

REVIEW:

The Author have evaluated the risk of DILI in covid-19 My comments are 1. Most of the drugs have been evaluated in this review. One of the off-label drug was tocilizumab. This review could help regarding the safety of this drugs DOI: 10.1055/a-1336-2371 2. What are the type of DILI in covid-19? , as we know there were three types. 3. What are the role of curcuminoid?

RESPONDA:

Dear reviewer,

We appreciate your considerations about the presented article.

Regarding question 2, DILI is classified as hepatocellular, cholestatic or mixed, as indicated by the ratio between alanine aminotransferase (ALT) and alkaline phosphatase (AP) markers, as well as the patient's signs and symptoms. As we found in the literature, the type and pattern of DILI in COVID-19 patients is yet to be understood given a scarcity of publications reporting liver signs and symptoms in addition to laboratory findings such as jaundice, hepatomegaly and ascites – liver biopsies are uncommon. The main marker of liver injury in COVID-19 is the elevation of aminotransferases, although this sign by itself is not sufficient to confirm the type of DILI. Also, as our article does not aim to discuss the state of the art of DILI and its physiological aspects, we decided to not discuss the types of DILI in depth. We present an overview of the types in page 9.

Regarding question: 3. What is the role of curcuminoid?

Evidence in the literature has shown that curcumin has beneficial effects against various diseases, including inflammatory, neurological, cardiovascular, pulmonary, metabolic and liver ones (1). Curcumin has also shown antiviral activities against several different viruses and, following this logic, it could be a therapeutic option for COVID-19 treatment. It is suggested that curcumin can prevent COVID-19 infections by inhibiting the pathogen entry, viral genome replication and steps in the endosomal pathway along with inhibition of T-cell signaling by impairing the autophagy-mediated antigen-presenting pathway (2). Moreover, its application in nanotechnology could improve its beneficial effects. Another important effect of curcumin is its prevention capacity and treatment of oxidative associated liver diseases (3).

Although curcuminoid is a promising alternative in the management of the infection and it could also be tested as a hepatocellular protector in liver injury cases of COVID-19, there is lack of clinical trials or retrospective/observational studies using this alternative in COVID-19 patients. Since curcuminoid remains in the theoretical field, for this case we decided to not insert this phytochemical compound in our review for clinical purposes. As more studies with this compound are published, drug therapy of COVID-19 and its side effects must be updated.

References:

1. Zahedipour F, Hosseini SA, Sathyapalan T, Majeed M, Jamialahmadi T, Al-Rasadi K, Banach M, Sahebkar A. Potential effects of curcumin in the treatment of COVID-19 infection. *Phytother Res.* 2020 Nov;34(11):2911-2920. doi: 10.1002/ptr.6738. Epub 2020 Jun 23. PMID: 32430996; PMCID: PMC7276879.

2. Dhar S, Bhattacharjee P. Promising role of curcumin against viral diseases emphasizing COVID-19 management: A review on the mechanistic insights with reference to host-pathogen interaction and immunomodulation. *J Funct Foods*. 2021 Jul;82:104503. doi: 10.1016/j.jff.2021.104503. Epub 2021 Apr 20. PMID: 33897833; PMCID: PMC8057770.
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