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(54) **Title:** THE ENHANCING EFFECT OF CANNABIDIOL (CBD) TO ANTI-INFLAMMATORY PLANT EXTRACTS HAVING A DUAL INHIBITORY EFFECT ON COX AND LOX

(57) **Abstract:** The present application provides a composition with an enhancing effect containing cannabidiol and anti- inflammatory herbal extracts having a weak dual inhibitory effect on COX (cyclooxygenase) and LOX (lipoxygenase). The herbal extracts are selected from Psoralea Corylifolia extract or betulin or Rosmarinus Officinalis extract or licorice (Glycyrrhiza Glabra) extract. A small amount of cannabidiol, max. 1.0% by volume, increases the therapeutic effect of individual herbal extracts. The composition can be used for treatment of skin inflammation, e.g. psoriasis, eczema, acne or allergic dermatitis, or for treatment of inflammation of internal organs, e.g. inflammation of pancreas or bowel or stomach or duodenum, or for the treatment of herpes virus. The form of the composition is cream, ointment, wax, capsule, paste, water, solution, emulsion or tablet.

THE ENHANCING EFFECT OF CANNABIDIOL (CBD) TO ANTI-INFLAMMATORY PLANT EXTRACTS HAVING A DUAL INHIBITORY EFFECT ON COX AND LOX

Technical Field

The invention relates to therapeutic compositions that act dually on both the COX enzyme and the LOX for the relaxation of both internal and external inflammatory diseases based on two natural substances, of which cannabidiol and / or hemp extract with equivalent CBD content is the basis of each composition. For the vast scope of the study (it is known that about twenty herbs and their extracts have a weak dual effect) it was not possible to trace all these new compositions from the practical point of view and therefore four herbs (extracts from them) were randomly selected and examined in the newly created compositions. However, unexpected results are sufficient to claim that by adding CBD to extracts with mild dual effects, the anti-inflammatory and regenerative effect of the newly formed compositions is enhanced.

The following compositions were studied:

Cannabidiol and Psoralea Corylifolia extrakt (Babchi), inhibitor COX a LOX.

Cannabidiol and Glycyrrhiza glabra L.extrakt (licorice), inhibitor COX a LOX.

Cannabidiol and *Rosmarinus officinalis* L. extrakt (rosemary), inhibitor COX a LOX.

Cannabidiol and Betulin extract, inhibitor COX a LOX.

Note: In the studies, pure 98% CBD and / or cannabis extract with an equivalent amount of CBD (hereinafter referred to as CBD) were used.

The efficacy of the composition was verified on the basis of the empirical research carried out, where the truths of hypotheses and hypotheses were confirmed.

Background Art

Nature is a great chemist and healer. Indians and wildlife knew that before. Until now, it is not known in some of the mixes that have emerged on the basis of empirical research by Indians, the principle of their effects and their effect on the cellular level. It is no wonder, therefore, that the new medicinal effects of plants are being sought and explored more and more intensively for their cheap and potentially unlimited source, which is suitable for the production of new therapeutic compositions.

New discoveries also use empirical sciences, which are an integral and important component of every discipline.

In general, the formation of all inflammations in general and cell proliferation and metastasis in carcinogenesis are predominantly controlled by pro-inflammatory mechanisms. Therefore, a great deal of effort is being made to develop eicosanoids / leukotrienes inhibiting / inhibiting agents, preferably with dual inhibitory effects on COX and LOX, without side effects.

Almost all inflammations in the human body, such as joint and muscle pain, allergic skin reactions, eczema, inflammation of other internal organs eg intestines, are mainly due to metabolic products of arachidonic acid.

Arachidonic acid is released from the cell membranes, in particular from the phospholipids that the cell membranes contain. E.g. when the skin is damaged, the skin cell is damaged and arachidonic acid is discharged from its phospholipid cover membrane. Arachidonic acid is rapidly metabolized to eicosanoids - prostaglandins, thromboxanes and leukotrienes that are most responsible for allergic, inflammatory, spasmolytic and spasmoconstriction reactions, and as local hormones (effects - not in the true sense of the hormones) affect smooth muscles, pain, affect blood clotting and cause a variety of other mechanisms such as redness and bleaching of the skin, splitting, pain, swelling, blood clotting, bronchial spasm - asthma, and the like.

To each of the major metabolites:

Prostaglandins are oxidized derivatives of arachidonic acid, participate in all inflammatory processes in the body, develop

their effects in a minimal amount and act as tissue hormones especially on smooth muscles, nerve cells, vascular system and reproductive apparatus. Prostaglandins cause vasodilation resulting in redness, hotness, increased permeability of blood vessels, which manifests swelling, affects pain and fever, reduces systemic arterial pressure, affects platelet aggregation. They are synthesized in most cells and act on virtually all of the body's metabolism by affecting the formation of hormones, digestive juices, influencing blood circulation, participating in immune and inflammatory processes, for example, causing stomach muscles (affecting smooth muscles) etc. Their effects vary according to the type of organ in which they form.
Thromoboxans are substances that form in the platelets, relaxing causing vasoconstriction (narrowing of the blood vessels) and clotting of blood platelets, thus contributing to blood clotting.

Leukotrienes are primarily found in leukocytes. Leukotrienes have a very strong bronchoconstrictor effect (it acts as a smooth muscle contraction). They increase the permeability of the blood vessels, act chemoactively and actively on leukocytes, mainly eosinophils and monocytes. At the onset of the allergic reaction, leukotrienes act as a very potent bronchoconstrictor, acting in a late allergic response to smooth muscle cells, epithelial cells and fibroblasts. Leukotrienes increase the ability of phagocytosis, inflammatory responses and immune defense against infections. They affect the onset or development of inflammatory diseases such as allergic rhinitis, bronchoconstriction, vasodilatation and vasoconstriction, reduction of mucociliary clearance, collagen deposition, proliferation of epithelial cells, smooth muscle proliferation, mucus formation.

The formation of prostaglandins and thromboxanes from arachidonic acid provides the enzyme cyclooxygenase and the formation of leukotrienes from arachidonic acid stimulates the enzyme 5-lipoxygenase.

Lipoxygenase (LOX) and cyclooxygenase (COX) are enzymes involved in the development and development of all inflammations of the organs of the human body such as skin inflammatory diseases (psoriasis, atopic eczema, allergic reactions, etc.), inflammatory diseases of the mucous

membranes of the internal organs such as Crohn's disease, colitis in general, gastritis, etc. They are also involved in the development and development of inflammation of the joints and, last but not least, in the onset of cancer.

COX and LOX are an important component of arachidonic acid metabolism (AA -arachidonic acid). Arachidonic acid (C19H31COOH, cis-5,8,11,14-eicosatetraenoic acid) is an unsaturated omega-6 fatty acid having 20 carbon atoms and four cis double bonds. In the human body AA gets food. It is most commonly found in vegetable oils, especially cannabis, sunflower and olives. It can also be produced directly in the body from essential linoleic acid (C17H31COOH, omega-6 fatty acid).

In AA we distinguish three metabolic pathways by which the eicosanoids are formed - the cyclooxygenase pathway, the lipoxygenase pathway and the epoxygenase pathway.

The cyclooxygenase pathway from AA is formed - by catalysis by the enzyme cyclooxygenase (COX) prostaglandin G2 (PGG2), which further generates prostaglandin H2 (PGH2). This is the starting material for other products - prostaglandin E2 (PGE2), D2 (PGD2), F2α (PGF2α), prostacyclin (PGI2) and thromboxane A2 (TXA2).

Lipoxygenase pathway is formed by lipoxygenase (LOX) enzyme catalysis 5-hydroxyeicosatetraenoic acid (5-HETE),

12-hydroxyeicosatetraenoic acid (12-HETE) and acid

15-hydroxyeicosatetraenoic acid (15-HETE). 5-HETE furthermore forms leukotrienes.

Cyclooxygenase (COX, prostaglandin endoperoxidase synthase) is an integral membrane bifunctional enzyme that is responsible for the formation of prostanoids from arachidonic acid. Three COX-1, COX-2 and COX-3 isoforms are known for COX, located on the nuclear membrane and on the inside of the endoplasmic reticulum.

COX-1 is a constitutive enzyme, which means that it occurs in many types of tissue in a constant amount and plays an important role in regulating homeostasis. At the site of inflammation, its activity increases two to four times.

COX-2 is an inducible enzyme that is found to be very small in most tissues or absent and its concentration rises to the site of inflammation by activating extracellular stimuli. The catalytic activity of inducible COX-2 may increase up to twenty times at the site of inflammation.

COX-3 (COX-1b) is a post-translational modified form of COX-1.

Nuclear COX-2 has an important regulatory role in mitogenesis. In tumor cells, COX-2 is located in mitochondria and lipid droplets (inclusions). Intracellular placement of COX-2 into mitochondria plays an important role in the protection against oxidative stress induced by apoptosis, whereas the location of COX-2 in lipid droplets critically affects tumor growth.

Lipoxygenases (LOX) are enzymes found in the plant kingdom, fungi and animals, including humans. The main function of lipoxygenase in humans is the provision of O2 (oxidation) of arachidonic acid to produce unstable hydroperoxyeicosatetraenoic acids (HPETEs) which are further reduced to hydroxyeicosatetraenoic acids (HETEs). Depending on the AA site (arachidonic acid), we divide the LOX enzyme into four categories for 5-LOX, 8-LOX, 12-LOX and 15-LOX.
In the 5-LOX pathway, 5-HPETE is metabolized to an unstable epoxide - leukotriene LTA4, resulting in leukotrienes LTB4, LTC4, LTD4, LTE4 and 5-HETE. Leukotrienes have pro-inflammatory effects, play a significant role in the pathogenesis of allergic inflammation, and can play a role in carcinogenesis.

5-LOX (5-lipoxygenase) is a 78 kDa protein. 5-LOX is primarily found in immune cells such as leukocytes, monocytes, macrophages and mast cells. The healthy tissue is level
5-LOX is almost undetectable; on the contrary, its concentration and activity are significantly increased in inflammatory or tumor-transformed tissues. There is a need for calcium and ATP to activate 5-LOX in AA metabolism. An integral 5-LOX enzyme for its proper function in leukotriene synthesis is 5-LOX activation protein (FLAP), the weight of which is 18 kDa. FLAP transmits arachidonic acid to the 5-LOX enzyme, allowing its oxidation in pro-inflammatory

leukotrienes. By inhibiting 5-LOX, leukotrienes are suppressed and thus inflammation is reduced.

Since cycloxygenase (COX) and lipoxygenase (LOX) are indispensable enzymes in the biosynthesis of pro-inflammatory eicosanoids (prostaglandins, prostacyclins, thromboxanes) and leukotrienes, the research and testing of inhibitors of these two significant arachidonic acid metabolism presently the subject of many studies and clinical work.

New inhibitors of these two enzymes can be generally very effective tools in the prevention and treatment of inflammatory diseases, allergic reactions and also in the prevention and progression of cancer.

Obviously, a great deal of effort has been made in recent years to research suitable inhibitors for both LOX and COX, which have the least adverse effects on the organism and are called dual agents / inhibitors.

For the treatment of inflammation in the human body, either steroid (hormonal) or non-steroidal (hormone-free) treatment is used.

Corticosteroid hormones (corticosteroid hormones) or corticoid hormones, which are synthetic cholesterol-synthesized corticosteroid hormone analogues, are used for steroid therapy. Corticosteroid and corticoid hormones prevent the release of arachidonic acid from cell membrane phospholipids (inhibit phospholipase) and thus prevent its metabolism to tissue hormones eicosanoids.

Undesirable effects of these corticosteroids and corticoids are skin thinning, red face, poor healing of wounds and lighter bruises, increased appetite for weight, and associated weight gain and poor fat loss with marigold, fat, abdominal fat, bullous hump - buffalo hump. Heavier unwanted symptoms, such as hypertension, bone thinning, hyperglycemia, negative nitrogen balance, and general infections, are known, as corticosteroids and corticosteroids reduce the immune system.

Non-steroidal treatments use chemical products that act anti-inflammatory in the absence of hormones. The most well-known substance is salicylic acid and its derivatives. It is used as pain relieving analgesic, an antipyretic for lowering body

temperature in fever. Because of its large anti-inflammatory effects it is also used as an anti-rheumatic agent and a remedy for the calming of skin inflammations. Salicylic acid blocks the conversion of arachidonic acid to prostaglandins and thromboxanes by irreversibly inhibiting the cyclooxygenase (COX) enzyme. Because salicylic acid blocks the formation of prostaglandins and especially thromboxanes, it suppresses the effects of inflammatory reactions, temperature and other cascade reactions of these two agents. However, salicylic acid does not treat the cause, it only suppresses the natural reaction of the organism.

The undesirable effect of nonsteroidal treatment is the development and development of gastric ulceration and reduction in blood clotting, which may be severe in some diseases such as esophageal varices and ulcerative colitis, and other latent bleeding disorders.
Recently, the development of drugs or compositions that would inhibit COX and LOX (so-called dual inhibitors) are being developed because they are shown to have better results in the fight against inflammatory diseases and transformation of cells with less side effects. Dual inhibitors (COX and LOX concurrently) therefore have a greater potential to suppress the development of inflammation than to inhibit only one of them (either COX or LOX only).

Pharmaceutical research feverishly searches for new substances and compositions that, while retaining their effectiveness, are free of the above-mentioned negative symptoms. Therefore, other dual drugs and compositions are intensively working on their huge contribution to the treatment of inflammation in general and pain. In the current state of the art, they are only synthetic pharmaceuticals and are in research phases. Natural dual drugs or composition on the market are missing. This deficiency is addressed by this patent application, which is based on the mild dual effects of plant extracts and their potentiation by adding CBD to produce a completely new, highly anti-inflammatory, curative composition.

The first synthetic dual drug is currently Licofelon, which reduces the levels of PGE2 and LTB4 and is free of gastrointestinal side effects. Another promising molecule is Propynon 50, which focuses on three major enzymes involved in

the metabolism of AA-COX-2, 5-LOX, and 15-LOX. He is in the phase of clinical studies.

The dual inhibitory effect of the compositions of the European patent EP 2 444 081 A1, wherein the COX inhibitor is cannabidiol, cannabis extract and 5-LOX inhibitor are Boswellia serrata.
It is a natural product that relaxes the inflammation of the skin. Its great disadvantage is that boswell acids, the Boswellie Serrata extract contained in this composition is not a natural dual inhibitor of COX and LOX but is only a 5-LOX inhibitor. Therefore, this composition does not have such an anti-inflammatory effect as the novel compositions of the present invention. After several years of experience with the composition described in the patent
EP 2 444 081 A1 and by its testing it has been found that lighter forms of skin inflammation in eczema in most cases are relaxed. For heavier forms of eczema, this composition behaves abnormally, and in many cases also aggravates eczema - for example, in acute exacerbation of eczema. This aggravation or allergic skin reaction is caused by Boswellie Serrata extract, which contains 65% to 75% of the potential extract in the rest of the extract with potential allergens.

Another drawback of this composition is that it does not have antipyretic effects. These disadvantages of EP 2 444 081 A1 completely eliminate the novel invention of the potentiation of anti-inflammatory dual plant extracts by Cannabidiol.

Pharmaceutical research feverishly searches for new substances and compositions that, while retaining their effectiveness, are free of the above-mentioned negative symptoms.

One possible solution is the present invention, which is intended to be inventive of a novel, natural, effective dual composition, the effect of which would be equal to or greater than previously known anti-inflammatory and analgesic non-steroidal agents, and at least identical to corticoids and corticosteroids but without side effects.

Summary of the invention

An unexpected and unique therapeutic, antiinflammatory effect of cannabidiol on individual extracts of various herbs that have a weak anti-inflammatory effect has been demonstrated. Their lesser anti-inflammatory effect is explained by a mild inhibitory effect on COX (Cyclooxygenase) and LOX (Lipoxygenase). The extracts were of the same 90% purity for the objective assessment of their anti-inflammatory effects.

It has been found that by adding a small amount (max. 1.0% by volume) of cannabidiol (hereinafter referred to as CBD) to individual herbal extracts, which in themselves had less anti-inflammatory properties, the therapeutic effect of the individual extracts was unexpectedly increased unusually, always an extract from a herb with inhibitory effect on COX and LOX and CBD.

In order to produce an effective new therapeutic composition, the herbal extract is a condition that has dual inhibitory properties on both COX and LOX. In an extract that inhibited only one lipoxygenase enzyme, the addition of CBD to the plant extract resulted in the formation of a dual composition (CBD is a COX inhibitor), but with the expected effect, i.e., a slight improvement in the healing of inflammatory diseases.

An unexpectedly high anti-inflammatory enhancing effect of CBD, which has been added to plant extracts with mild dual inhibitory effects on COX and LOX, has therefore been found empirically. Such new compositions are not known.

Patent EP 2 444 081 A1 is about adding the CBD to Boswell Srst. However, Boswellie Serrata does not have a dual effect on both COX and LOX at the same time but only on LOX and therefore the resulting composition is weak in its effects.

This research has the potential to justify applying this knowledge to all newly formed compositions which have been produced from a herb extract with a dual inhibitory effect on COX and LOX and with the addition of a CBD enhancer.

Synthetic inflammatory drugs can also be replaced by natural substances or medicinal plant extracts that contain anti-inflammatory ingredients (such as luteolin, psoralen, ursanic acid, lupenol) without side effects on the human organism. Their inhibitory effect on both COX and LOX is, however,

weaker than synthetic current medicaments. However, the potential for the use of this dual activity of the individual extracts is enormous and the effects of the newly formed compositions by the addition of CBD are unexpectedly and surprisingly better than some currently used non-steroidal synthetic COX and LOX inhibitors. This fact is addressed by this invention.

The invention and its essence is that natural extracts of individual herbs with mild dual effect are mixed with CBD (or cannabis extract with CBD) as a catalyst which unexpectedly and unilaterally potentiates their dual effect to produce a completely new, unique and hitherto unknown antiinflammatory and a regenerating CBD-containing composition.

One of the most important natural cyclooxygenase inhibitors (COX) is cannabidiol (CBD), which is contained in cannabis leaves and extracted by extraction to produce a hemp extract with high CBD content. This extract may be further separated to pure CBD with a purity of 98.8% purity. In cannabis, the most CBDs are mainly contained in leaves. Cannabis is a diverse plant with many applications; It contains over 400 unique compounds, including cannabinoids, terpenoids, flavinoids, alkaloids and others. Each of these compounds has unique and varied effects that are little known so far and other compounds are awaiting discovery. CBD is the drug of the future, just like the discovery of salicylic acid.

Long-term testing and observation of CBDs in compositions with the participation of a single plant extract with a weak dual effect revealed an unexpected improvement in the anti-inflammatory effects of plant extract on inflammatory diseases by the addition of CBD. After years of empirical studies, it has been concluded that cannabis extract containing CBD or CBD alone can highly potentiate / intensify its mild dual, anti-inflammatory effect in natural plant extracts, unpredictably, conspicuously and unusually. From this, the unusual property of CBD as a catalyst can be derived, increasing the anti-inflammatory effects of the observed plant extracts. Therefore, the pharmacokinetic interactions of the CBD with the other active compounds contained in the investigated extracts are more than likely as empirically demonstrated in this patent.

This hypothesis is borne out by the fact that CBD has been replaced by willow extracts (salicylic acid), which is itself a prominent COX inhibitor, similar to CBD. However, when mixing the willow extract with the dual plant extract, there was no unusual manifestation in terms of skin inflammation, as with the use of CBD.

This invention meets the novelty of the composition that has never been made and a new discovery in unexpected and high anti-inflammatory effect on the human organism.

A slight dual anti-inflammatory effect is known in several natural plant extracts. These anti-inflammatory properties and their inhibitory effects on COX and LOX were used to monitor the increased anti-inflammatory effects of these extracts upon addition of CBD or cannabis extract with CBD to form a new composition.

Description of individual plants from which extracts were used:

1) Psoralea corylifolia.

It is a small, upright, one-year herb growing to 60 to 120 cm high. The plant grows in tropical and subtropical regions of the world, including South Africa, China and India. For the production of extracts or medicinal components, seed, root and leaves are mainly used in this plant.

Psoralea corylifolia contains coumarin active ingredients: psoralen, isopsoralin, bavaquin, bavaquinin, isobavaquinin, bavachalcon, isobavachalcon, bakuchiol and raffinus. It has anti-inflammatory, analgesic, antioxidant and, according to other studies, anticancer effect on lung, stomach, prostate and lymph node cancer is possible. Antimycotic effect was detected on Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum and Microsporum gypseum.

The psoralea extract of corylifolia is also used primarily in Chinese medicine for osteoporosis, which promotes bone protection and growth, incontinence, lack of sperm, hair loss, psoriasis and vitiligo. Dilatates blood vessels, protects the liver, promotes bone growth, harmonises the activity of the intestines, the immune system, the heart, and has an antibiotic effect on gram-positive and gram-negative bacteria, Streptococcus mutans, Staphylococcus epidermidis and Staphylococcus aureus resistant to penicillin.
Reduces shrinkage.
The extract is mainly used for oral administration to alleviate arthritic pain and difficulty. The extract of psoralea corylifolia is itself a mild dual inhibitor of both COX and 5-LOX
(5-lipoxygenase).

2) BETULIN extract

Betulin, also betulinol, or betulol or lupendiol, is a triterpenic dibasic unsaturated alcohol contained mainly in the white pigment of birch bark of Betula pendula Roth. It is a white crystalline powder. It is obtained from birch bark with a common alcohol or chloroform extraction.
Betulin was one of the first triterpenoids, which succeeded in acquiring Löwitz in 1788 by sublimation from the birch bark as a pure chemical substance.
Betulin is studied for anti-inflammatory, hepatoprotective, analgesic, hypoglycaemic, hypolipidemic, antimicrobial, antimycotic, virostatic, immunomodulatory and tonic effects. It also has anti-tumor properties and anti-HIV activity - it has high antiviral properties.
Betulin is a COX and LOX inhibitor already in small concentrations (from 10 to 100 µg / ml of solution). Oral administration is a recommended dose of 0.1 to 0.25 mg / kg body weight. It also has a high antibacterial effect in these small concentrations especially Streptococcus pyogenes, Escherichia coli, Staphylococcus aureus and Enterococcus faecalis.

3) Licorice Glaze (*Glycyrrhiza glabra*)

Licorice is a healing plant of the legume family. Licorice is a 1m to 1.5m high perennial plant with a straight strong stem

and long roots. Flowers are arranged in pale violet straight grapes. Blooms in June and July. The fruit is a glabrous pod. The leaves are lichened, the individual leaves are ovate.
The roots of this plant belong to the important natural drugs used abundantly in both folk healing and practical medicine. The roots of liquorice glabrous are collected in autumn. Drying takes place at a temperature of about 30 ° C. Extract is prepared from the liquorice root.
Licorice was used in the healing of ancient Egypt. In the Czech Republic, the most popular use of medicinal liquorice effervescent was to cushion irritable cough. Liquorice substances support the formation of gastric juices and, on the contrary, act against the formation of gastric and duodenal ulcers. They also cause diluting dense mucus from the airways. It is therefore used as a supplement to relieve cough and to promote coughing during asthma or chronic bronchitis.
In small doses, liquorice promotes frequent urination, and at the higher doses, diuretic effects disappear. Other effects include inflammation in general and topical (psoriasis, eczema, allergic dermatitis) and increased muscular tension.
Excessive use of liquorice extract may be due to increased blood pressure and suppression of urination. With long-term consumption, liquorice substances are similar to corticosteroids, so long-term use is not recommended.
Licorice contains about 20% starch, 6% mustard, saponins - glycyrrhizin (50 times sweeter than sucrose), glabridin and isoliquiritigenin, monosaccharides, uronic acids and other substances. Licorice seeds contain toxic kanavanin.
Licorice has antimicrobial activity against gram-positive and gram-negative bacteria, mainly on Staphylococcus aureus, Mycobacterium tuberculosi, anti-fungicidal effects such as Mycobacterium smegmalis, Candida albicans and significantly suppresses herpes simplex viral activity which causes herpes. The root extract has a strong anti-angiogenic and anti-tumor effect. Liquorice extract is often used in traditional medicine to treat inflammatory and allergic diseases. Licorice extract has a moderate dual inhibitory effect on COX and LOC.

4) Rosmarinus officinalis L. - Rosemary

Rosemary (Rosmarinus officinalis L. Fam. Labiatae) is a green, blooming and bushy shrub, reaching a height of about one meter with an upright stem, whitish blue flowers and dark green

leaves. It grows wild along the northern and southern shores of the Mediterranean and also in the Himalayan region. He graduated in England, Germany, France, Denmark, Central America, Venezuela and the Philippines.

Rosemary (Rosmarinus officinalis Linn.) is used, for example, to flavor food, beverages as well as cosmetics; In folk healing, it is used, for example, as an anti-spasmolytic agent in kidney colic, but also to relieve the inflammation of the bronchi. The extract of rosemary relaxes the smooth muscle of the trachea and intestines, and has hepatoprotective and antitumor activity. The most important ingredients of rosemary are coffee acid and its derivatives, such as rosemary acid. These compounds have an antioxidant effect. Rosmarinic acid is well absorbed from the gastrointestinal tract and from the skin. Rosmarin acid increases the production of prostaglandin E2 and reduces the production of leukotriene B4 in human polymorphonuclear leukocytes and inhibits the complement system (COX and LOX). Years of experience have concluded that rosemary and its components, especially derivatives of coffee acids such as rosemary acid, may have therapeutic potential in the treatment or prevention of bronchial asthma, peptic ulcer, inflammatory diseases, prevention of atherosclerosis, affect ischemic heart disease, cataracts and possibly cancer. Rosemary is a weak inhibitor of COX and LOX.

Production Examples:

1) **Eczema cream:** A mixture of inflammatory and allergic processes in the skin

	Cebadex SE
RAW MATERIAL	Composition %
A	
Water demineralized - Aqua	40,19
Allantoin	0,2
Dow 2501 - Bis-PEG-18 Methyl Ether Dimethyl Silane	5
Glycerol 85% - Glycerin	5
B1	
White beeswax - Cera Alba	2
Polawax NF - Cetearyl alcohol, Polysorbate-60	6,5
Cutina® GMS V - Glyceryl monoStearate	2,5
White soft paraffin Ph.Eur.8.0. - Vazelína bílá	7
Saboderm OP - Ethylhexyl Palmitate	5
OEL M 500 - Dimethicone	5
dermosoft® GMCY - Glyceryl Caprylate	0,5
B2	
Tego SMO 80 V - Polysorbate 80	1
Sepimax ZEN - Polyacrylate-6	0,3
Cannabis oil raff	6
CBD extract	0,11
C	
Calcium Pantothenate	2
Water demineralized	5
D	
Rosemary extract	3,15
Salibide DMI - Dimethyl isosorbide	1,5
E	

Microcare SR8454 - Phenylpropanol, Decylen Glycol, Caprylyl Glycol		0,75	
Bisabolol		0,25	
Covi OX - Tocopherol		0,55	
Parfum Clear Crystal		0,5	
Total		100	

Technological process of production:

First, phase D is prepared - Rosemary extract dissolves in DMI. Stages A, B1 and B2 are particularly relevant.
Phase B2 is weighed and Sepimax ZEN polymer (Crosspolymer 6 polyacrylate) is completely dropped to volume.

Phase A without Dow 2501 is brought to a temperature of about 80-85 ° C. Upon reaching this temperature and just prior to mixing with B, DOW 2501 is added.
Phase B is also heated separately to 80-85 ° C. When this temperature is reached and immediately before mixing with A, the weighed phase B2 is added to B1. Mix B12 to A and mix.
The heating is switched off and the heating is switched on. Cool slowly, evenly with vigorous mixing.
Below 45 ° C, when solids are already solidified, phase D, C is added gradually and can be briefly mixed.
Under 35 ° C, phase E is added.
If about 60-40 ° C begins to separate or reverse the emulsion, it is only a rewetting feature, and it will be modified by cooling.
After finishing the production and cooling to room temperature, adjust the pH (4.5) and take the sample for microbiological control. The mass is transferred to the receptacles and stored in the semi-finished intermediate store.

Appearance:
- yellowish to brownish emulsion
- fragrance fresh
- pH 4.0-5.5
- dry matter min. 51%

2) Psoriasis cream: A mixture of excessive growth of skin cells and their rapid death

RAW MATERIAL	Raw material packaging number	COMPOSITION (%)	
A			
Water demineralized (aqua)		50,35	
Sepimax ZEN - Polyacrylate-6		1,5	
B			
Dow 2501 - Bis-PEG-18 Methyl Ether Dimethyl Silane		5	
dermosoft® decalact liquid - Sodium Caproyl/Lauroyl Lactylate, Triethyl Citrate		1	
C			
Tego SMO 80 V - Polysorbate 80		0,5	
Cutina® GMS V - Glyceryl monoStearate		1,5	
CBD extract		0,13	
Konopný olej raf		0,87	
dermosoft® GMCY - Glyceryl Caprylate		0,8	
Polawax NF - Cetearyl alcohol, Polysorbate -60		2,5	
Tego® Soft TN - C12-16 Alkyl benzoate		2	
ACE Fluid CPS - Cyclopentasiloxane		3	
D			

Covi OX - Tocopherol		0,4	
Microcare SR8454 - Phenylpropanol, Decylen Glycol, Caprylyl Glycol		0,75	
Bisabolol		1	
Parfum Adoré		0,7	
E			
Calcium Pantothenate		1	
Urea		5	
Hydrovance - Hydroxyethyl urea		3	
Water demineralized (aqua)		12	
F			
Psoralea Extract		2,0	
Salibide DMI - Dimethyl isosorbide		5	
Total		100	

Technological process of production:

The day before, Sepimax Zen (polyacrylate Crosspolymer 6) is swollen in water (phase A), and Psoralea corylifolia extract is dissolved in dimethyl isosorbide (phase F).

The prepared phase A is swollen after swelling and a gel is formed, and the evaporation of the recipe is completed. Phase A is warmed to about 50 ° C and phase B is stirred while stirring.
Particularly weigh phase C, which is heated up to approximately 80 ° C (Hemp extract and cyclopentasiloxane are added only after reaching the required temperature to avoid decomposition).
Phase C (80 ° C) was added to the AB phase (50 ° C) and mixed. The heating is switched off and very slowly and cool with vigorous stirring. There may be clumps - this is due to uneven cooling.

Cooling can then be interrupted and mixed only under natural cooling.
Stage E is prepared by dissolving the components in water. To the ABC phase, phase E, F is added under 40 ° C with stirring. D-phase components below 35 ° C are then progressively fed.

The pH is adjusted to 4.5-5.5, the sample is taken for the microbiological test and the mass is transferred to the intermediary containers of the blanks.

Appearance:
- yellowish to brownish emulsifier
- Fragrant floral
- pH 4.5-5.5
- dry matter min. 37%

2) Acne Cream: A mixture of follicular inflammation

RAW MATERIAL	Raw material packaging number	COMPOSITION (%)	
A			
Water demineralized		28	
MSM - Dimethyl sulfone		6	
Hydrovance - Hydroxyethyl urea		3	
Urea		6	
Dow 2501 - Bis-PEG-18 Methyl Ether Dimethyl Silane		5	
Glycerol 85% - Glycerin		3	
B1			
White beeswax - Cera Alba		3	
Polawax NF - Cetearyl alcohol, Polysorbate-60		6,1	
Cutina® GMS V - Glyceryl monoStearate		2,8	
White soft paraffin Ph.Eur.8.0. - Vazelína bílá		9	
OEL M 500 - Dimethicone		3	
dermosoft® GMCY - Glyceryl Caprylate		0,5	

B2			
Tego SMO 80 V - Polysorbate 80		1	
Sepimax ZEN - Polyacrylate-6		1,1	
Cannabis oil raff		10	
CBD extract		0,13	
B3			
7-dehydrocholesterol		0,15	
Retinyl Palmitate		0,3	
C			
Calcium Pantothenate		1	
Water demineralized		3,18	
D			
Licorice Glaze (Glycyrrhiza glabra) extrakt		0,1	
Salicylic acid		2	
Salibide DMI - Dimethyl isosorbide		5	
E			
Covi OX - Tocopherol		0,27	
Parfum Clear Crystal		0,37	
Total		100	

Technological process of production:

D phase D is first prepared - Liquorice glazed and Salicylic acid dissolved in DMI.
Stages A, B1 and B2 are particularly relevant.
Phase B2 is weighed and Sepimax ZEN polymer (Crosspolymer 6 polyacrylate) is completely dropped to volume.
Phase A without Dow 2501 is brought to a temperature of about 80-85 ° C. Upon reaching this temperature and just prior to mixing with B, DOW 2501 is added. Phase B is also heated separately to 80-85 ° C. When this temperature is reached and immediately before mixing with A, the weighed phase B2 is added to B1. Mix B12 to A, add B3, and mix.
The heating is switched off and the heating is switched on. Cool slowly, evenly with vigorous mixing.

Below 45 ° C, when solids are already solidified, phase D, C is added gradually and can be briefly mixed.
Under 35 ° C, phase E is added. If about 60-40 ° C begins to separate or reverse the emulsion, it is only a rewetting feature, and it will be modified by cooling.

After completion of production and cooling to room temperature, the pH is adjusted (4.5) and the sample is taken for microbiological control. The mass is transferred to the receptacles and stored in the semi-finished intermediate store.

Appearance:
- yellowish to brownish emulsion
- fragrance fresh
- pH 3.7-5.0
- dry matter min. 68%

4)Lupine shampoo - a mixture against the scaling of the skin in the hair

RAW MATERIAL	Raw material packaging number	COMPOSITION %
A		
Water demineralized		30,47
Urea		6,00
MSM - Dimethyl Sulfone		6,00
Sepimax ZEN - Polyacrylate-6		2,00
Chelaton III EDTA		0,10
B		
Dehyton PK 45 - Cocamidopropyl betaine		5,50
Texapon ALS Benz - Ammonium lauryl sulfate		20,00
Levenol H+B - Glycereth-2 Cocoate		2,00
Plantacare UP 818 - Coco Glucoside		5,00
C		
Amidet N - PEG-4 Rapeseed Amide		2,00

Cremophor CO 410 - PEG-40Hydrogenated Castor Oil		1,00
Varisoft EQ - Polyquaternium-98		1,50
Parfum Clear Crystal		0,30
Betulin - Betula Alba Bark Extract		0,10
CBD extract		0,03
D		
Texapon ALS Benz - Ammonium lauryl sulfate		12,00
Salicylic acid		3,00
E		
Oxetal VD 95 - Laureth -2, Peg-90 glyceryl isostearate		3,00
Total		100,00

Technological process of production:

Phase D is prepared to dissolve the salicylic acid in the surfactant without heating.

Prepare Phase A. Urea, MSM and Chelaton dissolve in the recirculating water under gentle warming to about 40-50 ° C. / Sepimax ZEN is a polyacrylate thickener already neutralized. Sepimax ZEN (Cross-Polymer 6 Polyacrylate) is wetted on the surface of this solution. After complete wetting, the evaporation of the recirculating water is added and the gel is mixed with warming while heating. A smooth gel is formed at a temperature of 40-50 ° C

Prepare phase C. Betulin is dissolved in a mixture of Amide N and Cremophor CO 410 with gentle heating. After the complete dissolution (it is possible to mix), the remainder of the phase C feedstock is added.

Phase B components are gradually weighed in order to warm up to 70-80 ° C. After reaching the homogeneous phase B, it is allowed to cool to 50 ° C and phase D is added, then phase A and homogenized by stirring. After the homogeneous mixture is formed (which is no longer heated), phase C is added and mixed well

Eventually it is ingested with phase E, Oxetal VD 95 can be dissolved into the liquid state prior to weighing in order to be better blended into volume.

Finally, after cooling, the pH is adjusted with a 10% NaOH solution to the desired 4.5-5.5, a microbiological control sample is taken and transferred to the storage containers in the intermediate storage of the blanks.

Appearance:

- Gel green to brownish color
- pH = 4.5-5.5
- fresh, herbal aroma
- dry matter approx. 44.5%

5) Regenerative ointment - wound healing

	A		
Petrolatum	Ad 100,00		
Cannabis sativa oil	20,00		
Betulin extract	3,0		
Isopropyl stearate	15,00		
Lanolin hydrogenated	6,00		
Cetyl and stearyl alcohol	5,00		
Benzyl alcohol	0,80		
Dehydroacetic	0,20		
Cannabidiol extractum	12,0		

Procedure: Heat to petroleum spirit with hydrogenated lanolin and fatty alcohols to melt, mix isopropyl myristate and finally add cannabidiol extract and solution of Betulin extract dissolved in DMI.

Benzyl alcohol and dehydroacetic acid are added to the solutions. Cool down and an ointment is created.

6) **Capsules for gastritis (inflammation and stomach and duodenal pain):**

Paste with extracts of Rosmarinus officinalis L. and cannabis extract with CBD for oral application. The components are in percent by weight. Use: Crohn's disease, ulcerative colitis, stomach ulcer.

		B	
Cannabis sativa oil		Ad 100,00	
Rosmarinus officinalis L. 65%		22,00	
Silica anhydrous		5,00	
Tocoferol acetate		0,95	
Butylhydroxyanisole		0,05	
Cannabidiol extractum cum CBD		0,01	

Hemp oil is homogenized with pyrogenic silica (anhydrous silica). Add to the gel the extract of Rosmarinus officinalis L. and Cannabidiol extracts cum CBD and then tocopherol acetate and butylhydroxyanisole. The paste can be filled into capsules.

7) **Arthritis capsules (inflammation and joint pain):**

Paste with cannabidiol complex and betulin extract designed for oral administration and given in capsules for arthritis, rheumatism, muscle pain and muscle strain.

Composition	(%)
Cannabis sativa oil	92,3
betulin extract	0,5

Cannabidiol 98%	0,2
Silica anhydrous	6
Tocoferol acetate	0,95
Butylhydroxyanisole	0,05

Preparation: Hemp oil is homogenized with pyrogenic silica (anhydrous silica). To the resulting gel we gradually add betulin extract, cannabis extract (CBD), tocopherol acetate and butylhydroxyanisole. Once the blending occurs, a paste can be formed which can be filled into a capsule.

8) **Haze composition: antiviral wax**

Phase A	
Aqua, water	32,37
betulin extract,	2,50
Sucralose	0,01
Sodium sorbate and Sodium benzoate, premix	0,15
Glycerin, glycerol 85%	6,00
Methylparaben, MP	0,10
Magnesium sulfate crystalspentahydrate	0,85
Phase B	
Beeswax, Apis melifica cera, Cera alba,	10,00
Glyceryl stearate, monoglycerid stearate, glyceryl monostearate	10,00
Butyrospermum parkii seed oil, Shea butter, cari	10,00
Vaselinum album, petrolatum, White beeswax	10,00
Butylhydroxytololum, BHT	0,02
Cetyl PEG/PPG-7/3 Dimeticone, cetyl dimetikon kopolyol, BC 99/012	7,50
Cannabis sativa leaves extract	10,00
Tocoferol acetate, Vitamin E	0,50

acetate	
Total	100

In the duplicator boiler, prepare phase B so that the first five components (wax, monoglyceride, shea butter, petrolatum and BHT) are heated to 60-65 ° C with stirring. Cetyl dimethicone copolyol, hemp oil, tocopherol acetate are then added gradually and with stirring.

Separately, phase A is prepared from the homogenization of the components: Betulin is dissolved in Salibide DMI and mixed with water to form an emulsion at 70 degrees.
Add the heated phase A slowly and with stirring to the heated phase B. Finally, at the elevated temperature in the liquid state, thoroughly homogenize with a colloidal mill and stir until solidified.

Industrial applicability

Cannabidiol-based or cannabisol-based cannabidiol-based cannabidiol extract as potentiator of anti-inflammatory properties of plant extracts with dual inhibitory effects on COX and LOX is useful in the wider treatment of all inflammatory diseases and their manifestations - swelling, redness, joint pain, stomach ache intestines, scaling of the skin. At the same time, betulin composition has pronounced antiviral therapeutic properties. The novel compositions of the present invention with their significance are fully consistent with the worldwide search for natural dual drugs to suppress and calm inflammations without undesirable side effects.
The composition according to this patent can be successfully used in the treatment of skin inflammations (eczema, atopic eczema, psoriasis, seborrhea, acne and other dermatitis including allergic manifestations), various haze, joint inflammation (rheumatism), swelling, muscle pain, contractions of muscles and other inflammations including, e.g., Crohn's disease, ulcerative colitis, bronchial asthma, gastric ulcer.

The dual anti-inflammatory and therapeutic agent of the invention is intended for both external use (mucosa, skin) in

the form of oils, creams, gels and ointments as well as for internal use (per os, per rectum) in the form of tablets, capsules, capsules, suppositories.

PATENT CLAIMS

1) The enhancing effect of cannabidiol (CBD) anti-inflammatory plant extracts having a dual inhibitory effect on COX and LOX, **characterized in** that each composition contains 98% cannabidiol or cannabis extract containing 98% cannabidiol, optionally other auxiliaries.

2) An enhancing effect of cannabidiol (CBD) anti-inflammatory plant extracts having a dual inhibitory effect on COX and LOX according to claim 1, **characterized in** that the composition contains cannabidiol and all herb extracts having dual effects on COX and LOX.

3) An enhancing effect of cannabidiol (CBD) anti-inflammatory plant extracts having a dual COX and LOX inhibitory effect according to any one of the preceding claims, **characterized in** that the composition contains cannabidiol cannabis extract and all herb extracts having dual effects on COX and LOX.

4) The enhancing effect of cannabidiol (CBD) anti-inflammatory plant extracts having a dual inhibitory effect on COX and LOX according to any one of the preceding claims, **characterized in** that the composition comprises cannabidiol cannabis extract and psoralea Corylifolia extract.

5) The enhancing effect of cannabidiol (CBD) anti-inflammatory plant extracts having dual inhibitory effect on COX and LOX according to any one of the preceding claims, **characterized in** that the composition comprises cannabidiol cannabidiol extract and betulin extract.

6) The enhancing effect of cannabidiol (CBD) anti-inflammatory plant extracts having dual inhibitory effect on COX and LOX according to any one of the preceding claims, **characterized in** that the composition comprises cannabidiol cannabis extract and licorice extract.

7) The enhancing effect of cannabidiol (CBD) anti-inflammatory plant extracts having a dual inhibitory effect on COX and LOX according to any one of the preceding claims, **characterized in** that the composition comprises cannabidiol cannabis extract and Rosmarinus officinalis extract.

8) The enhancing effect of cannabidiol (CBD) anti-inflammatory plant extracts having a dual inhibitory effect on COX and LOX according to any one of the preceding claims, **characterized in** that the other extracts are always in the range of 0.001% to 70%.

9) The enhancing effect of cannabidiol (CBD) anti-inflammatory plant extracts having a dual inhibitory effect on COX and LOX according to any one of the preceding claims, **characterized in** that the compositions are applied to skin inflammation, in particular to psoriasis, eczema, acne, allergic dermatitis.

10) The enhancing effect of cannabidiol (CBD) anti-inflammatory plant extracts having a dual inhibitory effect on COX and LOX according to any one of the preceding claims, **characterized in** that the compositions are applied to inflammations of inflammation of the internal organs, in particular pancreatic inflammation, bowel inflammation, inflammation of the stomach and duodenum.

11) The enhancing effect of cannabidiol (CBD) anti-inflammatory plant extracts having a dual inhibitory effect on COX and LOX according to any one of the preceding claims, **characterized in** that the compositions are applied as an antiviral agent to the herpes.

12) The enhancing effect of cannabidiol (CBD) anti-inflammatory plant extracts having a dual inhibitory effect on COX and LOX according to any one of the preceding claims, **characterized in** that the compositions may take various forms of embodiment, in particular they may be administered in the form of a cream, ointment, wax, paste, water, solution, emulsion, capsule, capsule, or tablet.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2018/001087

A. CLASSIFICATION OF SUBJECT MATTER

A61K31/05, A61K36/185, A61K36/487, A61K36/484, A61K36/53, A61P17/00, A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

CZ patent database

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Epoque x-full; STN - Caplus, DWPI; Google scholar:
Liquorice, betulin, babchi, glycyrrhiza, rosmarinus, licorice, Psoralea, corylifolia, Betula, birch, rosemary, Herpes virus, HSV, anti-inflammation, acne, eczema, lupus, psoriasis, COX, LOX, cyclooxygenase, lipoxygenase, cannabidiol, cannabis, hemp, CBD, herbal;
Google; Scholar: Skalický Jiří, Cebadex

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CZ31563U U1 (SKALICKY JIRI [CZ]) 21.3.2018; whole document ----	1-3, 5, 8-12
X	DE202016106651U U1 (CEBADEX SE [CZ]) 2.3.2018 whole document ----	1-3, 5, 8-12

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14.12.2018	15 January 2019 (15.01.2019)
Name and mailing address of the ISA/ VISEGRAD PATENT INSTITUTE Branch Office CZ Antonína Čermáka 2a, 160 68 Praha Czech Republic Facsimile No.: +420 224 324 718	Authorized officer Ing. Hana Voříšková Telephone No. +420 220 383

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT	International application No. PCT/IB2018/001087

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017059088 A1 (HOAG GEORGE EDWARD [US]) 6.4.2017, Example 23, fig. 23; claims 39, 48, 51-55	1-3, 7-9, 12

X	WO 2016123475 A1 (CONSTANCE THERAPEUTICS INC [US]) 4.8.2016, paragraph 0003, 0116, 0150; claims 1, 20-27	1-12

Y	Izzo, Angelo A., et al. "Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb." Trends in pharmacological sciences 30.10 (2009): 515-527., ISSN: 0165-6147 table 1, p. 519-520, and page 523	1-12

Y	Saeedi, Muadhamm, K. Morteza-Semnani, and M-R. Ghoreishi. "The treatment of atopic dermatitis with licorice gel." Journal of Dermatological Treatment 14.3 (2003): 153-157., ISSN: 0954-6634 whole document	1-3, 6, 8, 9, 12

Y	Beena, Gidwani, et al. "Evaluation of a novel herbal formulation in the treatment of eczema with Psoralea Corylifolia." Iranian Journal of Dermatology 13.4 (2010): 122-127., ISSN: 0021-082X abstract	1-4, 8-12

Y	Alam, Fiaz, Gul Nawaz Khan, and Muhammad Hassham Hassan Bin Asad. "Psoralea corylifolia L: Ethnobotanical, biological, and chemical aspects: A review." Phytotherapy Research 32.4 (2018): 597-615., published on 15.12.2017, https://doi.org/10.1002/ptr.6006 Chapter 5, especially 5.1 to 5.3	1-4, 8-12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2018/001087

Box. No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. Claims: 4 (completely); 1-3, 8-12 (partially)
   Composition containing cannabidiol (CBD) or cannabis extract containing CBD and Psoralea Corylifolia extract
2. Claims: 5 (completely); 1-3, 8-12 (partially)
   Composition containing CBD or cannabis extract containing CBD and betulin
3. Claims: 6 (completely); 1-3, 8-12 (partially)
   Composition containing CBD or cannabis extract containing CBD and licorice extract
4. Claims: 7 (completely); 1-3, 8-12 (partially)
   Composition containing CBD or cannabis extract containing CBD and Rosmarinus Officinalis extract

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

CZ31563U U1 (2018-03-21)	none	
DE202016106651U U1 (2018-03-02)	none	
WO2017059088 A1 (2017-04-06)	CN108697665A	2018-10-23
	JP2018529736A	2018-10-11
	EP3355874A1	2018-08-08
	CA3000398A1	2017-04-06
	US2018344676A1	2018-11-01
	US2018311184A1	2018-06-12
WO2016123475 A1 (2016-08-04)	EP3250200A1	2017-11-06
	EP3250200A4	2018-09-19
	MX2017009846A	2018-04-11
	CA2974292A1	2016-08-04
	US2016346339A1	2016-12-01
	AU2016211314A1	2017-08-17