Getting into the weeds on cannabis: Known potential side-effects and toxicity.

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Introduction

Cannabis sativa is one of the world's oldest cultivated plants[1], containing over 104 distinct cannabinoids and various other compounds, including terpenes, flavonoids, and other plant molecules[2]. For at least four millennia, humans have enjoyed the psychotropic and therapeutic potential of the full entourage of these compounds. Nevertheless, marijuana usage is linked to potential significant adverse effects, such as psychosis, cognitive impairment, and cardiovascular risks. Despite these potential side effects, in 2023, 50% of Americans stated having experimented with marijuana at least once. This percentage signifies a noticeable increase compared to the 45% reported in 2017 and 2019, emphasizing a consistent upward trend.[3]

Therapeutic Potential of Cannabis: Current Evidence

Current evidence reviewed in the 2017 National Academies of Science report supports some potential therapeutic benefits of cannabis.[4] These include its ability to manage chronic pain in adults, its antiemetic properties for combating chemotherapy-induced nausea and vomiting, and its effectiveness in alleviating symptoms associated with multiple sclerosis spasticity. However, there are still limitations in assessing cannabis's effectiveness against various other conditions and symptoms due to several challenges in cannabis research. These challenges include cannabis classification as a Schedule I substance, restricted access to the quality and strain necessary for comprehensive research, and the need to refine standardization and research methodologies.

Adverse Effects

Neuropsychiatric Adverse Effects

Psychosis. The use of marijuana is linked with a two to four times higher likelihood of developing psychosis among healthy individuals.[5]

Schizophrenia. Strong evidence demonstrates an association between cannabis use and the potential onset of schizophrenia, especially in individuals with a preexisting genetic susceptibility.[6]

Bipolar Disorder. In a cohort study involving over 6 million individuals, Jefsen et al. identified an association between cannabis use disorder and a higher risk of both psychotic and nonpsychotic bipolar disorder.[7]

Cognitive Impairment. Long-term cannabis users presented cognitive deficits and experienced impairments across various cognitive domains.[8]

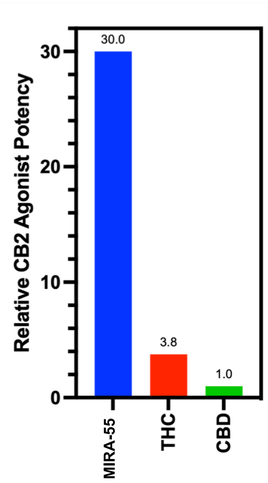
Other

Cardiovascular Risks. Frequent cannabis exhibited approximately a 33% higher likelihood of developing coronary artery disease (CAD) in comparison to those who had never used the substance.[9]

Addiction. Evidence demonstrates that approximately 9% of individuals who try marijuana will develop a cannabis use disorder.[10]

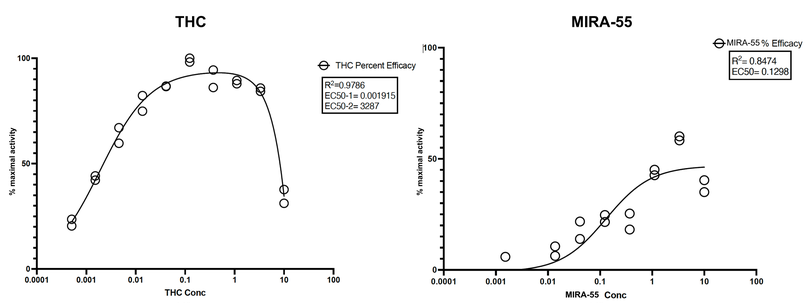
About MIRA-55

MIR-55 is a novel synthetic THC analog currently in development to treat cognitive decline, anxiety, and neuropathic pain. Unlike THC, which induces psychoactive effects through its activity at the CB1 receptor, MIRA-55 demonstrates lower potency at CB1 while maintaining a higher activation of CB2 receptors. This suggests that MIRA-55 may have the potential to be less intoxicating than THC while still delivering valuable therapeutic effects.



COMPARISON OF CB2 AGONIST POTENCY OF MIRA-55, THC AND CBD

In contrast to MIRA-55, THC displays a biphasic effect: Acting as an agonist at low doses (e.g. correlating with its anti-anxiety effects) and an antagonist at high doses (e.g. correlating with its pro-anxiety).
MIRA-55 exhibits a monophasic dose-response at CB1, suggesting a more stable anti-anxiety effect across its dosage range.[11]



DOSE RESPONSE OF MIRA-55 AND THC FOR AGONIST ACTIVITY AT THE CB1 RECEPTOR

Cognitive Performance: MIRA-55 has demonstrated its ability to enhance memory and improve cognitive performance in pre-clinical models involving wild-type mice.

Anti-Anxiety Effects: MIRA-55 has apparent potent anti-anxiety effects without sedation in the preclinical Elevated Plus Maze-Model of Anxiety.

Pain Reduction: MIRA-55 has demonstrated its ability to reduce and relieve pain in pre-clinical heat tolerance models.

Conclusion

In summary, while cannabis has shown benefits in managing some conditions, it is essential to acknowledge the potential adverse effects associated with its use. MIRA-55, a synthetic THC analog, represents a potential breakthrough in the field of cannabinoid therapeutics. It has shown promising results in preclinical studies, enhancing cognitive performance, reducing anxiety, and alleviating pain, all while demonstrating minimal side effects.

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