**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 modulator  Antagonist | THC-related adverse effects modulation \*\*, \*\*\*  Anxiolytic \*\*  Antidepressant \*\*  Vasorelaxant \*\* |
| CB2 | Partial agonist  Negative allosteric modulator  Antagonist | 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 | Agonist  Inverse 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) | Inhibitor  Activator | Anti-inflammatory \*, \*\*  Immunosuppressive \*, \*\*  Cytokine release reduction/increase \*, \*\*  Anti-arthritic \*\*  Multiple sclerosis amelioration \*\* |
| Gly-*α1* | Positive allosteric modulator  Agonist | 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 | Agonist  Inverse 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 | Agonist  Antagonist | Anti-psychoactive (*e.g.* reverse THC-induced psychoactive effects) \*\*  Analgesic \*\*  Anti-convulsant \*\*  Anti-epileptic \*  Hypophagia and weight reduction \*\*  Glycemic control improvement \*\*, \*\*\* |
| CB2 | Partial agonist  Antagonist | 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).