GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 7-8 (340-341) Июль-Август 2023

ТБИЛИСИ - NEW YORK

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press. Published since 1994. Distributed in NIS, EU and USA.

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

GEORGIAN MEDICAL NEWS
No 7 (340) 2023

Содержание:

GEORGIAN MEDICAL NEWS
No 7 (340) 2023

LIVER FIBROSIS: PATHOPHYSIOLOGY, DIAGNOSIS, AND EMERGING THERAPEUTIC TARGETS FOR A COMMON COMPLICATION OF CHRONIC LIVER DISEASES

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Abstract.

Fibrosis of the liver, which can be caused by either viral or chemical chronic liver illnesses, is a serious issue for the world's health. Collagen is crucial for the development of the illness and the possibility of developing hepatocellular carcinoma (HCC), which is linked to the progression of liver damage. Although there are various mechanisms for acute liver injury and diseases-specific cells response, almost all of fatty liver aetiologies share similar trends in the development of fibrous liver damage. The scientific community's knowledge of the fundamental causes of fibrosis of the liver has undergone a significant shift during the last ten years. It has been shown that the fundamental trigger, such as the control or management of an infectious disease, can be eradicated or eliminated in order to reverse liver fibrosis. Reversing frequently occurs prematurely or too rarely, particularly in severe fibrosis, to avoid possibly fatal effects. Therefore, there is an urgent need for anti-fibrotic medications to halt the progression of liver damage and the appearance of HCC. Even though various anti-fibrotic medication options have shown strong anti-fibrotic effects in lab animals, research studies have only seen a small amount or none of these advantages. There is not an approved remedy for the condition as a result. In this article, we give a general overview of the physiological and molecular origins of collagen in chronic liver disease and investigate how these causes can impact the quickly developing field of anti-fibrotic treatments.

Key words. Liver Fibrosis, Pathophysiology, Diagnosis, chronic liver diseases, Cells.

Introduction.

Every year, almost 2 million people pass away from persistent liver disorders, which place an enormous strain on global health. The fundamental aetiologies of chronic liver disease include linked to long-term liver damage, autoimmune and genetic diseases, non-alcoholic steatohepatitis (NAS), and alcoholic steatohepatitis (AS). Vascular scarring is a hallmark of the development of long-term inflammatory conditions and accounts for 45% of global mortality from all causes. Similarly, to this, the progression of cirrhosis in the liver mostly impacts outcome as well as quality of life [1].

Disorders that are pathogenic, toxic, metabolic, or virus cause damaged hepatocytes and immune system penetration, which trigger the trans-differentiation of hepatic stellate tissues (ICs) into myofibroblasts that produce gelatin Myofibroblasts are physically involved in organ regeneration; however, after a short-term insult, anti-fibrotic processes regulate this activity, resulting in myofibroblast deactivation or death and scarring clearance [2].

Lymphocytes and macrophages are drawn to and stimulated by hepatocyte mortality and the liver's creation of damage-associated motifs (DAMPs), encouraging ICs trans-differentiation and myofibroblast engagement [3]. On the one hand, specific monocyte groups that produce matrix-metalloproteinases (MMPs) are involved in wounding fibrosis. On a molecular level, pro-fibrogenic cell interactions are controlled by a complicated network of cytokine signals [4]. Illustrates the broad, etiology-unrelated interactions between cells that contribute to the growth of fibro depicted in Figure 1.

Stopping the growth of fibrogenesis is one method for preventing liver-related death. Many Over-vivo and in-vitro models have been created in the past few years to tackle the medical gap by designing effective and secure anti-fibrotic medications. Although we are learning more about the molecular mechanisms behind liver fibrogenesis, there is still no licensed medication for treating liver damage [5].

Study [6] evaluated to calculate the mediocre survival time and combined survival rate and to look into the mortality prognostic factors. To evaluate severity and distinguish between therapeutic therapies options is to use the MELD-Na model for severe liver disease, which includes serum sodium levels and physiological indicators.

Study [7] mentions that suffering from “type 2 diabetes mellitus, or T2DM, and non-alcoholic fatty liver disorder (NAFLD)”, a potentially dangerous condition that may have effects on the hepatic and extrahepatic levels need to be treated by endocrinologist physicians. Endocrinologists should be informed with the ADA's updated recommendations in order to address the management of NAFLD in patients with T2DM. These recommendations stress the significance of routinely checking individuals with hyperglycemia or diabetes who have steatosis or high plasma aminotransferases for progressive fibrosis. Additionally, more research is required to create fresh therapies that can effectively manage NAFLD in T2DM patients. Study [8] investigated how the gut microbiota affects the pathophysiologic causes of NAFLD and to evaluate the possibility of NAFLD treatments that target the microbiome. As a result, treating NAFLD patients with medications that successfully target the gut flora may be advantageous.

Study [9] critically examined the most recent definitions of hepatic encephalopathy (HE), investigate the causes and pathophysiological paths that lead to neurological deterioration in patients with end-stage liver disease, and assess management

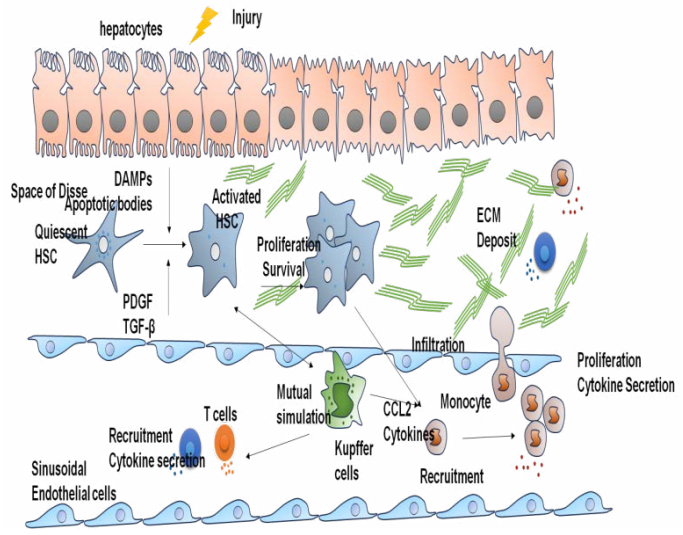

Figure 1. *Examples of fibrosis in the liver mechanistic ideas Damage-associated patterns (DAMPs) and apoptotic structures are released by chronic hepatocyte harm.*

techniques, diagnostic methods, currently accessible treatments, and novel treatment techniques for HE. The search covered scientific materials on hepatology and neurology as well as databases like PubMed an in-depth understanding of HE, the data that had been gathered was analysed, and the major assumptions were summarised. Study [10] examined the most recent pertinent literature and describe the current therapy options for NAFLD that target intermediate metabolism, insulin resistance, and T2DM. Numerous medications that are now recommended for hyperglycemia have produced favourable outcomes on NASH biomarkers because of the strong relationship between NAFLD and T2DM.

The genetics, aetiology, and pathology of mastocytosis are discussed in the paper [11], with a focus on novel diagnostic requirements and therapeutic approaches. Systemic mastocytosis (SM) or cutaneous mastocytosis are two possible illness manifestations. SM is classified into indolent, smouldering, aggressive, and MC leukaemia based on histological and molecular characteristics, clinical factors, and organ activation. Study [12] examined MSCs' and MSC-related secreted factors' therapeutic effects on ALD. Even while mounting data points to the medicinal value of MSCs and associated elements in ALD, the processes behind these elements' effects in this disease are not fully understood. The article increases our comprehension regarding the creation of efficient and secure treatments for ALD by providing details about existing or potential ALD therapies.

The treatment of cirrhosis of the liver, Study [13] suggested remodeling the microenvironment of the liver research. As a new ROS-responsive active targeted nanomedicine for the therapy of liver disease and hypertension at the portal vein in mice, the pPB-modified PEGylated hollow polydopamine nanoparticles packed with L-Argwere developed. The outcomes demonstrated that pPB peptides treatment may effectively direct nanoparticle distribution to HSCs, to prevent. Study [14] described Liver Diseases guidelines fibrosis score (NFS) and fibrosis-4 score (FIB4) for NAFLD as indicators of mortality and comorbidities in a sample of type 2 diabetics. All-cause mortality was predicted by the NFS and FIB4, especially in women and for categories other than heart disease. Negative renal events were anticipated by the NFS. These ratings for liver damage may help with classification of risk in people with diabetes and NAFLD. Study [15] discussed the macrovascular issues that have been linked to liver fibrosis, NAFLD and T2DM are closely related. Considering that severe fibrosis, as assessed by FibroScan, is individually related with a higher prevalence of macrovascular and microvascular difficulties, was instrument can now be used to thoroughly evaluate hepatic and vascular issues in patients with T2DM.

The mechanisms of fibrosis regression and the cytokines and chemokines that play a role in it are the primary topics of this study [16]. Here, they look at the role that mitochondria and metabolic alterations play in hepatic stellate cells' ability to fibrogenize.

Study [17] discussed many potential natural and synthetic activators of SIRT1 as a therapeutic therapy for liver disorders. NF-B is the primary regulator of the inflammatory response, and the metabolic sensor SIRT1, a class III histone deacetylase highly expressed in metabolic organs like the liver, has an inverse connection with it. Thus, targeting SIRT1 is gaining traction as a possible method of treating metabolic and/or inflammatory diseases.

In this article [18], we highlight recent developments in our knowledge of the physiological and molecular triggers of hepatic fibrosis in significant persistent liver disease aetiologies. In addition, clinically developing anti-fibrotic methods and medicines are covered.

Aetiology includes factors including intestinal dysbiosis, low-grade inflammation, elevated oxidative stress, and dysfunctional mitochondria. In addition to issues in the liver, patients with MAFLD are also at increased risk for developing cardiometabolic consequences [19].

Mechanistic concepts of liver fibrosis.

Liver fibrosis is exacerbated when free cholesterol accumulates in immune cells, specifically Kupffer cells. Elevated free cholesterol levels in hepatocytes of patients with non-alcoholic steatohepatitis (NASH) lead to cholesterol crystallization. KCs are attracted to hepatocytes containing cholesterol crystals, forming "crown-like structures." These activated KCsphagocytose the dead hepatocytes, transforming them into foam cells.

Kupffer cell activation causes a flow of cytokines that are pro-inflammatory throughout this procedure, which subsequently activates immune cells. The accumulation of free cholesterol in KCsactivates the TLR4 pathway, initiating the NF-kB and JNK pathways. Consequently, inflammatory and chemotactic cytokines are released, contributing to the growth of liver fibrosis. This highlights the role of cholesterol metabolism disruption and immune cell activation in promoting liver fibrosis, emphasizing the importance of managing lipid homeostasis to prevent fibrotic progression. Figure 2 depicts the Liver fibrosis score. This parameter measures the rate at which fibrosis progresses over time. By dividing the difference in fibrosis stage by the length of the gap, it may be estimated. It indicates a higher progression rate, meaning fibrosis is advancing more rapidly.

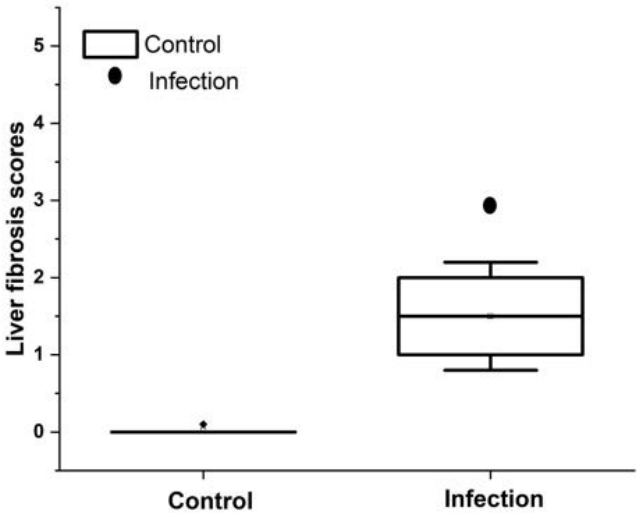

Figure 2. *Liver fibrosis score (Source: https://www.spandidos-publications.com/10.3892/etm.2019.8355).*

Liver fibrosis.

Liver fibrosis is a process that develops in response to a variety of liver ailments, including chronic viral hepatitis, alcoholic liver disease, and non-alcoholic fatty liver disease (NAFLD), autoimmune hepatitis, and more. In the liver, there is an overabundance of fibrous connective tissue (scar tissue). This buildup may be the consequence of prolonged liver cell injury and persistent inflammation.

Although the liver has a remarkable capacity for regeneration, chronic and ongoing injury may cause an unbalanced healing process that results in the deposition of scar tissue. The buildup of scar tissue may disturb the liver's natural design and affect how well it functions. Liver fibrosis is the term for this process.

Cirrhosis, a more serious illness, may ultimately result from liver fibrosis as it advances. Large-scale liver scarring, which may lead to decreased blood flow through the liver and diminished liver function, is a hallmark of cirrhosis. Ascites (fluid buildup in the abdomen), variceal haemorrhage (bleeding from dilated veins in the oesophagus or stomach), portal hypertension (raised pressure in the blood arteries of the liver), and an elevated risk of liver cancer are just a few of the consequences that may result from cirrhosis.

Using imaging methods like ultrasound, CT scans, or MRI, as well as blood tests that gauge liver function and the presence of certain enzymes and proteins, liver fibrosis and cirrhosis are often identified.

Addressing the underlying cause of liver damage is necessary for both preventing and controlling hepatic fibrosis. For instance, controlling viral hepatitis with antiviral drugs, establishing a healthy lifestyle to treat disorders like NAFLD, and limiting alcohol intake may all help to stop or decrease the development of liver fibrosis. In certain circumstances, medical procedures could be advised to control problems and enhance liver function.

ICs activation and myofibroblast progenitor cells

The control of fibrogenic responses in the liver is largely dependent on activated hepatic stellate cells (HSCs), often referred to as myofibroblast precursors or Ito cells (ICs). HSCs have a star-like appearance and a profusion of cytoplasmic lipid droplets while dormant. However, in response to liver damage, HSCs are activated and transdifferentiated into myofibroblasts, which can divide and contract. During this process, they lose their lipid droplets and develop a myofibroblastic phenotype that is characterized by the production of “tissue inhibitors of metalloproteinase 1 (TIMP1) and alpha-smooth muscle actin (α-SMA)”.

Extracellular matrix (ECM) components and inflammatory mediators are produced by activated HSCs, aiding the fibrotic process. After a liver injury has healed, myofibroblasts typically undergo apoptosis or become inactive. However, in cases of chronic liver injury, the continued activation of HSCs upsets the equilibrium between the creation and breakdown of ECM, causing hepatic fibrosis to advance. Additionally, the buildup of HSCs and myofibroblasts that have been activated can restrict the liver sinusoids, obstruct blood flow and nutrient exchange, and ultimately lead to liver failure.

Initiation and persistence are the two phases of HSC activation. Reactive oxygen species (ROS), lipid peroxides, and signals from KCsand endothelial cells are all involved in the early alterations in gene activity caused by damaged hepatocyte products. As a result of paracrine stimulation, increased proliferation, the generation of pro-inflammatory and chemoattractant chemicals, and ECM remodeling, the perpetuation stage entails the maintenance of a functional phenotype and the beginning of fibrosis. Cytokines that promote HSC activation and proliferation contain platelet-derived growth factor (PDGF) and transforming growth factor beta (TGF-). In addition, matrix-degrading enzymes secreted by HSCs, such as matrix metalloproteinases (MMPs), aid in the remodeling of the ECM. The development of fibrosis is aided by the buildup of ECM elements in the liver.

Further enhancing the pro-fibrogenic environment and maintaining HSC activation is the pro-inflammatory milieu and activation of other cell’s types, including Kupffer cell’s, invading immune cell’s, vascular cell’s, and platelets. In conclusion, by creating inflammatory mediators, remodeling the ECM, and assisting in the emergence of a pro-fibrogenic milieu, activated HSCs play a critical role in liver fibrosis. In fact, due to a disorder of constituent creation, the ECM remodeling entails modifications to the matrix's rigidity, flexibility, and density (Figure 3). The ECM is also not inert and may retain growth factors and cytokines generated by physiological processes, which further promotes fibrogenesis, hepatocyte proliferation, and carcinogenesis.

Although turned on ICs account for the majority of the collagen-producing tissues in the fibrous liver (> 90%), mounting evidence indicates that myofibroblasts can also originate from cells in the bone marrow, site fibroblasts, or “epithelial-to-mesenchymal tissue transition (EMT)” from liver cells or choanocytes. For instance, periportal fibrosis may be started by portal vein fibroblasts, which are primarily stimulated by cholestatic injury. In fact, after hepatic damage, observed that gateway cells make up more than 70% of myofibroblasts. Fibrocytes and Mesenchymal Stem Cells (MSCs) are possible origins of bone marrow-derived myofibroblasts. As they accumulate in the wounded tissues over time and have the

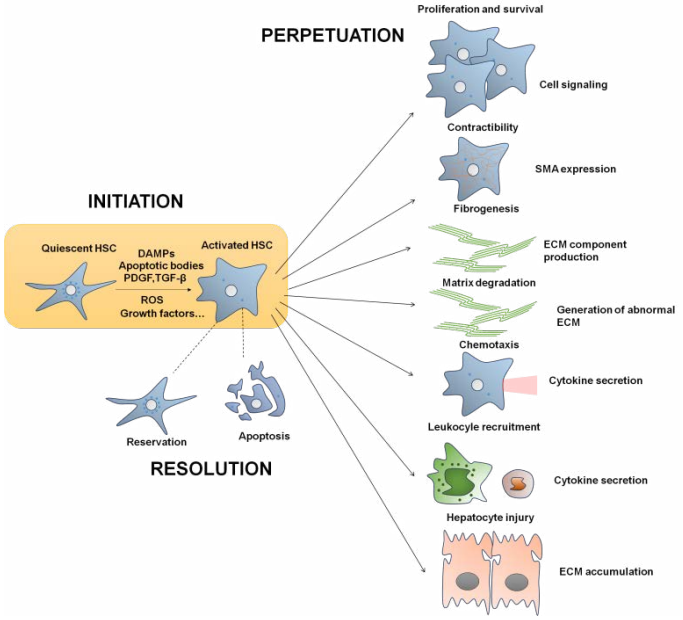

Figure 3. *Stimulation of ICs and subsequent pro-fibrogenic reactions.*

ability to develop into myofibroblasts, the fibrocytes may play a role in advanced illnesses.

Hepatocyte cell death and apoptosis

Hepatocyte loss is an essential early event in developing liver injury in various aetiologies. Dead hepatocytes' production of damaged-associated molecular patterns (DAMPs) is a warning signal, inducing inflammatory and fibrotic reactions in nearby KCsand immune cells (ICs). High-mobility group box 1 (HMGB1), a nuclear protein produced by necrotic hepatocytes capable of interacting with Toll-like receptors (TLRs) to trigger inflammatory and immunological responses, is one DAMP in liver illness that has been intensively researched. Additionally, HMGB1 has been observed to activate ICs and draw pro-inflammatory neutrophils to areas of necrosis in liver cells. Apoptotic structures, on the other hand, can encourage pro-fibrogenic responses and collagen synthesis, in part by activating Fas death receptors and TLR9 on ICs.

In contrast, apoptotic hepatocytes release fewer DAMPs. Lipotoxicity and hepatocellular apoptosis are brought on by hepatocyte lipid excess, notably the buildup of damaging lipid intermediates like saturated free fatty acids (FFAs). FFAs cause the production of ATP, which attracts monocytes, and the death of hepatocytes via the “Tumour Necrosis Factor-Related death-Inducing Ligand Receptor (TRAIL-R2)”. FFAs also cause cytokine release and inflammation by activating the TLR4 pathway in ICs and Kupffer cells. Hepatocyte apoptosis and necroptosis can be accelerated by disrupting the metabolism of cholesterol in hepatocytes, particularly higher free cholesterol levels. Hepatocyte cholesterol crystallization worsens liver fibrosis by recruiting KCsto create "crown-like structures," increasing the cytokines and activating IC. In conclusion, the buildup of lipids and cholesterol in hepatocytes causes hepatotoxicity, inflammation, and fibrosis.

Lymphocytes

Chronic liver damage causes the synthesis of inflammatory mediators and an invasion of leukocytes, especially lymphoid cells in the sub-endothelial region, as previously mentioned. Several chemokines are involved in relationships with vascular cells, further promoting the attraction of lymphocytes from circulation. Importantly, lymphocytes can interact with vascular cells and ECM elements via cell surface integrins, which support fibrogenic reactions and cell proliferation and development. Chemoattractant chemicals drive cells to the site of damage after moving through the endothelium via a complicated procedure. The stimulation of CXCR3 due to its ligands being, such as CXCL9, CXCL10, and CXCL11, generated by ICs and vascular cells, has been demonstrated to facilitate lymphocyte transendothelial motility. Additionally, myofibroblasts release cytokines encouraging lymphocyte migration, such as TGF-, IL-6, and hepatocyte growth factors.

Liver macrophages

The largest NC species in the liver, macrophages are crucial in starting liver failure and scarring. Hepatic macrophages comprise bone marrow-derived monocytes and persistent KCs from the liver. The ejection of DAMPs, the creation of ROS, the anti-viral response, and metabolic signaling brought on by fat accumulation all contribute to the stimulation of and the attraction of monocyte-derived tissues. From conventionally engaged pro-inflammatory macrophages (M1) to selectively engaged immunoregulatory monocytes (M2), monocytes can be categorized into a wide variety of distinct phenotypes. These subtypes have unique biomarkers and functional activities caused by various controllers. Tumor necrosis factor-alpha (TNF-alpha) interleukins are pro-inflammatory cytokines expressed by M1, whereas M2 produces anti-inflammatory cytokines. In reaction to many factors in their surroundings, hepatic macrophages show extraordinary flexibility and can transition to distinct phenotypes, occasionally exhibiting both hallmarks of M1 and M2 development. Numerous studies show that diverse intracellular divisions of macrophages reside in liver’s tissue and contribute to various fibrosis stages. However, it is hard to activities. It was shown that macrophage reduction during the initial stages of damage diminishes the inflammatory reaction, injury, and myofibroblast numbers. Conversely, the failure of ECM disintegration and a less effective repair result from macrophage reduction during healing.

Dysbiosis

The liver-gut axis is a two-way, close connection between the liver and the bacteria in the gut. As a result, the portal vein receives 75% of its blood from the soul with carries intestinal materials. The mucosal barrier, which is made up of the Dysbiosis vasculature barrier and gut epithelium barrier, shapes the interaction between the Dysbiosis microbiota and the liver. For the liver-gut axis to remain in equilibrium, the integrity of the intestine mucous barrier in addition to physiologic makeup of the intestinal microbiota is essential. By raising permeability in the intestines and changing the microbiota, body toxins, particularly alcohol misuse or a NAFLD low-fiber, high-fat diet, have been shown to disturb the equilibrium of the gut.

Consequently, the altered microbiome causes digestive bile acid deconjugation, which leads to the production of other BA that inhibit Farnesoid-X Receptor (FXR) signaling. Hepatic inflamed immune reactions and ICs activation are consequently

triggered by the overgrowth of possibly pathogenic bacteria. Bile acid activated nuclear receptor FXR controls the metabolism of BA, lipids, and glucoses.

Molecules and molecular signalling mechanisms in liver fibro genesis

Wnt/β-catenin signaling.

The "Wnt/-catenin" route is an important one in the field of medicine since it plays an important role in the development of organs. However, "Wnt/-catenin" signals have also been linked to the fibrosis of other organs, most notably the liver. The protein known as beta-catenin serves as the transcription factor and an adhesion molecule. The Wnt protein controls how it is expressed. Glycogen synthase and casein kinase constitute a component of destruction complicated that controls beta-catenin levels in the cytoplasm when the process is inactive. Instead, when the process is active, Wnt creates an arrangement with the proteins Frizzled and the protein linked to the lower-density lipoprotein receptors that stops catenin from being broken down. Catenin then manoeuvres within the cell's nucleus to start the transcription of relevant genes.

Oxidative stress

One of the main aspects causing liver's damage and the start of hepatic fibrosis is oxidation stress (OS). The generation of "ROS and reactive nitrogen species (RNS)" is related to a disturbed equilibrium between cellular pro-oxidant and protective components. ROS, which includes superoxide, hydrogen peroxide (H_2O_2), and hydroxyl radicals, are a family of pro-fibrotic facilitators. Particularly, the processes of Hepatocytes, ICs, and phagocytes exhibit oxidative phosphorylation and lipid peroxidation produce them during normal cell metabolism. ROS can operate as further communications to initiate various cell's' reactions at low concentrations. However, in high concentrations, they cause lipids, proteins, and DNA in cells to be disrupted, which causes hepatocyte necrosis and death. Activated ICs, KCs, and other pro-inflammatory tissues are also stimulated to produce pro-inflammatory and pro-fibrogenic factors by ROS. Ethanol, FFA buildup, iron buildup, and persistent infection by viruses all increase ROS generation.

NLRP3inflammasome -caspase1 signaling.

Hepatic injury and liver fibrosis are caused by liver inflammation, which is a common etiology. Hepatocytes and NCs, including ICs and KCs, exhibit internal complexes of multiple proteins called inflammatory tissues. The "NOD-like receptor (NLR) NLRP3 inflammasome" is the most well-known among the many inflammasomes. It has been shown to be crucial in transforming NAFLD into NASH. Pro-IL1 and pro-IL18 are converted into their mature forms by an internal multiprotein complex known as the NLRP3 inflammasome before caspase 1 is activated. The progression of liver's fibrosis is accelerated by important innate inflammatory response molecules including IL1 and IL18, which start and sustain an abnormal wound-healing response.

PDGF signaling.

PDGF is produced by platelets when the organism is healthy. When the liver is damaged, KCs contribute to the intrahepatic recruiting of platelet. Activated ICs, KCS, and endothelium tissues can all generate PDGF. Finally, because they are found on the surface of ICs, PDGF receptors (PDGFR) have the ability to initiate ICs in an autocrine manner. The division and stimulation of the PDGF-binding receptor causes phosphorylation of tyrosine residues on a variety of internal targets.

TGF-β signaling.

The ability of "PSMAD3L" to quickly translocate into the nucleus promotes the development of ICs and results in a pro-fibrogenic reaction. Due to its significance in activating ECM synthesis, this non-canonical pathway is increasingly considered a promising therapeutic target. TGF-non-canonical pathways like those for "mitogen-activated protein kinase (MAPK), mammalian target of rapamycin (mTOR)", and Rho GTPase have also been discovered in other investigations. The conventional and non-canonical routes each have a role in activating phagocytes, ICs, and both. Figure 4 shows TGF-β signaling.

Chronic liver disease-related pro-fibrogenic mechanisms

Chronic hepatitis B

Approximately 260 million individuals today have chronic HBV infection, primarily in Africa and Asia, despite the availability of effective vaccination. Vertical spread typically leads to persistent sickness, but horizontal transfer in adults frequently causes self-limiting acute infections. Interferon-based medicines and several nucleons (t)ide analogs are currently available as medicinal therapies for individuals with chronic conditions. Although nucleos(t)ide analogs seldom cure viral infections, they do slow down the disease's course, which can direct to liver's cirrhosis and HCC. Like chronic hepatitis C, hepatitis B causes persistent inflammation by releasing DAMPs and inducing the body's antiviral immune response. The precise role of HBV infection in ICs activation is still unclear, in contrast to HCV Higher values on the y-axis suggest a more favourable response to treatment, as seen in the higher reduction of the fibrosis stage, improved liver's function, or decreased levels of particular biomarkers.

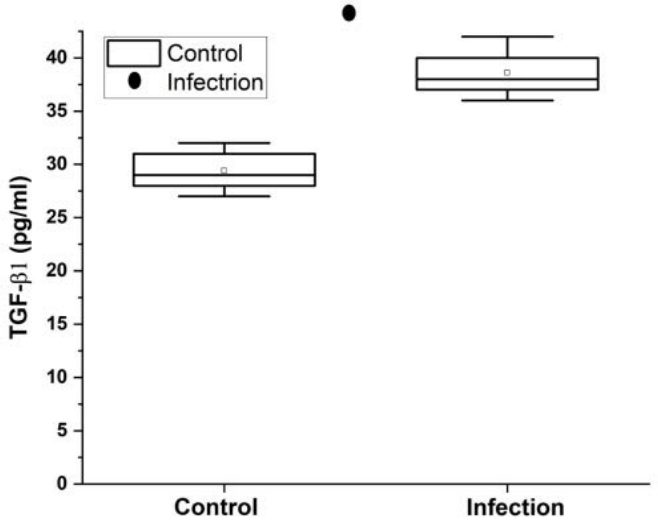

Figure 4. *TGF-β signaling (Score: https://www.spandidos-publications.com/10.3892/etm.2019.8355).*

Chronic hepatitis C

According to reports, human myofibroblasts express HCV host factors and are HCV-permissive. Enhanced collagen formation and multiplication in those tissues point to further possible acute pro-fibrogenic effects of HCV on this population of fibrosis-causing tissues. Although it has been demonstrated that curing HCV infection reduces the risks of liver disease and the chance of developing HCC, severe fibrosis still carries a sizable risk of HCC. According to various researches, chronic HCV infection causes ongoing genetic and transcriptional modifications related to the state of fibrosis and the risk of developing HCC.

Alcoholic liver disease

Globally, liver fibrosis is primarily caused by alcoholic liver damage. Prolonged alcohol consumption activates pro-fibrogenic processes: the conversion of alcohol to acetone in the liver results in the generation of ROS, which can paracrine stimulate ICs. Additionally, the alcohol molecule acetaldehyde is fibrogenic and stimulates TGF- release. Fibroblast to be expressed in ICs in response to acetaldehyde during hours. Several studies also point to alcohol-induced hepatocyte apoptotic as a cause of fibrosis in the livers. Fibrosis is caused by the removal or deactivation of ICs, which may be why the physiological equilibrium between pro- and anti-fibrogenic pathways in persistent ASH has been upset.

Non-alcoholic liver disease

It has been proposed that the name "metabolic-associated fatty liver disease (MAFLD)" be used to refer to the diverse group of patients with this condition. Rather, careful patient classification should be done following current risks and long-term contributors to enable preventative and therapeutic suggestions that treat the root cause of the illness in the complex. Since NAFLD is the cause of persistent liver disease spreading rapidly, it presently impacts 15–30% of adults worldwide and is predicted to develop exponentially over the coming years. NASH refers to the inflamed subtype of NAFLD that is at present characterized by the progression of the disease and elevated HCC risk. For a long time, other possible causes of persistent liver disease, such as drinking alcohol, had to be ruled out before NASH could be diagnosed. There is a connection, nevertheless, as a result of the diversity of aetiologies and diseases. For the diverse range of individuals with this condition, the phrase "metabolic associated fatty liver disease (MAFLD)" was recently proposed as a more relevant and characterizing terminology.

Resolution of liver fibrosis

High mortality and morbidity among those with chronic liver illnesses are caused by the development of liver fibrosis and cirrhosis, placing an enormous financial strain on society. Hepato complications and HCC development are risks that patients with recovered liver disease face on an annual basis of 2-7% and 1-7%, respectively. Collagen is the only histology characteristic in NASH patients independently corresponding with clinical results. At the time, tissue from liver fibrosis is the main cause deaths globally, emphasizing the urgent need for potent anti-fibrotic drugs.

Molecular mechanisms of fibrosis regression

ICs and myofibroblast deactivation or death are linked to fibrosis regression. Therefore, the end of tissues in ICs is a key process in resolving liver fibrosis, whereas enhanced cell mortality in hepatocytes causes' fibrosis. The matrix-degrading enzymes collagenase enzyme and MMPs, secreted by macrophages, play a major role in the fibrotic scar's disintegration. "Scar-associated macrophages (SAMs)", which display a phenotype not classified as M1/M2, have been linked to the resolution of hepatic fibrosis.

Therapeutic intervention

Phytomedicines with multidimensional liver fibrosis effects

During ancient times, patients with cirrhosis, chronic inflammatory conditions, and cytotoxic liver conditions have used silymarin. Due to studies suggesting that the primary ingredient, silibinin, may potentially reduce liver's injury caused by poisons and slow the course of fibrosis, the substance is considered a hepatoprotective drug. Additionally, silymarin has a long history of use in clinical settings to reduce hepatotoxicity caused by alpha-amanitin. As a result, silibinin is thought to be an exact antidote to amanitin. Regarding its medicinal applications, silymarin possesses antiviral properties, antioxidative, anti-inflammatory, and insulin-sensitizing properties in investigations on ALD, NASH, and viral hepatitis, among other aetiologies of persistent liver disease. In a CCl4-based rat model of liver fibrosis, silymarin treatment for twenty-eight days decreased antioxidant Activation, fibro score, and strain of ICs and KCs.

Immune modulation

Galectins bind carbohydrates and are released by various cell types in response to liver injury. They interact with the ECM or receptors located on tissues extracellularly. Elevated amounts of galectin have been seen in inflamed, fibrotic, or malignant liver tissue, according to multiple studies. Gal-3, which is mostly released by stimulated macrophages and has anti-apoptotic, cell distinguishing, and chemotactic capabilities, is entailed in the pathogenesis of Hepatic fibrosis. Patients with NASH tolerated the drug well. The majority of the time reported mild-moderate adverse events were connected-tissue problems, digestive tract, and musculoskeletal diseases.

Reduction of contractility and fibrotic scar evolution

In fibrotic livers, collagen 1 (Col1) is the most prevalent. In mouse models of hepatic were found selective suppression of Col1A1 siRNA, including lipoplexes. As a result, injections reduced collagen production by 90% and total collagen accumulation by 50%. Similar anti-inflammatory properties were also shown by another investigation using mice transgenic with inducible Col1 knockdown. Col1 chaperone Hsp47 can be knocked down by siRNA to stop collagen production. Employed Hsp47 siRNA-coupled liposomes, which are primarily taken up by ICs, to target principally cirrhosis-effector tissues and obtained substantial anti-fibrotic benefits in Three in-vivo models of fibrosis of the liver. Higher values on the y-axis suggest a more favourable response to treatment, as seen in the higher reduction of the fibrosis stage, improved liver function, or decreased levels of particular biomarkers, for example for figure 5 liver stage. This parameter measures the rate at which fibrosis progresses over time. Higher rate of advancement, which indicates that the fibrosis progression rate.

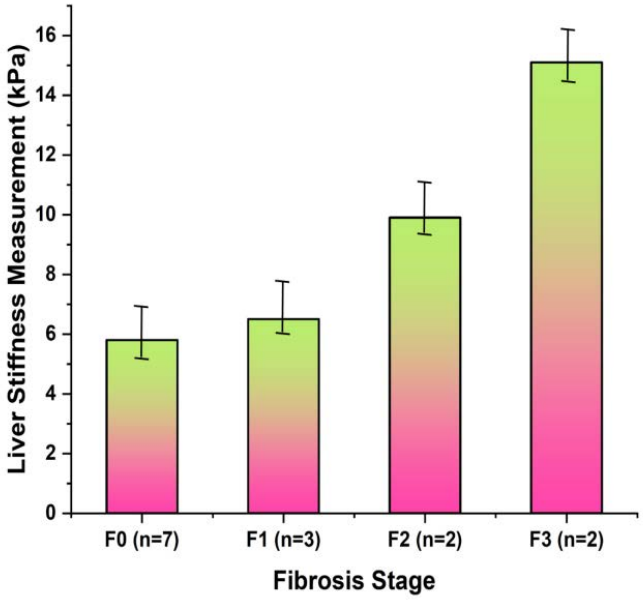

Figure 5. *Fibrosis stage (Source: https://www.researchgate.net/figure/Liver-stiffness-measurement-values-according-to-the-fibrosis-stage-in-patients-who_fig2_344353952).*

Inhibition of ICs activation

FXR ligands were initially created to treat secondary biliary cirrhosis, a kind of cholestatic liver disorder. The retinoid X receptor and FXR heterodimerize due to main BAbinding to FXR, activating the gene transcription function of the latter receptors. BA synthesis, export, as well as enteral and liver absorption are all down regulated as a result of FXR activity in hepatocytes and enterocytes. Additionally, it safeguards the gastrointestinal mucosal barrier, which contributes to preserving the healthy gut flora and, eventually, the liver-gut axis balance. Obeticholic acid (OCA), an FXR agonist, may help to restore the composition of the gut microbiome and lessen the translocation of bacteria and inflammation.

OCA, a synthetic FXR agonist, was developed and approved for use as a second-line therapy in PBC due to its effectiveness over cholestatic and other side effects. These compounds interfere with the physiologic feedback control system of bile acid synthesis. Current research investigations also show that long-term OCA medication improves patients with PBC's histological characteristics, particularly scarring.

Hepatic defense using lipid-lowering substances.

Statins are said to have favorable impacts on cardiovascular morbidity and death, which is particularly important for NASH patients. The reliability of this research is constrained by their retrospective methodology and the absence of strict clinical objectives, such as histologic evaluation of fibrosis, despite consistent evidence suggesting possible anti-fibrotic benefits. Further, the safety record of the drugs for individuals Having fibrosis and chronic liver failure need to be thoroughly assessed due to drug-induced liver damage, a rare but well- stated adverse effect of statins, as well as a higher likelihood of the breakdown of individuals with persistent liver disease due to compromised digestion in the organ.

Hepatic protection via restoration of gut microbiome

Transferring a fecal solution into a patient's body from a healthy donor gut is known as fecal microbiota transplantation or FMT. Fascinatingly, FMT lessened liver damage in a Chronic liver disease in a mouse model brought on by alcohol. Additionally, FMT outperformed probiotics in preventing liver damage because it had a protective impact on the function of the intestinal mucosal barriers. A few minor clinical studies have also shown possible preventive effects of FMT on the development of chronic hepatic disease.

Hepatic Protection Via Reduction of OX

Oxygenative Stress is a foremost contributor causing the onset of liver fibrosis, particularly in NASH. In order to reduce oxidative stress and fibrosis, numerous techniques have been developed and evaluated. Superoxides radicals are formed when bound to the membrane enzyme complexes called NOXs catalyze the reduction of NADH. In hepatic fibro genesis, NOX 1 plays an important role in IC activation, and NOX4 is also engaged in hepatocyte death. Studies conducted both in animal and vitro, the dual inhibitor dramatically reduced liver fibrosis in mouse strains of liver fibrosis based on CCl4 and bile duct closure.

Anti-Fibrotic Compounds Clinical Development: Challenges from Mice to Men

The active ingredient in turmeric, curcumin, has been studied in treating several medical conditions and has been shown to have anti-inflammatory, antiviral, and tumor-preventing properties. Therefore, in NASH in-vivo models, curcumin treatment decreased the onset and progression of liver steatosis, fibrosis, and inflammatory. Concerning the potentially beneficial effects of curcumin in chronic liver illnesses, there aren't many studies underway. Curcumin exhibits limited oral accessibility, similar to silymarin.

Conclusion.

Although there are many different causes of basic liver damage, the primary liver disease aetiologies share common patterns in the progression of fibrous fibrosis. Hepatic fibrosis is brought on by damage to hepatocytes or cholangiocytes regardless of the underlying cause, and the sickness advances predominantly as a result of dysregulated inflammatory responses. Because of this, a prolonged viral infection results in potent immunological reactions that continue to inflame the liver and promote hepatocyte death. A buildup of fatty in the hepatocytes which causes hepatocyte death and oxidative damage, is a hallmark of the evolution of ALD and NASH. The overabundance of ECM, the cellular counterpart of tissue fibrosis, is caused by collagen-producing myofibroblasts activated by recurrent Peak inflammatory responses followed. by antibacterial, repairing immune reactions. While many anti-fibrotic applicant drugs have demonstrated strong anti-fibrotic benefits in animal studies, these results are less certain in human clinical trials. It is conceivable to concentrate on liver fibrosis with medication because some anti-fibrotic drugs have demonstrated possible impacts on the progression of fibrosis in clinical studies. However, more clinical research is required to confirm the durability and long-term relevance of these results.

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