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Fig. 8

(57) Abstract: This disclosure is directed to compositions including a cannabinoid combination, a terpene combination, and a carrier, wherein the terpene combination includes β- caryophyllene, linalool, a-pinene and/or limonene, and wherein the terpene combination comprises about 3-30% by weight of the cannabinoid combination

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COMPOSITIONS AND METHODS FOR TREATMENT OF AUTISM SPECTRUM DISORDER

TECHNICAL FIELD

The present invention provides a composition comprising a cannabinoid combination and a terpene combination, and a method for treatment of autism spectrum disorder (ASD) by administration of said composition.

BACKGROUND ART

ASD is characterized by persistent challenges with social communication and social interaction, and by the presence of restricted, repetitive patterns of behavior, interests, or activities. These symptoms begin in early childhood and are expressed in almost all dimensions of the child's development. About 50% of the children and youth having ASD demonstrate self-injurious behavior (SIB) such as head-banging and self-biting, which has been found to correlate with intellectual disability.

No specific treatments are currently available and interventions are focusing on lessening of the disruptive behaviors, training, and teaching self-help skills for a greater independence.

Recently, CBD enriched cannabis has been shown to be beneficial for children with autism (Aran *et al.*, Cannabidiol based medical cannabis in children with autism - a retrospective feasibility study. *Neurology*, **2018**, 90). For instance, a study conducted by the Ben-Gurion University of the Negev and the Soroka University Medical Center, both in Israel, explored the connection between the use of medical cannabis and autism behavioral improvements in children with autism under the age of 18, and found cannabis to be a well-tolerated, safe and effective option to relieve symptoms including seizures, tics, depression, restlessness, and rage attacks.

According to said study, 188 ASD patients were treated with various medical cannabis products. The treatment in majority of the patients was based on cannabis oil containing 30% cannabidiol (CBD) and 1.5% Δ^9-tetrahydrocannabinol (Δ^9-THC). Symptoms, patient global assessment, and side effects after six months of treatment were assessed by structured questionnaires, and the results showed that about 80% of the

participants reported some level of improvement. Specifically, 30% of patients reported a significant improvement, 53.7% reported moderate improvement, and only 15% had slight improvement or no change.

The study mentioned above further explored the benefits of using cannabis on the life quality of patients with autism. For example, while good life quality, positive mood, and aspects of independence such as the ability to dress and shower independently, were reported by 31.3%, 42%, and 26.4% of the patients, respectively, prior to treatment initiation, these rates were remarkably improved to 66.8%, 63.5%, and 42.9% or the patients, respectively, after six months of treatment. As further shown, cannabis oil-based medication was able to significantly improve sleep and concentration to 24.7% and 14%, respectively, during an active treatment compared to 3.3% and 0% before treatment.

The exact mechanism of the cannabis effects in patients with ASD is not fully elucidated. Findings from ASD animal models indicate a possible dysregulation of the endocannabinoid system signaling behaviors, that was suggested to be also present in ASD patients. ASD is characterized by an excitation and inhibition imbalance of gamma-aminobutyric acid (GABA) and glutamate transmission regulation in different brain structures (Zamberletti *et al.*, The endocannabinoid system and autism spectrum disorders: insights from animal models. *International journal of molecular sciences*, **2017**, 18, 1916). The endocannabinoid system is involved in modulating imbalanced GABAergic (Piomelli, The molecular logic of endocannabinoid signaling. *Nature Reviews Neuroscience*, **2003**, 4, 873) and glutamatergic transmission (Colizzi *et al.*, Effect of cannabis on glutamate signaling in the brain: A systematic review of human and animal evidence. *Neuroscience & Biobehavioral Reviews*, **2016**, 64, 359-381).

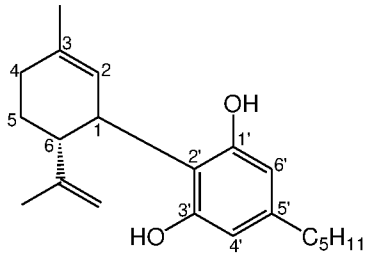
Other mechanisms of action can involve the neurotransmitters oxytocin and vasopressin, acting as important modulators of social behaviors (Meyer-Lindenberg *et al.*, Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. *Nature Reviews Neuroscience*, **2011**, 12, 524). Administration of oxytocin to patients with ASD has been shown to facilitate processing of social information, improve emotional recognition, strengthen social interactions, reduce repetitive behaviors and increase eye gaze. CBD was found to enhance oxytocin and vasopressin release during

activities involving social interaction. In addition, the two main active ingredients, THC and CBD, in the cannabis plant may have different psychoactive action mechanisms.

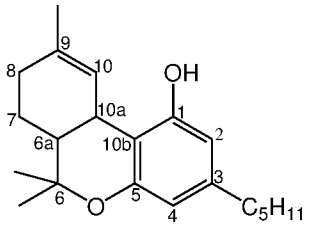
SUMMARY OF INVENTION

It has now been found, in accordance with the present invention, that a composition comprising a combination of purified cannabidiol (CBD) and Δ^9-tetrahydrocannabinol (THC) in a weight ratio of about 20:1, and a terpene combination comprising β-caryophyllene, linalool, α-pinene and limonene in a particular weight ratio, more specifically a composition referred to herein as "***Nitzan Spectrum composition***", was significantly more effective in limiting or attenuating co-morbid symptoms exhibited by children having ASD (e.g., hyperactivity, self-injury, social communication, and reaction to the flavor of the administered composition) than both a similar composition comprising a mixture of cannabis plant extracts as the CBD and THC sources, and a similar composition without said terpene combination, indicating that such a composition may be highly effective in treating children with ASD.

In one aspect, disclosed herein is a composition comprising a cannabinoid combination, a terpene combination, and a carrier, wherein said cannabinoid combination comprises of cannabidiol (CBD) or an enantiomer or diastereomer thereof in an, optionally partially or fully carboxylated at position 6' thereof, and Δ^9-tetrahydrocannabinol (Δ^9-THC; THC) or an enantiomer or diastereomer thereof, optionally partially or fully carboxylated at position 2 thereof (*see structures below*); and wherein said terpene combination consists of at least three terpenes selected from β-caryophyllene, linalool, α-pinene and limonene. According to some embodiment the CBD constitutes 5-30% by weight of the composition. According to some embodiment the THC constitutes 0.08-5.0% by weight of the composition. According to some embodiment, the CBD and the THC are present in a weight ratio of 20:1. According to some embodiment, the terpene combination comprises about 0.4-4.8% by weight of said composition. According to some embodiment, the terpene combination comprises about 3-30% or 3-20% by weight of said cannabinoid composition. Such compositions may be formulated as pharmaceutical or nutraceutical compositions, by optionally mixing with suitable one or more carriers and/or excipients.



CBD



THC

In another aspect, the present invention relates to a method for treatment of ASD in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a pharmaceutical composition according to any one of the embodiments above.

According to some embodiments, there is provided a composition comprising a cannabinoid combination, a terpene combination, and a carrier, wherein the cannabinoid combination comprises cannabidiol (CBD) or an enantiomer or diastereomer thereof, optionally partially or fully carboxylated at position 6' thereof, and Δ^9-tetrahydrocannabinol (Δ^9-THC) or an enantiomer or diastereomer thereof, optionally partially or fully carboxylated at position 2 thereof; wherein the terpene combination comprises at least three terpenes selected from β-caryophyllene, linalool, α-pinene and limonene, and wherein the terpene combination comprises about 3-30% by weight of the cannabinoid combination.

According to some embodiments, CBD constitutes 5-30% by weight of the cannabinoid combination.

According to some embodiments, the THC constitutes 0.08-3.0% by weight of the cannabinoid combination.

According to some embodiments, the CBD and the THC are present in a weight ratio of 20:1.

According to some embodiments, terpene combination constitutes about 0.4-4.8% by weight of said composition.

According to some embodiments, the cannabinoid combination consists of CBD and Δ^9-THC. According to some embodiments, cannabinoid combination consists of CBD in an amount of 5-27% by weight, and Δ^9-THC in an amount of 0.1-2.5% by weight.

According to some embodiments, the terpene combination comprises α-pinene, limonene, linalool, and β-caryophyllene. According to some embodiments, the terpene combination comprises β-caryophyllene, and at least two of α-pinene, limonene, and linalool. According to some embodiments, the terpene combination consists of α-pinene, limonene, linalool, and β-caryophyllene.

According to some embodiments, the β-caryophyllene constitutes about 50-90% by weight of the terpene combination. According to some embodiments, the linalool, when present, constitutes about 10-30% by weight of the terpene combination. According to some embodiments, each one of the α-pinene and limonene, when present, independently constitutes up to 5% by weight of the terpene combination.

According to some embodiments, the terpene combination comprises β-caryophyllene in an amount of about 70% of the terpene combination, linalool in an amount of about 20% of the terpene combination, α-pinene in an amount of up to 3% of the terpene combination, and limonene in an amount of up to 3% of the terpene combination.

According to some embodiments, the carrier is beeswax, honey, or a carrier oil. According to some embodiment, the carrier oil is selected from: a medium chain triglyceride (MCT), coconut oil, canola oil, olive oil, avocado oil, grapeseed oil, hempseed oil, sunflower oil, black seed oil, rosehip oil, argan oil, palm tree oil, and jojoba oil. Each possibility is a separate embodiment. According to some embodiments, the carrier oil is an MCT.

According to some embodiments, the composition further comprises at least one additional cannabinoid such as cannabidivarin (CBDV), cannabidivarinic acid (CBDVA), cannabidiphorol (CBDP), cannabidiol monomethyl ether (CBDM), cannabidiol-C4 (CBD-C4), cannabidiorcol (CBD-C1), Δ^9-tetrahydrocannabivarin (Δ^9-THCV), Δ^9-THCVA, Δ^8-THC, Δ^8-THCA, Δ^8-THCV, Δ^8-THCVA, Δ^9-tetrahydrocannabiphorol (Δ^9-THCP), iso-tetrahydrocannabinol-type (iso-THC), cannabinol (CBN), cannabinolic acid (CBNA), cannabinol-C4 (CBN-C4), cannabinol-C2 (CBN-C2), cannabiorcol (CBN-C1), cannabinol methyl ether (CBNM), cannabinodiol (CBND), cannabigerol (CBG), cannabigerovarin (CBGV), cannabigerolic acid (CBGA), cannabigerovarinic acid (CBGVA), cannabigerol monomethyl ether (CBGM), cannabigerolic acid monomethyl ether (CBGAM), cannabichromene (CBC), cannabichromenic acid (CBCA), cannabichromevarin (CBCV),

cannabichromevarinic acid (CBCVA), cannabichromanon (CBCN), cannabicyclol (CBL), cannabicyclolic acid (CBLA), cannabicyclovarin (CBLV), cannabivarin (CBV), cannabivarinic acid (CBVA), cannabielsoin (CBE), cannabielsoic acid A (CBEA-A), cannabielsoic acid B (CBEA-B), cannabitriol (CBT), cannabitriolvarin (CBTV), ethoxy-cannabitiolvarin (CBTVE), cannabifuran (CBF), dehydrocannabifuran (DCBF), cannabiripsol (CBR), or an enantiomer, diastereomer, racemate, or a salt thereof. Each possibility is a separate embodiment.

According to some embodiments, the at least one additional cannabinoid constitutes up to 5% by weight of the composition.

According to some embodiments, the composition is formulated as an emulsion, e.g., an oil-in edible solvent emulsion.

According to some embodiments, at least one of the CBD, the THC, the β-caryophyllene, the linalool, the α-pinene or the limonene is in a form of synthetic, purified, extracted or isolated molecules.

According to some embodiments, the composition is a pharmaceutical or a nutraceutical composition. According to some embodiments, the pharmaceutical composition is formulated for oral, buccal or sublingual administration, or for inhalation (e.g., vaporization). According to some embodiments, the pharmaceutical composition is formulated as a liquid dosage form, such as a solution, syrup and elixir; or as a solid dosage form such as a tablet, capsule, and pill. Each possibility is a separate embodiment. According to some embodiments, the nutraceutical composition is formulated as a food supplement, drink or beverage.

According to some embodiments, the composition is for use in the treatment of autism spectrum disorder (ASD).

According to some embodiments, the composition is suitable for use for reducing hyperactivity symptoms, reducing self-injury behavior, improving sleeping, and/or improving social communication in a suffering from autism spectrum disorder (ASD).

According to some embodiments, there is provided a method for treatment of autism spectrum disorder (ASD) in a subject in need thereof, the method comprising

administering to said subject a therapeutically effective amount of the herein disclosed composition.

Certain embodiments of the present disclosure may include some, all, or none of the above advantages. One or more technical advantages may be readily apparent to those skilled in the art from the figures, descriptions and claims included herein. Moreover, while specific advantages have been enumerated above, various embodiments may include all, some or none of the enumerated advantages.

In addition to the exemplary aspects and embodiments described above, further aspects and embodiments will become apparent by reference to the figures and by study of the following detailed descriptions.

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 shows the hyperactivity symptoms (e.g., how much calm the kid was, the rate of hyper events and duration thereof, and how easy was it to get the kid out of the event) in the participating kids. The Y axis shows the satisfaction level (scored by parents from 0-10; 10 being the highest positive score) and the X axis refers to the duration of testing (in weeks).

Fig. 2 shows the symptom of self-injury (e.g., self-harming, knocking the head in the wall, scratching the arms). The Y axis shows the satisfaction level (scored by parents from 0-10; 10 being the highest positive score) and the X axis refers to the duration of testing (in weeks).

Fig. 3 shows how much the sleeping problems (e.g., getting to sleep, waking at night, and disturbed sleeping) were improved during the trial time. The Y axis shows the satisfaction level (scored by parents from 0-10; 10 being the highest positive score) and the X axis refers to the duration of testing (in weeks).

Fig. 4 shows the improvement in social communications (e.g., making eye contact with the caretaker, reaction to physical contact, pronouncing the needs in words or gestures)

during the trial time. The Y axis shows the satisfaction level (scored by parents from 0-10; 10 being the highest positive score) and the X axis refers to the duration of testing (in weeks).

Fig. 5 shows the reaction to the taste of the medicine. The graph shows the improvement, according to the parents, in taking the medicine during the trial time. The Y axis shows the satisfaction level (scored by parents from 0-10; 10 being the highest positive score) and the X axis refers to the duration of testing (in weeks).

Fig. 6 shows the average of all the criterions tested in Figs. 1-5 (hyperactivity symptoms, self-injury, sleeping problems, social communication, and flavor improvement) according to a parent's report.

Fig. 7 shows ADOS social affect (SA), restricted and repetitive behaviors (RRB), total raw score, and calibrated severity score (CSS).

Fig. 8 shows Vineland total score and Socialization, Daily living and Communication subscale scores.

Fig. 9 shows efficacy data validated ASD questionnaires and analyzed in order to demonstrate the efficacy of Nitzan Spectrum in ASD population.

DETAILED DESCRIPTION

In one aspect, the present invention provides a composition comprising a cannabinoid combination, a terpene combination, and a carrier, wherein said cannabinoid combination consists of CBD or an enantiomer or diastereomer thereof, optionally partially or fully carboxylated at position 6' thereof, and THC or an enantiomer or diastereomer thereof, optionally partially or fully carboxylated at position 2 thereof; and wherein said terpene combination consists of at least three terpenes selected from β-caryophyllene, linalool, α-pinene and limonene. According to some embodiments, the CBD and the THC are present in a weight ratio of 20:1. According to some embodiment the CBD constitutes 5-30% by weight of the composition. According to some embodiment the THC constitutes 0.08-5.0% by weight of the composition. According to some embodiment the terpene combination comprises constitutes about 0.4-4.8% by weight of said composition.

According to some embodiment, the terpene combination comprises about 3-30%, 3-20%, 3-15%, 5-20% or 7-15% by weight of said cannabinoid composition. Each possibility is a separate embodiment.

The term "cannabinoid" as used herein refers to a chemical compound acting on cannabinoid receptors, i.e., a cannabinoid type 1 (CB1) and/or cannabinoid type 2 (CB2) receptor and/or the G protein-coupled receptor GPR55 and/or the N-arachidonoyl glycine (NAGly) receptor GPR18 and/or GPR119 and/or the PPAR family of nuclear hormone receptors . Ligands for these receptor proteins include the endocannabinoids produced naturally in the body; the phytocannabinoids found in *Cannabis sativa*, *Cannabis indica*, *Cannabis ruderalis*, and some other plants; and synthetic cannabinoids.

According to some embodiments, at least one of the CBD, the THC, the β-caryophyllene, the linalool, the α-pinene or the limonene is in a form of synthetic, extracted, isolated, or purified molecule.

As used herein, the term "synthetic" refers to a chemically synthesized molecule. As used herein, the term "extracted" refer to a molecule extracted from a natural source and added to the mixture. As a non-limiting example, an extracted terpene may also include additional components (e.g., additional terpenes), which are added to the composition, but which are not part of the plant/extract from which the cannabinoid combination. As used herein, the term "isolated" refers to a molecule which is extracted from a natural resource, so as to become the major component, but may also include smaller amounts of other component. As a non-limiting example, isolated linalool refers to an extract containing mostly linalool, e.g., at least 60%, at least 70% at least 80% or at least 90% linalool or at least 98% linalool. Each possibility is a separate embodiment. As used herein, the term "purified" refers to a molecule which is isolated from a natural resource, and purified so as to become the essentially only component, i.e., other component are present in residual amounts only. As a non-limiting example, purified α-pinene refers to an extract containing essentially only α-pinene, e.g., less than 90% or less than 95% or less than 98% of other components. Each possibility is a separate embodiment.

The composition disclosed herein comprises a cannabinoid combination and a terpene combination, also referred to herein together as "***the active agent combination***".

According to the invention, each one of the active agents comprised within the composition, i.e., each one of the cannabinoids and each one of the terpenes, can independently be either naturally produced and optionally purified, or synthetic. For the sake of simplicity, and if not otherwise explicitly specified, all references made throughout this specification to CBD refer to an enantiomer or diastereomer thereof as well, and all references made to THC also refer to an enantiomer or diastereomer thereof.

The composition disclosed herein comprises a cannabinoid combination consisting of CBD and THC, wherein the amount of each one of said cannabinoids is within the particular range disclosed, and the ratio between said CBD and THC thus ranges, e.g., between 100:1 to 6:1, 80:1 to 8:1, 60:1 to 10:1, 40:1 to 15:1, or 25:1 to 16:1, respectively. In particular embodiments, the amounts of said cannabinoids are determined such that the ratio between the CBD and THC ranges from about 24:1 to 18:1, e.g., about 22:1, 21:1, 20:1, 19:1, or 18:1, respectively.

Yet, it should be understood that some and even all of either or both the CBD and THC may exist as the carboxylated form thereof, i.e., as cannabidiolic acid (CBDA), or an enantiomer or diastereomer thereof; or Δ^9-tetrahydrocannabinolic acid (Δ^9-THCA), or an enantiomer or diastereomer thereof, Δ^8-tetrahydrocannabinolic acid (Δ^8-THCA), or an enantiomer or diastereomer thereof respectively (for the sake of simplicity, all references made herein to CBDA refer to an enantiomer or diastereomer thereof as well, and all references made to THCA also refer to an enantiomer or diastereomer thereof). In other words, the CBD comprised within the composition of the present invention may be partially or fully replaced with an equivalent molar amount of CBDA, and/or the THC comprised within said composition may be partially or fully replaced with an equivalent molar amount of THCA.

The terms "partially carboxylated" and "fully carboxylated" as used herein with respect to one or both of the cannabinoids comprised within the composition of the invention means that either a partial or full amount of said cannabinoid is carboxylated, i.e., present in the acidic form thereof. The term "equivalent molar amount" as used herein means that the amount of each one of CBDA and/or THCA, when present in the composition, is equivalent in moles to the amount of CBD and/or THC replaced by said CBDA and/or THCA, respectively. According to some embodiments the overall amount of CBD in the

composition, i.e., the amount of CBD present plus the amount of CBD obtainable by decarboxylation of said CBDA, when present, is 2-30%, 5-20% or 6-15% by weight. Each possibility is a separate embodiment. According to some embodiments, the overall amount of THC in the composition, i.e., the amount of THC present plus the amount of THC obtainable by decarboxylation of said THCA, when present, is 0.08-3.0%, 0.1-2% or 0.3-1% by weight. Each possibility is a separate embodiment.

In certain embodiments, the cannabinoid combination comprised within the composition of the invention consists of CBD and THC.

In other embodiments, the CBD is partially replaced by the carboxylated form thereof, i.e., said cannabinoid combination consists of CBD; CBDA; and THC. According to some embodiments, the amount of CBD present and the amount of CBD obtainable by decarboxylation of said CBDA sum up to 2-30%, 5-20% or 6-15% by weight. Each possibility is a separate embodiment.

In further embodiments, the CBD is fully replaced by the carboxylated form thereof, i.e., said cannabinoid combination consists of CBDA; and THC, wherein the amount of CBD obtainable by decarboxylation of said CBDA is 2-30%, 5-20% or 6-15% by weight. Each possibility is a separate embodiment.

In still other embodiments, the THC is partially replaced by the carboxylated form thereof, i.e., said cannabinoid combination consists of CBD; THC; and THCA, wherein the amount of THC present and the amount of THC obtainable by decarboxylation of said THCA sum up to 0.08-3.0%, 0.1-2% or 0.3-1% by weight.

In still further embodiments, the THC is fully replaced by the carboxylated form thereof, i.e., said cannabinoid combination consists of CBD; and THCA, wherein the amount of THC obtainable by decarboxylation of said THCA is 0.08-3.0%, 0.1-2% or 0.3-1% by weight. Each possibility is a separate embodiment.

In yet other embodiments, each one of the CBD and the THC is partially replaced by the carboxylated form thereof, i.e., said cannabinoid combination consists of CBD; CBDA; THC; and THCA, wherein the amount of CBD present and the amount of CBD obtainable by decarboxylation of said CBDA sum up to 12-30% by weight; and the amount

of THC present and the amount of THC obtainable by decarboxylation of said THCA sum up to 0.08-3.0%, 0.1-2% or 0.3-1% by weight. Each possibility is a separate embodiment.

In yet further embodiments, each one of the CBD and the THC is fully replaced by the carboxylated form thereof, i.e., said cannabinoid combination comprised within the composition of invention consists of CBDA; and THCA, wherein the amount of CBD obtainable by decarboxylation of said CBDA sum up to 2-30%, 5-20% or 6-15% by weight; and the amount of THC obtainable by decarboxylation of said THCA sum up to 0.08-3.0%, 0.1-2% or 0.3-1% by weight. Each possibility is a separate embodiment.

In certain embodiments, the cannabinoid combination comprised within the composition of the present invention consists of CBD, i.e., 2-[(1*R*,6*R*)-6-isopropenyl-3-methylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol, optionally partially or fully carboxylated at position 6' thereof; and THC, i.e., (6a*R*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromen-1-ol, optionally partially or fully carboxylated at position 2 thereof. In particular such embodiments, said cannabinoid combination consists of (i) CBD and THC only; (ii) a mixture of CBD and CBDA, and THC; (iii) CBD, and a mixture of THC and THCA; or (iv) a mixture of CBD and CBDA, and a mixture of THC and THCA, wherein the molar ratio between the CBD and CBDA, when both present, and the molar ratio between the THC and THCA, when both present, each independently is in a range of, e.g., about 100:1, 90:1, 80:1, 70:1, 60:1, 50:1, 40:1, 30:1, 20:1, 18:1, 16:1, 14:1, 12:1, 10:1, 9:1, 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, 2:1, 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:12, 1:14, 1:16, 1:18, 1:20, 1:30, 1:40, 1:50, 1:60, 1:70, 1:80, 1:90, or 1:100, respectively. In more particular such compositions, the overall amount of CBD is about 2-30%, 5-15% 12-30%, e.g., about 15-27%, about 17-23%, or about 20%, by weight, and the overall amount of THC is about 0.08-3%, about 0.1-2.5%, about 0.5-2%, or about 1-1.5%, by weight.

The term "terpene" as used herein refers to a hydrocarbon produced by a variety of plants and by some insects. Terpenes often have a strong odor, and may protect the plants producing them by deterring herbivores and by attracting predators and parasites of herbivores. Terpenes are also major biosynthetic building blocks. Steroids, for example, are derivatives of the triterpene squalene. The term "terpenoid" (also referred to as isoprenoid) as used herein refers to a modified terpene containing a functional group, usually an oxygen-containing group. As stated above, the terpenes comprised within the composition of the

invention may independently be either naturally produced and optionally purified, or synthetic.

Terpenes and terpenoids are the primary constituents of the essential oils of many types of plants and flowers. Essential oils are used widely as fragrances in perfumery and traditional medicine, such as aromatherapy. Synthetic variations and derivatives of natural terpenes and terpenoids also greatly expand the variety of aromas used in perfumery and flavors used in food additives.

Monoterpenes are a class of terpenes consisting of two isoprene units and having the molecular formula $C_{10}H_{16}$. Monoterpenes may be linear (acyclic) or contain rings (cyclic). Modified terpenes, such as those containing oxygen functionality or missing a methyl group, are called monoterpenoids. Monoterpenes and monoterpenoids are used in the pharmaceutical, cosmetic, agricultural, and food industries.

Sesquiterpenes are a class of terpenes consisting of three isoprene units and often have the molecular formula $C_{15}H_{24}$. Like monoterpenes, sesquiterpenes may be acyclic or contain rings, including many unique combinations. Biochemical modifications such as oxidation or rearrangement produce the related sesquiterpenoids.

Non-limiting examples of monoterpenes or monoterpenoids comprised within the terpene combination of the invention include a pinene selected from α-pinene, β-pinene, and γ-pinene, limonene, linalool, myrcene, camphene, nerol, geraniol, a terpineol selected from α-terpineol, β-terpineol, γ-terpineol, and terpinen-4-ol, or an enantiomer or diastereomer thereof; and non-limiting examples of sesquiterpene or sesquiterpenoid comprised within the terpene combination of the invention include longifolene, copaene, patchoulol, farnesol, humulene, farnesene, β-caryophyllene, or an enantiomer or diastereomer thereof.

In certain embodiments, the terpene combination comprised within the composition of the invention consists of at least three of α-pinene or an enantiomer thereof, limonene or an enantiomer thereof, linalool or an enantiomer thereof, and β-caryophyllene or an enantiomer or diastereomer thereof, e.g., α-pinene, limonene, and linalool; α-pinene, limonene, and β-caryophyllene; α-pinene, linalool, and β-caryophyllene; limonene, linalool, and β-caryophyllene; or α-pinene, limonene, linalool, and β-caryophyllene.

In particular such embodiments, the terpene combination comprised within the composition of the invention consists of β-caryophyllene, and at least two of α-pinene, limonene, and linalool. In particular such embodiments, the β-caryophyllene constitutes about 50-90%, e.g., about 60-80%, or about 70%, by weight of said terpene combination; the linalool, when present, constitutes about 10-30%, e.g., about 15-25%, or about 20%, by weight of said terpene combination; and each one of the α-pinene and limonene, when present, independently constitutes up to 5%, e.g., about 0.1-4%, 0.5-3.5%, or less than 3%, by weight of said terpene combination. More partiuclar such terpene combinations are those consisting of β-caryophyllene, linalool, and α-pinene; β-caryophyllene, linalool, and limonene; β-caryophyllene, α-pinene, and limonene; or β-caryophyllene, linalool, α-pinene, and limonene. Specific such terpene combinations consist of β-caryophyllene in an amount of about 70% of said terpene combination, linalool in an amount of about 20% of said terpene combination, α-pinene in an amount of up to 3% of said terpene combination, and limonene in an amount of up to 3% of said terpene combination.

The composition disclosed herein comprises, in addition to said cannabinoid and terpene combinations, a carrier. In certain embodiments, said carrier is beeswax or honey. In other embodiments, the carrier is a carrier oil, i.e., a vegetable oil (also known as base oil) derived from the fatty portion (usually from the seeds, kernels, or nuts) of a plant. Non-limiting examples of carrier oils include a medium chain triglyceride (MCT), coconut oil, canola oil, olive oil, avocado oil, grapeseed oil, hempseed oil, sunflower oil, black seed oil, rosehip oil, argan oil, palm tree oil, and jojoba oil. In particular such embodiments, the carrier oil comprised within the composition of the invention is an MCT. According to some embodiments, the carrier oil comprises olive oil. According to some embodiments, the carrier oil comprises an MCT alone or in combination with an oil, such as but not limited to olive oil.

Medium chain triglycerides (MCTs) are triglycerides with two or three medium chain fatty acids, i.e., fatty acids having an aliphatic tail of 6-12 carbon atoms such as hexanoic acid, octanoic acid, decanoid acid, and dodecanoic acid. MCTs are found in palm kernel oil and coconut oil, and may be separated by fractionation. Alternatively, they may be produced by, e.g., interesterification, i.e., a process that rearranges the fatty acids of a fat product.

In certain embodiments, the composition disclosed herein comprises a cannabinoid combination comprising CBD, i.e., 2-[(1*R*,6*R*)-6-isopropenyl-3-methylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol, optionally partially or fully carboxylated at position 6' thereof, and THC, i.e., (6a*R*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromen-1-ol, optionally partially or fully carboxylated at position 2 thereof, according to any one of the embodiments above; a terpene combination consisting of at least three of α-pinene, limonene, linalool, and β-caryophyllene; and MCT as a carrier oil. Particular such compositions comprise a trerpene combination consisting of α-pinene, limonene, and linalool; α-pinene, limonene, and β-caryophyllene; α-pinene, linalool, and β-caryophyllene; limonene, linalool, and β-caryophyllene; or α-pinene, limonene, linalool, and β-caryophyllene.

In particular such embodiments, said cannabinoid combination comprising CBD optionally partially or fully carboxylated at position 6' thereof, in an amount of about 2-30%, 5-15%, 15-27%, about 17-23%, or about 20%, by weight, and THC optionally partially or fully carboxylated at position 2 thereof, in an amount of about 0.1-2.5%, about 0.5-2%, or about 1-1.5%, by weight; and said terpene combination consists of β-caryophyllene, and at least two of α-pinene, limonene, and linalool, wherein the β-caryophyllene constitutes about 50-90% by weight of said terpene combination; the linalool, when present, constitutes about 10-30% by weight of said terpene combination; and each one of the α-pinene and limonene, when present, independently constitutes up to 5% by weight of said terpene combination. More particular such embodiments are those wherein said terpene combination consists of β-caryophyllene in an amount of about 70% of said terpene combination, linalool in an amount of about 20% of said terpene combination, and α-pinene and limonene, each in an amount of up to 3% of said terpene combination.

In certain embodiments, the composition of the invention, according to any one of the embodiments above, further comprises at least one additional cannabinoid, i.e., one, two, three, four, or more cannabinoids in addition to the CBD (and/or CBDA) and THC (and/or THCA) present. Examples of such cannabinoids include, without being limited to, cannabidivarin (CBDV), cannabidivarinic acid (CBDVA), cannabidiphorol (CBDP), cannabidiol monomethyl ether (CBDM), cannabidiol-C4 (CBD-C4), cannabidiorcol (CBD-C1), Δ^9-tetrahydrocannabivarin (Δ^9-THCV), Δ^9-THCVA, Δ^8-THC, Δ^8-THCA, Δ^8-THCV,

Δ^8-THCVA, cannabidiphorol (CBDP), iso-tetrahydrocannabinol-type (iso-THC), cannabinol (CBN), cannabinolic acid (CBNA), cannabinol-C4 (CBN-C4), cannabinol-C2 (CBN-C2), cannabiorcol (CBN-C1), cannabinol methyl ether (CBNM), cannabinodiol (CBND), cannabigerol (CBG), cannabigerovarin (CBGV), cannabigerolic acid (CBGA), cannabigerovarinic acid (CBGVA), cannabigerol monomethyl ether (CBGM), cannabigerolic acid monomethyl ether (CBGAM), cannabichromene (CBC), cannabichromenic acid (CBCA), cannabichromevarin (CBCV), cannabichromevarinic acid (CBCVA), cannabichromanon (CBCN), cannabicyclol (CBL), cannabicyclolic acid (CBLA), cannabicyclovarin (CBLV), cannabivarin (CBV), cannabivarinic acid (CBVA), cannabielsoin (CBE), cannabielsoic acid A (CBEA-A), cannabielsoic acid B (CBEA-B), cannabitriol (CBT), cannabitriolvarin (CBTV), ethoxy-cannabitiolvarin (CBTVE), cannabifuran (CBF), dehydrocannabifuran (DCBF), cannabiripsol (CBR), or an enantiomer, diastereomer, racemate, or a salt thereof. In particular such embodiments, said at least one additional cannabinoid constitutes up to 2.5% by weight of said composition, i.e., the overall amount of said additional cannabinoids sum up to not more than 5% by weight of said composition.

Each one of the cannabinoids comprised within the composition of the present invention, i.e., either or both of the CBD (when fully or partially present as CBDA) and THC (when fully or partially present as THCA), as well as any one of the additional cannabinoids when present, may be present in a salt, e.g., a pharmaceutically acceptable salt, form.

Suitable pharmaceutically acceptable salts include salts of ammonium (NH_4^+) or an organic cation derived from an amine of the formula R_4N^+, wherein each one of the Rs independently is selected from H, C_1-C_{22}, preferably C_1-C_6 alkyl, such as methyl, ethyl, propyl, isopropyl, *n*-butyl, sec-butyl, isobutyl, *tert*-butyl, *n*-pentyl, 2,2-dimethylpropyl, *n*-hexyl, and the like, phenyl, or heteroaryl such as pyridyl, imidazolyl, pyrimidinyl, and the like, or two of the Rs together with the nitrogen atom to which they are attached form a 3-7 membered ring optionally containing a further heteroatom selected from N, S and O, such as pyrrolydine, piperidine and morpholine. Additional suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g., lithium, sodium or potassium salts, and alkaline earth metal salts, e.g., calcium or magnesium salts.

Further pharmaceutically acceptable salts include salts of a cationic lipid or a mixture of cationic lipids. Cationic lipids are often mixed with neutral lipids prior to use as delivery agents. Neutral lipids include, but are not limited to, lecithins; phosphatidylethanolamine; diacyl phosphatidylethanolamines such as dioleoyl phosphatidylethanolamine, dipalmitoyl phosphatidylethanolamine, palmitoyloleoyl phosphatidylethanolamine and distearoyl phosphatidylethanolamine; phosphatidylcholine; diacyl phosphatidylcholines such as dioleoyl phosphatidylcholine, dipalmitoyl phosphatidylcholine, palmitoyloleoyl phosphatidylcholine and distearoyl phosphatidylcholine; phosphatidylglycerol; diacyl phosphatidylglycerols such as dioleoyl phosphatidylglycerol, dipalmitoyl phosphatidylglycerol and distearoyl phosphatidylglycerol; phosphatidylserine; diacyl phosphatidylserines such as dioleoyl- or dipalmitoyl phosphatidylserine; and diphosphatidylglycerols; fatty acid esters; glycerol esters; sphingolipids; cardiolipin; cerebrosides; ceramides; and mixtures thereof. Neutral lipids also include cholesterol and other 3β hydroxy-sterols.

Examples of cationic lipid compounds include, without being limited to, Lipofectin® (Life Technologies, Burlington, Ontario) (1:1 (*w/w*) formulation of the cationic lipid N-[1-(2,3-dioleyloxy)propyl]-N,N,N-trimethylammonium chloride and dioleoylphosphatidyl-ethanolamine); Lipofectamine™ (Life Technologies, Burlington, Ontario) (3:1 (*w/w*) formulation of polycationic lipid 2,3-dioleyloxy-N-[2(spermine-carboxamido)ethyl]-N,N-dimethyl-1-propanamin-iumtrifluoroacetate and dioleoylphosphatidyl-ethanolamine), Lipofectamine Plus (Life Technologies, Burlington, Ontario) (Lipofectamine and Plus reagent), Lipofectamine 2000 (Life Technologies, Burlington, Ontario) (Cationic lipid), Effectene (Qiagen, Mississauga, Ontario) (Non liposomal lipid formulation), Metafectene (Biontex, Munich, Germany) (Polycationic lipid), Eu-fectins (Promega Biosciences, San Luis Obispo, Calif.) (ethanolic cationic lipids numbers 1 through 12: $C_{52}H_{106}N_6O_4 \cdot 4CF_3CO_2H$, $C_{88}H_{178}N_8O_4S_2 \cdot 4CF_3CO_2H$, $C_{40}H_{84}NO_3P \cdot CF_3CO_2H$, $C_{50}H_{103}N_7O_3 \cdot 4CF_3CO_2H$, $C_{55}H_{116}N_8O_2 \cdot 6CF_3CO_2H$, $C_{49}H_{102}N_6O_3 \cdot 4CF_3CO_2H$, $C_{44}H_{89}N_5O_3 \cdot 2CF_3CO_2H$, $C_{100}H_{206}N_{12}O_4S_2 \cdot 8CF_3CO_2H$, $C_{162}H_{330}N_{22}O_9 \cdot 13CF_3CO_2H$, $C_{43}H_{88}N_4O_2 \cdot 2CF_3CO_2H$, $C_{43}H_{88}N_4O_3 \cdot 2CF_3CO_2H$, $C_{41}H_{78}NO_8P$); Cytofectene (Bio-Rad, Hercules, Calif.) (mixture of a cationic lipid and a neutral lipid), GenePORTER® (Gene Therapy Systems, San Diego, Calif.) (formulation of

a neutral lipid (Dope) and a cationic lipid) and FuGENE 6 (Roche Molecular Biochemicals, Indianapolis, Ind.) (Multi-component lipid based non-liposomal reagent).

Pharmaceutically acceptable salts of cannabinoids for use in the composition disclosed herein may be formed by conventional means, e.g., by reacting a free carboxylic acid-containing cannabinoid with one or more equivalents of an appropriate base in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is then removed *in vacuo* or by freeze drying, or by exchanging the cation of an existing salt for another cation on a suitable ion exchange resin.

In certain embodiments, the composition disclosed herein, according to any one of the embodiments above, consists essentially of a carrier as defined above, e.g., beeswax, honey, or a carrier oil such as MCT; and a cannabis plant extract, e.g., an extract obtained from the species *Cannabis sativa*, *Cannabis indica*, or *Cannabis ruderalis*, or from a hybrid cannabis strain, i.e., a mix (hybrid) of two classes of cannabis such as *Cannabis sativa*, *Cannabis indica*, a fraction thereof, or a combination thereof. Such extracts may be obtained by any method or technique known in the art, and from any part of the plant but preferably from the flowering. Particular such compositions exemplified herein essentially consist of mixtures of extracts obtained from *Cannabis TIL Tachllta* (Israel Plant Breeders' Rights Application No. 4837/19, filed 16.07.2019) and *Cannabis ZIV Sparkling Light* (Israel Plant Breeders' Rights Application No. 4852/19, filed 21.08.2019) (Israel Plant Breeders' Rights Gazette No. 94, July 1, 2019-December 31, 2019).

In other embodiments, the composition of the present invention, according to any one of the embodiments above, comprises a cannabinoid combination, a terpene combination, and optionally further one or more cannabinoids, wherein each one of the cannabinoids and terpenes composing said composition, or at least the majority thereof, is either synthetic or purified.

The term "consisting/consist essentially of" as used herein with respect to the disclosed composition means that all the components of said composition except for the carrier oil, i.e., the CBD (and/or CBDA) and THC (and/or THCA) constituting the cannabinoid combination, the terpenes constituting the terpene combination, as well as one or more of the additional cannabinoids optionally present, or at least the majority of said

components, each in the required weight percent thereof, are derived from a cannabis plant extract, a fraction thereof, or a combination thereof. Yet, it should be clear that compositions which are based on a cannabis plant extract (or fraction or combination thereof) may be enriched with purified and/or synthetic components so as to, e.g., increase the weight percentage of one or more of the cannabinoids and/or terpenes present in said extract (or fraction or combination thereof), or add one or more cannabinoid and/or terpene not present in said extract (or fraction or combination thereof).

In certain embodiments, the composition disclosed herein, according to any one of the embodiments above, is formulated as an emulsion, more particularly an oil-in-edible solvent emulsion. The term "edible solvent" as used herein means a solvent that is safe for human consumption, i.e., edible by human. Edible solvents may be polar or non-polar, and include water, as well as any edible organic solvent such as alcohols including ethanol (ethyl alcohol), propylene glycol (propane-1,2-diol), 1,3-butylene glycol, and glycerol (glycerine), diethyl ether (ether), vinegar (an aqueous solution of actic acid), and the like.

Particular such compositions may comprise a carrier oil as defined above, e.g., an MCT, coconut oil, canola oil, olive oil, avocado oil, grapeseed oil, hempseed oil, sunflower oil, black seed oil, rosehip oil, argan oil, palm tree oil, or jojoba oil, and be formulated as, e.g., an oil-in-water or oil-in-alcohol emulsions. Other compositions may be based on the the active agent combination, emulsified in either water or an edible alcohol using a surfactant (surface active substance), i.e., a compound that lowers the surface tension of a liquid, the interfacial tension between two liquids, or that between a liquid and a solid; and/or an emulsifier (also referred to as "emulgent"), i.e., a substance that stabilizes an emulsion by increasing its kinetic stability, e.g., a "surface active substance". Non-limiting examples of suitable surfactants include polysorbate surfactants such as Tween-80, Tween-60, Tween-40, Tween-20, Tween-65 and Tween-85, and sorbitane surfactants such as Span 20, Span 40, Span 60, Span 80 and Span 85. Particular such compositions, when formulated as an emulsion, comprises Tween-80 as a surface active substance.

Each one of the cannabinoids and terpenes comprised within the composition of the present invention may be derived from a cannabis extract, using any suitable extraction and purification procedures known in the art, or alternatively may be synthesized following any one of the procedures disclosed in the literature. For instance, CBD may be synthesized

following any one of the procedures known in the art, e.g., by acid condensation of *p*-mentha-2,8-dien-1-ol with olivetol. Optically active forms of CBD may be prepared using any one of the methods disclosed in the art, e.g., by resolution of the racemic form by recrystallization techniques; chiral synthesis; extraction with chiral solvents; or chromatographic separation using a chiral stationary phase. A non-limiting example of a method for obtaining optically active materials is transport across chiral membranes, i.e., a technique whereby a racemate is placed in contact with a thin membrane barrier, the concentration or pressure differential causes preferential transport across the membrane barrier, and separation occurs as a result of the non-racemic chiral nature of the membrane that allows only one enantiomer of the racemate to pass through. Chiral chromatography, including simulated moving bed chromatography, can also be used. A wide variety of chiral stationary phases are commercially available.

The compositions disclosed herein may be formulated as pharmaceutical compositions or nutraceutical compositions, optionally mixed with one or more suitable carriers and/or excipients.

In one particular such aspect, the composition of the present invention as defined in any one of the embodiments above is in a form of a pharmaceutical composition, i.e., the carrier comprised within said composition is a pharmaceutically acceptable carrier or pharmaceutically acceptable excipient.

The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" as used herein interchangeably refers to any and all solvents, dispersion media, preservatives, antioxidants, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. According to the present invention, the pharmaceutically acceptable carrier may further comprise ingredients aimed at enhancing the activity of the active agents, i.e., the cannabinoid combination and/or the terpene combination, or modulating the bioavailability thereof.

The term "acceptable" with respect to the pharmaceutically acceptable carrier denotes a carrier, excipient, or non-active ingredient that does not produce an adverse, allergic, or other untoward reaction when administered to a mammal or human as appropriate. For human administration, compositions should meet sterility, pyrogenicity,

and general safety and purity standards as required by, e.g., the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), the Therapeutic Goods Administration (Australia), the Medicines and Healthcare products Regulatory Agency (United Kigdom), or the Pharmaceuticals and Medical Devices Agency (Japan).

The pharmaceutical composition disclosed herein may be prepared by conventional techniques, e.g., as described in Remington: The Science and Practice of Pharmacy, 19th Ed., 1995. The compositions can be prepared, e.g., by uniformly and intimately bringing the active agents into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product into the desired formulation. The compositions may be formulated as a liquid dosage form, e.g., solution, emulsion, suspension, syrup, or elixir; or as a solid dosage form, e.g., a tablet, capsule, and pill, and may further include pharmaceutically acceptable fillers, carriers, diluents or adjuvants, and other inert ingredients and excipients. Preferred are compositions formulated as liquid dosage forms.

The pharmaceutical composition of the present invention may be formulated for any suitable route of administration, e.g., for oral, buccal, sublingual, or parenteral, e.g., intravenous, intraarterial, intramuscular, intraperitoneal, intrathecal, intrapleural, intratracheal, subcutaneous, or topical, administration, as well as for inhalation, e.g., cold or hot vaporization, but is preferably formulated for oral or sublingual administration, or for inhalation.

The pharmaceutical compositions of the invention, when formulated for oral administration, may be in any suitable form, e.g., tablets, troches, lozenges, aqueous, or oily suspensions, dispersible powders or granules, emulsions, solutions, hard or soft capsules, or syrups or elixirs. In certain embodiments, said tablets are in the form of matrix tablets in which the release of a soluble active is controlled by having the active diffuse through a gel formed after the swelling of a hydrophilic polymer brought into contact with dissolving liquid (*in vitro*) or gastro-intestinal fluid (*in vivo*). Many polymers have been described as capable of forming such gel, e.g., derivatives of cellulose, in particular the cellulose ethers such as hydroxypropyl cellulose, hydroxymethyl cellulose, methylcellulose or methyl hydroxypropyl cellulose, and among the different commercial grades of these ethers are those showing fairly high viscosity. In other embodiments, the tablets are formulated as bi- or multi-layer tablets, made up of two or more distinct layers of granulation compressed

together with the individual layers lying one on top of another, with each separate layer containing a different active agent. Bilayer tablets have the appearance of a sandwich since the edge of each layer or zone is exposed.

Pharmaceutical compositions for oral administration might be formulated so as to inhibit the release of one or both of the active agents, i.e., the cannabinoid combination and/or the terpene combination, in the stomach, i.e., delay the release of one or both of the active agents until at least a portion of the dosage form has traversed the stomach, in order to avoid the acidity of the gastric contents from hydrolyzing the active agent. Particular such compositions are those wherein the active agent is coated by a pH-dependent enteric-coating polymer. Examples of pH-dependent enteric-coating polymer include, without being limited to, Eudragit® S (poly(methacrylicacid, methylmethacrylate), 1:2), Eudragit® L 55 (poly (methacrylicacid, ethylacrylate), 1:1), Kollicoat® (poly(methacrylicacid, ethylacrylate), 1:1), hydroxypropyl methylcellulose phthalate (HPMCP), alginates, carboxymethylcellulose, and combinations thereof. The pH-dependent enteric-coating polymer may be present in the composition in an amount from about 10% to about 95% by weight of the entire composition.

In certain embodiments, the invention provides a pharmaceutical composition for oral administration, which is solid and may be in the form of granulate, granules, grains, beads or pellets, mixed and filled into capsules or sachets, or compressed to tablets by conventional methods. In some particular embodiments, the pharmaceutical composition is in the form of a bi- or multilayer tablet, in which each one of the layers comprise one of the two active agents, and the layers are optionally separated by an intermediate, inactive layer, e.g., a layer comprising one or more disintegrants.

Another contemplated formulation is depot systems, based on biodegradable polymers. As the polymer degrades, the active agent(s) is slowly released. The most common class of biodegradable polymers is the hydrolytically labile polyesters prepared from lactic acid, glycolic acid, or combinations of these two molecules. Polymers prepared from these individual monomers include poly (D,L-lactide) (PLA), poly (glycolide) (PGA), and the copolymer poly (D,L-lactide-co-glycolide) (PLG).

Pharmaceutical compositions for oral administration may be prepared according to any method known to the art and may further comprise one or more agents selected from sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active agents in admixture with non-toxic pharmaceutically acceptable excipients, which are suitable for the manufacture of tablets. These excipients may be, e.g., inert diluents such as calcium carbonate, sodium carbonate, lactose, calcium phosphate, or sodium phosphate; granulating and disintegrating agents, e.g., corn starch or alginic acid; binding agents, e.g., starch, gelatin or acacia; and lubricating agents, e.g., magnesium stearate, stearic acid, or talc. The tablets may be either uncoated or coated utilizing known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated using the techniques described in the US Patent Nos. 4,256,108, 4,166,452 and 4,265,874 to form osmotic therapeutic tablets for control release. The pharmaceutical composition of the invention may also be in the form of oil-in-water emulsion.

Useful dosage forms of the pharmaceutical compositions include orally disintegrating systems including, but not limited to, solid, semi-solid and liquid systems including disintegrating or dissolving tablets, soft or hard capsules, gels, fast dispersing dosage forms, controlled dispersing dosage forms, caplets, films, wafers, ovules, granules, buccal/mucoadhesive patches, powders, freeze dried (lyophilized) wafers, chewable tablets which disintegrate with saliva in the buccal/mouth cavity and combinations thereof. Useful films include, but are not limited to, single layer stand-alone films and dry multiple layer stand-alone films.

The pharmaceutical composition of the invention may comprise one or more pharmaceutically acceptable excipients. For example, a tablet may comprise at least one filler, e.g., lactose, ethylcellulose, microcrystalline cellulose, silicified microcrystalline cellulose; at least one disintegrant, e.g., cross-linked polyvinylpyrrolidinone; at least one binder, e.g., polyvinylpyridone, hydroxypropylmethyl cellulose; at least one surfactant, e.g., sodium laurylsulfate; at least one glidant, e.g., colloidal silicon dioxide; and at least one lubricant, e.g., magnesium stearate.

The pharmaceutical composition of the invention may be in the form of a sterile injectable aqueous or oleaginous suspension, which may be formulated according to the known art using suitable dispersing, wetting or suspending agents. The sterile injectable preparation may also be an injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Acceptable vehicles and solvents that may be employed include, without limiting, water, Ringer's solution, polyethylene glycol (PEG), 2-hydroxypropyl-β-cyclodextrin (HPCD), a surfactant such as Tween-80, and isotonic sodium chloride solution.

Pharmaceutical compositions according to the invention, when formulated for inhalation, may be in any suitable form, e.g., liquid or fine powder, and may be administered utilizing any suitable device known in the art, such as pressurized metered dose inhalers, liquid nebulizers, dry powder inhalers, sprayers, thermal vaporizers, electrohydrodynamic aerosolizers, and the like.

For instance, nebulizers use oxygen, compressed air or ultrasonic power to break up solutions and suspensions into small aerosol, i.e., a mixture of gas and solid or liquid particles, droplets that are inhaled from the mouthpiece of the device.

The pharmaceutical composition of the invention may be formulated for controlled release of one or more of the active agents, i.e., one or more of the cannabinoids and terpenes. Such compositions may be formulated as controlled-release matrix, e.g., as controlled-release matrix tablets in which the release of a soluble active agent is controlled by having the active diffuse through a gel formed after the swelling of a hydrophilic polymer brought into contact with dissolving liquid (*in vitro*) or gastro-intestinal fluid (*in vivo*). Many polymers have been described as capable of forming such gel, e.g., derivatives of cellulose, in particular the cellulose ethers such as hydroxypropyl cellulose, hydroxymethyl cellulose, methylcellulose or methyl hydroxypropyl cellulose, and among the different commercial grades of these ethers are those showing fairly high viscosity. In other configurations, the compositions comprise the active agent formulated for controlled release in microencapsulated dosage form, in which small droplets of the active agent are surrounded by a coating or a membrane to form particles in the range of a few micrometers to a few millimeters.

In another particular such aspect, the composition of the present invention as defined in any one of the embodiments above is in the form of a nutraceutical composition, i.e., the carrier comprised within said composition is a nutraceutically acceptable carrier, and may be formulated as a solid dosage form such as tablet, capsule, pill and powder, or as a liquid dosage form such as syrup and elixir, and may be prepared by conventional techniques known in the art. Particular such nutraceutical compositions are formulated as a food supplement (e.g., when comprising beeswax of honey as a carrier), drink or beverage.

The pharmaceutical or nutraceutical compositions of the invention are useful in treatment of ASD.

ASD encompasses a range of conditions classified as neurodevelopmental disorders in the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, published in 2013). Individuals diagnosed with ASD must present two types of symptoms: deficits in social communication and social interaction; and restricted, repetitive patterns of behavior, interests or activities. The DSM-5 redefined the ASDs to encompass the previous (DSM-IV-TR (DSM text revision, published in 2000) diagnoses of autism, Asperger syndrome, pervasive developmental disorder not otherwise specified (PDD-NOS), and childhood disintegrative disorder. Features of these disorders include social deficits, communication difficulties, stereotyped or repetitive behaviors and interests, sensory issues, and in some cases, cognitive delays.

Autism may be categorized as either syndromic (secondary) or non-syndromic. The traditional definition of syndromic ASD refers to a condition caused by a well-known genetic variant, i.e., a disorder with a clinically defined pattern of somatic abnormalities and a neurobehavioral phenotype that may include ASD. Syndromic autisms, which are so defined because they occur in individuals with neurological disorders such as fragile X mental retardation, tuberous sclerosis, or Rett syndrome, harbor a set of phenotypes that can be fully attributed to a mutation in a particular gene or a set of genes.

Non-syndromic autism, which comprises a vast majority of autism cases, is not linked to other neurological diseases (or syndromes) and is caused by unknown genetic or environmental cause. Moreover, many genes involved in non-syndromic intellectual disabilities and in epilepsy have also been implicated in the etiology of non-syndromic ADS

(Ivanov *et al.,* Autism spectrum disorder-a complex genetic disorder. *Folia medica*, **2015**, 57, 19-28; Fernandez and Scherer. Syndromic autism spectrum disorders: moving from a clinically defined to a molecularly defined approach. *Dialogues in clinical neuroscience*, **2017**, 19, 353).

Symptoms of ASD include behavioral problems that may be internalizing problems such as being emotionally reactive, depressed/anxious affect, expressing somatic complaints and withdrawal, or externalizing problems such as aggression, defiance and inattentiveness, tantrums and self-injury. Additionally, symptoms include restrictive/repetitive behavior and deficit in social communication/interaction behaviors (https://www.autismspeaks.org/what-autism/symptoms).

In another aspect, the present invention thus relates to a method for treatment of ASD in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a pharmaceutical composition according to any one of the embodiments above.

The term "subject" as used herein refers to any mammal, e.g., a human, non-human primate, horse, ferret, dog, cat, cow, and goat. In a preferred embodiment, the term "subject" denotes a human, i.e., an individual. In some embodiments, the subject is a child or adolescent.

The term "treatment" as used herein refers to the administering of a therapeutic amount of pharmaceutical composition as described above, which is effective to ameliorate undesired symptoms associated with said medical condition; prevent the manifestation of such symptoms before they occur; slow down the progression of said medical condition; slow down the deterioration of symptoms; enhance the onset of remission period; and/or lessen the severity of said medical condition.

The term "therapeutically effective amount" as used herein means an amount of said pharmaceutical composition that will elicit the biological or medical response of a tissue, system, animal or human that is being sought. The amount must be effective to achieve the desired therapeutic effect as described above, depending *inter alia* on the type and severity of the condition to be treated and the treatment regime. The effective amount is typically determined in appropriately designed clinical trials (dose range studies) and the

person versed in the art will know how to properly conduct such trials to determine the effective amount. As generally known, an effective amount depends on a variety of factors including the affinity of the ligand to the receptor, its distribution profile within the body, a variety of pharmacological parameters such as half-life in the body, on undesired side effects, if any, on factors such as age and gender, etc.

In certain embodiments, the pharmaceutical composition according to any one of the embodiments above, administered according to the method of the invention is useful for reducing hyperactivity symptoms, reducing self-injury behavior, improving sleeping, and/or improving social communication in said subject.

Unless otherwise indicated, all numbers expressing, e.g., weight ratios of the cannabinoids and terpenes comprised within the composition of the invention as defined above, used in this specification are to be understood as being modified in all instances by the term "about". Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification are approximations that may vary by up to plus or minus 10% depending upon the desired properties to be obtained by the present invention.

The following examples are presented in order to more fully illustrate some embodiments of the invention. They should in no way be construed, however, as limiting the broad scope of the invention. One skilled in the art can readily devise many variations and modifications of the principles disclosed herein without departing from the scope of the invention.

EXAMPLES

Study 1. Effects of medical cannabis-based treatment on children having ASD

Children with ASD exhibit co-morbid symptoms of hyperactivity, self-injury, aggressiveness, restlessness, anxiety and sleep disorders (Mannion and Leader, Comorbidity in autism spectrum disorder: A literature review. *Research in Autism Spectrum Disorders*, **2013**, 12, 1595-1616; South and Jacqui, Sensory, emotional and cognitive contributions to anxiety in autism spectrum disorders. *Frontiers in Human Neuroscience*, **2017**, 11, Article 20). Children with ASD are also known to suffer from susceptibility to flavors.

Previous studies have shown that a combination of CBD and THC at a weight ratio of 20:1 has beneficial results in treating children with ASD as compared to CBD only. There is much experience in Israel with the treatment of autism using 20:1 CBD:THC products in more than 1000 children. The adverse effects of such products are familiar and they are temporary and not significant (Aran *et al.*, Brief report: cannabidiol-rich cannabis in children with autism spectrum disorder and severe behavioral problems - A retrospective feasibility study. *J. Autism. Dev. Disord.,* **2019**, 49, 1284-1288).

Materials and methods

The present study utilized compositions each comprising a different combination of CBD and THC at a CBD:THC weight ratio of about 20:1; optionally a terpene combination comprising β-caryophyllene in an amount of about 70% of said terpene combination, linalool in an amount of about 20% of said terpene combination, α-pinene in an amount of up to 3% of said terpene combination, and limonene in an amount of up to 3% of said terpene combination; and MCT as a carrier oil. Each one of the various compositions was formulated as sublingual medicated drops each containing about 10 mg CBD and about 0.5 mg THC.

The study included four arms, each including five children at the age of 5-25 years old, diagnosed with ASD based on DSM IV (Diagnostic and Statistical Manual of Mental Disorders, American Psychiatric Association, 2000) or DSM V (Diagnostic and Statistical Manual of Mental Disorders, American Psychiatric Association, 2013) criteria, who were followed up for at least 30 days after commencement of treatment. Four ASD co-morbidity symptoms were evaluated: (a) hyperactivity symptoms (b) sleeping problems, (c) self-injury, and (d) social communication.

Patients in all arms were administered with a dose starting from 1 drop 4 times a day (i.e., about 40 mg CBD and 2 mg THC per 24 hour), which was increased, if necessary, up to 3 drops, 3 times a day, and 4 drops before sleep (i.e., about 130 mg CBD and about 6.5 mg THC per 24 hours).

Arm 1. Patients were treated with a composition comprising about 90% an extract obtained from *Cannabis ZIV Sparkling Light* (Israel Plant Breeders' Rights Application No.

4852/19; rich in CBD) and about 1.7% an extract obtained from *Cannabis TIL Tachllta* (Israel Plant Breeders' Rights Application No. 4837/19; rich in THC) and having CBD and THC in a ratio of about 20:1, respectively. The extractes were prepared by a cold wash ethanol extraction, more specifically by extracting (separating) the oil from a plant material of each one of the two species using cold ethanol (-20ºC; 190 proof (95%)) as the solvent; evaporating the ethanol from the fraction thus obtained using a rotary evaporator; and distilling the crude extract obtained using a wiped-film evaporator (WFE; Pope Scientific Inc., USA). The HPLC analysis of the two extracts are shown in **Table 1-2**.

Arm 2. Patients were treated with a composition similar to that used in Arm 1, but further comprising about 2% by weight of the terpene combination referred to above.

Arm 3. Patients were treated with a composition based on a mixture of purified CBD and THC (rather than a mixture of two cannabis plant extracts, each containing components in addition to CBD and THC, as in the composition administered to the patients in Arm 1).

Arm 4. Patients were treated with a composition similar to that used in Arm 3, but further comprising about 2% by weight of the terpene combination referred to above. This composition is also referred to herein as "***Nitzan Spectrum composition***".

Table 1. HPLC analysis of a *ZIV Sparkling Light* extract

Cannabinoid content [%w/w][a]												
CBDV	**CBDA**	CBG	**CBD**	CBGA	CBN	THC	Δ^8-THC	CBC	THCA	Total THC	**Total CBD**	Total CBG
0.17	**16.54**	0.70	**71.09**	0.08	0.40	2.86	nd	5.47	0.23	9.45	**85.47**	0.77

[a] Based on weight of extract. The values represent the average of two analyses (one sample per strain; samples were analyzed in duplicates).
nd - not determined

Table 2. HPLC analysis of the *TIL Tachllta* extract

Cannabinoid content [%w/w][a]												
CBDV	CBDA	CBG	CBD	CBGA	CBN	**THC**	Δ^8-THC	CBC	**THCA**	**Total THC**	Total CBD	Total CBG
nd	0.20	0.98	nd	4.21	0.25	**2.86**	nd	0.08	**93.77**	**85.09**	0.18	4.67

[a] Based on weight of extract. The values represent the average of two analyses (one sample per strain; samples were analyzed in duplicates).
nd - not determined

The content of cannabinoids (either a mixture of purified CBD and THC, or a mixture of the two extracts as CBD and THC sources) in each one of the various compositions used was about 20.1% by weight, and the content of the carrier oil (MCT) was either about 79.9% or about 77.9% by weight, depending on whether a terpene combination (2% by weight) was added or not.

The study was aimed at exploring the safety and efficacy of the compositions utilized, and testing their efficacy in treating children with ADS, more specifically in reducing, limiting, or attenuating each one of the co-morbid symptoms exhibited by these children. The compositions tested were orally administered to the children, according to the regimen described above, by their parents, who were also responsible for reporting the results based on their experience.

For each co-morbid symptom, the parents reported an improvement, no change, or worsening of symptoms, as compared to the baseline (i.e., the appearance of said symptom prior to the treatment). An overall change was defined based on the summation of all reports provided with respect to the children in each group. For all participating children, this was their first experience with CBD and no other cannabinoids were used before this study. During the first meeting, parents were instructed by an experienced authorized person how to administer the composition. Thereafter, a biweekly follow-up telephone interview was conducted with the parents, during which the parents were questioned regarding the status of the various ASD co-morbid symptoms exhibited by the particular kid (graded as improvement, no change, or worsening), emerging adverse effects, and medications that had been used during the study period.

Results and discussion

Fig. 1 shows the hyperactivity symptoms (e.g., how much calm the kid was, the rate of hyper events and duration thereof, and how easy was it to get the kid out of the event) in the participating kids. **Fig. 2** shows the symptom of self-injury (e.g., self-harming, knocking the head in the wall, scratching the arms). **Fig. 3** shows how much the sleeping problems (e.g., getting to sleep, waking at night, and disturbed sleeping) were improved

during the trial time. **Fig. 4** shows the improvement in social communications (e.g., making eye contact with the caretaker, reaction to physical contact, pronouncing the needs in words or gestures) during the trial time. **Fig. 5** shows the reaction to the taste of the medicine (the taste is a crucial element in children with ASD, since they are very sensitive to it, and in some cases, it prevents them from taking the medicine). The graph shows the improvement, according to the parents, in taking the medicine during the trial time. In all these figures, the Y axis shows the satisfaction level, and the X axis refers to the duration of testing. **Fig. 6** shows the average of all the criterions tested in **Figs. 1-5** (hyperactivity symptoms, self-injury, sleeping problems, social communication, and flavor improvement) according to a parent's report.

The results reported for the children of Arm 4 were the most significant, wherein said children demonstrated more presence, made eye contact more closely, and listened and learned more. Symptoms such as severe anger attacks, self-violence, and self-physical injuries, as well as violence in the surrounding, and long cries, faded and in some cases even disappeared.

In some of the children, but mainly and clearly in those of Arm 4, a substantial improvement in verbal capabilities was observed, and in some of the cases, treated children had started to talk for the first time.

The results presented herein, which are based on the reports provided by the parents of the children participating in the study, support previous publications suggesting that CBD, as well as CBD and THC combination at a weight ratio of 20:1, may be effective in improving co-morbid symptoms exhibited by children having ASD.

Yet, as surprisingly shown herein, a composition comprising a combination of purified CBD and THC in a weight ratio of about 20:1, and a terpene combination comprising β-caryophyllene, linalool, α-pinene and limonene in a particular weight ratio (Nitzan Spectrum composition), was significantly more effective in limiting or attenuating the co-morbid symptoms exhibited by said children than both a similar composition comprising a mixture of cannabis plant extracts as the CBD and THC sources, an a similar composition without said terpene combination, indicating that such a composition may be highly effective in treating children having ASD.

Furthermore, a product based on purified CBD and THC as exemplified herein was tastier than the corresponding product that is based on cannabis plant extracts as the CBD and THC sources; and the *Nitzan Spectrum composition* obtained after the addition of the terpene combination exemplified herein was superior to the product without the terpene combination, and had a better flavor.

Study 2: A phase III clinical trial designed to evaluate the safety and efficacy of Nitzan Spectrum on ASD pediatric population

Children with autism spectrum disorder (ASD) commonly exhibit comorbid symptoms such as aggression, hyperactivity and anxiety. Several studies are being conducted worldwide on cannabidiol use in ASD; however, these studies are still ongoing, and data on the effects of its use is very limited. The objective of this study was to report the experience of parents who administer, under supervision, oral cannabinoids to their children with ASD.

After obtaining a license from the Israeli Ministry of Health, parents of children with ASD were instructed how to administer oral drops of Nitzan Spectrum, medical cannabidiol oil. Information on comorbid symptoms and safety was prospectively recorded biweekly during follow-up interviews. An independent group of specialists analyzed these data for changes in ASD symptoms and drug safety.

Efficacy of treatment was tested using the Autism Diagnostic Observation Schedule (ADOS), 5 subtests of an age-appropriate Wechsler Intelligence Scale (WPPSI, WISC or WAIS), and the Vineland adaptive behaviors scale. All assessments were conducted before treatment initiation and again after 6 months. The ADOS was conducted by a trained and licensed speech therapist and cognitive testing was conducted by a licensed developmental psychologist. The Vineland was completed in a parent interview.

Study drug

All participants received Nitzan Spectrum, a medical cannabis extract infused in Medium-Chain Triglycerides (MCT) oil with a CBD:THC ratio of 20:1 for a period of six months. All participants started with one drop daily (each drop: 0.3mg THC and 5.7mg CBD) and increased gradually until improvement was reported by the parents. Final dose

did not exceed 10mg/kg/day (or total of 400mg per day) of CBD and 0.5mg/kg/day (or total of 20mg per day) of THC.

Method

Main inclusion criteria for the trial were –

- ASD patients, 5-25 yo
- Behavior problems, reported in last 6 months

Efficacy of treatment was tested using the Autism Diagnostic Observation Schedule (ADOS), 5 subtests of an age-appropriate Wechsler Intelligence Scale (WPPSI, WISC or WAIS), and the Vineland adaptive behaviors scale. All assessments were conducted before treatment initiation and again after 6 months. The ADOS was conducted by a trained and licensed speech therapist and cognitive testing was conducted by a licensed developmental psychologist. The Vineland was completed in a parent interview.

Cognitive assessments of children above the age of 6 years old included the Block design and Matrix subtests from the Perceptual Organization Index (POI), the Vocabulary and Similarities subtests from the Verbal Comprehension Index (VCI) and the Digit symbol-coding subtest from the Processing Speed Index (PSI). Children below the age of 6 years old preformed the Information subtest instead of the Similarities subtest.

Statistical analyses included paired T-tests to assess longitudinal changes in scores before and after treatment. Pearson correlation coefficients were used to assess relationships with age across scores of homological subscales.

Dosing

The average doses in the morning, noon, evening and the total for all day are presented in Table 3.

Table 3. Descriptive Statistics, Study drug dose

	N	Minimum	Maximum	Mean	Std. Deviation
Months follow-up	54	1.00	45.00	17.9815	7.86799
Mean Dose Morning	54	.75	8.55	4.0360	1.71257

Mean Dose Noon	38	.00	10.00	2.0240	2.27845
Mean Dose Evening	51	.00	7.10	3.0398	1.83711
Mean Dose_ all Day	35	.75	23.05	7.8824	4.24342

Safety Data

No abnormalities were observed during the trial.

Efficacy data

During the study the efficacy data was collected.

ADOS calibrated severity score (CSS) improved (decreased) significantly following treatment (M=-0.75, SD=1.24, t(31)=-3.41, p=0.002, Fig. 7). The total Vineland scores also improved (increased) significantly following treatment (M=5.46, SD=13, t(40)=2.69, p=0.01, Fig. 8). Improvements were apparent in the communication (M=5.65, SD=17.26, t(40)=2.1, p =0.042), daily living (M=6.05, SD=14.79, t(40)=2.62, p =0.012), and socialization (M=5.98, SD=15.19, t(40)=2.52, p=0.016) sub-scales. The Verbal Comprehension Index of the cognitive tests also improved significantly (M=0.65 SD=1.94, t(36)=2.04, p =0.048).

The efficacy data was collected also by validated ASD questionnaires and analyzed in order to demonstrate the efficacy of Nitzan Spectrum in ASD population. The data is presented in Fig. 9.

The data demonstrate a significant improvement in the communication and socialization skills of children administered with the herein disclosed Nitzan Spectrum composition, as demonstrated by the improvement in the ADOS calibrated severity score (CSS), the total Vineland scores and the Verbal Comprehension Index.

Importantly, a significantly life changing improvement in daily living and communication was reported by the parents whose kids were administered with the Nitzan Spectrum composition.

While certain embodiments of the invention have been illustrated and described, it will be clear that the invention is not limited to the embodiments described herein. Numerous modifications, changes, variations, substitutions and equivalents will be apparent to those skilled in the art without departing from the spirit and scope of the present invention as described by the claims, which follow.

CLAIMS

1. A composition comprising a cannabinoid combination, a terpene combination, and a carrier, wherein said cannabinoid combination comprising cannabidiol (CBD) or an enantiomer or diastereomer thereof, optionally partially or fully carboxylated at position 6' thereof; wherein the terpene combination comprises at least three terpenes selected from β-caryophyllene, linalool, α-pinene and limonene, and wherein the terpene combination comprises about 3-30% by weight of said cannabinoid combination.

2. The composition of claim 1, wherein the CBD constitutes 5-30% by weight of the cannabinoid combination.

3. The composition of any one of claims 1-2, wherein the THC constitutes 0.08-3.0% by weight of the cannabinoid combination.

4. The composition of of any one of claims 1-3, wherein the CBD and the THC are present in a weight ratio of 20:1.

5. The composition of any one of claims 1-4, wherein the terpene combination constitutes about 0.4-4.8% by weight of said composition.

6. The composition of any one of claims 1-4, wherein the cannabinoid combination further comprises Δ^9-tetrahydrocannabinol (Δ^9-THC) or an enantiomer or diastereomer thereof, optionally partially or fully carboxylated at position 2 thereof.

7. The composition of claim 6, wherein said cannabinoid combination consists of CBD and Δ^9-THC.

8. The composition of any one of claims 1-7, wherein said cannabinoid combination comprises CBD in an amount of 5-27% by weight, and Δ^9-THC in an amount of 0.01-2.5% by weight.

9. The composition of any one of claims 1-8, wherein said terpene combination comprises α-pinene, limonene, linalool, and β-caryophyllene.

10. The composition of any one of claims 1-8, wherein said terpene combination comprises β-caryophyllene, and at least two of α-pinene, limonene, and linalool.

11. The composition of claim 10, wherein the β-caryophyllene constitutes about 50-90% by weight of said terpene combination, the linalool, when present, constitutes about 10-30% by weight of said terpene combination; and each one of the α-pinene and limonene, when present, independently constitutes up to 5% by weight of said terpene combination.

12. The composition of claim 11, wherein said terpene combination comprises β-caryophyllene in an amount of about 70% of said terpene combination, linalool in an amount of about 20% of said terpene combination, α-pinene in an amount of up to 3% of said terpene combination, and limonene in an amount of up to 3% of said terpene combination.

13. The composition of any one of claims 1-12, wherein said carrier is beeswax, honey, or a carrier oil selected from a medium chain triglyceride (MCT), coconut oil, canola oil, olive oil, avocado oil, grapeseed oil, hempseed oil, sunflower oil, black seed oil, rosehip oil, argan oil, palm tree oil, and jojoba oil.

14. The composition of claim 13, wherein said carrier oil is an MCT.

15. The composition of any one of claims 1-14, further comprising at least one additional cannabinoid selected from cannabidivarin (CBDV), cannabidivarinic acid (CBDVA), cannabidiphorol (CBDP), cannabidiol monomethyl ether (CBDM), cannabidiol-C4 (CBD-C4), cannabidiorcol (CBD-C1), Δ^9-tetrahydrocannabivarin (Δ^9-THCV), Δ^9-THCVA, Δ^8-THC, Δ^8-THCA, Δ^8-THCV, Δ^8-THCVA, Δ^9-tetrahydrocannabiphorol (Δ^9-THCP), iso-tetrahydrocannabinol-type (iso-THC), cannabinol (CBN), cannabinolic acid (CBNA), cannabinol-C4 (CBN-C4), cannabinol-C2 (CBN-C2), cannabiorcol (CBN-C1), cannabinol methyl ether (CBNM), cannabinodiol (CBND), cannabigerol (CBG), cannabigerovarin (CBGV), cannabigerolic acid (CBGA), cannabigerovarinic acid (CBGVA), cannabigerol monomethyl ether (CBGM), cannabigerolic acid monomethyl ether (CBGAM), cannabichromene (CBC), cannabichromenic acid (CBCA), cannabichromevarin (CBCV), cannabichromevarinic acid (CBCVA), cannabichromanon (CBCN), cannabicyclol (CBL), cannabicyclolic acid (CBLA), cannabicyclovarin (CBLV), cannabivarin (CBV), cannabivarinic acid (CBVA), cannabielsoin (CBE), cannabielsoic acid A (CBEA-A), cannabielsoic acid B (CBEA-B), cannabitriol (CBT), cannabitriolvarin (CBTV), ethoxy-cannabitiolvarin (CBTVE), cannabifuran (CBF), dehydrocannabifuran (DCBF), cannabiripsol (CBR), or an enantiomer, diastereomer, racemate, or a salt thereof.

16. The composition of claim 15, wherein the at least one additional cannabinoid constitutes up to 5% by weight of the composition.

17. The composition of any one of claims 1-16, formulated as an emulsion.

18. The composition of any one of claims 1-17, wherein at least one of the CBD, the THC, the β-caryophyllene, the linalool, the α-pinene or the limonene is in a form of synthetic, purified, extracted or isolated molecules.

19. A pharmaceutical or nutraceutical composition according to any one of claims 1-18.

20. The pharmaceutical composition of claim 19, formulated for oral, buccal or sublingual administration, or for inhalation.

21. The pharmaceutical composition of claim 19, formulated as a liquid dosage form such as a solution, syrup and elixir; or as a solid dosage form such as a tablet, capsule, and pill.

22. The nutraceutical composition of claim 19, formulated as a food supplement, drink or beverage.

23. The pharmaceutical or nutraceutical composition of any one of claims 19-22, for treatment of autism spectrum disorder (ASD).

24. A method for treatment of autism spectrum disorder (ASD) in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a pharmaceutical composition according to any one of claims 19-23.

25. The method of claim 24, for reducing hyperactivity symptoms, reducing self-injury behavior, improving sleeping, and/or improving social communication in said subject.

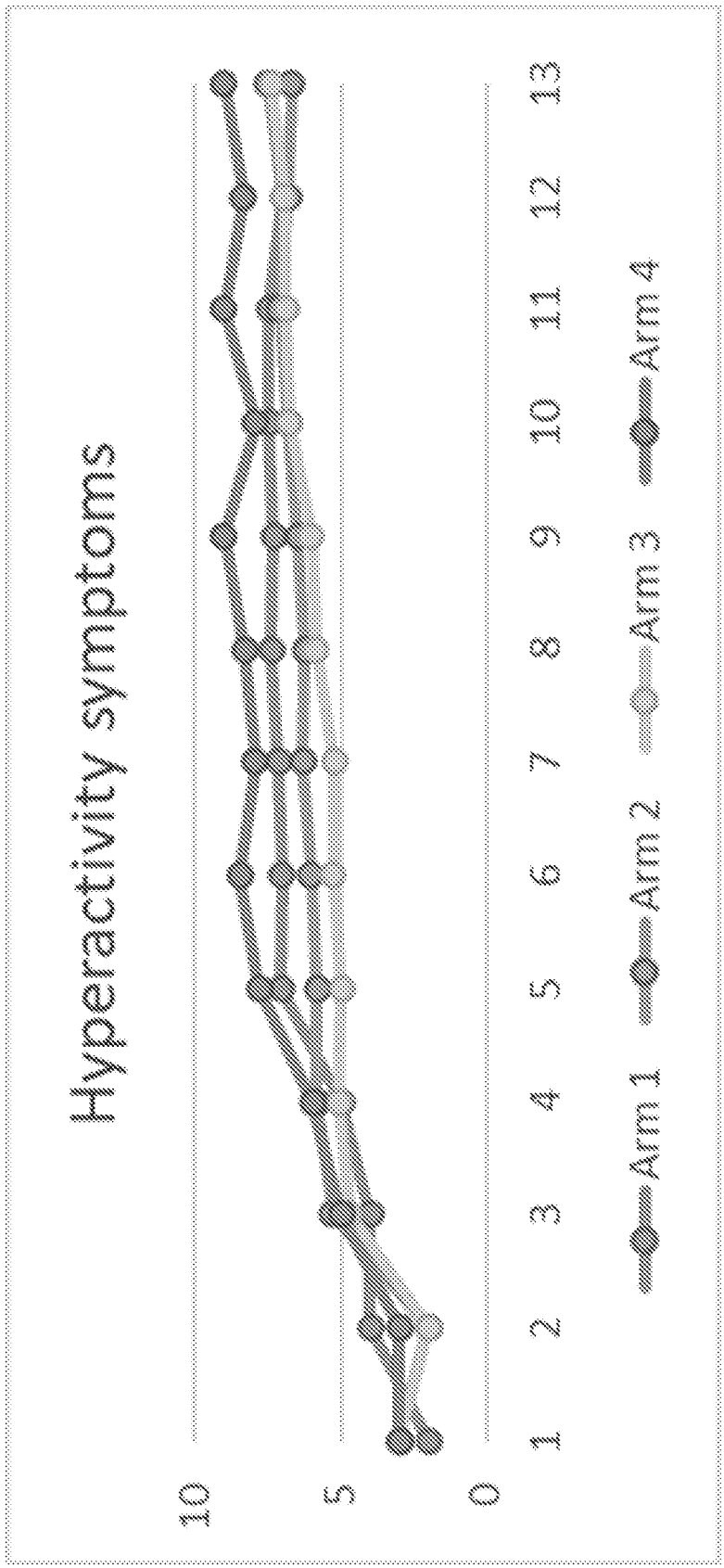

Hyperactivity symptoms
10
5
0
1
2
3
4
5
6
7
8
9
10
11
12
13
Arm 1
Arm 2
Arm 3
Arm 4

Fig. 1

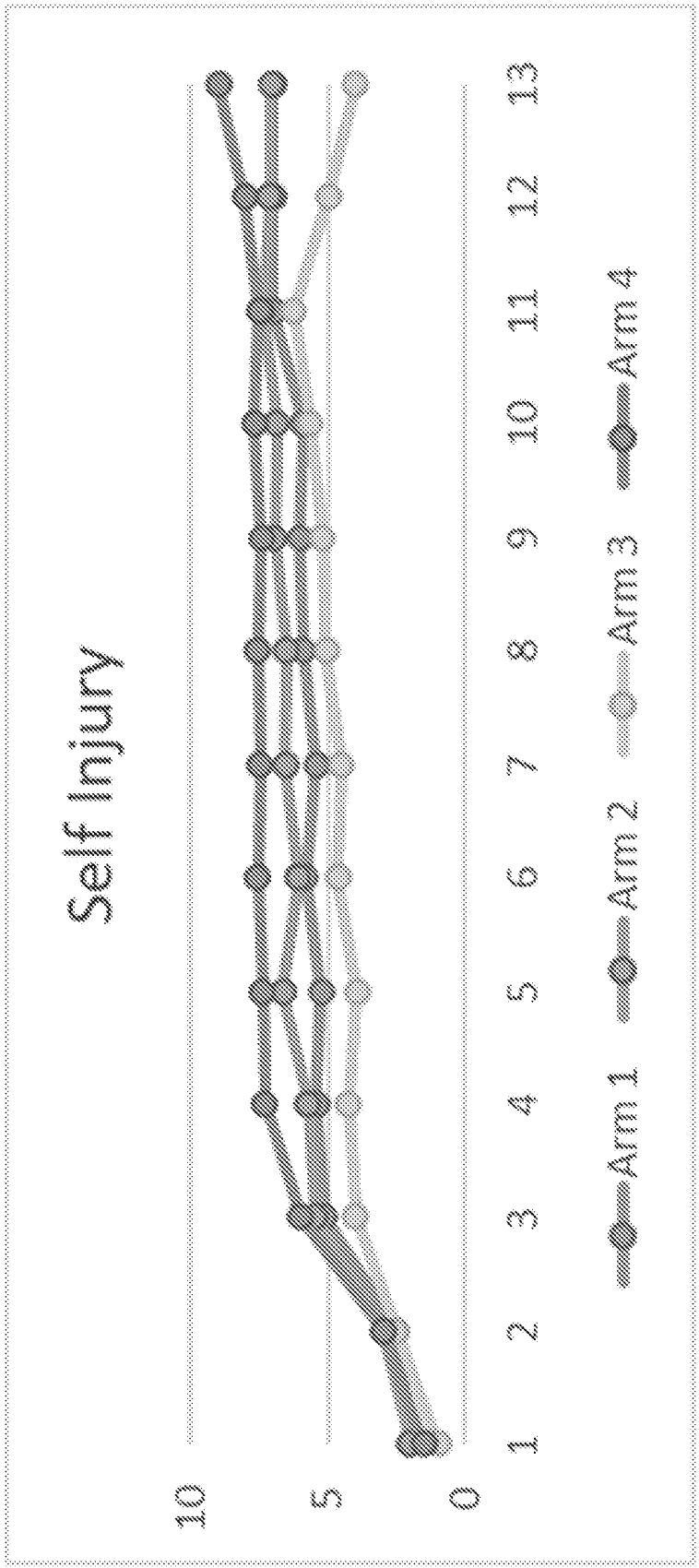
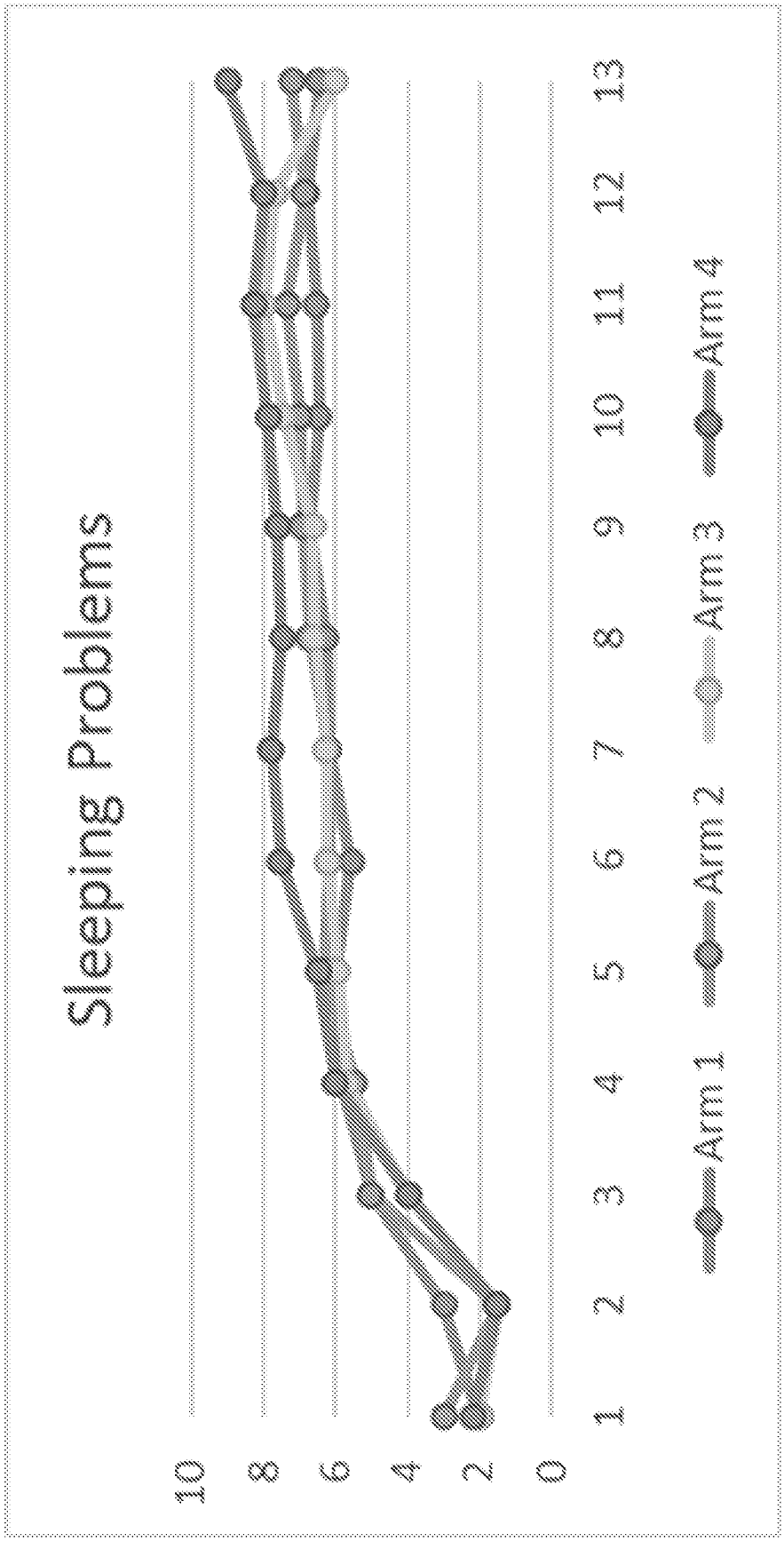


Fig. 2


Sleeping Problems
10
8
6
4
2
0
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2
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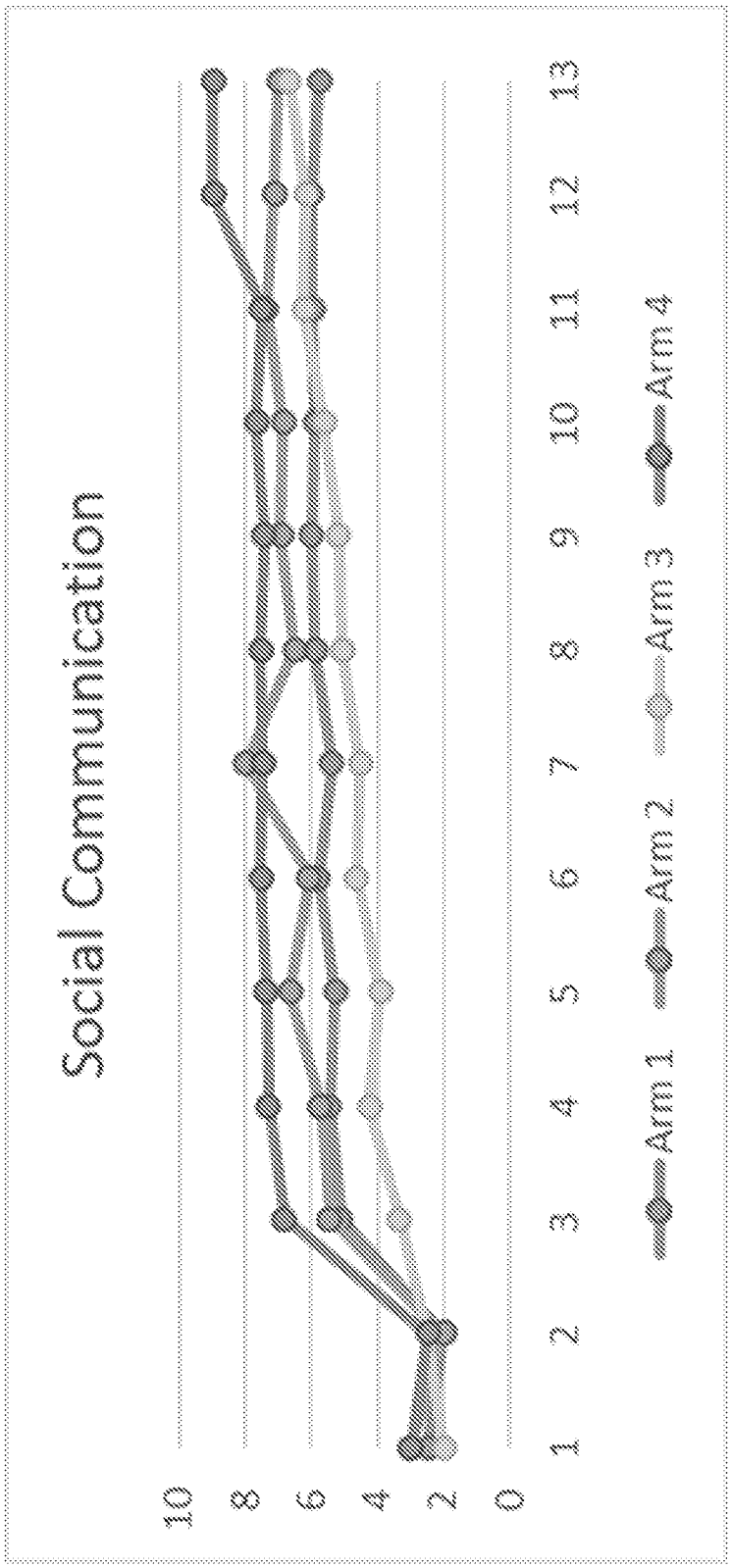
4
5
6
7
8
9
10
11
12
13
Arm 1
Arm 2
Arm 3
Arm 4

Fig. 3


Social Communication
10
8
6
4
2
0
1
2
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5
6
7
8
9
10
11
12
13
Arm 1
Arm 2
Arm 3
Arm 4

Fig. 4

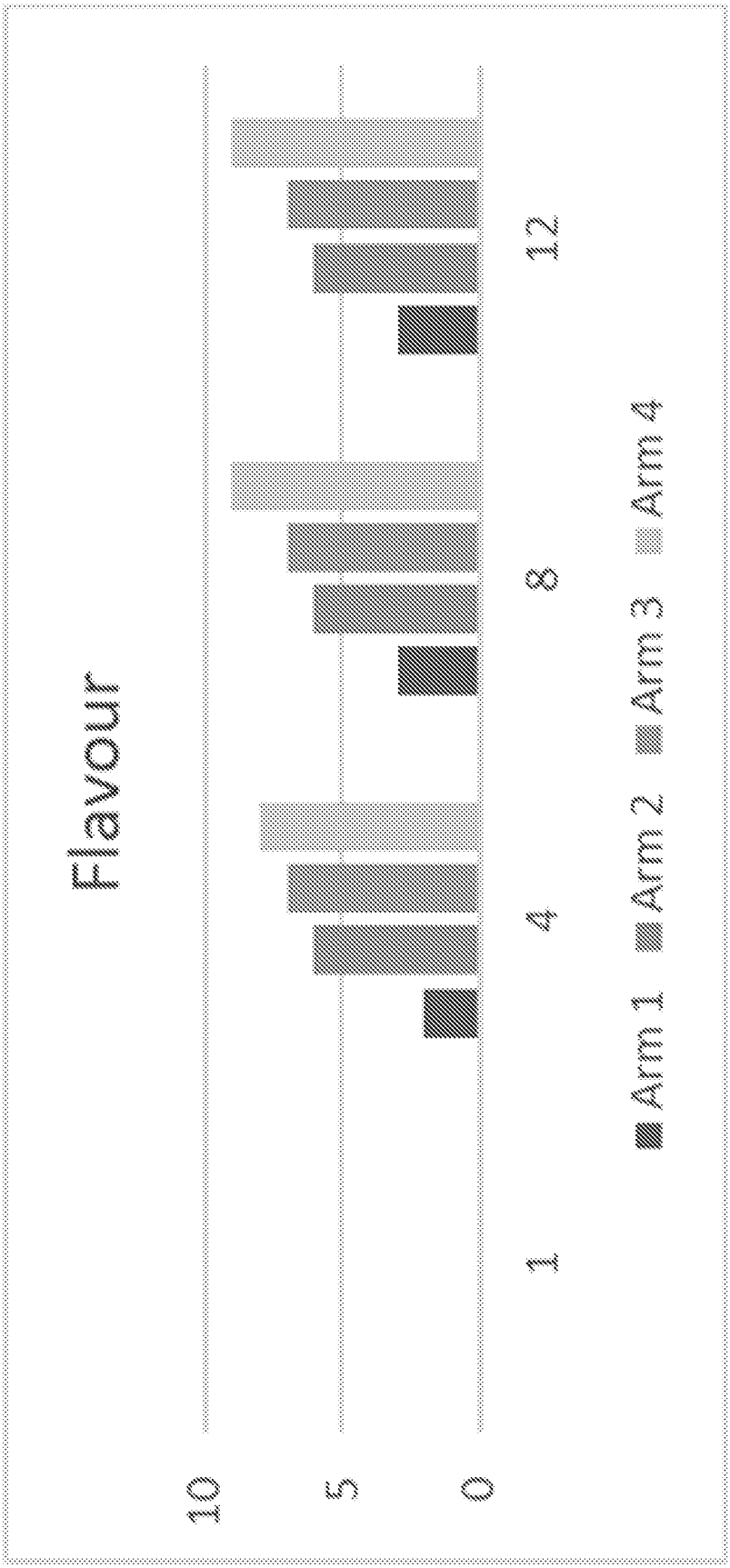


Fig. 5

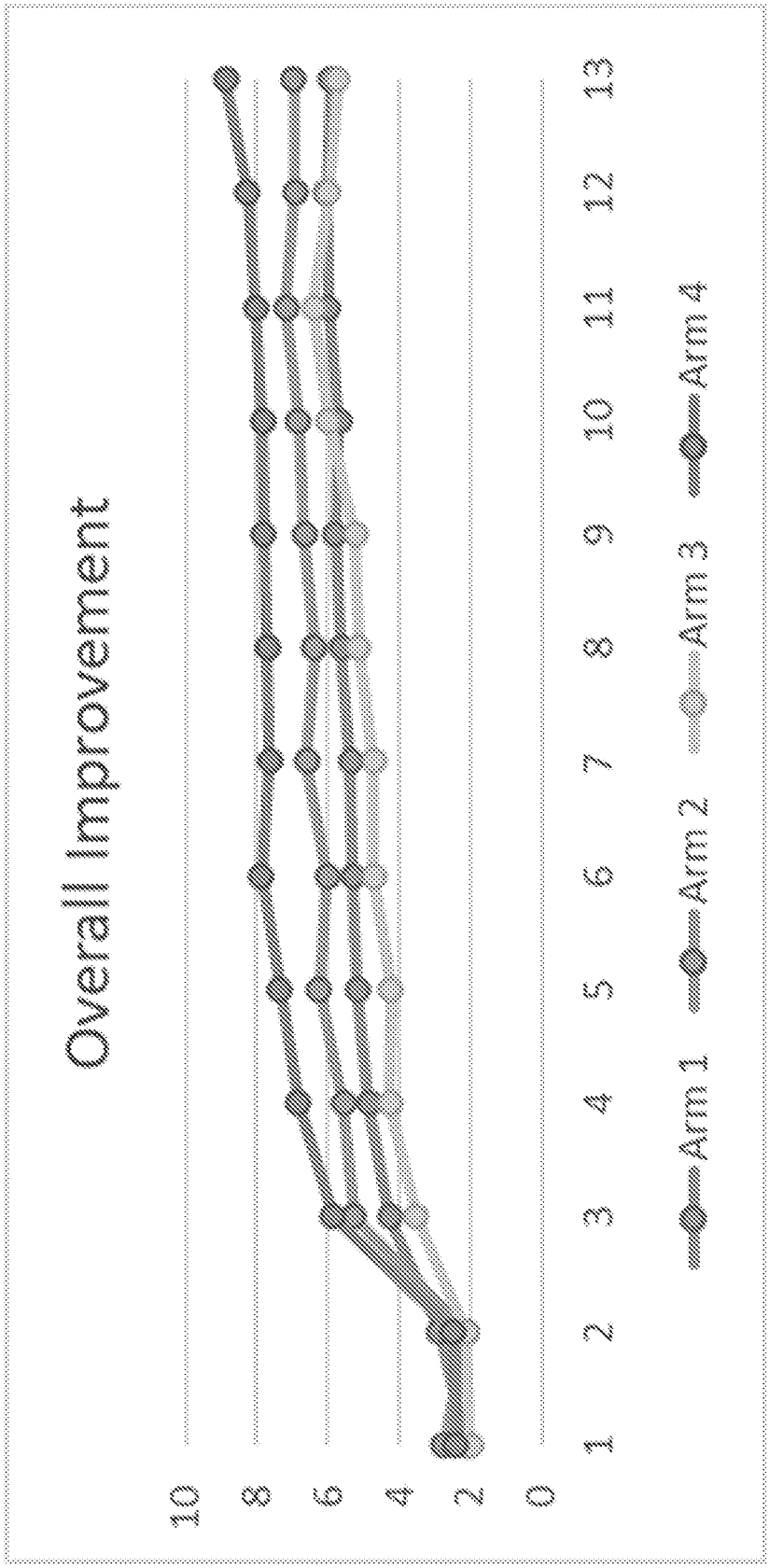

Overall Improvement
10
8
6
4
2
0
1
2
3
4
5
6
7
8
9
10
11
12
13
Arm 1
Arm 2
Arm 3
Arm 4

Fig. 6

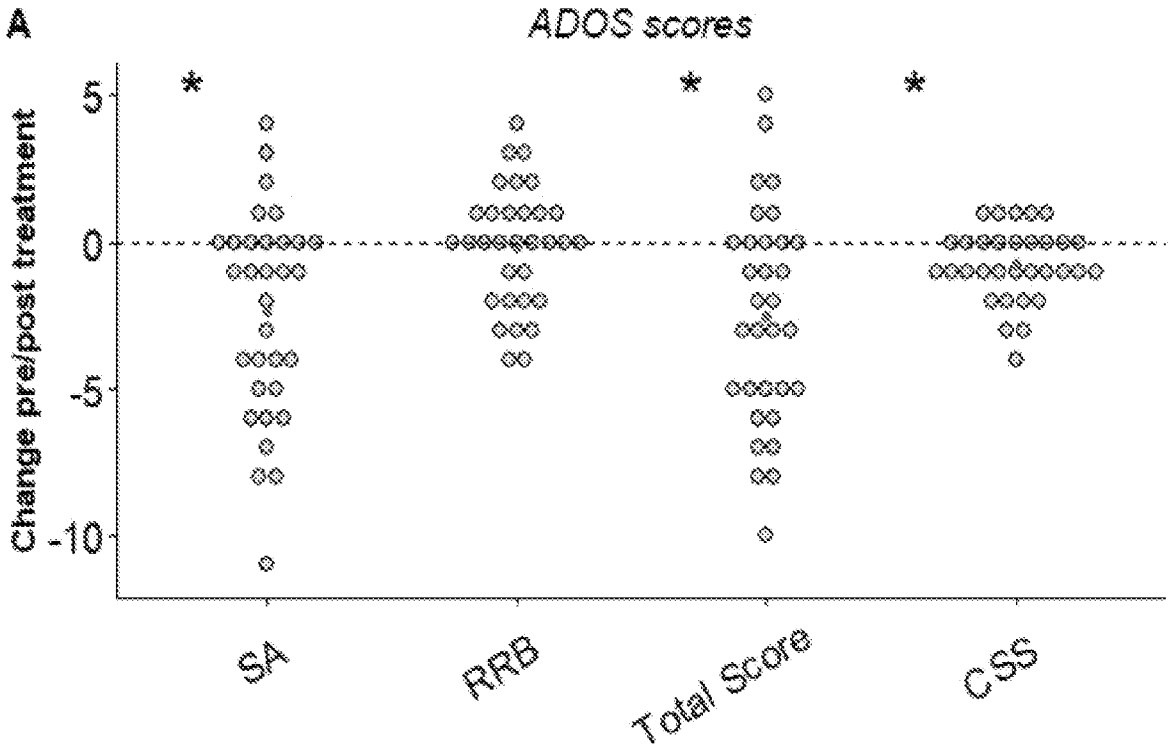
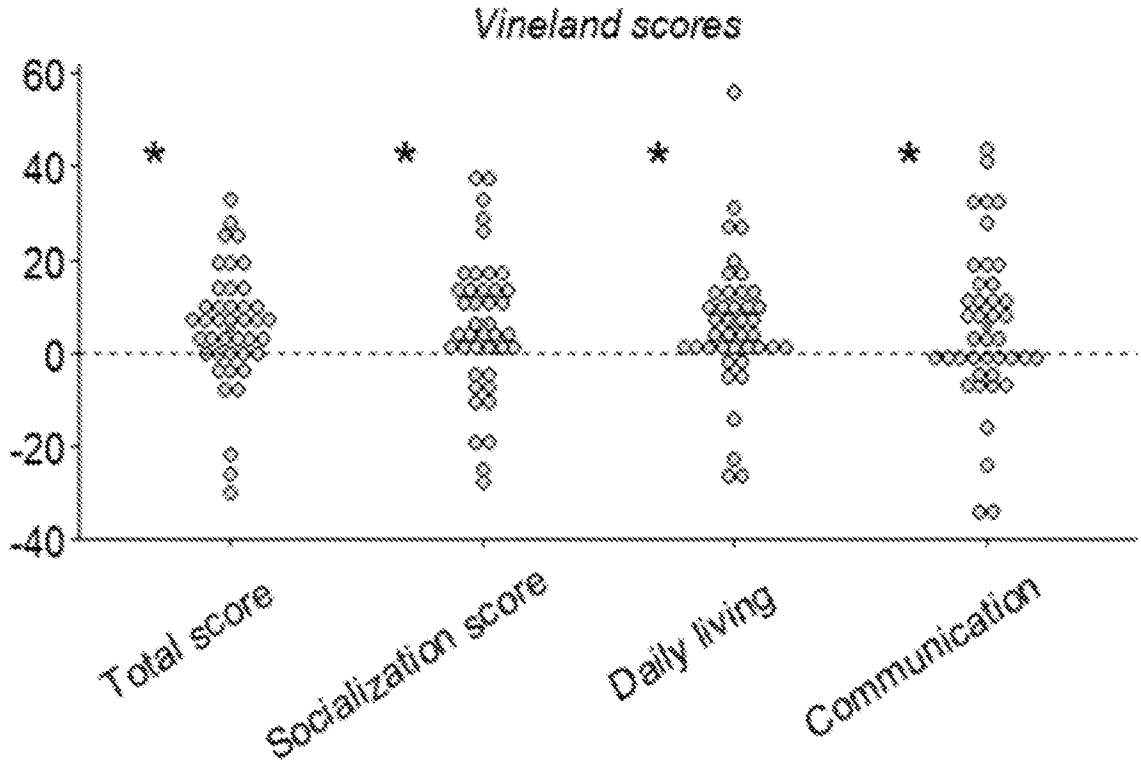

A
ADOS scores
Change pre/post treatment
5
0
-5
-10
*
*
*
SA
RRB
Total score
CSS

Fig. 7


Vineland scores
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40
20
0
-20
-40
*
*
*
*
Total score
Socialization score
Daily living
Communication

Fig. 8

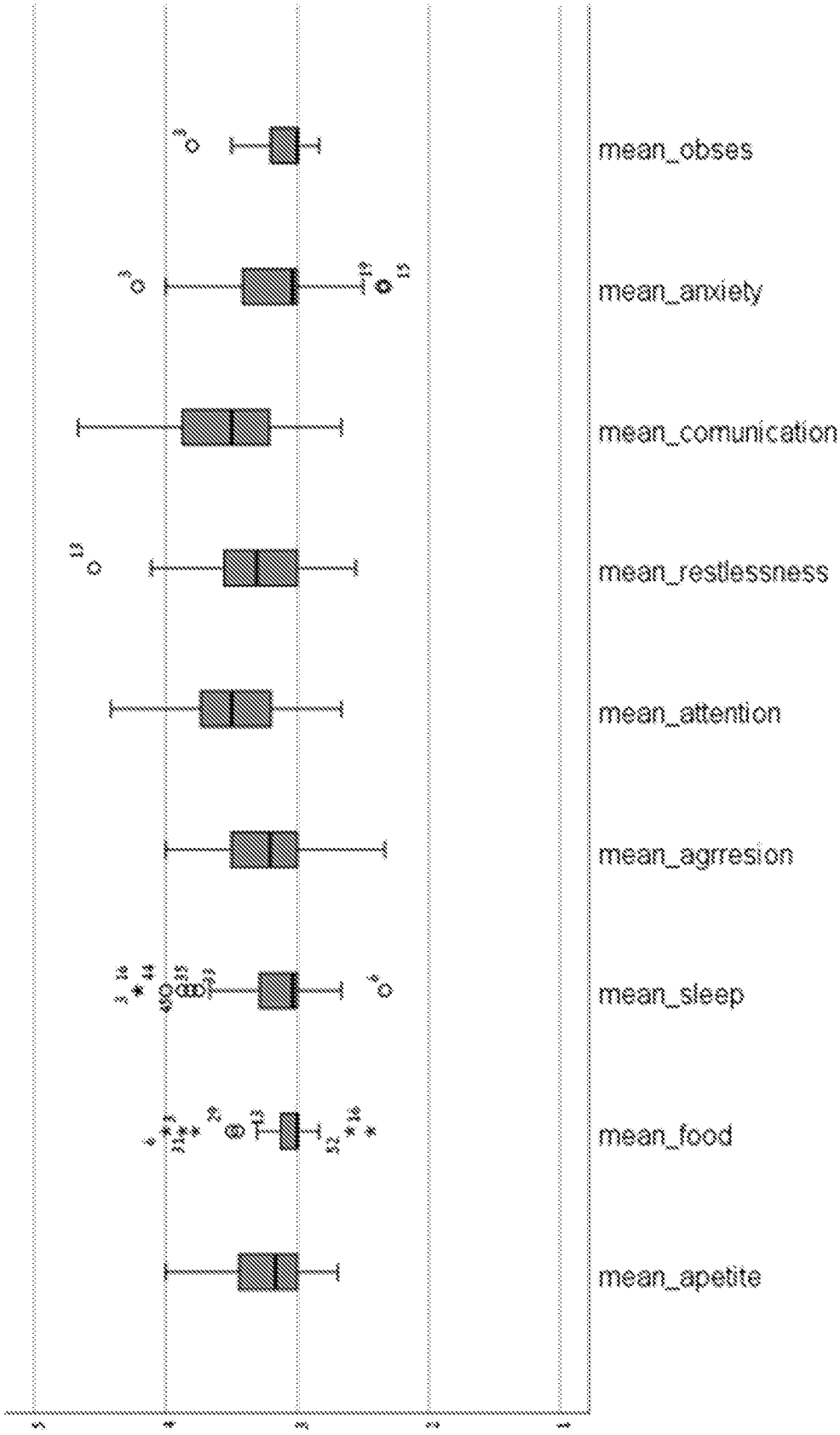
mean_obses
mean_anxiety
mean_comunication
mean_restlessness
mean_attention
mean_agrresion
mean_sleep
mean_food
mean_apetite

Fig. 9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2021/051254

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/352(2022.01)i; ***A61K 36/00***(2022.01)i; ***A61K 9/107***(2022.01)i; ***A61P 25/00***(2022.01)i
CPC:A61K 31/352; A61K 2300/00; A61K 36/00; A61K 9/107; A61P 25/00

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 31/352; A61K 36/00; A61K 9/107; A61P 25/00
CPC:A61K 31/352; A61K 2300/00; A61K 36/00; A61K 9/107; A61P 25/00

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

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

Databases consulted: NCBI, BLAST, Esp@cenet, Google Patents, CAPLUS, BIOSIS, MEDLINE, PubMed, Google Scholar, DWPI, Orbit Search terms used: CBD, cannabidiol, high-CBD, T1/C20, Avidekel, Nitzan, b-caryophyllene, linalool, a-pinene, limonene, ASD, autism spectrum disorder, hyperactivity, self-injury, sleep, social communication, anxiety

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
D,Y	Aran, Adi, et al.: "Brief report: cannabidiol-rich cannabis in children with autism spectrum disorder and severe behavioral problems—a retrospective feasibility study"; Journal of Autism and Developmental Disorders, Vol. 49, No. 3, P. 1284-1288, DOI: 10.1007/s10803-018-3808-2 (2018/10/31) Abstract, introduction p. 1284, methods p.1285	1-25
Y	WO 2020157639 A1 (BUZZELET DEVELOPMENT AND TECHNOLOGIES LTD [IL])06 August 2020 (2020-08-06) Abstract, para. [004], [0055], [0065], [0097], [0099], [00165], example 1, claims 1-2, 20 and 37	1-25
Y	Ryan, Lauren:" The Promising Emerging New Autism Drug: Cannabis"; retrieved from Linkedin: URL:< https://www.linkedin.com/pulse/promising-emerging-new-autism-drug-cannabis-lauren-ryan>, [Retrieved on 05/01/2022] (2020/01/28) Whole document	1-25

☑ 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
10 January 2022	**10 January 2022**

Name and mailing address of the ISA/IL	Authorized officer
Israel Patent Office **Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel** **Israel** Telephone No. **972-73-3927201** Email: **pctoffice@justice.gov.il**	**BERMAN ZAKEN Yael** Telephone No.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Russo, Ethan B.: "Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects"; British Journal of Pharmacology, Vol. 163, Issue 7, p. 1344-1364, DOI:10.1111/j.1476-5381.2011.01238.x (2011/07/12) Abstract, p.1348, 1350, 1352, table 1 and 2	1-25
Y	Finkle, Katie: "Top terpenes for patients with autism"; retrieved from the internet: URL:< https://keystoneshops.com/2019/11/21/top-terpenes-for-patients-with-autism/>, [Retrieved on 05/01/2022] (2019/11/21) Whole document	1-25
A	Internet archive: Tikun-Olam, Avidekel strain; retrieved from the internet: URL:< https://web.archive.org/web/20200921022601/https://www.tikun-olam.org.il/strain/%D7%90%D7%91%D7%99%D7%93%D7%A7%D7%9C/>, [Retrieved on 05/01/2022] (2020/09/21) Whole document	1-12,15,16,18,23-25

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2021/051254

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
WO 2020157639 A1	06 August 2020	WO 2020157639 A1	06 August 2020
		AU 2020215164 A1	16 September 2021
		EP 3917505 A1	08 December 2021
		IL 285156 D0	30 September 2021
		US 2021353638 A1	18 November 2021