**Table S1**. Selected *Cannabis sativa* L.-derived cannabinoids, their targets, mechanisms of action, and potential resultant pharmacological effects – Table adapted from (Christensen et al., 2023)

|  |  |  |  |
| --- | --- | --- | --- |
| **Structures** | **Targets** | **Mechanisms of Action** | **Potential Pharmacological effects** |
| A diagram of chemical structures  Description automatically generated with medium confidence**Δ9‑Tetrahydrocannabinol (THC) (2)** | CB1 | Partial agonist | Analgesic \*\*, \*\*\*Anti-convulsant \*\*Anti-epileptic \*\*Sleep improvement \*\*, \*\*\*Anti-anorectic \*\*, \*\*\*appetite stimulating \*\*, \*\*\*Anti-emetic \*\*, \*\*\*Anxiolytic \*\* |
| CB2 | Partial agonist | Analgesic \*\*, \*\*\* |
| GPR55 | Agonist | Not reported |
| GPR18 | Agonist | Not reported |
| 5-HT-3A | Antagonist | Anti-nociception \*Anti- emetic \* |
| DOR | Negative allosteric modulator | Not reported |
| MOR | Negative allosteric modulator | Not reported |
| PPAR-y | Agonist | Anti-cancer, anti-proliferative \*, \*\* |
| GlyR | Agonist | Analgesic \*, \*\* |
| TRPV2 | Agonist | Not reported |
| TRPV3 | Agonist | Not reported |
| TRPV4 | Agonist | Not reported |
| TRPA1 | Agonist | Not reported |
| TRPM8 | Antagonist | Not reported |
| **Cannabidiol (CBD) (3)**A diagram of chemical structures  Description automatically generated with medium confidence**Cannabidiol (CBD) (3)**A diagram of chemical structures  Description automatically generated with medium confidence**Cannabidiol (CBD) (3)**A diagram of chemical structures  Description automatically generated with medium confidence**Cannabidiol (CBD) (3)** | CB1 | Negative allosteric modulatorAntagonist | THC-related adverse effects modulation \*\*, \*\*\*Anxiolytic \*\*Antidepressant \*\*Vasorelaxant \*\* |
| CB2 | Partial agonistNegative allosteric modulatorAntagonist | Seizure reduction \*\*Anti-epileptic \*\*Anti-inflammatory \*\*Anti-cancer \*, \*\*Body weight decrease \*\*Neuroprotection \*\* |
| GPR3 | Inverse agonist | Alzheimer’s disease improvement \* |
| GPR6 | Inverse agonist | Parkinson’s disease improvement \* |
| GPR12 | Inverse agonist | Anti-cancer \* |
| GPR55 | Antagonist | Anti-epileptic \*\*, \*\*\*Seizure dampening \*\*Bone resorption inhibition \*\*Parkinson’s motor skills improvement \*\*Cancer cell migration inhibition |
| FAAH | Inhibitor | AEA increase and related effects \*Sleep induction \*, \*\*Stress reduction \*\*\*Anxiolytic \*\*\*Anti-depressant \*\* |
| 5-HT-1A | AgonistInverse agonist | Anti-emetic \*, \*\*Analgesic \*\*Chemotherapy induced neuropathic pain reduction \*, \*\*Anxiolytic \*\*Anti-depressant \*\*Cognitive performance improvement \*\*Anti-epileptic \*, \*\*, \*\*\*Seizure reduction \*\*Anti-stress \*\*Neuroprotection \*\* |
| 5-HT-3A | Antagonist | Anti-emetic \*\*Cardiovascular effects \*\* |
| A1A | Agonist | Anti-arrhythmic \*\*Analgesic \*\* |
| A2A | Agonist | Anti-inflammatory \*, \*\*Cognitive performance improvement \*\* |
| PPAR-*γ* | Agonist | *β*-amyloid-induced neuroinflammation reduction \*, \*\*Hippocampal neurogenesis \*, \*\*Alzheimer’s disease improvement \*, \*\* |
| Immune cell (not further specified) | InhibitorActivator | Anti-inflammatory \*, \*\*Immunosuppressive \*, \*\*Cytokine release reduction/increase \*, \*\*Anti-arthritic \*\*Multiple sclerosis amelioration \*\* |
| Gly-*α1* | Positive allosteric modulatorAgonist | Anti-inflammatory \*Neuroprotective \* |
| Gly-*α*3 | Positive allosteric modulator | Analgesic \*\* |
| GABA-A | Positive allosteric modulator | Anti-convulsant \*\*Anti-epileptic \*\* |
| TRPV1 | Agonist | Neuron anti-hyperexcitability \*Anxiolytic \*\*Anti-cancer, apoptosis \*Microglial phagocytosis enhancement \*Cardiovascular effects \*\* |
| TRPV2 | Agonist | Microglial phagocytosis enhancement \* |
| TRPV3 | Agonist | Not report |
| TRPV4 | Agonist | Not report |
| TRPA1 | Agonist | Analgesic \*\* |
| TRPM8 | Antagonist | Not reported |
| DOR | Negative allosteric modulator | Not reported |
| MOR | Negative allosteric modulator | Not reported |
| D2 | Partial agonist | Anti-psychotic\* |
| A black and white image of a molecule  Description automatically generated**Cannabigerol (CBG) (4)** | CB2 | Partial agonist | Anti-inflammatory \*, \*\*Colitis attenuation \*, \*\* |
| AEA uptake | Inhibitory | Various effects related to AEA \* |
| 5-HT-1A | Antagonist | Reverse anti-emetic effect of, *e.g.* CBD \*\* |
| A2A | Agonist | Not reported |
| TRPV1 | Agonist | Not reported |
| TRPA1 | Agonist | Not reported |
| TRPM8 | Antagonist | Colon anti-cancer \*\* |
| **Δ9-Tetrahydrocannabinolic acid (THCA) (5)**A black and white image of a molecule  Description automatically generated**Δ9-Tetrahydrocannabinolic acid (THCA) (5)** | CB1 | Partial agonist | Anti-nociceptive \*\*Anti-inflammatory |
| CB2 | Agonist | Not reported |
| PPAR-*γ* | Agonist | Adiposity reduction \*\*Metabolic syndrome prevention \*\*Anti-inflammatory \*\*Neuroprotective \*, \*\* |
| A group of chemical structures  Description automatically generated**Cannabichromene (CBC) (6)** | CB2 | Agonist | Anti-inflammatory \* |
| AEA uptake | Inhibitor | Various effects related to AEA \* |
| TRPV3 | Agonist | Not reported |
| TRPV4 | Agonist | Not reported |
| TRPA1 | Agonist | Anti-inflamatory \*\*Colitis reduction \*\*Analgesic \*\* |
| TRPM8 | Antagonist | Not reported |
| A group of chemical structures  Description automatically generated **Cannabinol (CBN) (7)** | CB1 | Agonist | Appetite increase \*\* |
| CB2 | AgonistInverse agonist | Not reported |
| TRPA1 | Agonist | Not reported |
| TRPM8 | Antagonist | Not reported |
| A group of chemical structures  Description automatically generated**Δ8-Tetrahydrocannabivarin (THCV) (8)****Δ8-Tetrahydrocannabivarin (THCV) (8)** | CB1 | AgonistAntagonist | Anti-psychoactive (*e.g.* reverse THC-induced psychoactive effects) \*\*Analgesic \*\*Anti-convulsant \*\*Anti-epileptic \*Hypophagia and weight reduction \*\*Glycemic control improvement \*\*, \*\*\* |
| CB2 | Partial agonistAntagonist | Anti-inflammatory \*\*Inflammatory pain reduction \*\* |
| 5-HT-1A | Agonist | Antipsychotic \*, \*\* |
| TRPV2 | Agonist | Not reported |
| TRPA1 | Agonist | Not reported |
| TRPM8 | Antagonist | Not reported |
| A group of chemical formulas  Description automatically generated**Cannabidiolic acid (CBDA) (9)** | CB2 | Partial agonist | Not reported |
| 5-HT-1A | Agonist | Anti-emetic \*\*Anti-convulsant \*\*Anxiolytic \*\* |
| TRPV1 | Agonist | Anti-heperalgesic \*\* |
| A group of chemical formulas  Description automatically generated**Δ8-Tetrahydrocannabinol** **(THC) (11)** | CB1 | Partial agonist | Appetite stimulant \*\* |
| CB2 | Agonist | Not reported |
| A group of chemical structures  Description automatically generated**Cannabivarin (CBDV) (24)** | GABA-A | Positive allosteric modulator | Anticonvulsive \*, \*\*\*Anti-epileptic \*, \*\*\* |
| TRPV1 | Agonist | Neuronal anti-heperexcitability \*Anti-convulsant \*\* |
| TRPV2 | Agonist | Not reported |
| TRPV3 | Agonist | Not reported |
| TRPA1 | Agonist | Not reported |

\*: Pre-clinical *in vitro* study; \*\*: pre-clinical *in vivo* study; \*\*\*: clinical study; N.B.: This table is non-exhaustive, broadly elucidating selected compounds and some of their potential pharmacological effects currently present in the pre-clinical literature. Depending on study parameters, the compounds show differing, sometimes biphasic, affinities and effects at different targets, thus highlighting the contradictory and equivocal evidence state. **Abbreviations:** 5-hydroxytryptamine receptor 1A (5-HT-1A); 5-hydroxytryptamine receptor 3A (5-HT-3A); adrenergic receptor alpha-1 (A1A); adrenergic receptor alpha-2 (A2A); anandamide endocannabinoid (AEA); cannabinoid receptor 1 (CB1); cannabinoid receptor 2 (CB2); delta-opioid receptor (DOR); dopamine D2 receptor (D2); fatty acid amide hydrolase enzyme (FAAH); gamma-aminobutyric acid type A receptor (GABA-A); glycine receptor (GlyR); glycine receptor type *α*1 (GlyR-*α*1); glycine receptor type *α* 3 (GlyR-*α*3 ); G-protein-coupled receptor 2 (GPR2); Gprotein- coupled receptor 3 (GPR3); G-protein-coupled receptor 6 (GPR6); G-protein-coupled receptor 12 (GPR12); G-protein-coupled receptor 18 (GPR18); G-protein-coupled receptor 55 (GPR55); Mu-opioid receptor (MOR); peroxisome proliferator-activated receptor gamma (PPAR-γ); transient receptor potential cation channel type A1 (TRPA1); transient receptor potential cation channel 8 (TRPM8); transient receptor potential vanilloid type 1 (TRPV1); transient receptor potential vanilloid type 2 (TRPV2); transient receptor potential vanilloid type 3 (TRPV3); transient receptor potential vanilloid type 4 (TRPV4).

**Table S2.** Selected Cannabis sativa L.-derived terpenes, their targets, mechanisms of action, and potential resultant pharmacological effects. Table adapted from (Christensen et al., 2023)

|  |  |  |  |
| --- | --- | --- | --- |
| **Structures** | **Targets** | **Mechanisms of Action** | **Potential Pharmacological effects** |
| **A group of chemical formulas  Description automatically generated****Myrcene (14)** | TRPV1 | Agonist | Analgesic \* |
| A2A | Agonist | Analgesic \*\* |
| **A group of chemical formulas  Description automatically generated****Limonene (17)** | 5-HT-1A | Agonist | Anti-stress \*\*Anxiolytic \*\*Anti-depressant \*\* |
| TRPA1 | Agonist | Analgesic \*\* |
| NFκB | Inhibitor | Anti-inflammatory \*\*, \*\*\*Analgesic \*\*Colitis reduction \*\* |
| A2A | Agonist | Not reported |
| FTase | Inhibitor | Anti-cancer \*\* |
| MAPK NFκB | Inhibitor | Anti-inflammatory \*\* |
| ERK/AKT | Agonist | Anti-cancer \*, \*\* |
| Virus particle (not further specified) | Inhibitor | Anti-viral \* |
| **A group of chemical formulas  Description automatically generated****Linalool (20)** | A1A | Agonist | Analgesic \*\* |
| A2A | Agonist | Analgesic \*\* |
| GABA-A | Agonist | Anxiolytic \*\* |
| Cancer cell (not further specified) | Inhibitor | Anti-cancer \*, \*\* |
| **Caryophyllene (21)****A group of chemical formulas  Description automatically generated****Caryophyllene (21)** | CB2 | Agonist | Analgesic \*\*Chemotherapy-induced peripheral neuropathy attenuation \*\*Anti-inflammatory\*\*Steatohepatitis protecting \*\*Metabolic dysregulation attenuation \*\* |
| PPAR-*α* | Agonist | Intracellular lipid modification\*Steatohepatitis protecting\* |
| PPAR-*γ* | Agonist | Intracellular lipid modification\*Steatohepatitis protecting\* |
| MAPK | Inhibitor Agonist | Chemotherapy-induced peripheral neuropathy attenuation \*\*Anti-cancer \* |
| TLR4 | Inhibitor | Microglial activation inhibition \*\*Neuroprotective \*, \*\*Anti-inflammatory \*, \*\* |

\* Pre-clinical *in vitro* study. \*\* Pre-clinical *in vivo* study. \*\*\* Clinical study. N.B.: This table is non-exhaustive, broadly elucidating selected compounds and some of their potential pharmacological effects currently present in the pre-clinical literature. Depending on study parameters, the compounds show differing, sometimes biphasic, affinities and effects at different targets, thus highlighting the contradictory and equivocal evidence state. **Abbreviations**: 5-hydroxytryptamine receptor 1A (5-HT-1A); adrenergic receptor alpha-1 (A1A); adrenergic receptor alpha- 2 (A2A); cannabinoid receptor 2 (CB2); Extracellular-regulated kinase/serine/threonine kinase (ERK/AKT); farnesyltransferase (FTase); gamma-aminobutyric acid type A receptor(GABA-A); mitogen-activated protein kinase (MAPK); Nuclear factor kappa B (NFκB); peroxisome proliferator-activated receptor alpha/gamma (PPAR- *α*/γ); Toll-like receptor 4 (TLR4); transient receptor potential cation channel type A1 (TRPA1); transient receptor potential vanilloid type 1 (TRPV1).