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Letter to the Editor

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# Cannabinoid Signal Transduction Explains Disconnect of Cannabis Effects in Experimental and Clinical Colitis

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We read with interest the review article of Tim Ambrose and Alison Simmons entitled 'Cannabis, Cannabinoids, and the Endocannabinoid System—Is There Therapeutic Potential for Inflammatory Bowel Disease?'.[1] Use of cannabis attracts widespread attention with regard to its potential usefulness in the management of inflammatory bowel disease, from patients and health care professionals. The study Ambrose and Simmons does an admirable job in summarising the existing body of contemporary biomedical literature, both with respect to clinical work regarding *Cannabis sativa* extracts for treating inflammatory bowel disease, and with respect to preclinical work on the potential of such extracts for constraining experimental colitis. Intriguingly, the authors conclude that there is a disconnect between experimental and clinical data. Whereas the evidence that cannabinoids can control experimental colitis, and especially chemical colitis, appears strong, the authors also observe that this does not translate in convincing indications that cannabinoids can be clinically effective.

The authors propose several interesting hypotheses that may account for the discrepancy observed. In particlar, they observe that some of the experimental work is done under normoxic conditions, whereas the human intestine is hypoxic. This point does not completely convince, however, in view of the fact that the intestine of experimental animals also is hypoxic. Here we would like to propose that the disconnect between experimental and clinical data lies in the effects of cannabinoid receptor activation on cellular signal transduction, and in how cannabinoid signal transduction influences experimental versus clinical colitis.

Recently we published a study in which volunteers and pancreatitis patients were challenged with medical cannabis preparations, and the kinomes of blood lymphocytes before and after medical cannabis were contrasted.[2] Especially prominent in our observations was that pro-inflammatory p38MAP kinase signalling and mTOR signalling were constrained following cannabis challenge. Importantly, p38MAP kinase inhibitors—although partially effective in chemical colitis—are not useful for treating clinical Crohn's disease.[3] Likewise, mTOR inhibitors attenuate chemical colitis in mice,[4] whereas a study evaluating the mTOR inhibitor everolimus in moderate-to-severe active Crohn's disease was prematurely terminated because of apparent lack of efficacy.[5] Thus cannabinoids act on inflammation by inhibiting p38MAP kinase and mTOR signalling, but for both inflammatory effector pathways there is a disconnect between what is observed in experimental colitis and what is observed in clinical inflammatory bowel disease. We feel that the discrepancy between experimental colitis and clinical colitis, with respect to its requirement for p38MAP kinase and mTOR signalling, constitutes a rational explanation for the apparent contradiction noted by Ambrose and Simmons with respect to cannabis effects.

## Conflict of Interest

The authors declare that they have no competing interests.

## Author Contributions

MP, KP, and GF wrote the paper. MP and GF had the original idea for the paper. All authors reviewed and approved the final draft of the paper.

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