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REVIEW

Chronic liver disease and management with silymarin: an introductory review of a clinical case collection

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Abstract

Chronic liver disease (CLD) is a significant global health concern and generally leads to fibrosis, cirrhosis and hepatocellular carcinoma. Various factors, such as metabolic abnormalities, viral infections, alcoholism, genetics and autoimmune responses, contribute to liver damage. CLD is characterized by different phenotypes, including non-alcoholic fatty liver disease, metabolic-associated fatty liver disease, drug-induced liver injury and alcoholic liver disease. These conditions have seen an increase in comorbidities and hospitalizations over the past decade, imposing a substantial burden on patients and healthcare systems. Understanding the underlying mechanisms of liver injury is crucial for effective management and reducing the clinical and economic burden of CLD. Although several attempts have been evaluated to find a drug therapy option for the management of non-alcoholic fatty liver disease and metabolic-associated fatty liver disease, there is no effective drug approved to date. However, different studies have demonstrated that silymarin, the milk thistle extract, could exert hepatoprotective, antioxidant, anti-inflammatory and antifibrotic properties and should therefore be considered an efficacious, tolerable and promising herbal product for the management of liver activity in CLDs. This review discusses the clinical features, diagnosis and available treatments for major liver diseases, acting as an introduction to a clinical case collection based on the management and treatment of major liver diseases with silymarin.

This article is part of the *Current clinical use of silymarin in the treatment of toxic liver diseases: a case series* Special Issue: https://www.drugsincontext.com/special_issues/current-clinical-use-of-silymarin-in-the-treatment-of-toxic-liver-diseases-a-case-series

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Introduction

Chronic liver disease (CLD) is a major cause of mortality and morbidity worldwide as well as a major factor in the utilization of healthcare resources.[1,2] CLD typically progresses to fibrosis, cirrhosis and, if untreated, hepatocellular carcinoma, resulting in approximately 2 million annual global deaths, 1 million due to cirrhosis complications and 1 million due to viral hepatitis and hepatocellular carcinoma.[1,3] CLD is also associated with an increased risk for cardiovascular disease (CVD), which represents the first cause of death in this clinical setting.[4] Pathophysiological conditions, such as metabolic abnormalities, viral infections, alcoholism, genetic inheritance, autoimmune responses, vascular conditions, drug use and toxins, can damage the liver.

CLD manifests in different phenotypes, including non-alcoholic fatty liver disease (NAFLD), metabolic-associated fatty liver disease (MAFLD), drug-induced liver injury (DILI) and alcoholic liver disease (ALD). Over the past decade, there has been a notable increase in CLD-related comorbidities and hospitalizations, imposing a substantial financial and resource burden on both patients and healthcare systems. A more comprehensive understanding and targeted approach to the primary pathophysiological mechanisms underlying liver injury hold promise for hepatoprotection, potentially alleviating the clinical and economic impact of CLD.[1]

This introductory review aims to provide a solid background on the main clinical features of liver diseases, how they are distinguished, how to diagnose them, and what treatments are currently available. This review is an opening paper to the clinical case collection entitled '*Current clinical use of silymarin in the treatment of toxic liver diseases: a case series*', focused on the management and treatment of major liver diseases with silymarin.[5–10]

Review

Phenotypes of CLDs

Non-alcoholic fatty liver disease

NAFLD is the predominant CLD in Europe, the USA and other regions, with almost 25% of the general population worldwide having NAFLD[11] and 70–90% of patients with obesity or type 2 diabetes (T2D) also being diagnosed with NAFLD.

NAFLD is characterized by the absence of substantial alcohol consumption as the primary causative factor and is closely linked to obesity, insulin resistance, T2D, hypertension, hyperlipidaemia and metabolic syndrome.[3] Patients may experience a spectrum of liver diseases ranging from simple fatty liver to the more advanced stages like non-alcoholic steatohepatitis (NASH), which can progress to cirrhosis, liver cancer and liver-related mortality. Histologically, NAFLD can be categorized into non-alcoholic fatty liver and NASH. Non-alcoholic fatty liver is defined by the presence of over 5% hepatic steatosis without evidence of hepatocellular injury, whilst NASH is characterized by over 5% hepatic steatosis and inflammation with hepatocyte injury, including ballooning, with or without fibrosis.[12]

The most important pathological event in NAFLD pathogenesis is oxidative stress, which refers to the abnormal accumulation of fat and reactive oxygen species (ROS) in liver cells, along with lipid peroxidation in the absence of any secondary cause of hepatic fat. ROS have the potential to inflict damage on cellular proteins, lipids and nucleic acids, resulting in cellular and tissue injury. Oxidative stress further disrupts hepatocyte function, activating inflammatory and fibrogenic pathways that contribute to the progression of NAFLD. Additionally, fat accumulation raises endotoxin levels in the liver, inducing M1 polarization of Kupffer cells – the primary contributors to ROS generation. M1-polarized macrophages produce ROS and pro-inflammatory cytokines, exacerbating liver damage and fostering hepatic fibrosis.[13]

It is recommended that all individuals affected by NAFLD undergo screening for metabolic syndrome.[1]

Metabolic-associated fatty liver disease

MAFLD is a new designation of NAFLD acknowledging metabolic syndrome as a key factor contributing to prolonged liver injury and encompassing a broad range of liver lesions associated with fat accumulation, specifically steatosis.[1,14,15] In the past, a diagnosis of NAFLD relied on the exclusion of significant alcohol consumption or drug-induced liver disease. However, the updated diagnostic criteria for MAFLD discard these exclusionary conditions and introduce 'positive' criteria. Consequently, a diagnosis of MAFLD now hinges on evidence of hepatic steatosis, identified through imaging, blood biomarkers or histology (liver biopsy), coupled with the presence of one of the following criteria: overweight or obesity, T2D, and/or indications of metabolic dysregulation. The latter includes at least two of the following seven alterations: increased waist circumference, low HDL-cholesterol, elevated triglyceridaemia, impaired fasting glucose, heightened blood pressure, elevated C-reactive protein and the presence of insulin resistance,[15] based on the presence of metabolic dysfunction, recognized as a primary driver of the disease. The diagnostic algorithm now relies on 'positive criteria' irrespective of alcohol consumption or concurrent liver diseases, facilitating the identification of a more homogeneous patient group. This shift is expected to guide efforts in stratifying patients with MAFLD and pave the way for a new multidisciplinary approach in the screening and management of fatty liver.[15,16]

Whilst most individuals with MAFLD are asymptomatic and do not experience progressive liver disease, incidental findings of alterations in liver function markers may raise suspicion of steatosis.[14] Individuals with MAFLD often exhibit numerous associated cardiovascular risk factors or comorbidities such as diabetes, atherogenic dyslipidaemia, metabolic syndrome and an elevated likelihood of cardiovascular events.

A recent consensus statement from multiple medical societies proposed a further refinement in nomenclature, replacing NAFLD with metabolic dysfunction-associated steatotic liver disease. This updated definition aims to reduce stigma surrounding the disease, enhance awareness and improve patient stratification. Notably, individuals with steatosis and any one of the cardiometabolic criteria (overweight or obesity, insulin resistance or T2D, treatment for T2D, hypertension or treatment for hypertension, high triglycerides, low HDL-cholesterol, or treatment for dyslipidaemia) are considered to have metabolic dysfunction-associated steatotic liver disease, underscoring the strong association between this liver disease and cardiometabolic abnormalities.[17]

Drug-induced liver injury and herbal-induced liver injury

Drugs represent an alternative cause of fatty liver disease, and DILI is characterized by intracellular lipid accumulation

in hepatocytes with steatotic changes as the predominant histopathological pattern.[18]

Over the past few decades, there has been a significant global surge in the use of herbal supplements, natural products and alternative/traditional medicines.[19,20] These drugs are typically obtained without a prescription, consumed without specific medical guidance or monitoring, and their safety and efficacy are not always well established. Notably, studies worldwide have underscored a rising incidence of herb-induced liver injury (HILI) in recent years, establishing traditional medicine and herbal/dietary supplements as prominent contributors to DILI. The diagnosis of DILI is based on the temporal association between drug administration and elevated levels of liver enzymes and/or alkaline phosphatase, with other causes of liver damage excluded.[18] DILI may either be intrinsic, depending on a specific drug causing dose-dependent hepatotoxicity, or more commonly, idiosyncratic, occurring only after several months of treatment. The pathogenesis of DILI is intricate, with drugs potentially enhancing the accumulation of ROS through various mechanisms.[21]

Alcoholic liver disease

ALD stands as a primary contributor to liver injury on a global scale. The World Health Organization reports that approximately 2 billion people engage in alcohol consumption, with up to 75 million diagnosed with alcohol disorders.[3] Alcohol is implicated in 30–50% of cirrhosis-related deaths worldwide. A concerning trend is the rise of weekend binge drinking, defined as the consumption of four/five or more standard drinks per day within 2 hours on at least one occasion in the last 30 days. This pattern is emerging as a significant health concern, particularly amongst young populations in Western societies.

Clinical manifestations of ALD encompass steatosis, fibrosis, alcoholic hepatitis and cirrhosis. The pathogenesis of ALD involves damage to mitochondrial membranes, accompanied by an escalation in lipid peroxidation. This process leads to discontinuation of the mitochondrial electron transport chain, generation of NADPH and instigation of hepatic inflammatory reactions and fibrosis.[3] Notably, ceasing alcohol consumption has the potential to reverse steatosis, highlighting the importance of intervention in mitigating the progression of ALD.[1]

Risk factors

As indicated previously, considerable evidence highlights that several metabolic syndrome components commonly occur in patients with NAFLD and other liver diseases. Indeed, obesity, insulin resistance, T2D, metabolic syndrome, dyslipidaemia, arterial hypertension and a sedentary lifestyle are common in NAFLD patients and are all risk factors for CVD, which stands as the primary cause of death in patients with NAFLD.

Alarming data on the worldwide obesity epidemic are contributing to a surge in complications associated with obesity, including NAFLD. Notably, the prevalence of NAFLD correlates with the rise in body mass index. Whilst the general population exhibits a NAFLD prevalence of approximately 25%, the prevalence increases to over 90% for individuals with extreme obesity undergoing weight reduction interventions and surgeries.[22]

Alongside the escalating obesity rates, T2D is also on the rise globally and represents a significant risk factor for both NAFLD and NASH, correlating with a more than two-fold elevation in the risk of advanced fibrosis, cirrhosis-related complications and liver disease mortality. The prevalence of NAFLD and NASH in patients with T2D exceeds 60%, and T2D appears to accelerate the progression of NAFLD, serving as a predictor of advanced fibrosis and mortality.[22]

Given the intimate connection between NAFLD, T2D and obesity along with the exploding prevalence of these comorbidities, it is anticipated that NAFLD, MAFLD and NASH prevalence are expected to increase, imposing a significant clinical, economic burden and adversely impacting patient-reported outcomes. This underscores the imperative to incorporate weight management and dietary modifications into any strategy addressing the NAFLD and MAFLD epidemic.[12,23]

With regards to DILI, older age, female sex, genetic factors, excessive alcohol consumption, virus infections and chronic concomitant medications or polypharmacy are all interrelated risk factors. Common triggers for DILI include certain medications such as antituberculosis drugs (anti-TB), antiepileptics and antibiotics.[10] Furthermore, the prolonged and excessive usage of herbal supplements, traditional medicines and dietary supplements has emerged as a significant contributor to HILI.[18,24] Notably, in the collection of clinical cases across the globe presented in this series,[5–10] at least one risk factor was found to be present in all the described CLD cases (except for DILI). This finding is in alignment with the available literature around NAFLD/MAFLD, where most patients have one or more risk factors, including overweight/obesity, T2D, dyslipidaemia or cardiovascular complications like hypertension. In cases with DILI, the common link was advanced age and long duration of hepatotoxic drug exposure. The collection of clinical cases describes the management of CLD with Legalon/silymarin.

Diagnosis and screening

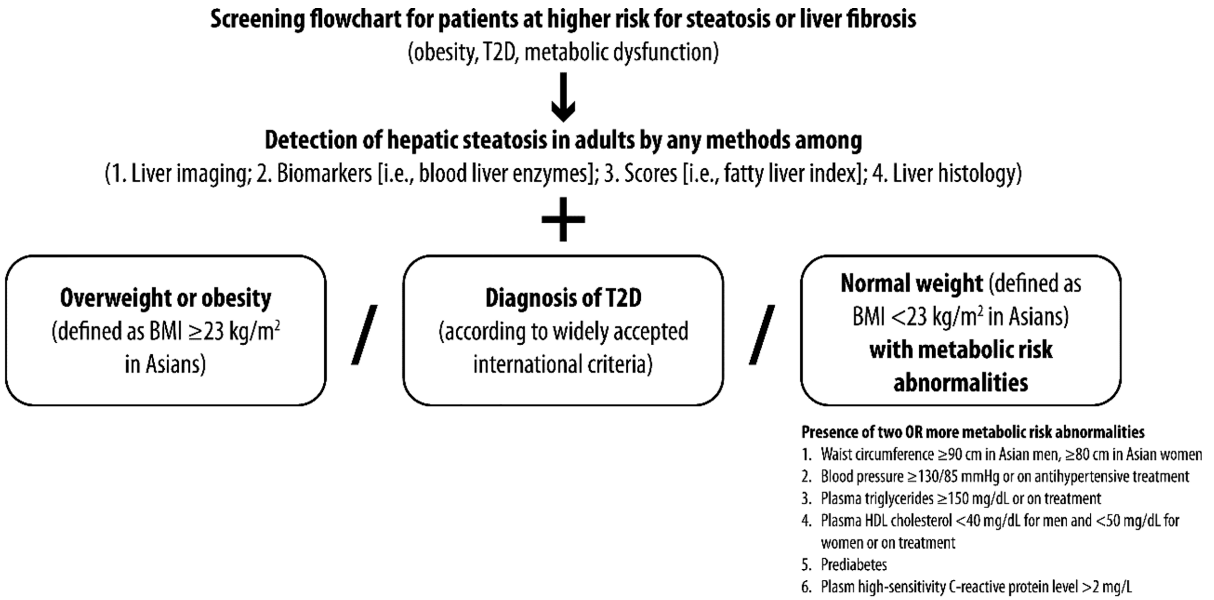
Most patients with NAFLD/NASH remain undiagnosed. Frequently, serum liver enzyme levels are within the normal

range, and patients exhibit no symptoms, rendering the condition asymptomatic. Consequently, it is advisable to consider screening, particularly in high-risk populations, such as in individuals with diabetes and obesity. It is noteworthy that NAFLD and MAFLD can manifest even in the absence of obesity. Hence, indicators like insulin resistance and altered body fat distribution may offer more accurate insights into the presence of fatty liver disease in these individuals. For patients without diabetes, the homeostatic model assessment for insulin resistance (HOMA-IR) serves as a viable tool for estimating insulin resistance.[25] In one of our clinical case collection cases, the HOMA-IR index was assessed.[5]

As stated above, the diagnosis of MAFLD relies on identifying the liver disease in conjunction with meeting at least one of three criteria, including overweight or obesity, T2D, or clinical indicators of metabolic dysfunction such as an elevated waist circumference and abnormal lipid or glycaemic profiles (Figure 1). Generally, the presence of metabolic risk factors may prompt the consideration of screening for fatty liver disease. If NAFLD/MAFLD is suspected, the patient should initially be evaluated by non-invasive tests.[26,27] After initial blood evaluation with liver function and lipid profile tests, detecting hepatic steatosis is crucial to diagnosing fatty liver disease. In the clinical setting, routine imaging, such as abdominal ultrasonography (ultrasound), is typically effective in identifying hepatic steatosis. Liver stiffness and controlled attenuation parameter measurements by vibration-controlled transient elastography (or Fibroscan system) are more sensitive than ultrasonography and could be employed to monitor alterations in hepatic steatosis over time (Figure 1).[26,27]

Equally important is the assessment of liver fibrosis given its strong correlation with future liver-related and CVD morbidity and mortality.[26–28] In particular, the extent of

Figure 1. Management algorithm for MAFLD/NAFLD.



LOW RISK	INTERMEDIATE RISK	HIGH RISK
Can be managed by non-liver specialist (primary care physician, endocrinologist, internist)	Multidisciplinary management, including liver specialist	Multidisciplinary management, including liver specialist
Periodic non-invasive assessment for fibrosis every 2–3 years	Yearly assessment for fibrosis progression	Yearly assessment for cirrhosis and cardiovascular disease
The risk factors, such as diabetes, obesity, hypertension and dyslipidemia, should be managed properly	The risk factors, such as diabetes, obesity, hypertension and dyslipidemia, should be managed properly	The risk factors, such as diabetes, obesity, hypertension and dyslipidemia should be managed properly
Initiate treatment (lifestyle change)	Initiate treatment (lifestyle change)	Treat to prevent liver cirrhosis and cardiovascular complications

Data from Eslam et al. 2020,[27] Cusi et al. 2022,[34] Rinella et al. 2023.[35]

liver fibrosis emerges as the sole indicator of liver damage with the ability to predict an elevated risk of cardiovascular complications.[28] Non-invasive tests of fibrosis can be classified into simple fibrosis scores (aspartate aminotransferase (AST)-to-platelet ratio index, fibrosis-4 index (FIB-4), NAFLD fibrosis score), specific fibrosis biomarkers, and imaging biomarkers. In this context, a FIB-4 index of ≥3.25 indicates a high risk for severe fibrosis (F3–F4).[29] These simple fibrosis scores are inexpensive and consist of clinical and laboratory parameters with modest accuracy and can serve as negative predictive values to exclude advanced fibrosis (Figure 1).

In situations where the existence or severity of concurrent CLD remains uncertain, or if non-invasive testing for fibrosis yields inconclusive results, a liver biopsy can provide valuable assistance in reaching a diagnosis.[25–27] On another front, early prediction of NAFLD and MAFLD, along with the assessment of risk and prognosis for cardiovascular and other potentially hazardous events, can be accomplished through laboratory testing (Figure 1).[26]

In our collection of clinical cases, patients at high risk were screened for CLD. Ultrasound was the most widely considered diagnostic method for evaluating liver damage and diagnosing NAFLD, MAFLD, DILI/HILI or steatohepatitis. Liver function tests and blood biomarkers were performed in all the clinical cases collected, both at baseline evaluation and at follow-up, to assess improvement in liver disease. In the case reports published by Chantarojanasiri[6] and Torre,[5] liver stiffness and controlled attenuation parameter assessments by transient elastography (Fibroscan system) were used to evaluate and monitor hepatic steatosis over time, whilst a hepatic fibrosis biomarker (FIB-4 index) was used to assess the degree of liver fibrosis in the case presented by Hashem.[7]

In agreement with the literature, a diagnostic liver biopsy is necessary only in rare cases with no conclusive evidence from non-invasive tests. In our cases, only one patient underwent liver biopsy because the assessment of fibrosis using non-invasive testing (ultrasound, elastography and platelet count) was inconclusive. In this case, liver biopsy helped the clinician to identify the severity and progression of MAFLD to metabolic-associated steatohepatitis (MASH) with steatosis and advanced fibrosis (F3–S3).[5] In addition, in the case presented by Lee and Tee,[8] an ultrasound-guided liver biopsy supported the diagnosis of grade II NASH.

Therapeutic approach

Management of CLDs has become a significant challenge to healthcare systems. The management should address both the liver disease and its associated metabolic comorbidities, including obesity, hyperlipidaemia, insulin resistance and T2D.[12] Indeed, a successful therapeutic strategy should aim to diminish steatosis and liver injury whilst enhancing the metabolic aspects and reducing the cardiovascular risk closely associated with liver damage. Therefore, lifestyle modification (incorporating dietary changes, weight loss and structured exercise interventions) remains the primary and cornerstone therapy for CLD.[27]

Non-pharmacological interventions

The modification of lifestyle, incorporating improvements in diet and exercise with a focus on weight loss, is advocated for the treatment of patients with NAFLD and MAFLD. It has been demonstrated that weight loss plays a pivotal role in enhancing the histopathological features of liver disease[12] and can lead to reductions in steatosis, resolution of steatohepatitis and fibrosis, and improve a patient's quality of life in a dose-dependent manner,[27] with studies showing that patients losing ≥5% body weight stabilized or improved fibrosis in 94% of cases. In addition, reducing daily caloric intake by at least 30%, or approximately 750–1000 kcal/day, has been shown to improve insulin resistance and hepatic steatosis. Additionally, maintaining physical activity for more than 150 minutes/week or increasing activity by more than 60 minutes/week has a significant impact on reducing liver enzymes, independent of weight loss.[27]

In line with non-pharmacological interventions, our clinical case collection supports the importance of weight loss in the management of fatty liver. A weight-control diet and regular exercise were recommended in various case reports.[5–7]

Pharmacological interventions

Numerous clinical studies have been conducted to find a drug therapy option for NAFLD and MAFLD management; however, despite these efforts, no effective drug has received approval to date, and therapeutic strategies remain largely empirical. However, several categories of drugs have been investigated to manage NAFLD and other liver diseases, aligning with the physiopathological mechanisms of liver injury. Oxidative stress stands out as a key mechanism responsible for liver damage and disease progression in NAFLD/MAFLD, and a therapeutic strategy targeting oxidative stress reduction has been proposed. Current guidelines recommend the use of drugs primarily in patients with biopsy-proven NASH with significant fibrosis, with substantial limitations and as off-label treatments. However, there is acknowledgement that individuals with less severe disease but at a high risk of disease progression could also be considered for treatment.[30]

Different antidiabetic medications have shown reported benefits for patients with fatty liver disease.

Pioglitazone

Pioglitazone, an insulin sensitizer, has demonstrated effectiveness in improving liver histology, including hepatic steatosis, aminotransferases, ballooning necrosis and inflammation, in patients both with and without T2D who have biopsy-proven NASH. It is important to note that, whilst pioglitazone has shown positive effects, its safety and efficacy in treating patients without diabetes and without histological confirmation have not been thoroughly evaluated.[12,30]

Metformin

Metformin has been associated with improvements in serum aminotransferases and insulin resistance. However, despite these positive effects, the use of metformin does not lead to significant improvements in liver histology in patients with NAFLD or NASH.[12]

Statins

The presence of metabolic syndrome increases cardiovascular risk in patients with NAFLD. To mitigate this risk, statins are frequently prescribed, demonstrating a significant reduction in cardiovascular mortality related to various CVDs.[31] Although statins have not been shown to exhibit notable beneficial effects on hepatic histology, they have shown efficacy in reducing cardiovascular morbidity and serum liver enzymes in individuals with fatty liver. Importantly, statins are generally safe with minimal liver toxicity, making them a viable consideration for all patients with MAFLD with hyperlipidaemia.[27] However, prescribing statins can pose challenges in patients with CLD, particularly in presence of an elevation of liver enzymes, and this challenge may contribute to the under-prescription of statins in patients with NAFLD.[32] General physicians often express hesitancy in recommending statin use for patients with baseline elevation of serum liver enzymes and may discontinue medication in the presence of minor alterations.[31] Nevertheless, a recent meta-analysis showed that patients with NAFLD-prescribed statins experienced a reduction of alanine aminotransferase (ALT), AST and gamma-glutamyl transferase, even when baseline liver enzyme levels were elevated.[31] This reinforces the evidence that statin therapy may be considered safe in patients with NAFLD even if liver damage is almost clinically evident.

Vitamin E

Therapeutic strategies targeting oxidative stress reduction have been proposed. Vitamin E has been reported to effectively improve hepatic histology in patients with steatohepatitis as an antioxidant.[27] Oxidative stress plays a crucial role in hepatocellular injury and disease progression in patients with fatty liver disease. The use of vitamin E in fatty liver diseases is linked to a reduction in aminotransferases and improvement in steatosis, inflammation and ballooning but did not exhibit any significant effect on hepatic fibrosis.

Vitamin E supplementation in patients with NAFLD has also been evaluated with a formulation of silymarin, resulting in significant improvements in both liver outcomes and biometric parameters. Thus, incorporating silymarin/vitamin E as a dietary adjunct appears to be potentially more effective than relying on diet alone and may improve patient motivation to sustain lifestyle changes over time.

Silymarin

The extract from milk thistle, known as silymarin, comprises a complex combination of plant-derived elements, predominantly consisting of flavonolignans, flavonoids and polyphenolic molecules. The primary flavonolignans within the silymarin complex include silibinin, silicristin, isosilibinin and silidianin, with silibinin being the most abundant and biologically active isomer.[21] These compounds exhibit antioxidant properties and have shown antifibrotic, anti-inflammatory and hepatoprotective effects in patients with NAFLD.[30] Indeed, several clinical studies on NAFLD, ALD and DILI/HILI have affirmed that silymarin can positively influence the progression of liver disease, alleviate symptoms, improve clinical conditions and enhance the quality of life in affected patients. Importantly, silymarin treatment has been shown to effectively reduce elevated levels of liver enzymes across various patient populations, including those with CLD.[30]

The clinical effects produced by silymarin are likely attributed to its antioxidant activity. Silymarin acts as a scavenger of free radicals, which induce lipid peroxidation, and influences enzyme systems associated with cellular damage, leading to fibrosis and cirrhosis. Through its role in reducing oxidative stress and cytotoxicity, silymarin protects intact liver cells or those not yet irreversibly damaged, earning it consideration as a hepatoprotective agent.[33]

For optimal benefit, the initiation of silymarin treatment is recommended as early as possible in patients with fatty liver (ALD or NAFLD) or DILI; this early intervention is particularly crucial when the liver's regenerative potential is high, and removal of oxidative stress - the underlying cause of cytotoxicity - can yield the most favourable results.[33]

Silymarin efficacy and safety have been demonstrated in all the cases of our collection, and its use was primarily aimed at reducing abnormal liver enzyme levels. Generally, silymarin 140 mg three times a day has been the standard dose to reduce deranged lover enzyme levels at the physiological range (mainly ALT and AST levels), ensuring good adherence and an acceptable safety

profile. Notably, the most promising results were observed in the case presented by Torre,[5] where 4 months of silymarin treatment reduced AST levels by 36 U/L, ALT levels by 74 U/L, and gamma-glutamyl transferase levels by 71 U/L. In a second case report by Lee and Tee,[9] the results were even more striking as, after only 1 month of silymarin treatment, a reduction of 302 U/L, 131 U/L and 74 U/L was observed for ALT, AST and alkaline phosphatase values, respectively, and the level of reductions was maintained for 4.5 years. This hepatic liver enzyme level normalization was consistently observed across all reported cases.

Conclusions

MAFLD is a new designation of NAFLD - the main chronic liver disease worldwide - that establishes a clearer diagnosis through a set of positive diagnostic criteria that allow clinicians to better tailor the practice to target individuals at high risk of developing complications or other metabolic comorbidities.

Silymarin should be considered as an efficacious, well-tolerated and promising herbal remedy for the management of liver function in chronic liver diseases. To maximize its benefits, the initiation of silymarin treatment is recommended at the earliest stages of liver disease, especially in cases of fatty liver disease and other distinct liver manifestations. This early intervention aligns with the heightened regenerative potential of the liver and provides an optimal window for addressing oxidative stress - the underlying cause of cytotoxicity - leading to the most favourable patient outcomes.

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