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(54) Benevnelse **SOLUBILISATE WITH CURCUMIN AND AT LEAST ONE OTHER ACTIVE SUBSTANCE**

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SOLUBILISATE WITH CURCUMIN AND AT LEAST ONE OTHER ACTIVE SUBSTANCE

Description

The invention relates to a solubilizate comprising curcumin and at least one further active substance for use according to claim 1. Furthermore, the invention relates to a fluid containing such a solubilizate, to a capsule filled with such a solubilizate or fluid, and to a dietary supplement and/or drug containing such a solubilizate. Curcumin is discussed as an active substance based on various potential pharmacological properties. For example, there are indications for the antioxidant and also for the anti-inflammatory effect of curcumin as well as for the effectiveness against viruses and bacteria and against cancer. Indications could therefore be, for example, Parkinson's, Alzheimer's, diabetes, colorectal tumors, pancreatic cancer, and liver dysfunction.

In order to be able to enter the bloodstream after oral intake, the active substance must pass through the small intestinal blood barrier, is then metabolized in the liver and enters the hepatic vein as a bioavailable fraction. The rest of the total active substance ingested and released in the body is either degraded microbially in the intestine or eliminated with the feces or bile.

The inventor has already created a curcumin solubilizate which has significantly increased bioavailability compared to native curcumin. This solubilizate is described in international patent application WO 2014094921 A1. Surprisingly, it has been found in several studies that alongside its high bioavailability, said curcumin solubilizate in its specific formulation also has an unexpectedly greater effect on the reduction of disease symptoms which are associated in particular with inflammation or cancer.

A toxicity due to the micellization of the active substance according to the invention in comparison to the native form could be ruled out on the basis of studies with MTT assays for cell viability. The verification of cell vitality by MTT assay is based on the reduction of the yellow water-soluble dye 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) into a blue-violet water-insoluble formazan.

US 2016/0081975 A1 discloses non-aqueous pre-gel concentrates which contain a water-soluble mixture of vitamin E derivatives or a polyethylene glycol (PEG) derivative of vitamin E, a non-polar substance which differs from the PEG derivative of vitamin E and a non-aqueous solvent. Table 5 shows a pre-gel concentrate comprising curcumin, *Boswellia* extract, hop extract and other constituents.

The inventor has therefore set himself the task of providing a formulation which makes the health-promoting to curative properties of curcumin, also when combined with at least one further active substance, available to the human or animal organism. In particular, it is an object of the invention to provide as high a bioavailability of curcumin as possible in combination with at least one active substance.

The inventor has recognized that the positive effect of curcumin on healing processes or on maintaining health can surprisingly be used, at least partially synergistically, in combination with further active substances.

The invention is defined in claims 1-15.

For the purposes of the present application, the term “active substance” refers to a substance that is provided in a pharmaceutically effective concentration and is preferably added for the purpose of having a pharmaceutical effect. Here, the name of the respective active substance is understood to encompass also substances that are converted in the body into the active substance and/or into its biologically active form.

“Active substances” within the meaning of the present application include secondary phytochemicals which are not produced as chemical compounds by plants in energy metabolism or in anabolic or catabolic metabolism. One group of secondary phytochemicals and thus active substances in the sense of the present application are flavonoids. The active substances in the sense of the present application also include natural polyphenols such as resveratrol or the polyphenols from licorice, and natural phenols, in particular chalcones such as xanthohumol. Also encompassed are plant extracts, i.e. substances that were extracted from plants or parts of plants using an extractant. These include extracts from hops or from the root material of the licorice plant. The active substance is referred to as

an “extract” even if it is still dissolved in the extractant. Also the term “essence” can be used for an extract.

The “active substances” in the sense of the present application also include enzymes. One example of an enzyme as an “active substance” in the present application is serrapeptase. However, the application is not limited to this enzyme.

The extract from the resin of the frankincense tree, *Boswellia serrata* extract, contains several pentacyclic triterpenes which together are often referred to as total boswellic acids (“total BAs”). The term "boswellic acids” refers to a group of chemical compounds naturally occurring in the resin of the frankincense trees mentioned above. The two basic structures are α-boswellic acid and β boswellic acid. Also, some derivatives of the boswellic acids are known, in particular compounds which carry a keto group at position 11 and/or which are acetylated at position 3. Boswellic acids that are currently considered to be significant in terms of pharmacological effects in particular include α-boswellic acid (αBA) and β-boswellic acid (βBA) and their derivatives 11 keto-β-boswellic acid (KBA; CAS 17019-92-0) and 3-O-acetyl-11-keto-β-boswellic acid (AKBA; CAS 67416-16-9), and 3-O-acetyl-α-boswellic acid (AαBA), and 3-O-acetyl-β-boswellic acid (AβBA). In particular the derivative AKBA is considered to have an anti-inflammatory effect. In the context of the present application, the term “Boswellia”, in particular in the term “Boswellia solubilizate” is used in the sense that the term “Boswellia” refers to the active substances from the resin of the frankincense tree, i.e. to at least one boswellic acid and/or at least one derivative of a boswellic acid. The term “boswellic acid solubilizate” refers to a micellar formulation of at least one boswellic acid which may also contain at least one boswellic acid derivative.

Xanthohumol is a flavonoid naturally occurring in hops. It is a prenylated plant polyphenol which is assigned to the chalcones and has only been identified in hops so far. The bitter hop varieties have a significantly higher content of xanthohumol than aroma varieties. In tests, xanthohumol was found to be effective against the emergence and development of cancer cells. In laboratory experiments, it was moreover found that xanthohumol is capable of protecting the nerve cells of the brain and thus could possibly help to slow down the course of diseases like Alzheimer's or Parkinson's.

Licorice flavonoid oil (LFO) consisting of hydrophobic polyphenols of the licorice in medium-chain triglycerides has a weight-reducing effect which is associated with reduced body fat. Antioxidant properties are also attributed to the ethanolic extracts of licorice. Licorice flavonoid oil having a glabridin concentration of 3 % goes by the brand name “KANEKA GLAVONOID™”. In the following, it shall also be referred to as “glavonoid”.

Resveratrol is a phytoalexin, which has antioxidant properties and belongs to the polyphenols. The substance can be found, for example, in grapes, in relatively large amounts in the skin of red grapes, but also in raspberries, mulberries, plums, peanuts and in Japanese knotweed. Resveratrol can also be isolated from the vine itself. According to the entry in the online encyclopedia “Wikipedia”, in-vitro studies have given an indication of possible efficacy against cancer cells and positive effects in diseases, such as arteriosclerosis, heart disease, Alzheimer's disease, arthritis, and some autoimmune diseases.

Serratia peptidase or serrapeptase is a proteolytic enzyme produced by the bacterium Serratia which lives in the intestine of the silkworm. Serrapeptase is said to have beneficial effects in relieving pain, inflammation, traumatic swelling, and excess mucus secretion by the organism. It is said to be effective like an anti-inflammatory and analgesic similar to acetylsalicylic acid, ibuprofen or other non-steroidal analgesics. It is also said to induce fibrinolytic anti-inflammatory and anti-oedematous activity in the tissue. Like all enzymes, serrapeptase is sensitive to the acids produced by the stomach. Therefore, the provision in a formulation that allows gastric passage is an object of the invention.

The solubilizate according to the invention may contain one or more boswellic acids and/or one or more boswellic acid derivatives in a total content of less than or equal to 10 wt.%, preferably less than or equal to 8 wt.%, most preferably 4.7 wt.% to 6.6 wt.%.

Due to the high proportion of Boswellia, the invention envisages, in an advantageous embodiment thereof, that the solubilizate contains an extract obtained from the resin of the plant *Boswellia serrata* by extraction using ethyl acetate as a source of the one or more boswellic acids and/or one or more

boswellic acid derivatives, with boswellic acids being contained in a concentration of at least 85 wt.% in this extract.

The solubilizate according to the invention may contain xanthohumol in an amount of less than or equal to 10 wt.%, preferably less than or equal to 5 wt.%, most preferably 1 wt.% to 3 wt.%.

Due to the high proportion of xanthohumol, the invention contemplates, in an advantageous embodiment thereof, that the solubilizate contains an ethanolic extract of hard resins from hops as a source of xanthohumol, with a xanthohumol concentration in this extract in a range between 65 wt.% and 95 wt.%, preferably in a concentration in a range from 80 % to 92 wt.%. In particular the products “Xantho-Flav Pure” or “Xantho-Flav” that will be discussed in more detail below can be used as a xanthohumol source in the context of the invention.

The solubilizate according to the invention may comprise a fluid containing licorice extract, in particular a hydrophobic solution of a licorice extract, preferably glavonoid and/or glabridin, with a proportion of less than or equal to 35 wt.%, preferably less than or equal to 20 wt.%, particularly preferably 0.3 wt.% to 17 wt.%.

The solubilizate according to the invention may contain resveratrol in the range between 1 wt.% and 15 wt.%, most preferably in the range between 5 wt.% and 10 wt.%.

The solubilizate according to the invention may contain serrapeptase in a range of up to 3 wt.%, preferably in a range between 0.1 wt.% and 2 wt.%, most preferably in a range between 0.18 wt.% and 0.35 wt.%.

The solubilizate according to the invention may contain coenzyme Q10 in the range of up to 10 wt.%, preferably in the range between 0.1 wt.% and 5 wt.%, most preferably in the range between 0.5 wt.% and 1.5 wt.%.

The solubilizate according to the invention may contain α-lipoic acid in the range of up to 10 wt.%, preferably in the range between 0.1 wt.% and 5 wt.%, most preferably in the range between 0.8 wt.% and 2.5 wt.%.

Also a solubilizate consisting of or containing curcumin and at least one further active substance may also advantageously be provided or used within the context of the invention for use in the prevention of diseases involving inflammation, cancer, Alzheimer's, Parkinson's, obesity, high cholesterol, elevated blood sugar, diabetes, metabolic syndrome and/or autoimmune diseases, multiple sclerosis (MS), for reducing visceral fat, for thermogenesis, for lowering cholesterol, in particular LDL cholesterol, and/or glucose in the blood and/or triglycerides in the blood, for improving macular pigment density, for reducing oxidative stress and/or for reducing the accumulation of fat in the hepatocytes, in particular as a pharmaceutical drug for treating and/or preventing fatty liver disease, Friedreich's ataxia, lysosomal diseases, in particular Tay-Sachs disease, arteriosclerosis, heart diseases, arthritis.

In particular, the invention provides the solubilizates as described above for use as an anti-inflammatory drug and/or as an antibiotic and/or as a pharmaceutical drug with an effect against cancer, Alzheimer's, Parkinson's, obesity, high cholesterol, elevated blood sugar, diabetes, metabolic syndrome, and/or autoimmune diseases, multiple sclerosis (MS), for lowering visceral fat, for thermogenesis, as a cholesterol-lowering pharmaceutical drug, in particular with respect to LDL cholesterol, and/or as a pharmaceutical drug with an effect for lowering glucose in the blood and/or triglycerides in the blood, for improving macular pigment density, for reducing oxidative stress and/or for reducing the accumulation of fat in the hepatocytes, in particular as a pharmaceutical drug with an effect against fatty liver, Friedreich's ataxia, lysosomal diseases, in particular Tay-Sachs disease, arteriosclerosis, heart diseases, arthritis.

In this context, too, it has proven to be advantageous that, for the solubilizate according to the invention, the total curcuminoid concentration in human blood plasma, measured one hour after oral administration of 500 mg curcumin in the form of the solubilizate according to any one of the preceding claims, is about 500 ng curcuminoid per mL of plasma ±100 ng curcuminoid per mL of plasma. The total curcuminoid concentration in human blood plasma over a period of 24 hours, measured as an area under the total curcumin plasma concentration-time curve

(AUC) is in the range from about 9,500 to about 10,000 nmol h/L. The solubilizate is thus available to the body to a great extent even after oral administration.

The invention advantageously provides solubilizates with very good anti-inflammatory properties. The anti-inflammatory activity measured as a concentration of C-reactive protein (CRP) in the blood serum of arthritic rats, after a single administration of the solubilizate according to the invention in a dose of 5 mg/kg body weight curcumin, is in the range from about 2,100 pg/mL to about 2,500 pg/mL and, after a single administration of the solubilizate in a dose of 10 mg/kg body weight curcumin, is in the range from about 1,400 pg/mL to about 1,800 pg/mL.

The anti-inflammatory effect measured as a concentration of myeloperoxidase (MPO) in the blood serum of arthritic rats, after a single administration of the solubilizate in a dose of 5 mg/kg body weight curcumin, is in the range from about 800 mU/mL to about 900 mU/mL. These are significantly lower than the values for native curcumin, as explained in more detail below.

The anti-inflammatory activity of a solubilizate of curcumin and Boswellia according to the invention measured as a concentration of C-reactive protein (CRP) in the blood serum of arthritic rats, after a single administration of the solubilizate in a dose of 5 mg/kg body weight curcumin and 10 mg/kg body weight boswellic acids, is in the range of about 1200 pg/mL to about 1500 pg/mL compared with about 3200 pg/mL to about 3500 pg/mL after administration of the same dose of native curcumin or Boswellia.

The anti-inflammatory effect of a solubilizate of curcumin and Boswellia according to the invention measured as a concentration of myeloperoxidase (MPO) in the blood serum of arthritic rats, after a single administration of the solubilizate in a dose of 5 mg/kg body weight curcumin and 10 mg/kg body weight of boswellic acids, is in the range from about 750 mU/mL to about 815 mU/mL, and thus significantly lower than about 1150 mU/mL to about 1250 mU/mL after administration of the same dose of native curcumin or Boswellia.

The enzyme unit (U) is a unit which has since been replaced by the katal to indicate enzymatic activity. Since the numerical values change when katal is used,

the enzyme unit (U) continues to be used in medicine and clinical chemistry. One enzyme unit U corresponds to one micro-mole substrate conversion per minute.

Furthermore, the invention offers the advantage of being able to provide the solubilizate according to the invention for use in agriculture, fish farming and/or in horticulture and/or in the field of food hygiene and/or for use as a disinfectant and/or in the field of packaging, preferably in the packaging of beef, poultry or fish, and/or for use as a disinfectant.

In particular for the solubilizate on its own with curcumin as an active substance, it was possible to demonstrate that the germ load of foodstuffs when treated with the solubilizate according to the invention leads to a significant reduction in the germ load. The curcumin acts as a photosensitizer. The latter is applied locally to a germ-infested surface where it is absorbed by the germs, wherein the surface is then exposed and the photosensitizer activated thereby. This then produces reactive oxygen species ("oxygen radicals") in the microbes, which are thereby killed.

In the food sector, for example in the case of antimicrobial packaging, the food, such as meat, can be sprayed with an aqueous solution of a solubilizate according to the invention and packed in PP, PE, PC or other transparent films and then exposed to thus keep the surface of already packaged foods sterile. Corresponding applications, also for the germ-free packaging of other objects, are also covered by the scope of the invention. This includes, for example, the packaging of surgical instruments and similar utensils.

The advantage of the formulation as a solubilizate according to the invention for this type of application is that the active substance, in particular the curcumin, can be used in a very high aqueous dilution so that color loading of the treated surface can be substantially completely ruled out. The high number of very small micelles results in uniform and adequate distribution of the active substance on the surface to be treated, even when the solubilizate has been strongly diluted. As a result, an application, for example in the field of packagings that are as sterile as possible, is facilitated by the invention in a simple and very cost-effective manner.

In order to provide stable micelles of the active substances, within the context of the invention the polysorbate content must be at least 70 wt.%, preferably in the

range between 75 wt.% and 95 wt.%, most preferably in the range between 79 wt.% and 88 wt.%.

Depending on the specific application case, the solubilizate of the invention may contain up to 20 wt.%, preferably up to 15 wt.% of ethanol, for example, and/or up to 25 wt.%, preferably between 12 wt.% and 20 wt.%, most preferably up to 10 wt.% of glycerol, and/or additionally up to 10 wt.%, preferably up to 7 wt.% of water. The addition of ethanol allows the content of polysorbate to be reduced, which is an advantage in view of the ADI value for polysorbate (25 mg/kg body weight), as recommended by WHO. The content of polysorbate may also be reduced by adding glycerol.

The solubilizates of the invention have a narrow particle size distribution with small mean particle sizes, even under the physiological conditions of a gastric passage; the diameter distribution of the micelles in a dilution of the solubilizate with distilled water in a ratio of 1:500 at pH 1.1 and 37 °C ranges from about d_{10} = 6 nm to about d_{90} = 20 nm. These values were determined from a volume distribution. Details of particle size analysis of the micelles of the solubilizates will be explained below.

An indication of the improved bioavailability, compared to compositions of curcumin or of curcumin and at least one further active substance that have not been micellated according to the invention, is obtained by the determination of the turbidity of the solubilizate which is much easier to measure. As a result of the formulation according to the invention, the turbidity of the solubilizate is preferably less than 25 FNU, more preferably less than 3 FNU, as measured by scattered light measurement using infrared light in compliance with the specifications of the ISO 7027 standard at a dilution of the solubilizate in a ratio of 1:50 or 1:500 in water under physiological conditions (pH 1.1 and 37 °C).

In order to make oral administration of the solubilizate according to the invention more simple and convenient for the consumer or patient, the invention also provides a capsule filled with a solubilizate as described above, wherein the capsule is in the form of a soft gelatin capsule or a hard gelatin capsule or a soft gelatin-free capsule or a hard gelatin-free capsule, for example a cellulose capsule.

Moreover, in the context of the invention, the solubilizate according to the invention may be incorporated into other fluids, in particular liquids. The active substance-filled small micelles will be retained when doing so. Thus, the invention also provides a fluid containing the solubilizate as described above, wherein the fluid is selected from the group comprising foods, dietary supplements, beverages, cosmetics, and pharmaceutical products. In the context of the invention, the fluid may in particular comprise an aqueous dilution of the solubilizate.

In a preferred embodiment of the solubilizate according to the invention, the solubilizate is designed for use as a food supplement and/or drug in a curcumin dose in the range from 0.5 mg/kg body weight up to 1 mg/kg body weight, preferably with a dose of 0.81 mg/kg body weight.

In a preferred embodiment of the solubilizate according to the invention, the solubilizate is designed to be used as a food supplement and/or drug in a Boswellia dose in the range from 1 mg/kg body weight up to 2 mg/kg body weight, preferably with a dose of 1.62 mg/kg body weight.

In a preferred embodiment of the solubilizate according to the invention, the solubilizate is designed to be used as a food supplement and/or drug in a xanthohumol dose in the range from 0.5 mg/kg body weight up to 1 mg/kg body weight, preferably with a dose of 0.81 mg/kg body weight.

To produce a solubilizate according to the invention comprising curcumin and at least one further active substance, it is possible either to mix together individually prepared solubilizates, or to directly prepare a solubilizate that contains curcumin and at least one further active substance.

The invention furthermore provides methods for producing a solubilizate as described above. If co-micellization of curcumin and at least one further active substance is desired, the invention provides the following first variant of a preparation method having the steps of

a) providing polysorbate 80 and/or polysorbate 20 and/or a mixture of polysorbate 20 and polysorbate 80

b) adding at least one further active substance, in particular *Boswellia* serrata extract and/or xanthohumol,

c) adding curcumin powder,

wherein, in step a), heating to a temperature in the range from 40 °C to 62 °C, preferably to a temperature in the range from 45 °C to 57 °C, particularly preferably to a temperature in the range between 48 °C and 52 °C, takes place, and wherein, in step b), the temperature remains unchanged with respect to step a) or heating to a temperature in the range from 60 °C to 75 °C, preferably to a temperature in the range from 61 °C to 70 °C, particularly preferably to a temperature in the range between 63 °C and 67 °C takes place,

and wherein, in step c), heating to a temperature in the range from 82 °C to 97 °C, preferably to a temperature in the range from 83 °C to 92 °C, most preferably to a temperature in the range between 85 °C and 89 °C takes place.

This preparation method makes it possible to produce a solubilizate which, in an aqueous dilution, is able to form micelles loaded with curcumin and with at least one further active substance. For this purpose, it is also possible to mix the at least two active substances with one another in a preparatory step under appropriately adapted temperature control, and then to add them in combined form, as a mixture.

In particular, a step b1) adding water at a temperature in the range from 40 °C to 62 °C, preferably at a temperature in the range from 45 °C to 57 °C, most preferably at a temperature in the range between 48 °C and 52 °C, can be carried out before step b).

Additionally or alternatively, in step b1) also the addition of ethanol can be carried out at a temperature in the range from 40 °C to 62 °C, preferably at a temperature in the range from 45 °C to 57 °C, most preferably at a temperature in the range from 48 °C to 52 °C.

The invention provides another possibility for a production method involving co-micellization of curcumin and at least one further active substance with the following second variant involving a method having the steps of

a) preparing a first batch by providing polysorbate 80 and/or polysorbate 20 and/or a mixture of polysorbate 20 and polysorbate 80 and at least one first active substance, in particular α-lipoic acid,

b) preparing a second batch by providing water and at least one further active substance, in particular serrapeptase

c) adding at least one further active substance, in particular xanthohumol and/or Boswellia serrata extract and/or glavonoid and/or resveratrol and/or coenzyme Q10, and adding curcumin powder to the second batch from step b)

d) combining the first batch from step a) and the second batch from step c),

wherein the temperature during the performance of steps a) to d) is in the range from 18 °C to 22 °C,

e) heating to a temperature in the range from 80 °C to 97 °C, preferably to a temperature in the range from 83 °C to 92 °C, most preferably to a temperature in the range between 85 °C and 89 °C;

In step c), ethanol and/or glycerol and/or MCT oil and/or polysorbate 20 and/or polysorbate 80 and/or a mixture of polysorbate 20 and polysorbate 80 can also be added.

The invention provides another possibility for a production method involving co-micellization of curcumin and at least one further active substance with the following third variant having a method having the steps of

a) providing polysorbate 80 and/or polysorbate 20 and/or a mixture of polysorbate 20 and polysorbate 80 and glycerol and ethanol,

b) adding at least one further active substance, in particular an ethanolic extract of the hard resins from hops, in particular Xantho-Flav Pure powder,

wherein, in step a), heating to a temperature in the range from 40 °C to 62 °C, preferably to a temperature in the range from 45 °C to 57 °C, particularly preferably to a temperature in the range between 48 °C and 52 °C, takes place, and wherein, in step b), heating to a temperature in the range from 60 °C to 75 °C,

preferably to a temperature in the range from 61 °C to 70 °C, particularly preferably to a temperature in the range between 63 °C and 67 °C, takes place,

c) adding curcumin powder at a temperature in the range from 70 °C to 92 °C, preferably at a temperature in the range from 75 °C to 87 °C, most preferably at a temperature in the range between 78 °C and 82 °C,

d) adding glavonoid while heating to a temperature in the range from 80 °C to 97 °C, preferably to a temperature in the range from 83 °C to 92 °C, most preferably to a temperature in the range between 85 °C and 89 °C;

The invention also provides a method for producing a solubilizate as described above by mixing a curcumin solubilizate and a solubilizate of at least one other active substance, in particular in a quantitative ratio of 1:1. In this respect, the invention also provides solubilizates which, immediately after their preparation, both on their own with curcumin and on their own with another active substance in each case, exhibit loaded micelles in aqueous dilution.

The invention will now be explained in more detail by way of exemplary embodiments. The following components were used:

Curcumin

The product named “Turmeric Oleoresin Curcumin Powder 95 %” with the product code EP-5001 from Green Leaf Extraction Pvt Ltd., Kerala, India, was used as the curcumin. The curcumin powder has CAS Number 458-37-7. It is a natural product obtained by solvent extraction of the rhizomes of *Curcuma longa*. The curcumin content of the powder is at least 95 %, according to manufacturer specifications. This curcumin content is determined by ASTA method 18.0.

As an alternative to the “oleoresin turmeric 95 %” curcumin powder from Green Leaf mentioned above, it is also possible for the exemplary embodiments described below to use, as the curcumin, 95 % curcumin extract by Neelam Phyto-Extracts, Mumbai, India, or curcumin BCM-95-SG or curcumin BCM-95-CG from eurochem GmbH, Gröbenzell, Germany, or Curcuma Oleoresin 95 % from Henry Lamotte OILS GmbH, Bremen, Germany, for example.

Boswellia

In the context of the present application, the term “Boswellia” in particular refers to an extract from the resin of the frankincense plant. Specifically, an extract of the species *Boswellia serrata* has been used, which was an extract obtained by extraction with ethyl acetate from the resin of the plant with the botanical name *Boswellia serrata* with the product code “HC22519” manufactured by Frutarom Belgium N.V., Londerzeel, Belgium. A solubilizate containing this extract is also referred to as “boswellic acid solubilizate” because of its content of boswellic acids.

Besides extracts from the resin of the frankincense plant, it is also possible to use boswellic acids and/or derivatives of boswellic acids for the purposes of the solubilizates according to the invention. In particular, the following may be considered: alpha-boswellic acid (CAS number 471-66-9), beta-boswellic acid (CAS number 631-69-6) and their derivatives, 3-O-acetyl-alpha-boswellic acid (CAS number 89913-60-0), 3-O-acetyl-beta-boswellic acid (CAS number 5968-70-7), 11-keto-beta-boswellic acid (KBA, CAS number 17019-92-0), and 3-O-acetyl-11-keto-beta-boswellic acid (AKBA, CAS number 67416-61-9).

Xanthohumol

The products “Xantho-Flav” or “Xantho-Flav Pure” of the brand “Hopsteiner” by Simon H. Steiner, Hopfen, GmbH, Mainburg, Germany were used as the xanthohumol source. Both are natural products produced from hops. The active substance is the hop polyphenol xanthohumol. This is a yellow colored powder with a xanthohumol content between 65 % and 85 % in “Xantho-Flav” and at least 85 % in “Xantho-Flav Pure”, according to manufacturer specifications.

The concentrations of xanthohumol and isoxanthohumol in “Xantho-Flav Pure” are quantified by the manufacturer according to UV spectrophotometric analysis or HPLC EBC 7.8 using external calibration standard pure XN (370 nm) or IX (290 nm). “Xantho-Flav Pure” contains the prenylated flavonoid xanthohumol in a very high concentration. For the exemplary embodiments in the context of the present application, “Xantho-Flav Pure” of batch number 9432 was used.

Glavonoid / glabridin

"Glavonoid" is the product name for a composition by Kaneka Corporation, Osaka, Japan, which contains glabridin as the active substance. Glabridin is a flavonoid of real licorice (*Glycyrrhiza glabra*). The product “Kaneka Glavonoid” contains 30 % licorice extract and 70 % edible oil according to the manufacturer's specifications. According to the manufacturer's specifications, "Kaneka Glavonoid" is standardized to 3 % glabridin, which is the main component of the polyphenols of pure licorice. The CAS no. of glabridin is 59870-68-7.

Resveratrol

The “eveResveratrol” product was used as resveratrol. This is transresveratrol, which was obtained by fermentation. The product is provided as a whitish powder without the addition of additives. The proportion of transresveratrol is at least 98 wt.%, and the remainder is water. The product has the CAS number 501-36-0 and the product code RSXOL 9800.

Serrapeptase

The product named Serratiopeptidase by Shaanxi Pioneer Biotech Co. Ltd. with batch number PBD 20170708 was used as the serrapeptase. This is a greyish white to light-brown powder.

Coenzyme Q10

Co-enzyme Q10 was purchased from the Xiamen Kingdomway Group Company. It was produced by microbial fermentation and, according to the manufacturer's specifications, contains less than 0.5 % of the cis isomer.

α-lipoic acid ("alpha"-lipoic acid)

Alpha-lipoic acid was purchased from Jiangsu Tohope Pharmaceutical Co. Ltd, China.

Polysorbate 80

The source of polysorbate 80 was the material “TEGO SMO 80 V FOOD” with the specification code “K04 EU-FOOD” from Evonik Nutrition & Care GmbH, Essen, Germany. The product complies with the EU requirements for the food additive E

433. As an alternative to the TEGO SMO 80 V from Evonik mentioned above, it is also possible to use TEGO SMO 80 V from InCoPA Gmbh, Illertissen, Germany, or Crillet 4/Tween 80-LQ-(SG) from CRODA GmbH, Nettetal, Germany, or Lamesorb SMO 20 and Kotilen-O/1 VL from Univar or from Kolb Distributions AG, Hedingen, Switzerland, as the polysorbate 80 in the exemplary embodiments described below.

Polysorbate 20

The source of polysorbate 20 was the material “TEGO SML 20 V FOOD” with the specification code “K09 EU-FOOD” from Evonik Nutrition & Care GmbH, Essen, Germany. The product complies with the EU requirements for food additive E 432. As an alternative to the TEGO SML 20 from Evonik mentioned above, it is also possible to use Crillet 1/Tween 20-LQ-(SG) from CRODA GmbH, Nettetal, Germany, as the polysorbate 20 within the context of the invention.

Ethanol

In the context of the present application, ethanol was purchased from Berkel Pfälzische Spritfabrik GmbH & Co. KG. According to the specification for “undenatured neutral alcohol 1411U taxed”, the content of ethanol of this product is about 92.6 to 95.2 wt.%.

Glycerol

The product used as glycerol in the context of the present application was “Glycamed 99.7 %” from Glaconchemie GmbH, Merseburg, Germany. The glycerol content of this product is at least 99.5 %, according to manufacturer specifications.

Medium-chain triglycerides

Medium-chain triglycerides (MCTs) are triglycerides that contain medium-chain fatty acids. Medium-chain fatty acids include caproic acid, caprylic acid, capric acid and lauric acid. These are saturated fatty acids which naturally occur in tropical vegetable fats such as coconut oil and palm kernel oil. To a small extent they are also contained in milk fat. There is no pure MCT oil in nature; however, pure MCT

oils can be obtained synthetically. In the context of the invention, individual MCTs or a mixture of different MCTs can be used as medium-chain triglycerides. Medium-chain triglycerides were used in the form of MCT oil Delios VK Kosher, manufactured by Cognis GmbH, Monheim, Germany, or in the form of MCT oil (70/30) Rofetan GTCC 70/30 manufactured by DHW Deutsche Hydrierwerke Rodleben GmbH, Dessau-Roßlau, Germany, CAS number 73-398-61-5.

Furthermore, medium-chain triglycerides can be used in the form of the product ROFETAN DTCC 70/30 (Ph. Eur.). This is a caprylic/capric acid triglyceride with CAS number 73398-61-5. The product corresponds to the monograph “medium-chain triglycerides” of the European Pharmacopoeia valid at the filing date. Manufacturers are Ecogreen Oleochemicals DHW, Deutsche Hydrierwerke GmbH, Rodleben, Germany.

Mixed tocopherol

70 % mixed tocopherol in vegetable oil, Vitapherole T-70 non-GMO, from the manufacturer VitaeNaturals can be used, for example, as mixed tocopherol (E306, CAS numbers 59-02-9, 16698-35-4, 54-28-4 and 119-13-1).

If is added in the preparation of a solubilizate, distilled water is used.

At the University of Cairo in the Faculty for Pharmacy in the Institute of Pharmacology, Prof. Dr. M. T. Khayyal carried out investigations into the anti-inflammatory effect of curcumin and combinations of curcumin with Boswellia or xanthohumol in each case in native form or in the solubilized form according to the invention.

Anti-inflammatory markers and antioxidant capacity were determined. Female Wistar rats having a body weight between 150 and 200 g were subjected to “Adjuvant induced arthritis” in accordance with “Pearson et al. (1956)”. 0.1 ml Freund's Adjuvans (FCA) was administered into the right rear paw of the animals on day 0 via a subplanar injection. The animals were divided at random into 12 groups of 8 animals in each case.

Group 1 formed the control group.

Group 2 received diclofenac as a reference active substance in a dose of 3 mg/kg body weight.

Group 3 received native curcumin in a dose of 5 mg/kg body weight.

Group 4 received curcumin solubilized according to the invention in a dose of 5 mg/kg body weight.

Group 5 received native curcumin in a dose of 10 mg/kg body weight, and

Group 6 received the same dose of solubilized curcumin.

Group 7 received native xanthohumol in a dose of 5 m/kg body weight, and

Group 8 received solubilized xanthohumol in the same dose.

Group 9 received a mixture of native curcumin in a dose of 5 mg/kg body weight and native Boswellia extract in a dose of 10 mg/kg body weight.

Group 10 received a mixture of solubilized curcumin and solubilized Boswellia in the same dose in each case.

Group 11 received a mixture of native curcumin in a dose of 5 mg/kg body weight and native xanthohumol in a dose of 5 mg/kg body weight, and

Group 12 received a mixture of solubilized curcumin and solubilized xanthohumol in the same dose in each case.

After inoculation with the adjuvant, all extracts or solubilizates were administered orally once a day from day 0 to day 21. After day 21, the animals were killed and serum samples were prepared and stored at -80 °C. Myeloperoxidase (MPO), C-reactive protein (CRP), the total antioxidant capacity (TAC) and the (thiobarbituric acid reactive substances) (TBARS) were measured.

The results are explained below with reference to the accompanying drawings. The drawings show:

Fig. 1a the effect of curcumin in native and solubilized form and of diclofenac on the serum content of CRP (pg/L),

Fig. 1b the effect of curcumin (5 mg/mL) in native and solubilized form, given together with either Boswellia or xanthohumol, on the serum content of CRP (pg/L) compared with diclofenac,

Fig. 2 the effect of curcumin in native and solubilized form and of diclofenac on the serum content of MPO (mU/mL),

and Fig. 3 the effect of curcumin in native and solubilized form, given together with either Boswellia or xanthohumol on the serum content of MPO (mU/mL) compared with diclofenac.

First, the effects on the C-reactive protein (CRP) were investigated. C-reactive protein is a specific marker for anti-inflammatory activity. Both the native and the solubilized form of curcumin inhibited the CRP serum level of the rats in a dose-dependent manner, although the solubilized form was twice as effective as the native and significantly more effective than diclofenac in the selected dose (Figure 1a).

If Boswellia is administered together with curcumin both in native form, the inhibitory effect on the CRP serum does not change significantly (Figure 1b). However, if curcumin and Boswellia are administered together and in a corresponding dose in solubilized form, the anti-inflammatory effect is enhanced. In this relation, Boswellia is superior to xanthohumol in potentiating the effect of curcumin at the doses under consideration.

Myeloperoxidase (MPO) in plasma plays a central role as a pro-inflammatory mediator in rheumatoid arthritis and is an indicator of the migration of neutrophilic granulocytes into the affected tissue. Its concentration is increased in patients with rheumatoid arthritis and causes oxidative stress. In the studies, the concentration of MPO was efficiently reduced by solubilized curcumin, this being in the same way as and not significantly different from diclofenac for both doses considered. However, native curcumin did not influence the MPO level (Figure 2). The administration of Boswellia together with curcumin, both in native form and in solubilized form, did not improve the effect of the curcumin in reducing the MPO concentration.

Oxidative stress is one of the main factors contributing to joint destruction in rheumatoid arthritis (RA). An increase in the production of so-called “reactive oxigen species (ROS)” leads to a reduced supply of endogenous antioxidants and ultimately results in the destruction of cells. Neutrophilic granulocytes that are released in the rheumatoid joint produce free oxygen radicals resulting in increased formation of lipid peroxides, which manifest themselves in a rise in TBARS serum. Therefore, the increase in antioxidant status, which is represented by an increase in TAC, can be used as an indicator of protection against the development of degenerative inflammatory processes. There is an inverse relationship between the level of TAC and that of the TBARS, a high level of the antioxidant capacity TAC corresponds to a low concentration of TBARS.

The studies carried out showed that the native form of curcumin has no significant impact on the levels of TBARS or TAC at either dose under consideration. Solubilized curcumin according to the invention reduced the level of TBARS at both selected doses and increased the TAC, wherein hardly any differences can be identified with respect to the effect of diclofenac.

These data are compiled in the following table. The table contains data relating to the effect of curcumin and Boswellia in native form and in solubilized form, either given alone or in combination with diclofenac in a dose of 3 mg/kg body weight once a day over 21 days, on the antioxidant capacity TAC and the thiobarbituric acid reactive substances TBARS in the serum of arthritic rats (n=8). Mean values ± standard errors SEM are given.

Group	TAC (nmol/microliter)	TBARS (nmol/L)
Arthritic control group	57.26 ± 3.36	13.10 ± 0.39
Diclofenac (3 mg/kg)	82.08 ± 2.96	7.93 ± 0.84
Native curcumin (5 mg/kg)	60.31 ± 3.25	11.64 ± 0.39
Solubilized curcumin (5 mg/kg)	77.01 ± 0.73	5.97 ± 0.47
Native curcumin (10 mg/kg)	68.41 ± 1.09	13.18 ± 0.46
Solubilized curcumin (10 mg/kg)	87.15 ± 5.27	6.82 ± 0.56
Native curcumin (5 mg/kg) + Boswellia (10 mg/kg)	64.56 ± 1.45	12.08 ± 0.52

Group	TAC (nmol/microliter)	TBARS (nmol/L)
Solubilized curcumin (5 mg/kg) + Boswellia (10 mg/kg)	76, 94 ± 2.17	6.81 ± 0.19

The administration of Boswellia together with curcumin, each in native form, did not demonstrate any significant effect in reducing oxidative stress, according to the results shown in the table. However, in solubilized form, these combinations were equally as effective as diclofenac in reducing TBARS and increasing TAC in the serum of arthritic rats.

First investigations on the application of the curcumin solubilizate according to the invention in fighting cancer cells of the (MCF-7) and (T47D) lines for breast cancer, (Hepg-2) for liver cancer, (HCT-116) for colon cancer and (PC3) for prostate cancer demonstrate very good results in terms of achieving the smallest possible proportion of cells which survive treatment. The curcumin solubilizate allowed for a reduction to a “surviving fraction” in the range from about 15 % to about 25 %.

The particle size analyses of the micelles in aqueous dilutions of solubilizates according to the invention were measured according to the principle of dynamic light scattering using laser light of 780 nm wavelength, unless stated otherwise. The particle size measurements were performed using the ParticleMetrix NANO-flex backscatter particle analyzer. The measuring principle is based on dynamic light scattering (DLS) in a 180° heterodyne backscattering setup.

For the experimental determination of turbidity of the solubilizates according to the invention, the turbidity meters are calibrated with a standard suspension. Thus, instead of measured light intensity, the concentration of the calibration suspension is indicated. So, when any arbitrary suspension is measured, the indication means that the respective liquid causes the same light scattering as the standard suspension at the indicated concentration. The internationally defined turbidity standard is formazine. The most common units include the indication FNU, i.e. Formazin Nephelometric Units. This is the unit used in water treatment, for

example, for measuring at 90° in compliance with the requirements of the ISO 7072 standard.

To prepare a solubilizate according to the invention having the active substances curcumin and at least one further active substance, it is possible either to mix individually prepared solubilizates with one another or to directly prepare a solubilizate that contains curcumin and at least one other active substance or several further active substances.

Curcumin solubilizates

By way of example, a 7 % curcumin solubilizate is prepared. To this end,

925 g	polysorbate 80
75 g	curcumin powder 95 % (= 71.2 g of curcumin)

The polysorbate 80 is heated to between 48 and 52 °C. The curcumin powder is added to the polysorbate under stirring, while further heating to a temperature in the range from 95 to 97 °C. The powder is added at an appropriate rate so as to be evenly drawn into the emulsifier during stirring. After cooling to a temperature below a maximum of 60 °C, the curcumin solubilizate is bottled. This solubilizate was used for the preparation of a curcumin and Boswellia solubilizate.

At a dilution ratio of 1:500 in water at pH 1.1 and a temperature of 37 °C, the 7 % curcumin solubilizate exhibits an average turbidity of 0.9 FNU.

However, it should be noted that the curcumin content can be further increased without having to accept adverse consequences, for example in terms of the stability of the micelles. A composition of 100 g of 95 % curcumin powder and 900 g of polysorbate 80 is just as likely to result in a stable product as a composition of 120 g of 95 % curcumin powder and 880 polysorbate 80 or 70 g of 95 % curcumin powder and 930 g of polysorbate 80.

Also, polysorbate 80 may be entirely or partially replaced by polysorbate 20. For example, for preparing a curcumin solubilizate with polysorbate 20 alone, 894 g of polysorbate 80 and 106 g of 95 % curcumin powder can be used. The polysorbate

20 is heated to between about 63 °C and about 67 °C. While stirring, the curcumin powder is slowly added to the polysorbate 80. While adding the curcumin powder, heating is continued to between about 83 °C and about 87 °C. The resulting solubilizate is slowly cooled to below about 45 °C and is then ready for being bottled.

Otherwise, the preparation of these variants corresponds to that described above. Solubilizates of up to about 11 % can be produced in this way.

1.5 % serrapeptase solubilizate

The following are used:

15 g serrapeptase:

serratiopeptidase 20,000 U/mg = 300,000,000 U,

15 g water

16.5 g MCT oil,

953.5 g polysorbate 80.

At a temperature in the range between 18 and 22 °C, water is mixed with serrapeptase, and the mixture is homogenized. This means that the serrapeptase is distributed as evenly as possible in the water. This creates the conditions for the serrapeptase to be largely completely dissolved in the water. While heating to a temperature in the range between 83 and 87 °C, MCT oil is incorporated into the water-serrapeptase mixture under constant stirring. The stirring is performed vigorously enough for the serrapeptase to dissolve evenly in the water. At unchanged temperature, polysorbate 80 is added under stirring and is homogenized. The stirring is performed vigorously enough so that the polysorbate 80 is evenly distributed. The product is then cooled to a temperature below 60 °C and bottled. It is then stored in the dark at not more than 25 °C.

300,000 U/g corresponds to 15 mg/g of 1.5 % serrapeptase in enzymatic units. At a dilution in water of 1:50, the turbidity of this solubilizate was determined under physiological conditions at pH 1.1 and 37 °C. The resulting value was 1.8 FNU.

For particle size analysis of the serrapeptase solubilizate, this solubilizate was initially diluted in a ratio of 1:500 with distilled water and brought to 37 °C with constant stirring using a magnetic stirrer and with the aid of a hotplate. The pH was then adjusted to 1.1 using 32 % hydrochloric acid. The samples were then immediately measured. The results are compiled in the following table. The data of two measurements were averaged.

	d_{10} (nm)	d_{50} (nm)	d_{90} (nm)	d_{99} (nm)
Intensity distribution	9.23	10.47	12.23	13.56
Volume distribution	9.10	10.18	11.82	13.12

10 % resveratrol solubilizate

The following are used:

100 g resveratrol

45 g MCT oil,

600 g polysorbate 80

180 g polysorbate 20 and

75 g mixed tocopherol.

At a temperature in the range between 18 and 22 °C, the polysorbates, the mixed tocopherol and the MCT oil are mixed with one another and homogenized. Stirring is performed vigorously enough for the components to be distributed evenly. With heating to a temperature in the range between 83 and 87 °C, the resveratrol is added to the mixture or solution of polysorbate MCT oil and mixed tocopherol. The mixture is stirred vigorously enough that the resveratrol is drawn uniformly into the emulsifier-containing receiver. As soon as a homogeneous and transparent product is provided, it is cooled to a temperature below 30 °C and bottled. The product is transparent yellowish and viscous and is stored in the dark at a temperature of 25 °C.

If the administration of 3,500 mg of the native form of the resveratrol raw material is used for therapy purposes, the following calculation applies to the equivalent amount of solubilizate:

Three capsule fillings each with 675 mg of solubilizate correspond to an amount of 2,025 mg per day or 200 mg of active ingredient resveratrol and 100 mg of mixed tocopherol. With a DV factor of 1:17, 200 mg x 17 = 3,400 mg of pure substance resveratrol.

The turbidity was also determined for this solubilizate under physiological conditions (pH 1.1; 37 °C) and with a dilution in water of 1:50. The resulting value was 16.1 FNU.

5 % coenzyme Q10 solubilizate

The following are used:

57.5 g coenzyme Q10

160 g MCT oil and

782.5 g polysorbate 80.

The polysorbate is heated to a temperature in the range between 83 °C and 87 °C. The coenzyme Q10 powder is then incorporated with stirring. Stirring is performed vigorously enough for the components to be distributed evenly. While maintaining the temperature or repeatedly heating to a temperature in the range between 83 and 87 °C, coenzyme Q10 is dissolved in polysorbate 80. The MCT oil is then incorporated at a constant temperature. As soon as a homogeneous and transparent product is produced, it is cooled to a temperature below 60 °C and bottled. The product is orange-red, transparent and partially solid at room temperature. It is stored in the dark at a temperature of 25 °C.

The measurement of the turbidity under physiological conditions (pH 1.1; 37 °C) with a dilution in water of 1:50 resulted in a value of 11.9 FNU as an average of three measurements (11.4 FNU; 10.5 FNU; 13.9 FNU).

A particle size analysis for a sample of 20 microliters in a dilution ratio of 1:50 in a solution of sodium chloride (50 mmol/L) and sodium azide (200 mg/L) by the Wyatt Technology Europe GmbH in the “Eclipse Program”, i.e., by means of field flow fractionation, resulted in a peak with a radius of 16.5 nm for the micelles of this solubilizate. The diameter of the micelles is therefore 33 nm.

10 % α-lipoic acid solubilizate

The following are used:

896.7 g	polysorbate 80
103.3 g	α-lipoic acid.

The polysorbate 80 is heated to between 28 and 32 °C. With stirring, the α-lipoic acid powder is added to the polysorbate and incorporated. The powder is added at an appropriate rate so as to be evenly drawn into the emulsifier during stirring. Heating to a temperature in the range between 83 °C and 87 °C is then carried out. As soon as a homogeneous and transparent product is produced, it is cooled to a temperature below 60 °C and bottled. The product is yellow and viscous and is stored in the dark at a temperature of 25 °C.

The product can also be prepared using polysorbate 20 or a mixture of polysorbate 80 and polysorbate 20.

At a dilution ratio of 1:50 in water at a pH 1.1 and a temperature of 37 °C, the solubilizate exhibits an average turbidity of 2.9 FNU.

A particle size analysis of a sample of 20 microliters at a dilution ratio of 1:50 in a solution of sodium chloride (50 mmol/L) and sodium azide (200 mg/L) by the Wyatt Technology Europe GmbH in the “Eclipse Program”, i.e., by means of field flow fractionation, resulted in a peak with a radius of below 10 nm for the micelles of this solubilizate. The diameter of the micelles is therefore at most 20 nm.

10 % Xantho-Flav Pure solubilizate (≙ 9.2 % xanthohumol) with ethanol

The following are used:

100 g Xantho-Flav Pure (≙ 92 g xanthohumol),
150 g ethanol (96 %) of neutral alcohol grade 1411U,
and
750 g polysorbate 80.

First, the Xantho-Flav Pure powder is dissolved in ethanol while being heated to a temperature in the range between 48 and 52 °C. A homogeneous solution is created. Polysorbate 80 is then added to the solution of Xantho-Flav Pure in ethanol while heating to between 83 and 87 °C. The adding is done at a rate such that the two fluids homogenize well under stirring. The resulting solubilizate is cooled to below 60 °C and is bottled and stored in the dark and cool, i.e. at temperatures below 25 °C.

15 % glavonoid solubilizate (= 0.45 % glabridin) with glycerol

The following were used:

150 g glavonoid (= 4.5 g glabridin)
100 g 99 % glycerol
750 g polysorbate 80.

First, glycerol and glavonoid were mixed and homogenized at a temperature in the range from 18 to 22 °C. While heating to 83 to 87 °C, polysorbate 80 was added to the fluid consisting of glycerol and glavonoid while stirring. Stirring was vigorous enough for a homogeneous solubilizate to be obtained. This was allowed to cool to a maximum of 30 °C and bottled and then stored in the dark at a temperature below 25 °C.

The solubilizates described above can be used to prepare the solubilizate according to the invention comprising curcumin and at least one a further active substance by mixing. This is described below on the basis of Embodiments 3, 5, 6 and 7.

Embodiment 1

Solubilizate of 5.4 % curcumin/6.6 % boswellic acid

This embodiment of the solubilizate according to the invention was prepared directly. The active ingredients were co-micellized. For this purpose, the following were used:

82 g	80 % Boswellia serrata extract (= 65.6 g boswellic acid),
57 g	95 % curcumin powder (= 54.1 g curcumin)
70 g	water
350 g	polysorbate 20
441 g	polysorbate 80.

While heating to a temperature in the range from 48 to 52 °C, polysorbate 20 and polysorbate 80 are homogenized with each other while being dissolved in each other, under stirring. While maintaining the temperature, the emulsifier mixture is mixed with the water. while stirring is performed vigorously enough so that the water and the ethanol are dissolved evenly in the emulsifier solution. Without changing the temperature, the Boswellia serrata extract is incorporated into the water-diluted emulsifier mixture while stirring. The Boswellia serrata extract is added at such a slow rate that it is uniformly drawn into the diluted emulsifier solution while stirring. Subsequently, the temperature is increased to a range between 63 °C and 67 °C under vigorous stirring. The curcumin powder is incorporated while stirring. The temperature is further increased to a value in the range between 85 °C and 89 °C while stirring vigorously enough so that the curcumin is evenly distributed in the preparation and homogenized.

At a dilution ratio of 1:500 in water at a pH of 1.1 and a temperature of 37 °C, the solubilizate exhibits an average turbidity of 1.9 FNU.

In the context of the present application, a verification about whether the homogenization of the components to form a solubilizate according to the invention has been sufficiently completed in the preparation of any solubilizates is obtained by measurements of the clarity of the product, which indicates complete micellization, using a laser beam. Such a laser beam measurement may be

performed, for example, by illuminating the sample using a commercially available laser pointer, in particular with a wavelength in the range between 650 nm and 1700 nm (spectral color red), and subsequent visual inspection of the illuminated or irradiated solubilizate. The verification is not achieved by sampling and thus outside the reaction vessel, but in the reaction vessel. The laser beam is directed through a sight glass which is located on the front of the reaction vessel, perpendicularly to the reaction vessel. If merely a point of light appears on the rear inner surface of the reaction vessel, completely free of scattering, the resulting particle structures in the reaction vessel are smaller than the wavelength of the visible light, which is thus a visual confirmation that the process of micellization has been completed.

Within the scope of the invention, the contents of curcumin and Boswellia extract in the individual solubilizates can also be set to be significantly higher than in the example shown, depending on the application.

Embodiment 2

Solubilizate of 3.3 % curcumin /3.6 % boswellic acid with 1.8 % xanthohumol

The following are used:

45 g	80 % *Boswellia serrata* extract (= 36 g boswellic acid),
35 g	95 % curcumin powder (33.25 g curcumin)
23 g	Xantho-Flav containing at least 80 % of xanthohumol (18.4 g xanthohumol),
60 g	water
50 g	ethanol (96 %) of neutral alcohol grade 1411U,
350 g	polysorbate 20
437 g	polysorbate 80.

While heating to a temperature in the range from 48 to 52 °C, polysorbate 20 and polysorbate 80 are homogenized with each other while being dissolved in each other, under stirring. While maintaining the temperature, the emulsifier mixture is mixed with the water and ethanol, while stirring is performed vigorously enough so

that the water and the ethanol are dissolved evenly in the emulsifier solution. At unchanged temperature, the Boswellia serrata extract and the xanthohumol are incorporated into the water-diluted emulsifier mixture while stirring. The adding is performed at a rate slow enough so that the Boswellia serrata extract and the xanthohumol are evenly drawn into the dilute emulsifier solution under stirring. Subsequently, the temperature is increased to a range between 63 °C and 67 °C under vigorous stirring. The curcumin powder is incorporated while stirring. The temperature is further increased to a value in the range between 85 °C and 89 °C while stirring vigorously enough so that the curcumin is evenly distributed in the preparation and homogenized.

This is followed by cooling to a temperature of less than or equal to 45 °C. The dark-yellow viscous preparation comprising a solubilizate of curcumin and boswellic acid and xanthohumol is then bottled and stored in a cool, dark place, i.e., below 25 °C.

At a dilution ratio of 1:500 in water at a pH of 1.1 and a temperature of 37 °C, the solubilizate exhibits an average turbidity of 1.9 FNU.

Unless stated otherwise, for a particle size analysis of a solubilizate according to the invention, this solubilizate were initially diluted in a ratio of 1:500 with distilled water and brought to 37 °C with constant stirring using a magnetic stirrer and with the aid of a hotplate. The pH was then adjusted to 1.1 using 32 % hydrochloric acid. The samples were then immediately measured. The results are compiled in the following table.

	d_{10} (nm)	d_{50} (nm)	d_{90} (nm)	d_{99} (nm)
Intensity distribution	10.18	15.70	533.0	3080
Volume distribution	7.90	10.96	15.21	20.37

Embodiment 3 (not according to the invention)

Solubilizate of 1.5 % curcumin/3 % boswellic acid/2 % xanthohumol/0.35 % serrapeptase

The following are used:

250 g 7 % curcumin solubilizate,
250 g 12 % Boswellia solubilizate,
250 g 9.2 % xanthohumol solubilizate and
250 g 1.5 % serrapeptase solubilizate.

All four solubilizates can be heated to a temperature in the range from 50 °C to 60 °C to lower their viscosity and thus enhance flowability. Then they are mixed together by stirring. Once a homogeneous complete product is obtained, it is optionally cooled to a temperature below 60 °C and bottled.

Prior to further processing such as filling into capsules, it is favorable to again stir the product to homogenize it, and if necessary to this end to heat it moderately, i.e. to a temperature of about 40 °C to 50 °C.

With a dilution ratio of 1:500 in water at a pH of 1.1 and a temperature of 37 °C, the solubilizate exhibits an average turbidity of 1.0 FNU.

The results of the particle size analysis are compiled in the following table.

	d_{10} (nm)	d_{50} (nm)	d_{90} (nm)	d_{99} (nm)
Intensity distribution	9.08	15.64	292.7	615
Volume distribution	6.35	9.36	14.10	20.16

Embodiment 4

Solubilizate of 5 % glavonoid (= 1.8 % glabridin)/

3 % curcumin/3.5 % xanthohumol

The following are used:

32 g 95 % curcumin powder (= 30.4 g curcumin)
44 g Xantho-Flav Pure powder (= 35.2 g xanthohumol)

60 g Kaneka glavonoid (= 1.8 g glabridin)
60 g 96 % ethanol of neutral alcohol grade 1411U,
44 g glycerol 99.5 %
760 g polysorbate 80.

Polysorbate 80 and glycerol are mixed with stirring and heated to a temperature in the range from 48 to 52 °C in order to homogenize the mixture effectively. Ethanol is incorporated into the polysorbate-glycerol mixture while stirring vigorously enough that a homogeneous solution is formed. The temperature is kept constant. Xanthohumol is then incorporated into the solution of polysorbate, glycerol and ethanol. The temperature is increased to a value in the range between 63 and 67 °C. The mixture is stirred vigorously enough that xanthohumol combines homogeneously with the solution provided.

Subsequently, curcumin powder is incorporated into the xanthohumol solubilizate. The temperature is increased to a value in the range between 78 and 82 °C. As in the case of xanthohumol and also in the incorporation of glavonoid described below, stirring is performed vigorously enough each time that the newly added component of the solubilizate bonds homogeneously to the solubilized product in the fluid provided. The temperature is further increased to a value in the range between 85 and 98 °C for the glavonoid to be added.

The product is a solubilizate with co-micellated curcumin, xanthohumol and glavonoid. The solubilizate is allowed to cool to a value of at most 45 °C while stirring and then bottled.

Embodiment 5 (not according to the invention)

Solubilizate of 1.5 % curcumin/2 % xanthohumol/3.5 % glavonoid (0.1 % glabridin)/1.2 % coenzyme Q10

The following are used:

250 g 7 % curcumin solubilizate,
250 g 9.2 % xanthohumol solubilizate

250 g 15 % xanthohumol solubilizate and

250 g 5 % enzyme Q10 solubilizate.

All four solubilizates can be heated to a temperature in the range from 50 °C to 60 °C to lower their viscosity and thus enhance flowability. Then they are mixed together by stirring. Once a homogeneous complete product is obtained, it is optionally cooled to a temperature below 60 °C and bottled.

Prior to further processing such as filling into capsules, it is favorable to again stir the product to homogenize it, and if necessary to this end to heat it moderately, i.e. to a temperature of about 40 °C to 50 °C.

The results of the particle size analysis are compiled in the following table.

	d_{10} (nm)	d_{50} (nm)	d_{90} (nm)	d_{99} (nm)
Intensity distribution	8.22	10.88	14.80	450
Volume distribution	7.78	10.06	13.10	16.39

Embodiment 6 (not according to the invention)

Solubilizate of 1.3 % curcumin/1,6-%xanthohumol/3 % glavonoid (0.09 % glabridin)/1 % coenzyme Q 10/2 % α-lipoic acid

The following are used:

200 g 7 % curcumin solubilizate,

200 g 9.2 % xanthohumol solubilizate

200 g 15 % glavonoid solubilizate

200 g 5 % enzyme Q10 solubilizate and

200 g 10 % a-lipoic acid solubilizate.

All five solubilizates can be heated to a temperature in the range from 50 °C to 60 °C to lower their viscosity and thus enhance flowability. Then they are mixed

together by stirring. Once a homogeneous complete product is obtained, it is optionally cooled to a temperature below 60 °C and bottled.

Prior to further processing such as filling into capsules, it is favorable to again stir the product to homogenize it, and if necessary to this end to heat it moderately, i.e. to a temperature of about 40 °C to 50 °C.

The results of the particle size analysis are compiled in the following table.

	d_{10} (nm)	d_{50} (nm)	d_{90} (nm)	d_{99} (nm)
Intensity distribution	8.85	11.64	17.05	981
Volume distribution	7.16	9.41	12.36	15.43

Embodiment 7 (not according to the invention)

Solubilizate of 0.8 % curcumin 1 1.5 % boswellic acid/1 % xanthohumol/1.8 % glavonoid (0.05 % glabridin)/0.18 % serrapeptase/1.2 % resveratrol/0.6 % coenzyme Q10/1.2 % α-lipoic acid

The following are used:

125 g 7 % curcumin solubilizate,
125 g 12 % Boswellia solubilizate,
125 g 9.2 % xanthohumol solubilizate
125 g 15 % glavonoid solubilizate
125 g 1.5 % serrapeptase solubilizate
125 g 10 % resveratrol solubilizate
125 g 5 % co-enzyme Q10 solubilizate and
125 g 10 % a-lipoic acid solubilizate.

All eight solubilizates can be heated to a temperature in the range from 50 °C to 60 °C to lower their viscosity and thus enhance flowability. Then they are mixed together by stirring. Once a homogeneous complete product is obtained, it is optionally cooled to a temperature below 60 °C and bottled.

Prior to further processing such as filling into capsules, it is favorable to again stir the product to homogenize it, and if necessary to this end to heat it moderately, i.e. to a temperature of about 40 °C to 50 °C.

With a dilution ratio of 1:50 in water at a pH of 1.1 and a temperature of 37 °C, the solubilizate exhibits an average turbidity of 12.5 FNU.

The results of the particle size analysis are compiled in the following table.

	d_{10} (nm)	d_{50} (nm)	d_{90} (nm)	d_{99} (nm)
Intensity distribution	8.09	10.91	15.19	425
Volume distribution	6.90	9.26	12.37	15.71

Embodiment 8 (not according to the invention)

Direct preparation of solubilizate of 0.8 % curcumin 1 1.5 % boswellic acid/1 % xanthohumol/1.8 % glavonoid (0.05 % glabridin)/0.18 % serrapeptase/1.2 % resveratrol/0.6 % coenzyme Q10/1.2 % α-lipoic acid

The following are used:

9.375 g	95 % curcumin powder,
19 g	Boswellia serrata extract (15.2 boswellic acid),
12.5 g	Xantho-Flav powder (at least 80 % xanthohumol = 10 g xanthohumol),
18.75	glavonoid (0.56 g glabridin)
1.875 g	serrapeptase (37,500,000 U),
12.5 g	resveratrol
7.19 g	co-enzyme Q10
12.5 g	α-lipoic acid
7.875 g	water
18.75 g	ethanol
12.5 g	Glycerol

9.375 g	mixed tocopherol
27.685 g	MCT oil
122.5 g	polysorbate 20, and
707.225 g	polysorbate 80.

Polysorbate 80 is mixed with α-lipoic acid at a temperature in the range between 18 and 22 °C. while stirring vigorously enough so that a homogeneous mixture is obtained. Separately, the serrapeptase is dissolved in water in the same way at a temperature in the range from 18 to 22 °C. The further ingredients ethanol, xanthohumol, curcumin, Boswellia, glavonoid, resveratrol, co-enzyme Q10, mixed tocopherol, glycerol, MCT oil and polysorbate 20 are slowly and successively metered into the mixture or solution of serrapeptase and water while constantly stirring. The temperature is further in the range between 18 and 22 °C. Good mixing and homogeneity of the product is to be ensured. If appropriate, pauses are taken between the addition of a substance and the addition of the next substance. The adding is conducted slowly enough, while stirring, so that the particular ingredient to be added is evenly incorporated into the preparation.

Next, both mixtures, i.e., the polysorbate 80 and α-lipoic acid sample and the remaining mixture of all the other ingredients are combined and continue to be stirred at a temperature in the range from 18 to 22 °C. A homogeneous paste-like mass is produced which is similar to a “pulp.” This is heated to a temperature in the range from 85 °C to 89 °C. Heating is carried out slowly with constant stirring such that the

"pulp" that is heating up always remains mixed as homogeneously as possible. After cooling to a temperature below 60 °C, the product is bottled. It is dark and viscous and is stored in the dark at temperatures of not more than 25 °C. Prior to further processing such as filling into capsules, it is favorable to again stir the product to homogenize it and, if necessary to this end, to heat it moderately, i.e. to a temperature of about 40 °C to 50 °C.

With a dilution ratio of 1:50 in water at a pH of 1.1 and a temperature of 37 °C, the solubilizate exhibits a turbidity of 1.0 FNU.

The results of the particle size analysis are compiled in the following table.

	d_{10} (nm)	d_{50} (nm)	d_{90} (nm)	d_{99} (nm)
Intensity distribution	8.66	11.01	14.58	220.4
Volume distribution	7.96	9.87	12.59	15.52

Embodiment 9

Solubilizate of 3 % curcumin/3.2 % boswellic acid/1.6 % xanthohumol/1 % CBD oil

The following are used:

40.5 g	80 % *Boswellia serrata* extract (32.4 % boswellic acid),
31.5 g	95 % curcumin powder (29.925 g of curcumin),
20.7 g	Xantho-Flav powder containing at least 80 % of xanthohumol (16.5 g xanthohumol),
54 g	water
45 g	ethanol
315 g	polysorbate 20
483 g	polysorbate 80
10 g	CBD oil: 30 % cannabidiol.

Cannabidiol (CBD) is a barely psychoactive cannabinoid derived from the female hemp *Cannabis sativa* or *Cannabis indica*. A non-THC-free CBD oil was used, which means that it may contain traces of THC. Tetrahydrocannabinol (THC) is responsible for the psychedelic effects of hemp plants.

While heating to a temperature in the range from 48 to 52 °C, polysorbate 20 and polysorbate 80 are homogenized with each other while being dissolved in each other, under stirring. While maintaining the temperature, the emulsifier mixture is mixed with the water and ethanol, while stirring is performed vigorously enough so that the water and the ethanol are dissolved evenly in the emulsifier solution. At unchanged temperature, the Boswellia serrata extract and the xanthohumol are incorporated into the water-diluted emulsifier mixture while stirring. The adding is

performed at a rate slow enough so that the Boswellia serrata extract and the xanthohumol are evenly drawn into the dilute emulsifier solution under stirring. Subsequently, the temperature is increased to a range between 63 °C and 67 °C under vigorous stirring. The curcumin powder is incorporated while stirring. The temperature is further increased to a value in the range between 85 °C and 89 °C while stirring vigorously enough so that the curcumin is evenly distributed in the preparation and homogenized. Subsequently, the CBD oil is incorporated into the mixture while stirring vigorously enough so that the CBD oil is evenly distributed in the preparation and homogenized.

This is followed by cooling to a temperature of less than or equal to 45 °C. The dark-yellow viscous preparation comprising a solubilizate of curcumin and boswellic acid and xanthohumol and CBD oil is then bottled and stored in the dark and cool, i.e. below 25 °C. The solubilizate and the aqueous solution therefrom are stable homogeneously or soluble in the same crystal-clear manner as the solubilizate according to Embodiment 2.

It will be apparent to a person skilled in the art that the invention is not limited to the examples described above, but rather can be varied in various ways. It is in particular possible to combine or swap the features of the individually illustrated examples.

PATENTKRAV

1. Solubilisat, som inneholder og spesielt består av

kurkumin i et innhold fra 3 vekt-% til 7 vekt-%;

og minst ett ytterligere virkestoff,

som omfatter ett eller flere stoffer valgt fra gruppen bestående av xanthohumol, planteekstrakter, særlig fra harpiksen fra røkelsestreet, lakris, cannabinoider, enzymer, særlig serrapeptase, koenzym Q_{10}, α-lipoinsyre, resveratrol; og

minst én emulgator med en HLB-verdi i et område under 18, foretrukket mellom 13 og 18, nemlig polysorbat 80 eller polysorbat 20 eller en blanding av polysorbat 20 og polysorbat 80;

hvor polysorbatinnholdet er minst 70 vekt-%, foretrukket i området mellom 75 vekt-% og 95 vekt-%, mest foretrukket i området mellom 79 vekt-% og 88 vekt-%;

for anvendelse i behandling og/eller forebygging av sykdommer som involverer betennelse, kreft, Alzheimers, Parkinsons, fedme, høyt kolesterol, forhøyet blodsukker, diabetes, metabolsk syndrom og/eller autoimmune sykdommer, multippel sklerose (MS), for å redusere visceralt fett, for termogenese, for å senke kolesterol, spesielt LDL-kolesterol, og/eller glukose i blodet og/eller triglyserider i blodet, for å forbedre makulær pigmenttetthet, for å redusere oksidativt stress og/eller for å redusere akkumuleringen av fett i hepatocyttene, spesielt som et farmasøytisk legemiddel for behandling og/eller forebygging av fettleversykdom, Friedreichs ataksi, lysosomale sykdommer, spesielt Tay-Sachs sykdom, arteriosklerose, hjertesykdommer, artritt.

2. Solubilisat ifølge krav 1,

for anvendelse som et antiinflammatorisk kosttilskudd og/eller som et farmasøytisk legemiddel med en effekt mot kreft, Alzheimers, Parkinsons, fedme, høyt kolesterol, forhøyet blodsukker, diabetes, metabolsk syndrom, og/eller autoimmune sykdommer, multippel sklerose (MS), for å senke visceralt fett, for

termogenese, som et kolesterolsenkende farmasøytisk legemiddel, spesielt med hensyn til LDL-kolesterol, og/eller som et farmasøytisk legemiddel med en effekt for senkning av glukose i blodet og/eller triglyserider i blodet, for å forbedre makulær pigmenttetthet, for å redusere oksidativt stress og/eller for å redusere akkumuleringen av fett i hepatocyttene, spesielt som et farmasøytisk legemiddel med en effekt mot fettleversykdom, Friedreichs ataksi, lysosomale sykdommer, spesielt Tay-Sachs sykdom, arteriosklerose, hjertesykdommer, artritt.

3. Solubilisat, som inneholder og spesielt består av

kurkumin i et innhold fra 3 vekt-% til 7 vekt-%;

og minst ett ytterligere virkestoff,

som omfatter ett eller flere stoffer valgt fra gruppen bestående av xanthohumol, planteekstrakter, særlig fra harpiksen fra røkelsestreet, lakris, cannabinoider, enzymer, særlig serrapeptase, koenzym Q_{10}, α-lipoinsyre, resveratrol; og

minst én emulgator med en HLB-verdi i et område under 18, foretrukket mellom 13 og 18, nemlig polysorbat 80 eller polysorbat 20 eller en blanding av polysorbat 20 og polysorbat 80;

hvor polysorbatinnholdet er minst 70 vekt-%, foretrukket i området mellom 75 vekt-% og 95 vekt-%, mest foretrukket i området mellom 79 vekt-% og 88 vekt-%,

til bruk i landbruk, fiskeoppdrett og/eller hagebruk og/eller på feltet mathygiene og/eller for bruk som desinfeksjonsmiddel og/eller på feltet emballasje, helst i emballasjen til storfekjøtt, fjørfe eller fisk, og/eller for bruk som desinfeksjonsmiddel.

4. Solubilisat for anvendelse ifølge krav 1 eller 2 eller solubilisat ifølge krav 3,

karakterisert ved at

solubilisatet inneholder opptil 20 vekt-%, foretrukket opptil 15 vekt-% etanol

og/eller **ved at**

solubilisatet inneholder opptil 25 vekt-%, foretrukket mellom 12 vekt-% og 20 vekt-%, mest foretrukket opptil 10 vekt-% glyserol;

og/eller **ved at**

solubilisatet i tillegg inneholder opptil 10 vekt-%, foretrukket opptil 7 vekt-% vann

og/eller **ved at**

diameterfordelingen av micellene i en fortynning av solubilisatet med destillert vann i et forhold på 1:500 under fysiologiske forhold (pH 1,1 og 37 °C) er i et område fra ca. d_{10} = 6 nm til ca. d_{90} = 20 nm

og/eller **ved at**

turbiditeten til solubilisatet er mindre enn 25 FNU, foretrukket mindre enn 3 FNU, målt ved måling av spredt lys ved anvendelse av infrarødt lys i henhold til spesifikasjonene i ISO 7027-standarden ved en fortynning av solubilisatet i et forhold på 1:50 eller 1:500 i vann under fysiologiske forhold (pH 1,1 og 37 °C).

5. Kapsel fylt med et solubilisat for anvendelse ifølge krav 1 eller 2 eller 4 eller med et solubilisat ifølge krav 3 eller 4,

karakterisert ved at

kapselen er i form av en myk gelatinkapsel eller en hard gelatinkapsel eller en myk gelatinfri kapsel eller en hard gelatinfri kapsel, for eksempel en cellulosekapsel.

6. Fluid, som inneholder et solubilisat for anvendelse ifølge krav 1 eller 2 eller 4 eller med et solubilisat ifølge krav 3 eller 4,

karakterisert ved at

fluidet velges fra gruppen bestående av matvarer, kosttilskudd, drikkevarer, kosmetikk og farmasøytiske produkter,

og/eller **ved at**

fluidet omfatter en vandig fortynning av solubilisatet.

7. Solubilisat ifølge ett av krav 1 til 4 eller kapsel ifølge krav 5 eller fluid ifølge krav 6 for oral anvendelse for behandling og/eller forebygging av sykdommer som involverer betennelse, kreft, Alzheimers, Parkinsons, fedme, høyt kolesterol, forhøyet blodsukker, diabetes, metabolsk syndrom og/eller autoimmune sykdommer, multippel sklerose (MS), for å redusere visceralt fett, for termogenese, for å senke kolesterol, spesielt LDL-kolesterol, og/eller glukose i blodet og/eller triglyserider i blodet, for å forbedre makulær pigmenttetthet, for å redusere oksidativt stress og/eller for å redusere akkumuleringen av fett i hepatocyttene, spesielt som et farmasøytisk legemiddel for behandling og/eller forebygging av fettleversykdom, Friedreichs ataksi, lysosomale sykdommer, spesielt Tay-Sachs sykdom, arteriosklerose, hjertesykdommer, artritt.

8. Solubilisat for anvendelse ifølge krav 7,

karakterisert ved at

solubilisatet administreres til kosttilskuddsforbrukeren eller pasienten i en kurkumindose som varierer fra 0,5 mg/kg kroppsvekt til 1 mg/kg kroppsvekt, foretrukket i en dose på 0,81 mg/kg kroppsvekt, særlig én gang daglig

og/eller **ved at**

solubilisatet administreres til kosttilskuddsforbrukeren eller pasienten i en Boswellia-dose som varierer fra 1 mg/kg kroppsvekt til 2 mg/kg kroppsvekt, foretrukket i en dose på 1,62 mg/kg kroppsvekt, særlig én gang daglig

og/eller **ved at**

solubilisatet administreres til kosttilskuddsforbrukeren eller pasienten i en xanthohumoldose som varierer fra 0,5 mg/kg kroppsvekt til 1 mg/kg kroppsvekt, foretrukket i en dose på 0,81 mg/kg kroppsvekt.

9. Fremgangsmåte for å produsere et solubilisat som inneholder og særlig består av

kurkumin i et innhold fra 3 vekt-% til 7 vekt-%;

og minst ett ytterligere virkestoff,

som omfatter ett eller flere stoffer valgt fra gruppen bestående av xanthohumol, planteekstrakter, særlig fra harpiksen fra røkelsestreet, lakris, cannabinoider, enzymer, særlig serrapeptase, koenzym Q_{10}, α-lipoinsyre, resveratrol; og

minst én emulgator med en HLB-verdi i et område under 18, foretrukket mellom 13 og 18, nemlig polysorbat 80 eller polysorbat 20 eller en blanding av polysorbat 20 og polysorbat 80;

hvor polysorbatinnholdet er minst 70 vekt-%, foretrukket i området mellom 75 vekt-% og 95 vekt-%, mest foretrukket i området mellom 79 vekt-% og 88 vekt-%, særlig et solubilisat ifølge krav 4;

som omfatter følgende trinn

(a) å tilveiebringe polysorbat 80 og/eller polysorbat 20 og/eller en blanding av polysorbat 20 og polysorbat 80;

(b) å tilsette minst ett ytterligere virkestoff, særlig *Boswellia serrata*-ekstrakt og/eller xanthohumol;

(c) å tilsette kurkuminpulver;

hvor trinn (a) omfatter oppvarming til en temperatur i et område fra 40 °C til 62 °C, foretrukket til en temperatur i et område fra 45 °C til 57 °C, mest foretrukket til en temperatur i et område fra 48 °C til 52 °C; og

hvor trinn (b) omfatter å holde temperaturen uendret sammenlignet med trinn a), eller oppvarming til en temperatur i et område fra 60 °C til 75 °C, foretrukket til en temperatur i et område fra 61 °C til 70 °C, mest foretrukket til en temperatur i et område fra 63 °C til 67 °C; og

hvor trinn (c) omfatter oppvarming til en temperatur i et område fra 82 °C til 97 °C, foretrukket til en temperatur i et område fra 83 °C til 92 °C, mest foretrukket til en temperatur i et område fra 85 °C til 89 °C.

10. Fremgangsmåten ifølge krav 9, hvor et trinn (b1) utføres før trinn (b),

omfattende å tilsette vann ved en temperatur i et område fra 40 °C til 62 °C, foretrukket ved en temperatur i et område fra 45 °C til 57 °C, mest foretrukket ved en temperatur i et område fra 48 °C til 52 °C.

11. Fremgangsmåten ifølge krav 9 eller 10, hvor trinn

(b1) videre omfatter å tilsette etanol ved en temperatur i et område fra 40 °C til 62 °C, foretrukket ved en temperatur i et område fra 45 °C til 57 °C, mest foretrukket ved en temperatur i et område fra 48 °C til 52 °C.

12. Fremgangsmåte for å produsere et solubilisat som inneholder og særlig består av

kurkumin i et innhold fra 3 vekt-% til 7 vekt-%;

og minst ett ytterligere virkestoff,

som omfatter ett eller flere stoffer valgt fra gruppen bestående av xanthohumol, planteekstrakter, særlig fra harpiksen fra røkelsestreet, lakris, cannabinoider, enzymer, særlig serrapeptase, koenzym Q_{10}, α-lipoinsyre, resveratrol; og

minst én emulgator med en HLB-verdi i et område under 18, foretrukket mellom 13 og 18, nemlig polysorbat 80 eller polysorbat 20 eller en blanding av polysorbat 20 og polysorbat 80;

hvor polysorbatinnholdet er minst 70 vekt-%, foretrukket i området mellom 75 vekt-% og 95 vekt-%, mest foretrukket i området mellom 79 vekt-% og 88 vekt-%, særlig solubilisat ifølge krav 4;

med følgende trinn

(a) klargjøre et første preparat ved å tilveiebringe polysorbat 80 og/eller polysorbat 20 og/eller en blanding av polysorbat 20 og polysorbat 80 og minst et første virkestoff, særlig α-lipoinsyre;

(b) klargjøre et andre preparat ved å tilveiebringe vann og minst ett ytterligere virkestoff, særlig serrapeptase;

(c) tilsette minst ett ytterligere virkestoff, særlig xanthohumol og/eller *Boswellia serrata*-ekstrakt og/eller glavonoid og/eller resveratrol og/eller koenzym Q_{10}, og tilsette kurkuminpulver til det andre preparatet fra trinn (b);

(d) kombinere det første preparatet fra trinn (a) og det andre preparatet fra trinn c); hvor temperaturen er i et område fra 18 °C til 22 °C under gjennomføringen av trinn (a) til (d);

(e) varme opp til en temperatur i et område fra 80 °C til 97 °C, foretrukket til en temperatur i et område fra 83 °C til 92 °C, mest foretrukket til en temperatur i et område fra 85 °C til 89 °C.

13. Fremgangsmåte ifølge krav 12, hvor trinn

(c) videre omfatter å tilsette etanol og/eller glyserol og/eller MCT-olje og/eller polysorbat 20 og/eller polysorbat 80 og/eller en blanding av polysorbat 20 og polysorbat 80.

14. Fremgangsmåte for å produsere et solubilisat som inneholder og særlig består av

kurkumin i et innhold fra 3 vekt-% til 7 vekt-%;

og minst ett ytterligere virkestoff,

som omfatter ett eller flere stoffer valgt fra gruppen bestående av xanthohumol, planteekstrakter, særlig fra harpiksen fra røkelsestreet, lakris, cannabinoider, enzymer, særlig serrapeptase, koenzym Q_{10}, α-lipoinsyre, resveratrol; og

minst én emulgator med en HLB-verdi i et område under 18, foretrukket mellom 13 og 18, nemlig polysorbat 80 eller polysorbat 20 eller en blanding av polysorbat 20 og polysorbat 80;

hvor polysorbatinnholdet er minst 70 vekt-%, foretrukket i området mellom 75 vekt-% og 95 vekt-%, mest foretrukket i området mellom 79 vekt-% og 88 vekt-%, særlig solubilisat ifølge krav 4,

med følgende trinn

(a) å tilveiebringe polysorbat 80 og/eller polysorbat 20 og/eller en blanding av polysorbat 20 og polysorbat 80 og av glyserol og etanol;

(b) å tilsette minst ett ytterligere virkestoff, særlig et etanolisk ekstrakt av harde harpikser fra humler;

hvor

trinn (a) omfatter oppvarming til en temperatur i et område fra 40 °C til 62 °C, foretrukket til en temperatur i et område fra 45 °C til 57 °C, mest foretrukket til en temperatur i et område fra 48 °C til 52 °C;

og hvor

trinn (b) omfatter oppvarming til en temperatur i et område fra 60 °C til 75 °C, foretrukket til en temperatur i et område fra 61 °C til 70 °C, mest foretrukket til en temperatur i et område fra 63 °C til 67 °C; og

(c) tilsetning av kurkuminpulver ved en temperatur i et område fra 70 °C til 92 °C, foretrukket ved en temperatur i et område fra 75 °C til 87 °C, mest foretrukket ved en temperatur i et område fra 78 °C til 82 °C;

(d) tilsetning av glavonoid under oppvarming til en temperatur i et område fra 80 °C til 97 °C, foretrukket til en temperatur i et område fra 83 °C til 92 °C, mest foretrukket til en temperatur i et område fra 85 °C til 89 °C.

15. Fremgangsmåte for å produsere et solubilisat som inneholder og særlig består av

kurkumin i et innhold fra 3 vekt-% til 7 vekt-%;

og minst ett ytterligere virkestoff,

som omfatter ett eller flere stoffer valgt fra gruppen bestående av xanthohumol, planteekstrakter, særlig fra harpiksen fra røkelsestreet, lakris, cannabinoider, enzymer, særlig serrapeptase, koenzym Q_{10}, α-lipoinsyre, resveratrol; og

minst én emulgator med en HLB-verdi i et område under 18, foretrukket mellom 13 og 18, nemlig polysorbat 80 eller polysorbat 20 eller en blanding av polysorbat 20 og polysorbat 80;

hvor polysorbatinnholdet er minst 70 vekt-%, foretrukket i området mellom 75 vekt-% og 95 vekt-%, mest foretrukket i området mellom 79 vekt-% og 88 vekt-%, særlig et solubilisat ifølge krav 4,

ved å blande et kurkuminsolubilisat og et solubilisat av minst ett ytterligere virkestoff, særlig i et kvantitativt forhold på 1:1 av de individuelle solubilisatene.

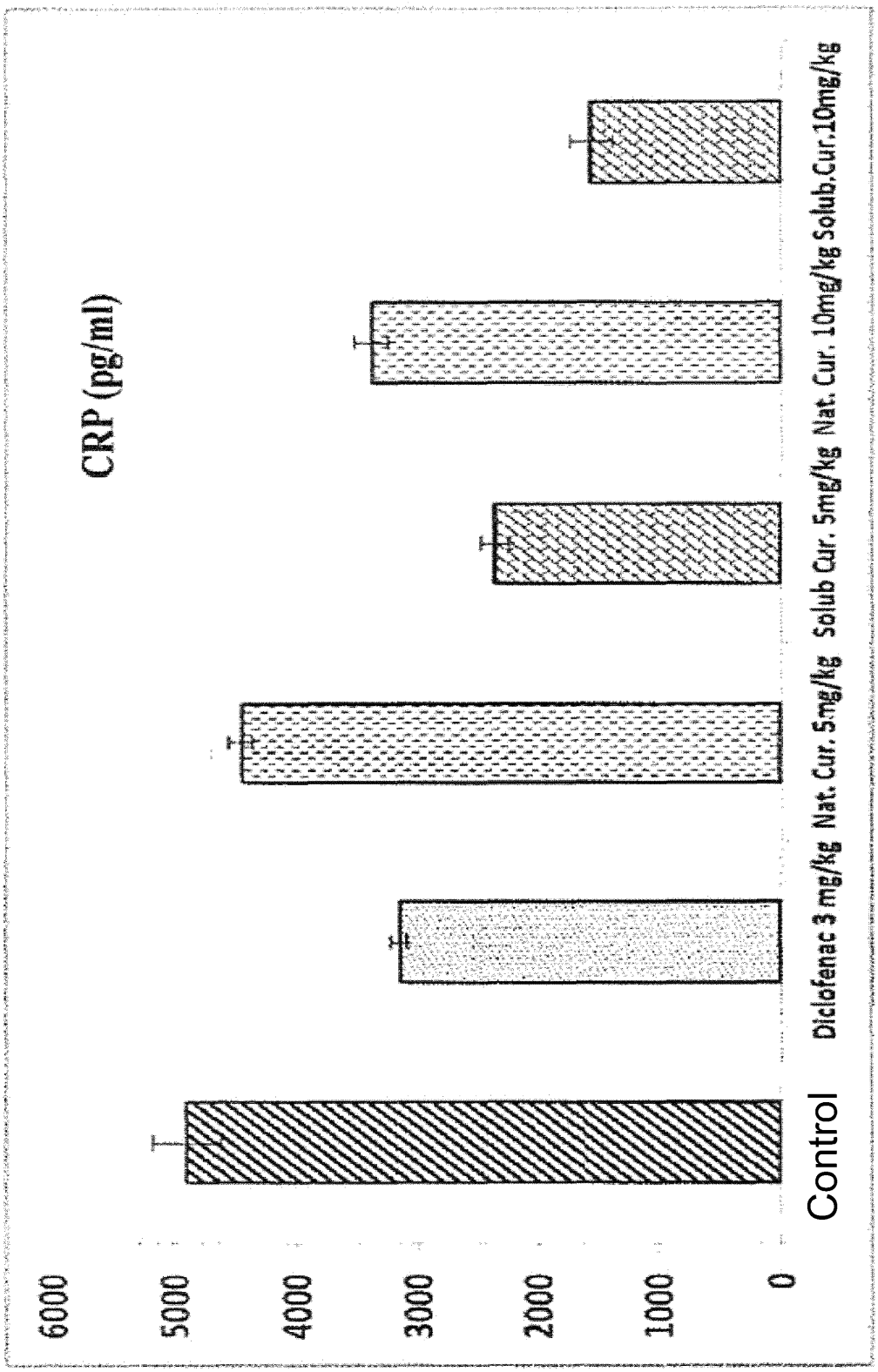
CRP (pg/ml)
6000
5000
4000
3000
2000
1000
0
Control
Diclofenac 3 mg/kg
Nat. Cur. 5mg/kg
Solub Cur. 5mg/kg
Nat. Cur. 10mg/kg
Solub.Cur.10mg/kg

Fig. 1a

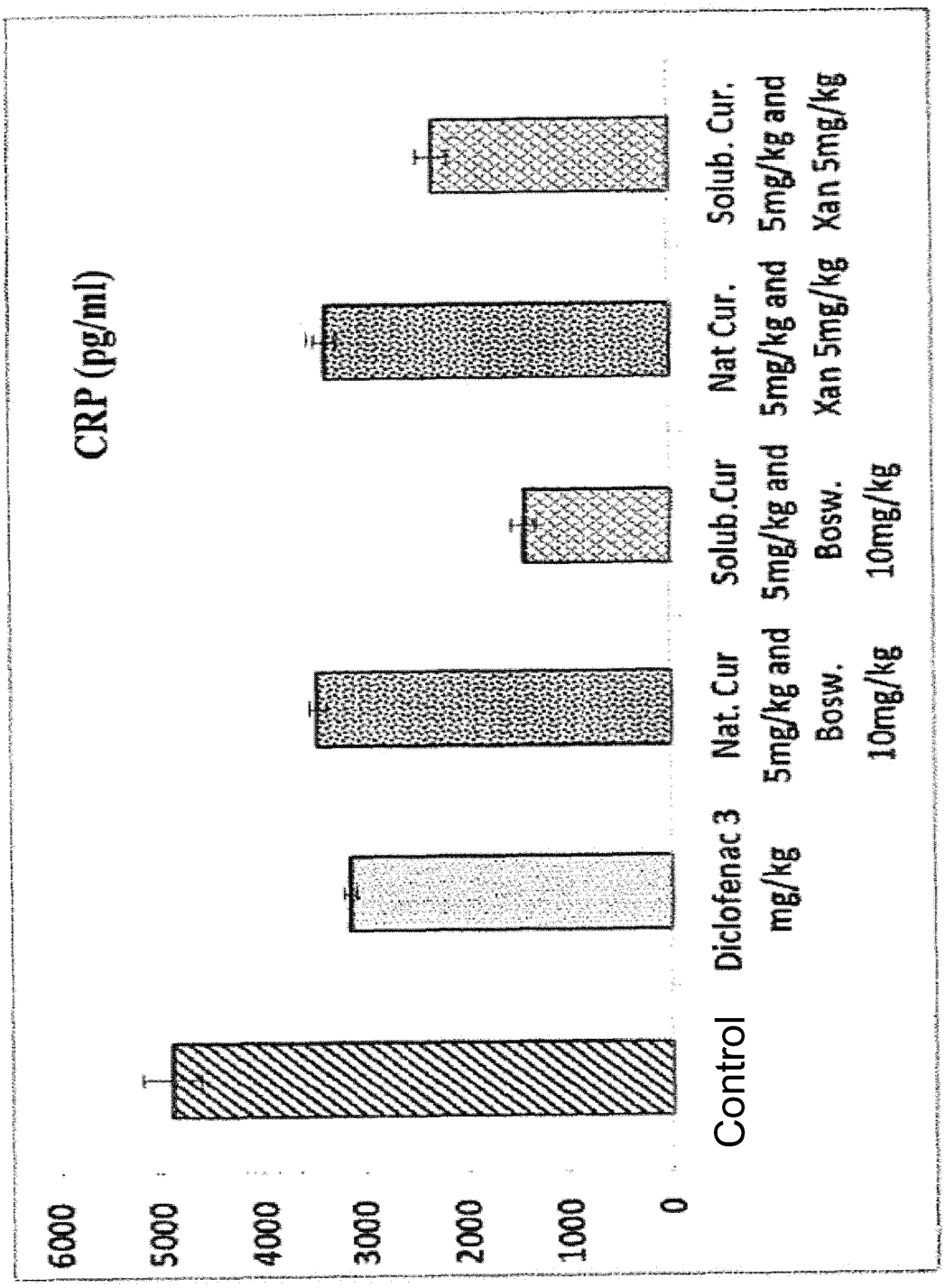
CRP (pg/ml)
6000
5000
4000
3000
2000
1000
0
Control
Diclofenac 3 mg/kg
Nat. Cur 5mg/kg and Bosw. 10mg/kg
Solub.Cur 5mg/kg and Bosw. 10mg/kg
Nat Cur. 5mg/kg and Xan 5mg/kg
Solub. Cur. 5mg/kg and Xan 5mg/kg

Fig. 1b

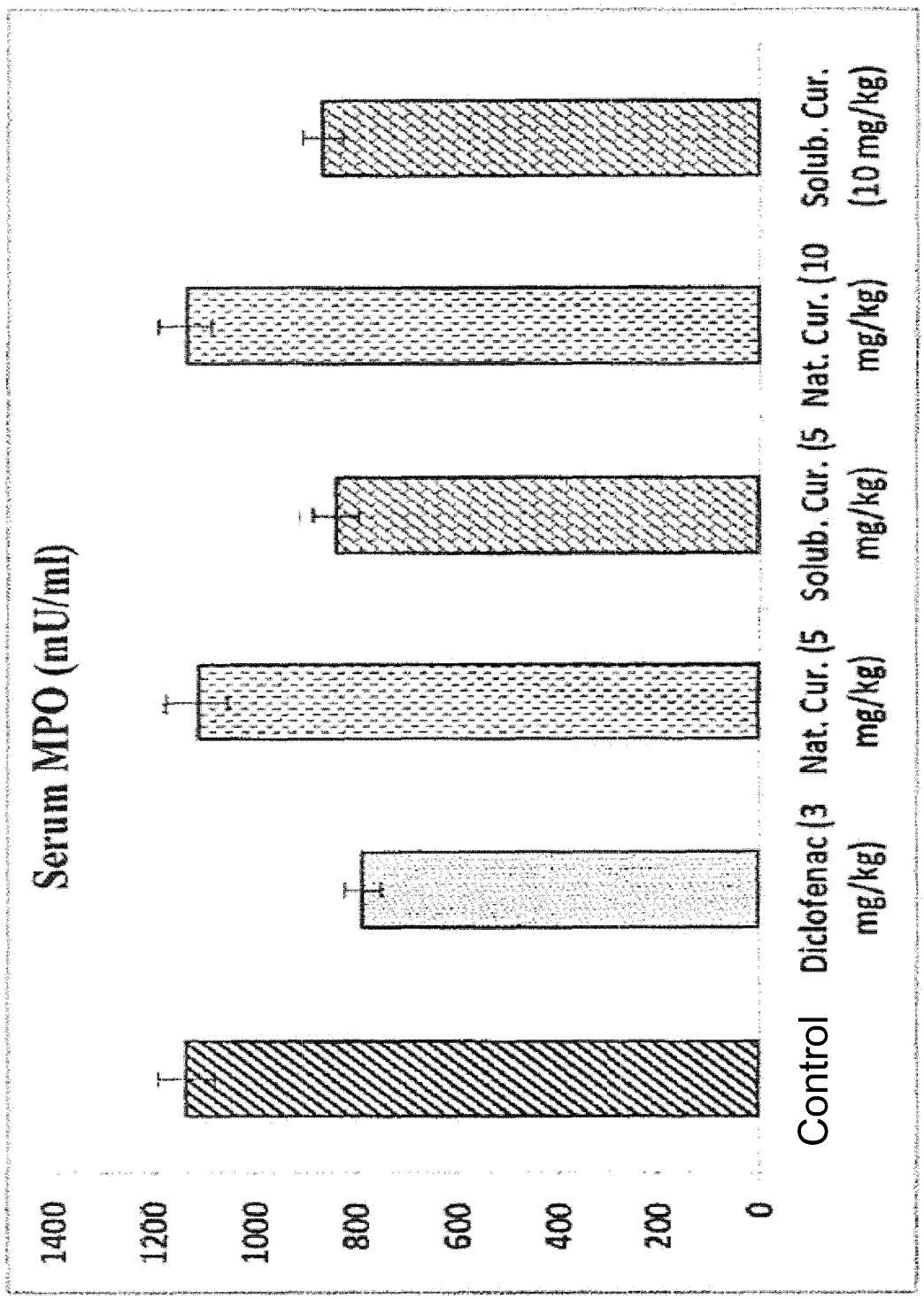
Serum MPO (mU/ml)
1400
1200
1000
800
600
400
200
0
Control
Diclofenac (3 mg/kg)
Nat. Cur. (5 mg/kg)
Solub. Cur. (5 mg/kg)
Nat. Cur. (10 mg/kg)
Solub. Cur. (10 mg/kg)

Fig. 2

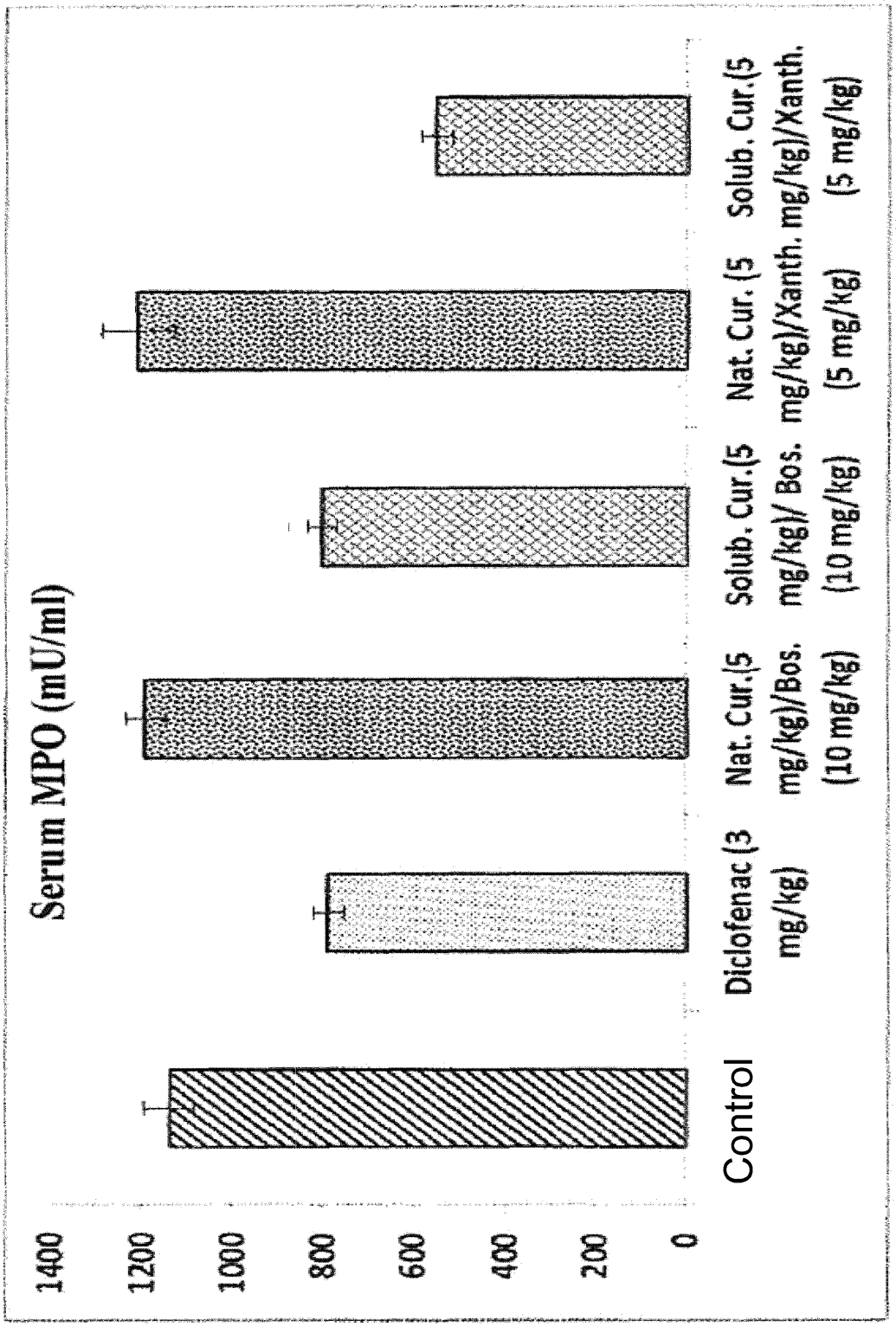
Serum MPO (mU/ml)
1400
1200
1000
800
600
400
200
0
Control
Diclofenac (3 mg/kg)
Nat. Cur.(5 mg/kg)/Bos. (10 mg/kg)
Solub. Cur.(5 mg/kg)/ Bos. (10 mg/kg)
Nat. Cur. (5 mg/kg)/Xanth. (5 mg/kg)
Solub. Cur.(5 mg/kg)/Xanth. (5 mg/kg)

Fig. 3