This Clinical Monograph is only to be used by health professionals.

Public Monograph for general Suggested Use of our supplements is at: https://quality.cannacea.life/SM.FSHO.EN.pdf

DISCLAIMER: **This information is developed from the cited references and has not been evaluated by the US Pharmacopeia (USP), the US Food and Drug Administration (FDA), the European Commission (EC), the UK Food Standards Agency (FSA), or any other regulatory agency unless specifically noted. While we endeavor to reference trustworthy peer-reviewed scientific sources, we make no representations as to the accuracy, completeness, or usefulness of this information or references. By applying or using the educational information provided or cited here, you agree Cannacea and its affiliates will not be liable for any consequences of such application or use.**

OVERVIEW: **Read carefully before recommending use, especially if patient has a medical condition, takes medicine, is pregnant or nursing (or plans to be), or is a child. Intended for adults. To be kept out of child's reach. Contains no more than 0.2% THC. Low THC level may result in a failed drug test.**

These statements have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure or prevent any disease.

Supplement Facts, Suggested Use and Ingredient Listing for our products can be found on product labeling and online at https://www.cannacea.life. Website also describes details of our extraction and production processes. Comprehensive batch-specific constituency, potency and purity Certificates of Analysis by ISO/IEC 17025 accredited laboratories available by scanning QR code on labeling and online by LotID at https://quality.cannacea.life.

KEY WARNINGS AND PRECAUTIONS

- **Maximum intakes, THC advisory, and Drug Test advisory:** Section 3
- **Contraindications, Hypersensitivities, and Allergies:** Section 4
- **Drowsiness, Sedation, and other potential Adverse Effects:** Section 5
- **Drug and Supplement Interactions:** Sections 6 and 7
- **Pregnancy and Nursing Contraindication details:** Section 8
- **Hepatic Impairment and CYP450 Polymorphism advice:** Section 8
- **Anti-Epileptic Drug concomitant use advice:** Sections 6 and 8
- **Seizure patient Withdrawal advisory:** Section 11

1. MODE OF ACTION

This supplement contains phytocannabinoids naturally produced within Hemp (*Cannabis sativa*) including Cannabidiol (CBD), Cannabigerol (CBG), Cannabichromene (CBC), Δ9-Tetrahydrocannabinol (THC), Cannabidivarin (CBDV), Cannabinol (CBN), and others *(see lot-specific lab results)*. These can supplement endogenous endocannabinoid neurotransmitters such as arachidonoyl ethanolamide (AEA, "anandamide") and 2-arachidonoyl glycerol (2-AG) that modulate the receptors, enzymes, and functioning of the Endocannabinoid System (ECS) acting across our bodies[1]. Alongside are countless known and unknown phytoterpenes, phytonutrients, minerals and other natural factors acting synergistically with the phytocannabinoids.

2. METHODS OF USE

Shake well before use (phytocompounds can settle differentially with time).

Take directly in mouth or mix into food or drink. Taking along with a fat-rich food or drink significantly increases phytocannabinoid absorption compared with taking in a fasted state[2]. Taking with a fat-rich snack away from meals may accelerate absorption compared with taking at the end of a large meal that may delay absorption. **Users sensitive to the flavor or direct intake of hemp oil may prefer it mixed and diluted into a morsel, snack, or meal before intake.**

This hemp oil can also be used externally for direct topical Endocannabinoid supplementation of affected areas, **avoiding eyes or open wounds**.

Bottle must be kept cool, dry, and away from light. Phytocannabinoids are sensitive to heat, oxygen, and especially light once in solution. Avoid having moisture or debris adhering to dropper or entering bottle, so keep glass dropper clean and use with care. Dropper pipette is marked in 0.25 mL increments, use oil meniscus to align.

With Macadamia Nut Oil as carrier, **this oil should remain primarily fluid if refrigerated for freshness** (best kept in fridge door). If fats appear in cooled oil, to melt leave bottle for a few minutes at room temperature or carry it in a pocket, shaking well before serving. These tips can also apply during the winter. If stored in fridge, sufficiently re-warm bottle before opening so the bottle is no longer "sweating" with condensation when wiped dry, to **avoid formation of condensation inside refrigerated bottle once opened**.

3. SUPPLEMENT INTAKES

The safety of chronic human CBD intakes up to 20-50 mgCBD/kg/day have been studied[3,4,5,6]. **Clinicians directing supplement intakes are advised:**
1) **Know and monitor for potential adverse & drug interaction effects, typically intake-proportional, factoring for Special Populations** *(see Sections 4 - 8)*.
2) **Start with low intakes (0.1 – 1 mgCBD/kg/day, depending on severity of case). If greater therapeutic effects are desired, raise intake as gradually as possible, raising daily intake by a *maximum* 5 mgCBD/kg/day in a week, and keep intake as low as possible that achieves desired effects.**
3) **Best not to exceed often-studied 20 mgCBD/kg/day chronic intake ceiling.**
Full spectrum oils have been shown to achieve intended effects at lower CBD intakes than purified CBD or isolates[7].

THC advisory: Contains low levels of psychotropic Δ9-Tetrahydrocannabinol (THC) that has a mean acute Lowest Observed Effect Level (LOEL) of 2.5 mgTHC in clinical studies[8]. **This supplement provides less than 2 mgTHC per mL**.

While CBD may suppress some THC effects[9], **physicians directing high intakes of this supplement are advised to monitor for any psychotropic, psychotomimetic, anxiogenic, arrhythmic, tachycardic, hypertensive, orthostatic hypotensive, hypothermic or other pharmacological effects of THC**. Any potential THC effects experienced at a given corresponding CBD intake level should decrease by taking a hemp supplement having higher CBD:THC ratio.

ACTIVATED 40 is > 25:1 CBD:THC	**TAGRID'S 100 is > 70:1 CBD:THC** for sensitive persons requiring maximum supplementation

(With natural variations, see lab results for lot-specific CBD:THC ratios. Full spectrum oils lose ~25% THC a year / CBD:THC rises ~33% a year.)

Supplement use may result in a failed drug test. Human trials showed THC drug test metabolites are detectable in blood and urine during and days after intake of full spectrum cannabis oil having 22:1 CBD:THC ratio taken at 120 mgCBD/day and above for 7 days [10]. *(details in Section 9)*

4. CONTRAINDICATIONS

This supplement is contraindicated for use in any persons having a history of hypersensitivity to CBD, cannabinoids or any ingredient in the product, including allergy to Hemp, Macadamia nuts or tree nuts.

Supplement is contraindicated for use in pregnant and nursing women. ***(See Section 8)***

5. ADVERSE EFFECT POTENTIAL

Intake-dependent drowsiness, fatigue, lethargy, sedation, diarrhea and reduced appetite can commonly occur at high supplement intakes. Pyrexia, rash and upper respiratory infection were also reported in clinical trials using high intakes of purified CBD and concomitant anti-epileptic drugs. [3, 4]

A human trial of full spectrum cannabis oil of 22:1 CBD:THC ratio only showed higher adverse effect rates than placebo at CBD intakes exceeding 240 mgCBD per day (exceeding 120 mgCBD 2x per day).[10]

Users should not drive or operate machinery before acclimating to intake levels and determining how such activities might be affected, especially at higher intakes.

Hepatic Effects: Human epilepsy trials of purified CBD given at 10 - 20 mgCBD/kg/day showed a low incidence rate of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevation greater than 3 times the upper limit of normal (ULN) in patients taking CBD alone. ALT or AST elevations were correlated with CBD intake and were significantly greater with concomitant valproate. As there were no significant elevations of bilirubin (above 2x ULN) no drug-induced liver injury was inferred.[6, 11]

Baseline and ongoing serum levels of ALT, AST, and bilirubin may need monitoring in persons taking this supplement at levels corresponding to an intake of 10 mgCBD/kg/day or above. *(Special advice for Persons with Hepatic Impairment in Section 8)*

6. DRUG INTERACTION POTENTIAL

Ensure the potential interactions between this hemp supplement and any administered drugs are known, in all cases monitoring for signs of drug interaction with a readiness to adjust drug dosages and/or supplement intakes where clinically appropriate.

Clinician-oriented resource listing over 1,000 potential supplement-drug and supplement-supplement interactions can be accessed online at:

https://clinic.cannacea.life/CannabinoidInteractions.pdf

Effect of Supplement on Drugs: CBD and other phytocannabinoids in this supplement affect Cytochrome P450 enzymes that metabolize many drugs, (**bold** if well-established) possibly inhibiting CYP1A1, **1A2**, 1B1, 2A6, **2B6**, **2C8**, **2C9**, **2C19**, **2D6**, **3A4**, 3A5, and 3A7, and inducing **CYP1A2**, **2B6**, and **3A4** [12, 13]. CBD can inhibit phase II metabolic enzymes UGT1A9 and 2B7 [12, 13], and can inhibit the P-glycoprotein (P-gp) transporter [3]. The CBD inactive metabolite 7-COOH-CBD can inhibit transport mediated via BCRP and BSEP [12]. An inhibitory enzyme interaction for a drug can increase that drug's plasma levels, usually increasing its intended, adverse and/or interactive effects. An inductory enzyme interaction for a drug can decrease that drug's plasma levels, usually decreasing its effects.

Effect of Drugs on Supplement: CBD and the other phytocannabinoids are primarily metabolized by CYP2C9, 2C19 and 3A4, and phase II UGT1A7, 1A9, and 2B7 enzymes [12, 13]. Taking supplement with inhibitors of these enzymes can increase plasma levels of CBD and other phytocannabinoids, increasing their intended, adverse and/or interactive effects. Taking with inducers of these enzymes can decrease plasma levels of CBD and other phytocannabinoids, reducing their effects and efficacy of supplementation.

Concomitant Valproate/Clobazam/Stiripentol: Taking supplement with valproate, and to a lesser extent with clobazam, may increase incidence of ALT or AST elevation. Human trials coadministering purified CBD and clobazam showed increases in plasma concentrations of 60% for clobazam and 300%-500% for N-desmethylclobazam (the clobazam active metabolite), increasing risk of clobazam-related adverse effects, with increases of 40%-70% in plasma levels of CBD and its active metabolite 7-OH-CBD. CBD coadministration with stiripentol also increased stiripentol plasma levels.[12, 13, 14]

Concomitant CNS Depressants and Alcohol: Taking this supplement with central nervous system depressants (CNS depressants) such as alcohol, barbiturates, benzodiazepines, muscle relaxants and others increases risk of drowsiness and sedation.[12, 13]

7. SUPPLEMENT INTERACTION POTENTIAL

Ensure the potential interactions between this hemp supplement and any other herbs or supplements taken in combination are known, in all cases monitoring for signs of interaction with a readiness to adjust herb and/or supplement intakes as appropriate, including intakes of this supplement.

Taking this hemp supplement with other herbs or supplements may cause their intended, adverse and/or drug interaction effects to be increased or decreased, depending whether our hemp oils inhibit or induce the enzymes that metabolize their active ingredients. Inversely, taking other herbs or supplements that affect the enzymes metabolizing the CBD and other phytocannabinoids in our hemp oils may increase or decrease the intended, adverse and/or drug interaction effects of our hemp oils. *(see Section 6 for the enzymes affected by phytocannabinoids, and which enzymes metabolize phytocannabinoids. The online* ***Interactions List*** *linked above includes some supplements having potential interactions with our hemp oils, with some listed in following subsection for "Drowsiness")*

Drowsiness: Some sleep-promoting herbs or supplements may cause excessive drowsiness when combined with our hemp oils[12], such as: **Calamus**, **California poppy**, **Catnip**, **Chamomile**, **5-HTP**, **GABA**, **Glycine**, **Hops**, **Jamaican dogwood**, **Kava**, **Lavender**, **L-tryptophan**, **Melatonin**, **Passionflower**, **SAMe**, **Sassafras**, **Skullcap**, **St. John's wort**, and **Valerian**. Special care must be taken when combining this hemp supplement with other herbs or supplements that promote sleep to determine any additive effects.

Grapefruit Interaction: The consumption of grapefruit or its juice is known to inhibit the CYP3A4 liver enzyme, which could increase the intended, adverse and/or drug interaction effects of this supplement. This will be dependent on the concentration, dose and preparation of grapefruit or its juice. If ingesting grapefruit or its juice while taking this supplement, monitor this supplement's effects and lower or adjust intakes accordingly.[15]

8. SPECIAL POPULATIONS

Pregnancy: Supplement is contraindicated in women who are pregnant. There may be potential for embryofetal developmental toxicity if pregnant while taking phytocannabinoids. Animal studies show cannabinoids readily cross the placenta to the fetus in mammals, increasing the incidence of teratogenicity dose-dependently [4, 16, 17]. **Supplement should not be used during pregnancy.**

Lactation: Supplement is contraindicated in women who are nursing. There may be potential for postnatal infant developmental toxicity if nursing while taking phytocannabinoids. Human studies show cannabinoids like THC and CBD accumulate in breast milk where they can be detected up to 6 weeks after intake cessation, have detectable metabolites in infant feces, and may retard infant motor development [18, 19]. At high maternal CBD intakes, animal studies show dose-dependent postnatal developmental toxicity in infant rats [4], while CBD and THC show dose-dependent teratogenic potential in other animal studies [4, 16, 17]. **Supplement should not be used while nursing an infant or during the preceding 6 weeks.**

Phytocannabinoid teratogenicity seems due to influence on endocannabinoid activities that are key for the proper development of embryo and fetus.[17, 20]

Hepatic Impairment: Persons with moderate hepatic impairment (Child-Pugh B) or severe hepatic impairment (Child-Pugh C) are known to have significantly elevated CBD plasma concentrations compared with healthy populations.[21]

CYP450 Polymorphisms: Persons with Cytochrome P450 polymorphisms having atypical "variant" or "wild type" alleles encoding the CYP2C9, 2C19 or 3A4 enzymes may be "poor" or "ultra-rapid" metabolizers of CBD and the other phytocannabinoids, thus increasing or decreasing, respectively, their plasma levels, intended effects, adverse effects and/or interactive effects.[22]

Anti-Epileptic Drugs: Persons taking Anti-Epileptic Drugs (AEDs) might experience some drug interactions and other reactions if concomitantly taking this supplement, including: 1) potential for transaminase elevation *(see Sections 5 and 6)*, 2) potential for an increase in plasma levels of the AED(s), CBD and/or the other phytocannabinoids if there is a drug interaction *(see Section 6)*, and 3) increased risk of suicidal ideation or behavior as sometimes seen when administering AEDs.[12]

9. CLINICAL PHARMACOLOGY

Enzymes that metabolize CBD and other phytocannabinoids in supplement are in *Section 6*. Important food effects on absorption are in *Section 2*.

CBD Oral Pharmacokinetics: CBD is primarily metabolized by the liver, and somewhat the GI tract, into active 7-OH-CBD that gets converted to inactive 7-COOH-CBD. Taken in oil form, CBD is subjected to significant first-pass liver metabolism before entering the blood, having ~80% transformed into 7-COOH-CBD, ~10% into 7-OH-CBD, with ~10% remaining as parent CBD. CBD metabolites are excreted into urine and feces, but not into oral fluid or sweat.[10, 23, 24]

A trial of 32 humans taking 60-240 mgCBD 2x/day (120-480 mgCBD/day) using 22:1 CBD:THC full spectrum cannabis oil for 7 days showed dose-proportional CBD plasma level with 7.2-36.3 ngCBD/mL mean peak plasma level (C_{max}) across intake range. On day 7, 7-COOH-CBD comprised 91%-95% of plasma exposure for all intakes, with the remainder split between 7-OH-CBD and parent CBD. Following data apply for all intakes in the study: CBD plasma levels reached steady-state within 7 days. Mean time to C_{max} peak (t_{max}) was 4-6 h for CBD and 7-OH-CBD, and 4-8 h for 7-COOH-CBD, without significant differences from day 1 to day 7. Mean half-life in plasma ($t_{1/2}$) was 4-6 h for CBD and 7-OH-CBD after 7 days ($t_{1/2}$ for 7-COOH-CBD was above quantification limit due to low clearance). Mean clearance (CL/F) on day 7 was 1,200-2,800 L/h for CBD and 7-OH-CBD, and 30-100 L/h for 7-COOH-CBD. Clearance rate for 7-COOH-CBD showed clear decrease as intake increased, which somewhat occurred for CBD as well.[10]

A trial of 13 humans taking a single ~1mg CBD and ~3mg CBDA dose using ~1:1 CBD:THC full spectrum cannabis oil showed mean plasma C_{max} for CBDA 70x higher than CBD. 7-COOH-CBD again dominated overall plasma exposure, though 7-OH-CBD had 2x higher mean C_{max} than 7-COOH-CBD, in contrast with the above higher-dose study (perhaps due to CBDA effects or low doses in this study). Mean t_{max} was 1.5-2 h for CBD and 7-OH-CBD, and 6h for 7-COOH-CBD. In urine, active 7-OH-CBD was found at ~4x higher mean concentration than inactive 7-COOH-CBD.[23]

THC Oral Pharmacokinetics: THC is metabolized into active 11-OH-THC that gets converted to inactive 11-COOH-THC. Similarly to CBD, taken in oil-form, THC is subjected to significant first-pass liver metabolism before entering the blood, with ~80% transformed into 11-COOH-THC, ~10% into 11-OH-THC, and ~10% remaining as parent THC.[24]

A 7-day human trial using 22:1 CBD:THC full spectrum cannabis oil taken at 60-240 mgCBD with 2.7-10.8 mgTHC 2x/day (120-480 mgCBD/day, 5.4-21.6 mgTHC/day) resulted in undetectable THC levels in plasma for all intakes (0.78 ng/mL LOQ). 11-OH-THC was detected in plasma after 7 days with 5.4-10.8 mgTHC 2x/day intake levels, but not on day 1. THC drug-test metabolite 11-COOH-THC was detected in plasma throughout the study for all intake levels (>0.78 ng/mL), and was detectable above 50 ng/mL in urine for all intake levels, particularly for the 120-240 mgCBD + 5.4-10.8 mgTHC 2x/day intakes, for at least 3-6 days after cessation of intake.[10]

10. ABUSE, DEPENDENCE & WITHDRAWAL ADVISORY FOR SEIZURES

CBD is the major phytocannabinoid (PC) in supplement (>80% of PC w/w), hence the following Abuse, Dependence and Withdrawal focus is on CBD.

Abuse: Human and animal studies show CBD does not produce THC-like behavioral responses or rewarding effects.[25]

Human studies show acute administration of CBD to adults at doses of 750, 1500, and 4500 mg in the fasted state (10, 20, and 60 mg/kg for 75 kg adults, respectively) produced responses on positive subjective measures (e.g., "Drug Liking" and "Take Drug Again") within acceptable placebo range, unlike significantly higher responses for THC or alprazolam.[26]

Dependence: Administration of CBD at 1500 mg/day (2x 750 mg) to adults for 28 days did not produce signs or symptoms of withdrawal over a 6-week assessment period after CBD discontinuation.[27]

Withdrawal for Seizures: Notwithstanding the lack of withdrawal symptoms in typical adult populations cited above, **for persons experiencing seizures, abrupt discontinuation of high CBD intakes should be avoided to minimize risk of increased seizure frequency and/or intensity**. High intakes of CBD in these persons should be decreased gradually.

11. GENERAL SAFETY

Human studies using full spectrum and purified CBD show no adverse effects with acute intakes up to at least 120 mgCBD and 240 mgCBD/day, typically.

The safety of acute and chronic CBD intakes up to 1500 mg or 20 mg/kg per day has been fairly well-studied in humans.[3, 4, 10]

A human trial with oral CBD-rich hemp oils ranging from full spectrum to CBD isolate taken for at least 60 days showed no evidence of liver disease in the 839 participants, with no increase in the prevalence of elevated liver function tests when compared to a population with a similar incidence of medical conditions.[28]

12. NONCLINICAL TOXICOLOGY

Hemp Extract: Hemp extract containing 26% phytocannabinoids (25% CBD, 1% others), 13% non-cannabinoid phytocompounds (terpenes, sterols, tocopherols and fatty alkanes), and 61% edible fatty acids, was administered to Wistar rats at 100-760 mgExtract/kg/day for 90 days. A No Adverse Effect Level (NOAEL), including fertility effects, of 100 mgExtract/kg/day for males (providing 25 mgCBD/kg/day), and of 360 mgExtract/kg/day for females (providing 90 mgCBD/kg/day) was determined in the rats. There was no evidence of genotoxicity for the hemp extract in a bacterial reverse mutation test (Ames), in vitro mammalian chromosomal aberration test, or in vivo mouse micronucleus study.[29]

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