Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

Specific Comments to Authors: This review is of importance to understand present status and perspectives of cirrhosis-resoluting bioengineering. 1. I recommend to figure our limitation and future direction as Figure 3.

Answer: Ok, we added and additional figure that resume the challenges and limitations

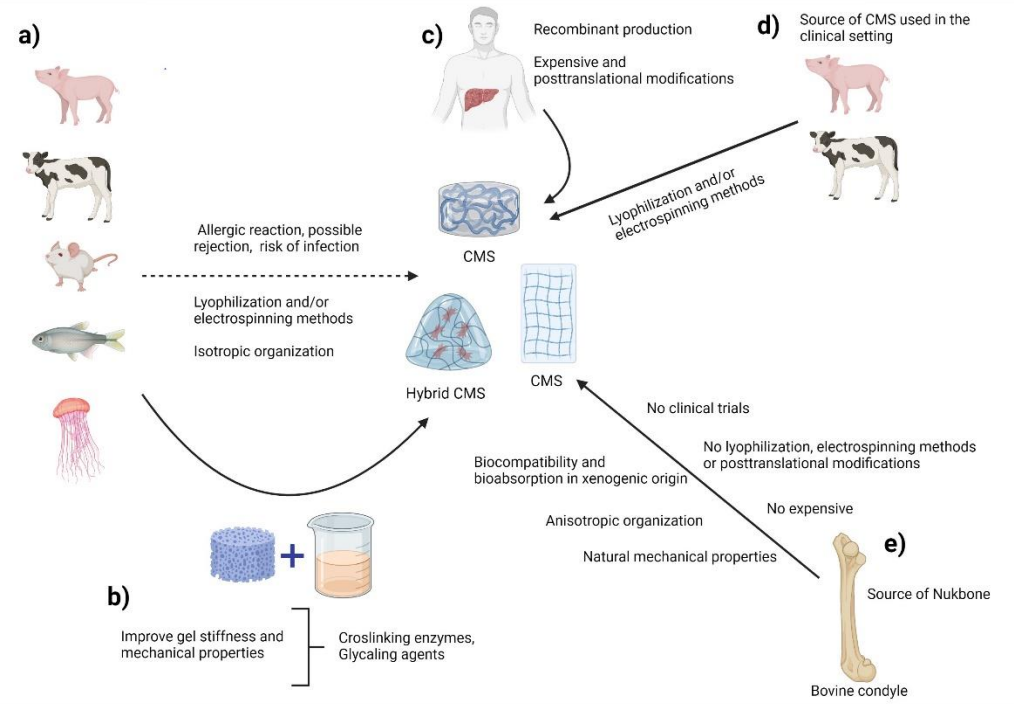

Figure 3. Challenges and Limitations of Collagen Matrix Scaffolds. **a**) Xenogenic sources of collagen promote allergic reactions, rejection or risk of infections (e.g., bovine spongiform encephalopathy). Lyophilization and/or electrospinning methods are used to obtain CMSs, which alter their natural properties, including isotropic organization. b) Hybrid collagen matrices using crosslinking enzymes (e.g., lysyl oxidase and transglutaminase) and glycating agents (high concentrations of ribose) to improve mechanical properties and stiffness. c) The production of human recombinant collagen is expensive, and current recombinant systems lack native prolyl 4-hydroxylase activity. d) The available sources of CMS are obtained from bovines and pigs using lyophilization and/or electrospinning methods. e) Nukbone obtained from bovine condyles as a CMS source showed great advantages; however, it is important to validate its use in clinical trials. The next step of CMS is explored in the context of the different stages of CLD induced by distinct liver insults.

2. The authors described as a limintation "it is important to research the implication of the use of different types of collagen in the context of CLD including fibrosis, cirrhosis, and HCC induced by the different etiologies". Do you have any findings or manuscripts supporting your statement? Please describe this point in more detail.

Answer: There are available information reported since 2014 about the production of different collagen types from early to advanced stages of liver fibrosis. In 2014, was reported that collagens III, IV, V, and VI showed significant increases from early to late fibrosis (F4 or cirrhosis) in hepatitis C. Additionally, the authors concluded that collagen IV was the most useful discriminator between early and late stages, whereas collagen V and VI showed strongest expression in early fibrosis stages (1). On the other hand in Hepatitis B virus, was reported that the S protein promotes collagen I expression in hepatic stellate cells (LX-2 cells) by virtue of hepatocytes (HepG2, hepatoma cells) secreting TGF-β1 (2). Recently (2021), the formation and degradation of collagens were evaluated in alcohol-related liver fibrosis. The study provide evidence that patients with alcohol liver diseases showed higher levels of type III collagen in cirrhosis stage compared with healthy controls. Moreover, they showed that collagen III formation progressively superseding degradation of this type of collagen, in contrast the degradation of collagen VI (CM6) is higher compare with its synthesis (PRO-C3) (3). In a similar manner, in nonalcoholic fatty liver disease (NAFLD), was reported that PRO-C3 was adapted to ADAPT model, allowing discriminate F3 and F4, with superior ROCs aspartate aminotransferase to platelet ratio index (APRI), FIB-4, and NAFLD fibrosis score (NFS)(4). Taken together, these studies provide evidence that synthesis and degradation of collagens is not a static process, showiest that synthesis and degradation occurs is in accordance with the liver insult and the fibrosis stage.

1. Chen W, Rock JB, Yearsley MM, Ferrell LD, Frankel WL. Different collagen types show distinct rates of increase from early to late stages of hepatitis C-related liver fibrosis. Hum Pathol. 2014;45(1):160-5.
2. Liu X, Tu Y, Deng X, Liang J. The S protein of hepatitis B virus promotes collagen type I expression in hepatic stellate cells by virtue of hepatocytes. Biomed Rep. 2014;2(1):97-100.
3. Thiele M, Johansen S, Gudmann NS, Madsen B, Kjaergaard M, Nielsen MJ, et al. Progressive alcohol-related liver fibrosis is characterised by imbalanced collagen formation and degradation. Aliment Pharm Ther. 2021;54(8):1070-80.
4. Daniels SJ, Leeming DJ, Eslam M, Hashem AM, Nielsen MJ, Krag A, et al. ADAPT: An Algorithm Incorporating PRO-C3 Accurately Identifies Patients With NAFLD and Advanced Fibrosis. Hepatology. 2019;69(3):1075-86.

3. Please check grammatical errors before resubmission.

Answer: Ok, we check all the manuscript again and send the manuscript to American Journal Experts for language correction.

Reviewer #2:
Scientific Quality: Grade A (Excellent)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: The authors present a review summarizing the state of the art on research based on the use of CMS to understand and combat CLD. In my view, this is an interesting topic that deserves attention and that the authors describe and discusse brilliantly. There are a couple of minor questions that might be considered:

1. A list of abbreviations would facilitate the reading of the manuscript, mainly for non-specialized readers.

Answer: We include a list of abbreviations as the reviewer suggested

2. The manuscript provides the main ideas in the field in a comprehensive manner. However, although the information provided is valuable, I miss a more detailed discussion and conclusions after several statements (for an example, in the second paragraph on CMS in liver cancer or after the reference to Nukbone); observations are described but their relevance and future implications are elusive.

Answer: Thanks for your comment, in general we written the manuscript in a general context (opinion-review) of the collagen matrix scaffold (CMS) and Chronic liver disease (CLD). The main intention was just providing clues for the readers about the future and implications of CMS and CLD, allowing readers to make their own judgment. About Nukbone, we decide does not include a lot information to avoid self-citation and not create a bias in this field, because we are part of the group of research. Thus, maintaining ethics in the dissemination of science. Nevertheless, we include additional information as the reviewer suggest.