellia species with a water immiscible organic solvent and filtering the extract carefully to remove the insoluble resin material,

b) washing the organic solvent extract repeatedly with an aqueous alkali solution such as aqueous potassium hydroxide,

c) washing the organic layer obtained after the alkali wash, with water and brine,

d) evaporating the said organic layer under vacuum and high temperature to obtain the oily residue and,

e) removing the volatile compounds from the said oily residue under high vacuum and high temperature to obtain BLPRE.

Another representative procedure for obtaining Boswellia low polar gum resin extract (BLPRE) comprises:

a) preparing the alcohol or hydroalcohol extract of Boswellia gum resin,

b) partitioning the alcohol extract between an aqueous alkali solution and a water immiscible organic solvent,

c) separating of the organic solvent layer, followed by evaporation of the solvent to obtain oily residue and,

d) removing of volatile compounds from the said oily residue under high temperature and high vacuum to obtain BLPRE.

Yet another representative procedure for obtaining Boswellia low polar gum resin extract (BLPRE) comprises:

a) extracting the gum resin of Boswellia species with alcohol or hydro alcohol,

b) evaporating the organic solvent to an optimum level of total solids and then

c) adjusting the pH to the alkaline side, preferably pH 9 – 12,

d) repeatedly extracting the solution with an organic solvent,

e) evaporating the organic solvent under vacuum and high temperature to obtain the oily residue and,

f) evaporating the volatiles from the said oily residue under high vacuum and high temperature to obtain BLPRE.

A representative procedure for obtaining *Boswellia serrata* volatile oil (BsVOIL) comprises:

a) procuring the gum resin of *Boswellia serrata* and

b) separating the Volatile oil component by either steam distillation or distillation under high vacuum, low temperature from the said gum resin to obtain BsVOIL.

Yet another representative procedure for obtaining *Boswellia carterii* volatile oil (BcVOIL) comprises:

a) procuring the gum resin of *Boswellia carterii* and

b) separating the Volatile oil component by either steam distillation or distillation under high vacuum, low temperature from the said gum resin to obtain BcVOIL.

The representative processes for obtaining Boswellia volatile oil (BVOIL) from *Boswellia serrata, Boswellia carterii* are described above. However, a similar process or processes can be applied to any of the gum resin obtained from Boswellia species for producing Boswellia volatile oil (BVOIL).

A representative procedure for obtaining *Boswellia serrata* low polar gum resin extract (BsLPRE) comprises:

a) Procuring the gum resin of *Boswellia serrata*

b) extracting with an water immiscible organic solvent and the insoluble gum materials were separated by filtration and discarded,

c) washing the organic solvent extract repeatedly with dilute aqueous alkali solution to remove the acidic compounds,

d) washing the organic layer successively with water and brine,

e) evaporating the organic layer under vacuum at 60 - 70°C to obtain an oily residue and,

f) removing the volatile components are then removed from the said oily residue under high vacuum and high temperature to obtain a viscous oil, which is referred hereinafter as *Boswellia serrata* low polar gum resin extract (BsLPRE).

Alternatively, the BsLPRE can also be prepared by a process comprising:

a) preparing the alcohol or hydroalcohol extract of *Boswellia serrata* gum resin,

b) partitioning the alcohol extract between an aqueous alkali solution and a water immiscible organic solvent,

c) separation of the organic solvent layer , followed by evaporating the organic layer under vacuum at 60 - 70°C to obtain an oily residue and,

d) removing the volatile components are then removed from the said oily residue under high vacuum and high temperature to obtain a viscous oil , which is referred herein after as *Boswellia serrata* low polar gum resin extract (BsLPRE) .

A representative procedure for obtaining *Boswellia carterii* low polar gum resin extract (BcLPRE) comprises:

a) procuring the gum resin of *Boswellia carterii*,

b) extracting the gum resin with an water immiscible organic solvent and the insoluble gum materials were separated by filtration and discarded,

c) washing the organic solvent extract repeatedly with dilute aqueous alkali solution to remove the acidic compounds,

d) washing the organic layer successively with water and brine,

e) evaporating the organic layer under vacuum at 60 - 70°C to obtain an oily residue and

f) removing the volatile components are then removed from the said oily residue under high vacuum and high temperature to obtain a viscous oil, which is referred hereinafter as *Boswellia carterii* low polar gum resin extract (BcLPRE).

Alternatively, the BcLPRE can also be prepared by process comprising:

a) preparing the alcohol or hydroalcohol extract of *Boswellia carterii* gum resin,

b) partitioning the alcohol extract between an aqueous alkali solution and a water immiscible organic solvent,

c) separation of the organic solvent layer, followed by evaporating the organic layer under vacuum at 60 - 70°C to obtain an oily residue,

d) the volatile components are then removed from the said oily residue under high vacuum and high temperature to obtain a viscous oil, which is referred herein after as *Boswellia carterii* low polar gum resin extract (BcLPRE).

The representative processes for obtaining Boswellia low polar gum resin extract (BLPRE) from *Boswellia serrata* and *Boswellia carterii* are described above. However, a

similar process or processes can be applied to any of the gum resin obtained from Boswellia species for producing the low polar gum resin extract.

The said intact Boswellia oil (BOIL) or Boswellia volatile oil (BVOIL) or Boswellia low polar gum resin extract (BLPRE) constitute significant components in Boswellia gum resin. However, it has very limited commercial utility and it is mostly discarded as a waste material. Potential utilization of these fractions has been long overdue. The inventors found very unexpectedly that *Boswellia serrata* low polar gum resin extract (BsLPRE), a fraction obtained after removing the volatile compounds from the *Boswellia serrata* oil, has several beneficial properties.

In our earlier Indian patent application 2229/CHE/2008 filed 15th September, 2008 and PCT application # PCT/IN2009/000505 filed 14th September, 2009 we disclosed synergistic compositions comprising AKBA enriched fraction and *Boswellia serrata* non-acidic extract (BNRE). BNRE composition and method of identification are also disclosed.

In our recent Indian patent application 394/CHE/2010 filed 15th February, 2010 we disclosed non Boswellic acid fraction and its synergistic compositions.

During the search for bioenhancing agents, the inventors accidentally found that non-acidic Boswellia low polar gum resin extract fraction (BLPRE), Boswellia volatile oil fraction (BVOIL) or Boswellia oil fraction (BOIL) comprising BLPRE and BVOIL enhance the bioavailability of bioactive agents. The compositions LI13108F containing *Boswellia serrata* low polar gum resin extract (BsLPRE; LI13115) and Boswellia serrata extract selectively enriched to 30% 3-O_acetyl-11-keto-β-boswellic acid (AKBA) and LI13119F containing *Boswellia serrata* volatile oil fraction (BsVOIL) and Boswellia serrata extract selectively enriched to 30% 3-O_acetyl-11-keto-β-boswellic acid (AKBA) were supplemented to Albino Wistar rats. The control group of animals was supplemented with Boswellia serrata extract selectively enriched to 30% AKBA. Blood samples were collected from all animals prior to oral administration of test products and at 0.5, 1, 2, 4, 8 and 12 hrs after oral administration. The comparative oral bioavailability of AKBA from these Boswellia products was evaluated by measuring the serum AKBA concentration for each test animal using LC-MS.

Surprisingly, both the compositions LI 13108Fand LI 13119F showed better oral bioavailability with AUCs 14.08 and 11.23 respectively compared to AUC 9.825 shown by individual ingredient Boswellia serrata extract containing 30% AKBA (LI 13115). The bioavailability (in terms of AUC) of LI 13108F is 43.33% more than LI 13115. The bioavailability of LI 13119F is 14.33% more than that of LI 13115. The study details are summarized in example-5 and depicted in Figure II.

To exert optimal therapeutic efficacy, an active substance should reach systemic circulation and site of its action in an effective concentration during the desired period. Improving bioavailability and reducing dosage frequency without losing therapeutic benefit is crucial in achieving therapeutic efficacy and patient compliance in chronic treatment regimes. The present invention achieves this objective by enhancing the oral bioavailability of AKBA in compositions containing BsLPRE or BsVOIL.

The bioavailability enhancing effect of BsLPRE was further confirmed by evaluating the composition LI13124F1 containing BsLPRE and a novel curcumin compound called bisdemethylcurcumin (LI01008) in comparison with LI01008 alone in Alibino Wistar rats. Bisdemethylcurcumin is a potent curcuminoid, far superior to other naturally occurring curcuminoids with respect to antioxidant and other biological activities commonly exhibited curcumins.The composition LI13124F1 showed better bioavailability of LI01008 in serum samples compared to the animals supplemented with LI01008 alone. The serum samples of animals supplemented with LI13124F1 showed 75% better bioavailability compared to the serum samples of the animals supplemented with LI01008 alone. The experimental studies are discussed in example-6 and depicted in Figure III.

The foregoing thus suggest that the non-acidic Boswellia low polar gum resin extract fraction (BLPRE), Boswellia volatile oil fraction (BVOIL) or Boswellia oil fraction (BOIL) comprising BLPRE and BVOIL enhance the bioavailability of bioactive agents. These bio-enhancing agents thus can be useful to improve the efficacy and reduce the dose of bioactive agents.

Different embodiments of the present invention are as outlined below:

In an important aspect, the invention provides bioenhancing agents selected from intact Boswellia oil (BOIL), Boswellia volatile oil (BVOIL) and Boswellia low polar gum resin extract (BLPRE) obtained from Boswellia gum resin of Boswellia species for increasing the bioavailability of biological agents.

In an important aspect, the invention provides compositions comprising one or more ingredients selected from intact Boswellia oil (BOIL), Boswellia volatile oil (BVOIL) and Boswellia low polar gum resin extract (BLPRE) obtained from Boswellia gum resin of Boswellia species in combination with a biological agent for increasing the bioavailability of biological agent.

In another aspect, the invention provides Boswellia derived bioenhancing agents for improving the bioavailability and/or bio-efficacy of nutraceuticals or dietary supplements *is also relevant to animal health besides being important for humans.*

In another aspect the invention provides Boswellia derived bioenhancing agents for increasing the bioavailability of one or more biological ingredient(s) or functional ingredient(s).

In another aspect the invention provides Boswellia derived bioenhancing agents for increasing the bioavailabilityof one or more Boswellia derived components.

In another aspect the invention provides Boswellia derived bioenhancing agents for increasing the bioavailability of one or more Curcuma longa derived components.

In another aspect the invention provides the method of using Boswellia derived bioenhancing agents for enhancing the bioavailability of biological agents.

In another aspect, the invention provides bioenhancing agents, which function through one or more of the mechanisms comprising increasing the bioavailability, enhancing the serum concentration, improving gastrointestinal absorption, improving systemic utilization and improving cross over through certain biological barriers like respiratory lining, urinary lining, blood brain barrier and skin.

In another aspect, the invention provides bio-enhancing agents Boswellia oil (BOIL), Boswellia volatile oil (BVOIL) and Boswellia low polar gum resin extract (BLPRE)derived from the gum resin of Boswellia where in the gum resin can be obtained from one or more of the Boswelliaspecies selected from *Boswellia serrata*, *Boswellia carterii* and *Boswellia papyrifera*.

In another aspect the invention provides compositions for bioenhancing the activity ofbiological agents in warm blooded animals in need thereof.

In another aspect the invention provides compositions comprising Boswellia oil (BOIL),Boswellia volatile oil (BVOIL) and Boswellia low polar gum resin extract (BLPRE) for enhancing the bioavailability of nutraceutical or dietetical ingredients in warm blooded animals in need thereof.

The nutraceutical/dietetical acceptable agents comprise one or more ingredients selected from phytochemicals, Nootropic agents, anti obese agents, antiinflammatory agents, anti cholesterol agents, anti arthritic agents, anti diabetic agents,anti microbial agents, anti fungal agents, anti cancer agents, anti hypertensive agents, analgesic agents, anti platelet aggregation agents, anti atherosclerotic agents, antioxidants, anti thrombotic agents, antibiotic agents, anti malarial agents, anti osteoporotic agents, probiotics agents, anti fungal agents, immune potentiating agents, anti viral agents, anti histamines, muscle relaxants, anti depressants, hypnotic agents and their salts thereof.

In another aspect the invention provides composition(s) for increasing the bioavailability of one or more biological ingredient(s) selected from biologically active ingredient(s), functional ingredient(s), herbal ingredient(s), dietary supplement(s), nutrient(s), anti-oxidant(s),vitamin(s), mineral(s), amino acid(s), and oil(s) their mixtures obtained from plant(s)/animal(s)/microorganism(s)/ synthesis/semi-synthesis.

The functional ingredient(s) comprise one or more ingredients selected from nutrients, dietary supplements, nutritional ingredients, herbal ingredients, phytochemicals, animal

proteins, glucosamine, chondroitin, plant proteins, fruit extracts, animal extracts, algae extracts, probiotics and their salts thereof.

The herbal ingredient(s) comprise one or more ingredients selected fromextracts/fractions/phytochemicals and their salts derived from *Withania somnifera, Bacopa monniera, Boswellia species, Curcuma species, Centella asiatica, Sphaeranthus indicus, Annona squamosa, Holoptelia integrifolia, Piper betel, Dolichos biflorus, Moringa oleifera* and *Murraya koenigii.*

The anti-oxidant(s) comprise one or more ingredients selected from vitamin A, vitamin C,vitamin E, alpha-carotene, trans-beta-carotene, betacryptoxanthin, lycopene, lutein/zeaxanthin, pine bark bioflavonals complex, germanium, selenium and zinc.
The vitamin(s) comprise one or more water soluble vitamins selected from vitamin B1,vitamin B2, niacinamide, vitamin B6, vitamin B12, folic acid and vitamin C; fat-soluble vitamins selected from vitamin A, vitamin D, vitamin E and vitamin K.
The mineral(s) comprise one or more minerals selected from calcium, iron, zinc, vanadium, selenium, chromium, iodine, potassium, manganese, copper and magnesium.
The amino acid(s) comprise one or more amino acids selected from lysine, isoleucine, leucine, threonine, valine, tryptophan, phenylalanine, methionine , L-selenomethionine and their mixtures thereof.
The oil(s) comprise one or more oils selected from omega-3 fatty acid, flaxseed oil, fish oils, krill oil, essential oils and volatile oils.

The biological activity of Boswellia derived compounds/phytochemicals that can be enhanced by bioenhancing agents include extracts of fractions standardized to one or more boswellic acids selected from α-Boswellic acid, β-Boswellic acid, 3-O-acetyl-α-Boswellic acid, 3-O-acetyl-β-Boswellic acid, 3-O-acetyl-11-keto-α-Boswellic acid,11-keto-β-Boswellicacid and 3-O-acetyl-11-keto-β-Boswellic acid.

In another aspect, the invention provides bio-enhancing agents selected from Boswellia oil (BOIL), Boswellia volatile oil (BVOIL) and Boswellia low polar gum resin extract (BLPRE) derived from the gum resin of Boswellia for enhancing the bioavailability of

extracts/fractions particularly standardized to 3-O-acetyl-11-keto-β-Boswellic acid (AKBA).

In another aspect, the invention provides Boswellia derived agents and compositions for enhancing the bioavailability of the phytochemicals derived from Boswellia species including but not limited to boswellic acids selected from α-boswellic acid, β-boswellic acid, 3-acetyl-α-boswellic acid, 3-acetyl-β-boswellic acid, 3-acetyl-11-keto-α-boswellic acid and 3-acetyl-11-keto-β-boswellic acid or mixtures thereof.

The Boswellia species that can be used for producing the oil (BOIL) or volatile oil (BVOIL) or low polargum resin extract (BLPRE) from the gum resin comprise one or more species selected from *Boswellia serrata, Boswellia carterii, Boswellia payrifera. Boswellia ameero, Boswellia bullata, Boswellia dalzielii, Boswellia dioscorides, Boswellia elongata, Boswellia frereana, Boswellia nana, Boswellia neglecta, Boswellia ogadensis, Boswellia pirottae, Boswellia popoviana, Boswellia rivae, Boswellia sacra and Boswellia socotrana.*

In another aspect, the invention provides Boswellia oil orBoswellia volatile oil or Boswellia low polar gum resin extract for enhancing thebioavailability of one or more Curcuma derived extracts/fractions/components/phytochemicals that can be enhanced by bioenhancing agents include extracts of fractions standardized to selected from curcumin, demethoxycurcumin, bisdemethoxycurcumin, monodemethylcurcumin, bisdemethylcurcumin, tetrahydrocurcumin, tetrahydrodemethoxycurcumin, tetrahydro bisdemethoxycurcumin and ar-turmerone or mixtures thereof.

In another aspect, the invention provides bio-enhancing agents Boswellia oil (BOIL),Boswellia volatile oil (BVOIL) and Boswellia low polar gum resin extract (BLPRE) derived from the gum resin of Boswellia for enhancing the bioavailability of extracts/fractions particularly standardized to curcumin or demethoxycurcumin or bisdemethoxycurcumin or mixtures thereof.

In another aspect, the invention provides Boswellia derived bioenhancing agents and for enhancing the bioavailability of the one or more phytochemicals derived from Curcuma species selected from curcumin, demethoxycurcumin, bisdemethoxycurcumin, monodemethylcurcumin, bisdemethylcurcumin, tetrahydrocurcumin, tetrahydrodemethoxycurcumin, tetrahydro bisdemethoxycurcumin and ar-turmerone or mixtures thereof.

The Curcumin derived components that can be bioenhanced are derived from *Curcuma longa, Curcuma aromatica, Curcuma domestica, Curcuma aeruginosa, Curcuma albicoma, Curcuma albiflora, Curcuma alismatifolia, Curcuma angustifolia, Curcumaelata, Curcuma ferruginea, Curcuma flaviflora, Curcuma yunnanensis* and *Curcuma zedoaria*.

In another aspect the invention provides the representative processes for obtaining Boswellia oil (BOIL) comprising:

a) procuring the gum resin of one or more of the plant(s) selected from but not limited to *Boswelliaserrata*or *Boswelliacarterii*or *Boswellia papyrifera* or mixtures thereof,

b) extraction of the gum resin with a water immiscible organic solvent,

c) filtering the extract carefully to remove the insoluble resin material,

d) washing the organic solvent extract repeatedly with an aqueous alkali solution such as aqueous potassium hydroxide,

e) washing the organic layer with water and brine,

f) evaporating the organic layer under vacuum and high temperature to obtain the oily residue (BOIL).

In another aspect the invention provides a representative procedure for obtaining Boswellia volatile oil (BVOIL) comprising:

a) procuring the gum resin of Boswellia,

b) separating the Volatile oil component by either steam distillation or distillation under high vacuum and temperature from the said gum resin to obtain BVOIL.

c) alternatively, the BVOIL fraction can be separated from the BOIL fraction described above by vacuum distillation under high vacuum and temperature.

In another aspect, the invention provides a process for producing Boswellia low polar gum resin extract (BLPRE) comprising the following steps:

a) extraction of the gum resin of Boswellia species with a water immiscible organic solvent and filtering the extract carefully to remove the insoluble resin material,

b) washing the organic solvent extract repeatedly with an aqueous alkali solution such as aqueous potassium hydroxide,

c) washing the organic layer obtained after the alkali wash, with water and brine,

d) evaporating the said organic layer under vacuum and high temperature to obtain the oily residue,

e) removing the volatile compounds from the said oily residue under high vacuum and high temperature to obtain BLPRE.

The water immiscible organic solvent used for extraction can be selected from the groupcomprising but not limited to 1,2-dichloroethane, hexane, dichloromethane, chloroform,ethyl acetate, n-butanol, methyl iso-butyl ketone (MIBK) or their suitable combinationthereof.The alkali solution used for washing the organic solvent extract can be selected from Group-I or Group-II metal hydroxides, which include but not limited to Sodium hydroxide, Potassium hydroxide, Calcium hydroxide and Magnesium hydroxide or mixtures thereof

In another aspect, an alternative process for producing BLPRE comprises:

a) preparing the alcohol or hydroalcohol extract of Boswellia gum resin,

b) partitioning the alcohol extract between an aqueous alkali solution and a water immiscible organic solvent,

c) separation of the organic solvent layer, followed by evaporation of the solvent to obtain oily residue,

d) removal of volatile compounds from the said oily residue under high temperature and high vacuum to obtain BLPRE.

In another aspect, a further alternative process for producing Boswellia low polar gum resin extract (BLPRE) comprise,

a) extracting the gum resin of Boswellia species with alcohol or hydro alcohol,

b) evaporating the organic solvent to an optimum level of total solids and then

c) adjusting the pH to the alkaline side, preferably pH 9 – 12,

d) repeatedly extracting the solution with an organic solvent,

e) evaporating the organic solvent under vacuum and high temperature to obtain the oily residue,

f) evaporating the volatiles from the said oily residue under high vacuum and hightemperature to obtain BLPRE.

The alcohol used for extraction can be selected from the group comprising but not limitedto methanol, ethanol and propanol or their suitable combination thereof.

In another aspect, the invention provides a Boswellia low polar gum resin extract(BLPRE) from *Boswellia serrata*, wherein the said extract comprises one or more phytochemical marker compounds selected from but not limited to guiol (**1**), nephthenol (**2**), serratol (**3**),diterpene X (**4**), lupeol (**5**), olean-12-ene-3β-ol (**6**), olean-12-ene-3α-ol (**7**), lanosta-8,24-diene-3α-ol (**8**) and urs-12-ene-3α-ol (**9**).

In another aspect, the invention provides a Boswellia low polar gum resin extract obtained after selectively removing the acidic and volatile compounds.

The composition(s) of the present invention containing the bioenhancer and the biological agent is administered through oral, dermal, intravenous, subcutaneous, intra-peritoneal, rectal, intra-muscular or any suitable route inwarm blooded animals.

The effective daily dosage of the Bioenhancer(s) in warm blooded animals is in the range of 0.001 to 1500 mg/kg body weight.

The effective daily dosage of the Bioenhancer(s) in warm blooded animals is in the range of 0.01 to 500 mg/kg body weight.

The effective daily dosage of the Bioenhancer(s) in warm blooded animals is in the range of 0.1 to 150 mg/kg body weight.

The effective daily dosage of the Bioenhancer(s) in warm blooded animals is in the range of 1.5 - 15 mg/kg body weight.

Examples:

Example 1

<u>A process for preparation of the Boswellia oil (BOIL):</u>

The process for preparing Boswellia oil comprises:

a) procuring the gum resin of one or more of the plant(s) selected from but not limited to *Boswellia serrata* or *Boswellia carterii* or *Boswellia papyrifera* or mixtures thereof,
b) extraction of the gum resin with a water immiscible organic solvent,
c) filtering the extract carefully to remove the insoluble resin material,
d) washing the organic solvent extract repeatedly with an aqueous alkali solution such as aqueous potassium hydroxide,
e) washing the organic layer with water and brine, and
f) evaporating the organic layer under vacuum and high temperature to obtain the oily residue (BOIL).

Example 2:

A process for preparation of the Boswellia volatile oil (BVOIL):

The process for preparing Boswellia volatile oil comprises:
a) procuring the gum resin of one or more of the plant(s) selected from but not limited to *Boswellia serrata* or *Boswellia carterii* or *Boswellia papyrifera* or mixtures thereof,
b) separating the volatile oil component by either steam distillation or distillation under high vacuum, low temperature from the said gum resin to obtain Boswellia volatile oil (BVOIL).

Example 3:

Preparation of *Boswellia serrata* low polar gum resin extract (BsLPRE):

The *Boswellia serrata* gum resin (100 g) was dispersed in 600 mL of methyl isobutylketone (MIBK) solvent and stirred at room temperature for 60 min. The insoluble gum materials were separated by filtration. The MIBK solution was extracted repeatedly with2% KOH solution (3 x 200 mL) to remove the acidic compounds. The MIBK layer was then washed successively with water (400 mL) and brine (200 mL). The MIBK layer was evaporated under reduced pressure at 60 – 70°C and the volatile components are then removed from the oily residue under high vacuum at 75 – 100°C to obtain *Boswellia serrata* low polar gum resin extract or BsLPRE as a viscous oil (12 g).

Alternatively, the gum resin (250 g) collected from *Boswellia serrata* was extracted with methanol (300 mLx3) and the combined methanol extract was concentrated. The residue (50 g) was dissolved in ethyl acetate (400 mL) and extracted thrice with 1N KOH (3 x100

mL). The organic layer was washed with water (2 x 200 mL) and brine (200 mL) and evaporated to obtain Boswellia oil. The volatile compounds were evaporated from the oil under high vacuum at 75-100°C to obtain 22 g of BsLPRE.

The BsLPRE was subjected to column chromatography over normal silica gel using solvents of increasing polarity starting from hexane to hexane/ethyl acetate mixtures to ethyl acetate. The identical fractions were combined based on TLC and the combined fractions were subjected individually to repeated column over silica gel using mixtures of hexane/ethyl acetate or hexane/acetone as eluants to obtain pure compounds. Some of the impure fractions were further subjected to preparative HPLC using a reversed phase C18silica column to obtain pure compounds. The structures of individual compounds were established by analyzing the ^{1}H NMR, ^{13}C NMR, DEPT, HSQC and HMBC and mass spectral data and then comparing the data with that of known compounds. Nine of the prominent compounds are identified as guiol (**1**), nephthenol (**2**), serratol (**3**), diterpene X(**4**), lupeol (**5**), olean-12-ene-3β-ol (**6**), olean-12-ene-3α-ol (**7**), lanosta-8,24-diene-3α-ol(**8**) and urs-12-ene-3α-ol (**9**) as depicted in **Figure I**. The pure compounds were then utilized to standardize the *Boswellia serrata* low polar gum resin extract (BsLPRE) using HPLC method. The novel composition of BsLPRE, evaluated based on analytical HPLC method, along with the retention times (Rt) is summarized in **Table 1**.

Table 1

Composition of *Boswellia serrata* low polar gum resin extract (BsLPRE)

S. No	Test substance	R_t in min	Percentage
1	Guiol (1)	4.5	0.96
2	Nephthenol (2)	7.087	2.01
3	Serratol (3)	8.027	13.32
4	Diterpene X (4)	15.777	0.12
5	Lupeol (5)	26.901	0.06
6	Olean-12-ene-3β-ol (6)	31.460	1.29
7	Olean-12-ene-3α-ol (7)	33.718	5.36
8	Lanosta-8,24-diene-3α-ol (8)	35.371	1.34
9	Urs-12-ene-3α-ol (9)	37.207	4.55

Example 4

Preparation of *Boswellia carterii* low polar gum resin extract (BcLPRE):

The *Boswellia carterii* gum resin (100 g) was dispersed in 600 mL of methyl iso butyl ketone (MIBK) solvent and stirred at room temperature for 60 min. The insoluble gum materials were separated by filtration. The MIBK solution was extracted repeatedly with2% KOH solution (3 x 200 mL) to remove the acidic compounds. The MIBK layer was then washed successively with water (400 mL) and brine (200 mL). The MIBK layer was evaporated under reduced pressure at 60 – 70°C and the volatile components are then removed from the oily residue under vacuum at 75 – 85°C to obtain *Boswellia carterii* low polar gum resin extract or BcLPRE as a viscous oil (9.5 g).

Alternatively, the gum resin (250 g) collected from *Boswellia carterii* was extracted with methanol (300 mLx3) and the combined methanol extract was concentrated. The residue (50 g) was dissolved in ethyl acetate (400 mL) and extracted thrice with 1N KOH (3 x100 mL). The organic layer was washed with water (2 x 200 mL) and brine (200 mL) and

evaporated to obtain Boswellia oil. The volatile compounds were evaporated from the oil under vacuum at 75-85°C to obtain 17.75 g of BcLPRE.

Example 5

Comparative bioavailability of 3-O-acetyl-11-keto-β-boswellic acid (AKBA) from different boswellia products:

Albino Wistar rats were quarantined and healthy rats were selected for the study. The selected animals were acclimatized for 7 days prior to the study initiation in the allocated room. Animals employed for the study were randomized into various treatment groups, fasted overnight at free access to water, body weights were noted and individual doses were calculated based on the body weights. Blood samples were collected from all animals prior to oral administration of test products and at 0.5, 1, 2, 4, 8 and 12 hrs after oral administration. Collected blood samples were allowed to clot for 10 min and centrifuged at 4^0C at 1800 g for 10 min. The serum samples were deprotenized with 100μL TCA (20%) and 1.8 mL of HPLC grade methanol, centrifuged at 4^0C at 1800 g for 10min and supernatants were subjected to LCMS analysis for total AKBA. The Composition LI 13108F comprising *Boswellia serrata* extract selectively enriched to 30% 3-O-acetyl-11-keto-β-boswellic acid (AKBA) (LI 13115) and *Boswellia serrata* non-volatile oil (BsLPRE) in the ratio 2:1; and composition LI13119F comprising *Boswellia serrata* extract standardized to 30% AKBA and *Boswellia serrata* steam distilled oil (BVOIL) in the ratio 2:1 showed better oral bioavailability with Area under the curve (AUC) 14.08 and 11.23 respectively compared to individual *Boswellia serrata* extract standardized to 30% AKBA (LI 13115) (AUC: 9.825). The bioavailability [in terms of [AUC] of LI 13108F is 43.33% more than LI 13115. The bioavailability of LI 13119F is 14.33% more than that of LI 13115. The serum concentration of AKBA in animals of various treatment groups at various time points was summarized in **Table-2**. The serum concentration against time was plotted and the details are summarized in Figure II.

Table-2

Mean Serum AKBA concentration µg/mL			
Time (h)	**LI 13115** (Mean±SE)	**LI 13108F** (Mean±SE)	**LI 13119F** (Mean±SE)
0	0.000 ± 0.00	0.000 ± 0.00	0.000 ± 0.00
0.5	1.200 ± 0.19	1.533 ± 0.06	1.805 ± 0.21
1	1.545 ± 0.28	1.853 ± 0.11	1.865 ± 0.32
2	1.980 ± 0.45	2.000 ± 0.16	1.750 ± 0.26
4	0.850 ± 0.32	2.147 ± 0.41	1.100 ± 0.07
8	0.452 ± 0.22	0.520 ± 0.16	0.645 ± 0.13
12	0.095 ± 0.10	0.199 ± 0.14	0.200 ± 0.20
AUC	9.825	14.0825 (43.33%)	11.2325 (14.33%)

Example 6:

Comparative Bioavailability of LI01008 and its composition:

LI13124F1Animals (Wistar Rats) were acclimatized for 7 days prior to study initiation. Six animals were divided randomly into 2 groups, each comprised of 3 animals. The body weights were noted and doses were calculated based on initial body weights. Animals were treated orally with 450 mg dose of a composition (LI13124F1) containing bisdemethylcurcumin (LI01008) and BsLPRE (LI13115) in 2:1 ratio or 300 mg/kg LI01008 as suspension in 0.5% CMC. Blood samples were collected before treatment and several time intervals after treatment at 0.5, 1, 2, 4, 6, 8 and 12 hours. Collected blood samples were processed in a refrigerated centrifuge and serum samples were deprotenized using HPLC grade methanol, mixed thoroughly and centrifuged to remove precipitated proteins clear supernatants were subjected for LI01008 estimation by HPLC. The data is summarized in table 3 below.

As per the data, the bioavailability of LI01008 in the composition LI13124F1 is 75% better compared to that when LI01008 is administered alone.

Table 3

S.No	Time after Admn.	LI13124F1 suspension in 0.5% CMC	LI01008 suspension in 0.5% CMC
1	0	0	0
2	0.5	0.1075	0.07
3	1	0.16	0.1085
4	2	0.105	0.078
5	4	0.065	0.035
6	6	0.032	0.00535
7	8	0.0085	0
8	12	0	0

It will be appreciated by those of ordinary skilled in the art that changes could be made to the embodiments described above without departing from the broad inventive concept thereof. It is understood, therefore, that this invention is not limited to the particular embodiments or examples disclosed, but is intended to cover modifications within the embodiments and scope of the present invention.

We claim,

1. Use of an agent selected from intact Boswellia oil (BOIL), Boswellia volatile oil (BVOIL) and Boswellia low polar gum resin extract (BLPRE) or mixtures thereof derived from the gum resin of Boswellia species as a bio-enhancing agent in enhancing the bioavailability of biological agents.

2. Use of a composition comprising one or more ingredients selected from intact Boswellia oil (BOIL), Boswellia volatile oil (BVOIL) and Boswellia low polar gum resin extract (BLPRE) or mixtures thereof obtained from Boswellia species in combination with biological agents as a bio-enhancing composition in enhancing the bioavailability of said biological agents.

3. The use of the bio-enhancing agent or the composition according to claim 1 or 2, wherein the Boswellia gum resin originates from one or more of the Boswellia species selected from *Boswellia serrata, Boswellia carterii*and*Boswellia papyrifera.*

4. The use of the bio-enhancing agent or the composition according to claim 3, wherein said biological agents are selected from biologically active ingredient(s), functional ingredient(s), herbal ingredient(s), dietary supplement(s), nutrient(s), antioxidants), vitamin(s), mineral(s), amino acid(s) and oil(s) or their mixtures.

5. The use of the bio-enhancing agent or the composition according to claim 4, wherein the said biologically active ingredients are selected from dietetically acceptable active ingredient(s), compound(s), extract(s), fraction(s), phytochemical(s), synthetic drug(s) or their salts or mixtures thereof.

6. The use of the bio-enhancing agent or the composition according to claim 4, wherein the said functional ingredient comprises one or more ingredients selected from herbal ingredients, dietary supplements, antioxidants, vitamins, minerals, amino acids, fatty acids, essential oils, fish oils, enzymes, glucosamine, chondroitin and probiotics or their salts or mixtures.

7. The use of the bio-enhancing agent or the composition according to claim 5 or 6, wherein said biologically active ingredient(s) and functional ingredient(s) is/are obtained from plant(s), animal(s), microorganism(s), by synthesis or by semi-synthesis for enhancing the bioavailability.

8. The use of the bio-enhancing agent or the composition according to claims 4 or 6, wherein the herbal ingredient comprises one or more ingredients selected from extracts/fractions/phytochemicals and their salts derived from *Withaniasomnifera, Bacopamonniera, Boswellia species, Curcuma species, Centellaasiatica, Sphaeranthus indicus, Garciniamangostana, Annonasquamosa, Holopteliaintegrifolia, Piper betel, Dolichosbiflorus, Moringaoleifera and Murrayakoenigii* or mixtures thereof.

9. The use of the bio-enhancing agent or the composition according to claim 8, wherein the extracts/fractions phytochemicals derived from Boswellia species include extracts or fractions standardized to one or more boswellic acids selected from α-boswellic acid, β-boswellic acid, 3-O-acetyl-α-boswellic acid, 3-O-acetyl-β-boswellic acid, 3-O-acetyl-11-keto-α-boswellic acid and 3-O-acetyl-11-keto-β-boswellic acid or mixtures thereof.

10. The use of the bio-enhancing agent or the composition according to claim 8, wherein the extracts/fractions/phytochemicals derived from Boswellia species include extracts or fractions standardized to 3-O-acetyl-11-keto-β-boswellic acid.

11. The use of the bio-enhancing agent or the composition according to claim 8, wherein the phytochemicals derived from Boswellia species include boswellic acids selected from α-boswellic acid, β-boswellic acid, 3-O-acetyl-α-boswellic acid, 3-acetyl-β-boswellic acid, 3-O-acetyl-11-keto-α-boswellic acid and 3-O-acetyl-11-keto-β-boswellic acid or mixtures thereof.

12. The use of the bio-enhancing agent or the composition according to claim 8, wherein the extracts/fractions/phytochemicals derived from Curcuma species include

extracts or fractions standardized to one or more components selected from curcumin, demethoxycurcumin, bisdemethoxycurcumin, monodemethylcurcumin, bisdemethylcurcumin, tetrahydrocurcumin, tetrahydrodemethoxycurcumin, tetrahydrobisdemethoxycurcumin and ar-turmerone or mixtures thereof.

13. The use of the bio-enhancing agent or the composition according to claim 8, wherein the Curcuma species derived extracts/fractions are particularly standardized to curcumin.

14. The use of the bio-enhancing agent or the composition according to claim 8, wherein the phytochemicals derived from Curcuma species include curcumin, demethoxycurcumin, bisdemethoxycurcumin,monodemethylcurcumin, bisdemethylcurcumin, tetrahydrocurcumin, tetrahydrodemethoxycurcumin, tetrahydrobisdemethoxycurcumin and ar-turmerone or mixtures thereof.

15. The use of the bio-enhancing agent or the composition according to claims 4 and 6, wherein the antioxidant comprises one or more ingredients selected from vitamin a, vitamin c, vitamin e, alpha-carotene, transbeta-carotene, betacryptoxanthin, lycopene, lutein/zeaxanthin, pine bark bioflavonals complex, germanium, selenium and zinc.

16. The use of the bio-enhancing agent or the composition according to claims 4 and 6, wherein the vitamins comprise one or more water soluble vitamins selected from vitamin b1, vitamin b2, niacinamide, vitamin b6, vitamin b12, folic acid and vitamin c; fat-soluble vitamins selected from vitamin a, vitamin d, vitamin e and vitamin k.

17. The use of the bio-enhancing agent or the composition according to claims 4 and 6, wherein the minerals comprise one or more selected from calcium, iron, zinc, vanadium, selenium, chromium, iodine, potassium, manganese, copper and magnesium.

18. The use of the bio-enhancing agent or the composition according to claims 4 and 6, wherein the amino acids comprise one or more selected from lysine, isoleucine, leucine, threonine, valine, tryptophan, phenylalanine, methionine, 1-selenomethionine or mixtures thereof.

19. The use of the bio-enhancing agent or the composition according to claims 4 and 6, wherein the oil(s) comprise one or more selected from omega-3 fatty acid, flaxseed oil, fish oils, essential oils and volatile oils.

20. The use of the bio-enhancing agent or the composition according to claim 3, wherein the boswellia species that can be used for producing the oil or volatile oil or low polar gum resin extract from the gum resin according to claim 3, are selected from Boswellia ameero, Boswellia bullata, Boswellia dalzielii, Boswellia dioscorides, Boswellia elongata, Boswellia frereana, Boswellia nana, Boswellia neglecta, Boswellia ogadensis, Boswellia pirottae, Boswellia popoviana, Boswellia rivae, Boswellia sacra and Boswellia socotrana.

21. The use of the bio-enhancing agent or the composition according to claim 1 or 2, wherein the biological agents are 3-O-acetyl-11-keto-β-boswellic acid and/or bisdemethylcurcumin.