Weed, sex and influenza

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Shareable abstract (@ERSpublications)
The study by Milad *et al.* presents data addressing how inhalation of cannabis smoke affects influenza infections in mice, and uncovers responses that are different in male and female mice
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The use of cannabis, often referred to as marijuana, to treat ailments such as pain, chemotherapy side-effects and neurological disorders has increased worldwide. Cannabis was federally legalised in Canada in 2018, joining an increasing number of countries and states in which using cannabis recreationally is permitted. This has stimulated the debate over how compounds contained in cannabis, including Δ-9-tetrahydrocannabinol (9-THC) and cannabidiol (CBD), work on a cellular level, and how the use impacts essential biological pathways and human health. 9-THC and CBD undergo first-pass metabolism in the liver, catalysed by cytochrome P450 (CYP)2C9, CYP2C19 and CYP3A4 [1]. While oral availability is delayed and limited (only about 10–20%) due to metabolism, inhaled delivery of cannabis results in instant (within 6–10 min) and substantial systemic absorption [2]. There are numerous ongoing clinical trials examining the pharmacology and toxicology of smoked or vapourised CBD products to uncover the therapeutic potential and safety of inhaled cannabis products. Cannabinoids, including THCs and CBD, have been shown to reduce inflammation, but whether and how these effects could modify the susceptibility to and severity of respiratory infections is an important knowledge gap. Some anecdotal reports and social media sites suggest that cannabis could relieve some of the symptoms associated with influenza A virus (IAV) infections due to its presumed anti-inflammatory function. However, no controlled study has either substantiated or debunked this notion. The lack of clinical evidence is partially due to regulatory and ethical considerations, along with the complex nature of cannabis compounds, which have impeded extensive research on their effects on viral infections.

The pre-clinical study presented by Milad *et al.* [3] fills an area of much needed research: how does inhaled cannabis smoke affect respiratory host defence function? Through a series of integrated analyses, the authors demonstrate that in mice, daily exposure to cannabis smoke increased IAV burden in the lung, which was accompanied by decreased total leukocytes, including macrophages, monocytes and dendritic cell populations in the lungs, suggesting immune suppression. In addition, certain cytokines and markers of adaptive immune responses (*e.g.* circulating IAV-specific antibodies) were decreased by cannabis smoke in female mice but not male mice, indicating sex-specific differences in cannabis-induced immune suppression. Interestingly, cannabis smoke alone had little impact on these markers in uninfected mice, suggesting that the effect on immune competence was dependent on an activated antiviral defence response. However, it is unclear how inhaled cannabis mediates these effects. Receptors for cannabinoids include cannabinoid-1 receptor (CB1-R), which is the receptor mediating central nervous system effects, and CB2-R, which is more abundant on immune cells including B-cells, macrophages, monocytes, natural killer cells and T-cells. Hence, the effects of cannabinoids on reducing inflammation are thought to be mediated at least partially through CB2-R. Since CB2-R is expressed on various adaptive and innate immune cells, this suggests a potential mechanism by which cannabinoids can affect both arms of the immune system. Indeed, previous studies have demonstrated that oral administration of 9-THC impaired influenza-induced immune responses and myeloid cell immune function in mice, and that the role for CB1-R and/or CB2-R [4] depends on the specific immune cell activation pathway [5, 6]. Other (orphan)

receptors, such as GPR5, GPR18, GPR55, GPR92 and GPR119, can also mediate cannabinoid effects, yet their specific role in the effects of cannabinoids on inflammatory and immune responses is not clear. Additionally, cannabinoids are known modulators of transient receptor potential channels (TRP) [7].

For example, CBD has been shown to be a TRPV1 agonist while both CBD and 9-THC are TRPV2 agonists. Previous evidence from TRPV1 knockout mice indicates that TRPV1 may play an important role in CBD-mediated immune suppression *via* the release of myeloid-derived suppressor cells [8].

Assuming the impairment of host defence responses observed by Milad *et al*. [3] is part of a larger biological paradigm and is not dependent on the virus, cannabis use could have much broader public health implications. Since cannabis does impair virus-induced innate and adaptive immune responses, it will likely have significant effects on other respiratory infections. While CBD can potentially reduce infection with SARS-CoV-2 [9], cannabis use was associated with poorer COVID-19 survival [10]. However, no significant effect of cannabis use was seen in COVID-19 vaccine antibody responses [11]. For non-respiratory virus infections, effects of cannabis use are consistent with its known anti-inflammatory effects and preserved HIV-specific T-cell responses [12]. Thus, additional studies carefully examining the effects of cannabinoids on antiviral host defence responses in humans are needed.

Since cannabis use is twice as prevalent among male compared to female adults [13], understanding sex-specific effects of cannabis is important. The study presented here did show some sex-dependent differences. For example, in addition to IAV-specific antibody levels, which were decreased by cannabis smoke only in female mice, cannabis-induced changes in viral load were only observed in female mice. While sex differences exist in the expression of endogenous cannabinoid receptors, the subjective effects of cannabis and cannabis metabolism are also different in males and females. As indicated above, THC is primarily metabolised by CYP2C9 and CYP2C19 to its major metabolite 11-hydroxyl-THC, which is also psychoactive, and then into 11-carboxyl-THC, which is not psychoactive [14]. Studies examining potential differences in pharmacokinetics of oral and vapourised cannabis showed potential sex-dependent differences in metabolism and potential bioavailability [15]. In addition, oral contraceptives significantly inhibit CYP2C19, thus potentially affecting the metabolism of cannabinoids [16]. As a result, whether and how sex or sex hormones affect cannabis pharmacology remains an important knowledge gap, especially in the context of IAV infections, which are known to have strong sex differences [17].

In conclusion, considering that cannabis use is on the rise, the study presented by Milad *et al*. [3] provides much needed evidence that inhaled cannabis smoke can significantly affect the susceptibility to and severity of IAV infections. and that these effects are likely to be different in males and females. This is of additional significance as cannabis use is prevalent in already immunocompromised individuals, such as cancer patients using it to overcome side-effects caused by chemotherapy. Hence, the data presented here provide the basis for additional clinical studies translating these findings into humans *in vivo* and providing much needed data to understand how the increase in inhaled cannabis product use could affect respiratory virus infections.

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