Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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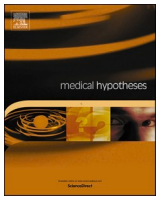

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Diethylcarbamazine as potential treatment of COVID-19 lung fibrosis

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ABSTRACT

Diethylcarbamazine, the antiparasitic drug, also possesses anti-inflammatory and immunomodulatory activities. The anti-fibrotic activity of diethylcarbamazine makes it a potential candidate to treat coronavirus disease 2019 (COVID-19)-related pulmonary fibrosis. Experimental and clinical studies should assess this possible effect.

To the Editor

We, with great interest, read the proposal by Abeygunasekera and Jayasinghe [1] describing the use of diethylcarbamazine (DEC; N, N-Diethyl-4-methyl-1-piperazincarboxamid, $C_{10}H_{21}N_3O$) as an adjuvant for treating coronavirus disease 2019 (COVID-19). DEC is a safe and non-expensive drug with side effects mainly related to parasitic infection. The recently reported activities of DEC include immunomodulatory [2,3], anti-inflammatory [4], and antifibrotic activities [5,6]; hence, the potential of DEC is beyond its original use as an antifilarial agent. DEC protects against acute lung injury [7] and shows an antifibrotic effect in experimental liver fibrosis [5,6], a condition that shares common pathways with lung fibrosis [8]. We believe that the antifibrotic activity suggests a significant potential of DEC for treating COVID-19-related lung damage. DEC reduces the production of fibrotic factors and collagen [9–11] and the expression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [11], thus inhibiting the production of the profibrotic cytokines, interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α. IL-1β and IL-6 influence the inflammatory and fibrotic response by inducing the activation and accumulation of neutrophils and lymphocytes to the injury site and promoting the activation of fibroblasts and collagen synthesis [12]. DEC reduces the expression of transforming growth factor (TGF)-β [5,6], a potent profibrotic cytokine, that induces the production and deposition of extracellular matrix (ECM) [13].

Additionally, DEC decreases tissue inhibitor of metalloproteinase (TIMP)-1 expression, further increasing metalloproteinase (MMP)-2 expression, ECM accumulation, and fibrosis [5,6]. It would be clinically relevant to determine whether DEC may reduce the tissue damage leading to fibrosis or act upon already established lesions in patients in the acute stage or those recovering from post-COVID-19 fibrosis. Evidence suggest that the effect of DEC is dose-dependent, hence determining the effective therapeutic dose is critical [2,4]. We believe that the mechanisms described above suggest DEC as a potential alternative for treating COVID-19-related pulmonary fibrosis and even lung fibrosis of another origin. Extensive experimental and clinical testing, including *in silico* screening for additional mechanisms, may provide the degree of evidence necessary to repurpose [1,14] this known, but remarkable and resourceful drug.

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Consent statement/Ethical approval

Not required.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Abeygunasekera A, Jayasinghe S. Is the anti-filarial drug diethylcarbamazine useful to treat COVID-19? Med Hypotheses 2020;143:109843. https://doi.org/10.1016/j.mehy.2020.109843.
[2] García-Hernández M, Castro-Corona MA, Segoviano-Ramírez JC, Brattig NW. Medina-De la Garza CE. Immunomodulatory effect of diethylcarbamazine in mice infected with *Nocardia brasiliensis*. Int Immunopharmacol 2014;23:113–20.
[3] Medina-De la Garza CE, Guerrero-Ramírez G, García-Hernández M, Castro-Corona MA, Torres-López E, Brattig NW, et al. Immunomodulatory activity of diethylcarbamazine on humoral, cellular cytokine response and respiratory burst in BALB/c mice. Immunopharmacol Immunotoxicol 2012;34(3):477–83.
[4] Peixoto CA, Silva BS. Anti-inflammatory effects of diethylcarbamazine: a review. Eur J Pharmacol 2014;734(1):35–41.
[5] Rodrigues GB, Oliveira EE, Mendonça-Junior FJB, dos Santos LAM, de Oliveira WH, de França MER, et al. A new diethylcarbamazine formulation (NANO-DEC) as a therapeutic tool for hepatic fibrosis. Int Immunopharmacol 2018;64:280–8.
[6] Rocha SWS, de França MER, Rodrigues GB, Barbosa KPS, Nunes AKS, Pastor AF. Diethylcarbamazine reduces chronic inflammation and fibrosis in carbon tetrachloride- (CCl_4) induced liver injury in mice. Mediators Inflamm 2014;2014. https://doi.org/10.1155/2014/696383.
[7] Ribeiro EL, de Souza Barbosa KP, Fragoso IT, Donato MAM, Oliveira dos Santos Gomes F, da Silva BS, et al. Diethylcarbamazine attenuates the development of Carrageenan-induced lung injury in mice. Mediators Inflamm 2014;2014:1–12. https://doi.org/10.1155/2014/105120.
[8] Makarev E, Izumchenko E, Aihara F, Wysocki PT, Zhu Q, Buzdin A, et al. Common pathway signature in lung and liver fibrosis. Cell Cycle 2016;15(13):1667–73.

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[9] de França MER, Rocha SWS, Oliveira WH, Santos LA, de Oliveira AGV, Barbosa KPS, et al. Diethylcarbamazine attenuates the expression of pro-fibrogenic markers and hepatic stellate cells activation in carbon tetrachloride-induced liver fibrosis. Inflammopharmacol 2018;26(2):599–609.
[10] El-Sisi A-D-S, Sokar SS, Shebl AM, Mohamed DZ. Antifibrotic effect of diethylcarbamazine combined with hesperidin against ethanol induced liver fibrosis in rats. Biomed Pharmacother 2017;89:1196–206.
[11] Rodrigues GB, Rocha SWS, Santos LAMD, de Oliveira WH, Gomes FODS, de França MEdR, et al. Diethylcarbamazine: possible therapeutic alternative in the treatment of alcoholic liver disease in C57BL/6 mice. Clin Exp Pharmacol Physiol 2015;42(4):369–79.
[12] She YX, Yu QY, Tang XX. Role of interleukins in the pathogenesis of pulmonary fibrosis. Cell Death Discov 2021;7(1). https://doi.org/10.1038/s41420-021-00437-9.
[13] John AE, Joseph C, Jenkins G, Tatler AL. COVID-19 and pulmonary fibrosis: a potential role for lung epithelial cells and fibroblasts. Immunol Rev 2021;302(1):228–40.
[14] Oh KK, Adnan MD, Cho DH. Drug-repurposing against COVID-19 by targeting a key signaling pathway: an in silico study. Med Hypotheses 2021;155:110656. https://doi.org/10.1016/j.mehy.2021.110656.

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