Journal Pre-proof

A response to Kong et al.'s January 2021 article "*Cannabinoids in dermatologic surgery*".

Tasnim Abdalla, BHSc, Yuliya Lytvyn, PhD, Katherine Ann McDonald, MD, Asfandyar Mufti, MD, Afsaneh Alavi, MD, MSc

PII: S0190-9622(21)00912-9

DOI: https://doi.org/10.1016/j.jaad.2021.04.068

Reference: YMJD 15965

To appear in: Journal of the American Academy of Dermatology

Received Date: 31 March 2021

Accepted Date: 9 April 2021

Please cite this article as: Abdalla T, Lytvyn Y, McDonald KA, Mufti A, Alavi A, A response to Kong et al.'s January 2021 article "*Cannabinoids in dermatologic surgery*". , *Journal of the American Academy of Dermatology* (2021), doi: https://doi.org/10.1016/j.jaad.2021.04.068.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2021 Published by Elsevier on behalf of the American Academy of Dermatology, Inc.



1	Journal of the American Academy of Dermatology
2	Article Type: Notes & Comments
3	A response to Kong et al.'s January 2021 article "Cannabinoids in dermatologic
4	surgery".
5	
6	Title: A response to "Cannabinoids in Dermatologic Surgery": The added considerations of
7	factors affecting tissue perfusion, wound healing, and modes of administration in safety and
8	efficacy of cannabinoids
9	
10	Authors: Tasnim Abdalla ¹ , BHSc; Yuliya Lytvyn ¹ , PhD; Katherine Ann McDonald ² , MD;
11	Asfandyar Mufti ² , MD; Afsaneh Alavi ² , ³ , MD, MSc
12	
13	Affiliations
14	¹ Temerty Faculty of Medicine, University of Toronto, Canada
15	² University of Toronto, Division of Dermatology, Toronto, Canada
16	³ Mayo Clinic, Department of Dermatology, Rochester, Minnesota.
17	
18	Conflicts of Interest: None declared.
19	Funding: None declared.
20	
21	Corresponding author:
22	Katherine Ann McDonald
23	Phone: 613-883-5023; Email: kmcdo026@uottawa.ca
24	RKS Dermatology Clinic, Women's College Hospital
25	76 Grenville St, Toronto, ON M5G 1N8

26	
27	Word Count: 471
28	Reference Count: 5/5
29	Tables or figures: 0
30	
31	Key words: dermatologic surgery; cannabinoids; cannabidiol (CBD); tobacco smoking;
32	marijuana; wound healing; inflammation; pain
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	

51

52 To the Editor:

53

54 Kong et al. comprehensively reviewed the impact of cannabinoids on inflammation, 55 proliferation, fibrosis, pain management and wound healing with a focus on implications for 56 dermatologic surgery.¹ We would like to extend this thorough discussion to include the effect 57 of cannabinoids on tissue perfusion, chronic wound healing, and potential concerns with 58 cannabinoid modes of administration.

59

Studies examining the impact of cannabinoids on tissue perfusion report mixed results. In a 60 study of 18 patients, administration of HU210 cannabinoid receptor agonist showed 61 decreased blood flow as measured by a laser doppler.² However, a recent systematic review 62 outlines literature on both the vasodilatory and vasoconstrictive effects of cannabinoids.³ In 63 this review, it was suggested that the vascular impacts of endocannabinoids may depend on 64 the dose, time since administration, use of anesthesia, and baseline arterial pressure. 65 Although there is currently limited and poor-quality evidence to definitively conclude how 66 cannabinoids effect post-operative tissue perfusion and chronic wound healing, it is an 67 important area of future study. 68

69

The anti-inflammatory and analgesic effects of cannabinoids may positively impact chronic wound healing. While the exact mechanisms are unclear, it has been postulated that cannabinoids decrease levels of $TNF\alpha$, reactive oxygen species, and lipoxygenases resulting in beneficial effects on peri-wound tissues and improved wound healing.⁴ Although the current data suggesting cannabinoid use may be beneficial in wound healing is limited to a few case reports, several higher quality studies are underway. An ongoing open label clinical

Journal Pre-prooi

trial of 35 patients is examining the effect of topical cannabis-based medicine, which includes a mixture of cannabinoids, terpenes, and flavonoids, on chronic wound healing and wound related pain (ISRCTN16488940). Preliminary results from two elderly female patients with recalcitrant non-uremic calciphylaxis leg ulcers demonstrated complete wound closure after mean of 76 days with no adverse effects.⁴ The results of the ongoing and future larger clinical trials will help establish whether topical cannabinoids may be an effective and safe treatment for chronic wounds.

83

Finally, the method of cannabis administration and the type of vehicle are important 84 85 considerations in the efficacy of wound healing, given the numerous systemic formulations 86 available (smoking, vaping, edibles, patches, as well as topical formulations with oils, creams and sprays). Patients who smoke cannabis are more likely to smoke tobacco compared to 87 88 patients who do not and may not disclose that tobacco is rolled in with the marijuana. Mechanistically, heated tobacco, nicotine, and the gaseous by products cause tissue hypoxia 89 via vasocontraction and increased blood viscosity. This ultimately leads to poor wound 90 healing,⁵ and is an important confounder to consider clinically. Given this potential risk, 91 92 restriction of smoking both cannabis and tobacco pre-operatively may be warranted.

93

94 In summary, taking into consideration factors affecting tissue perfusion, the role in wound 95 healing, and the method of administration are substantial in evaluation of safety and efficacy 96 of cannabinoids in relation to medical and surgical dermatology. High quality clinical trials 97 are warranted to help establish future recommendations and guidelines.

98

99

100

102	References
103	
104	1. Kong HE, Pollack BP, Blalock TW. Cannabinoids in dermatologic surgery. J Am Acad
105	Dermatol 2021.
106	2. Dvorak M, Watkinson A, McGlone F , Rukwied R. Histamine induced responses are
107	attenuated by a cannabinoid receptor agonist in human skin. Inflamm Res 2003;52:238-45.
108	3. Richter JS, Quenardelle V, Rouyer O, Raul JS, Beaujeux R, Geny B et al. A Systematic
109	Review of the Complex Effects of Cannabinoids on Cerebral and Peripheral Circulation in
110	Animal Models. Front Physiol 2018;9:622.
111	4. Maida V, Shi RB, Fazzari FGT , Zomparelli L. Topical cannabis-based medicines - A
112	novel paradigm and treatment for non-uremic calciphylaxis leg ulcers: An open label trial. Int
113	Wound J 2020;17:1508-16.
114	5. McDaniel JC , Browning KK. Smoking, chronic wound healing, and implications for
115	evidence-based practice. J Wound Ostomy Continence Nurs 2014;41:415-23; quiz E1-2.